Helping Hands for
Blood Conservation Techniques
and Perioperative Planning
Part 1a May 2001

PREOPERATIVE TREATMENT

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PREOPERATIVE TREATMENT

Introduction

Are There Risks which have to be taken, when using Blood Free Management?

A. Preoperative Risk Management

1. Preoperative Risk Management General Aspects

(1) Koperna T, Semmler D, Marian F.

*RISK STRATIFICATION IN EMERGENCY SURGICAL PATIENTS: IS THE APACHE II SCORE A RELIABLE MARKER OF PHYSIOLOGICAL IMPAIRMENT?*


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HYPOTHESES: The APACHE II (Acute Physiology and Chronic Health Evaluation II) score used as an intensive care unit (ICU) admission score in emergency surgical patients is not independent of the effects of treatment and might lead to considerable bias in the comparability of defined groups of patients and in the evaluation of treatment policies. Postoperative monitoring with the APACHE II score is clinically irrelevant. DESIGN: Inception cohort study. SETTING: Secondary referral center. PATIENTS: Eighty-five consecutive emergency surgical patients admitted to the surgical ICU in 1999. The APACHE II score was calculated before surgery; after admission to the ICU; and on postoperative days 3, 7, and 10. MAIN OUTCOME MEASURES: APACHE II scores and predicted and observed mortality rates. RESULTS: The mean +/- SD APACHE II score of 24.2 +/- 8.3 at admission to the ICU was approximately 36% greater than the initial APACHE II score of 17.8 +/- 7.7, a difference that was highly statistically significant (P<.001). The overall mortality of 32% favorably corresponds with the predicted mortality of 34% according to the initial APACHE II score. However, the predicted mortality of 50% according to the APACHE II score at admission to the ICU was significantly different from the observed mortality rate (P =.02). In 40 long-term patients (>/=10 days in the ICU), the difference between the APACHE II scores of survivors and
patients who died was statistically significant on day 10 (P =.04). CONCLUSIONS: For risk stratification in emergency surgical patients, it is essential to measure the APACHE II score before surgical treatment. Longitudinal APACHE II scoring reveals continuous improvement of the score in surviving patients but has no therapeutic relevance in the individual patient.


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PROBLEM: Due to their impaired immune function, unusual multimorbidity, and extensive concomitant medication HIV-infected patients impose special and specific demands on those who deal with their perioperative care. PREOPERATIVE ASSESSMENT: Beside standardized diagnostic and therapeutic preparations the preoperative knowledge, quantification, and treatment of HIV-associated opportunistic disorders and chronic organ damage are of particular importance. This requires an extended problem-orientated work-up. Furthermore, antiretroviral medication may interact with perioperatively administered pharmaceutics and lead to hardly foreseeable synergistic and antagonistic adverse effects. In contrast, "drug holidays" favor the development of HIV drug resistance. OPERATIVE MANAGEMENT: Anesthetic and surgical procedures basically depend on the underlying indication and consequently follow common principles. Laparoscopic techniques do not have any specific advantage in HIV-infected subjects. PERIOPERATIVE MORBIDITY: During their postoperative course, HIV-infected patients have to be more often admitted to intensive care unit and kept on artificial respiration unplannedly. Perioperative morbidity of HIV-infected patients increases with the stage of their disease. It is, however, not significantly elevated compared to that of HIV-negative subjects in similar preoperative health condition.


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BACKGROUND: A single preoperative high dose of methylprednisolone (15 to 30 mg/kg) has been advocated in surgery, because it may inhibit the surgical stress response and thereby improve postoperative outcome and convalescence. However, these potential clinical benefits must be weighed against possible adverse effects. OBJECTIVE: To conduct a risk-benefit analysis using a meta-analysis, to compare complication rates and clinical advantages associated with the use of high dose methylprednisolone in surgical patients. METHODS: Randomised controlled trials of high dose methylprednisolone in elective and trauma surgery were systematically searched for in various literature databases. Outcome data on adverse effects, postoperative pain and hospital stay were extracted and statistically pooled in fixed-effects meta-analyses. RESULTS: We located 51 studies in elective cardiac and noncardiac surgery, as well as traumatology. Pooled data failed to show any significant increase in complication rates. In patients treated with corticosteroids, nonsignificantly more gastrointestinal bleeding and wound complications were observed; the 95% confidence interval boundaries of the numbers-needed-to-harm were 59 and 38, respectively. The only significant finding was a reduction of pulmonary complications (risk difference -3.5%; 95% confidence interval -1.0 to -6.1), mainly in trauma patients. CONCLUSION: For patients undergoing surgical procedures, a perioperative single-shot administration of high dose methylprednisolone is not associated with a significant increase in the incidence of adverse effects. In patients with multiple fractures, limited evidence suggests promising benefits of glucocorticoids on pulmonary complications.


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Breast cancer management requires a multidisciplinary approach that is tailored to the patient's stage at presentation, desire for breast conservation or reconstruction, estimation of risk of recurrence, and assessment of the benefits and toxicities of potential adjuvant therapies. At the Lahey Clinic Medical Center, breast surgeons, plastic surgeons, radiation oncologists, and medical oncologists staff the Breast Cancer Treatment Clinic, and work closely together to formulate treatment plans that will optimize the likelihood for cure with an acceptable cosmetic result. This involves careful preoperative work-up, surgical axillary staging, breast irradiation in the setting of breast conservation, and selection of chemotherapy or hormonal therapy if appropriate. Newer aspects of breast cancer care, including sentinel lymph node biopsy, postmastectomy radiation therapy, expanded use of hormonal therapy in younger women, new agents and chemotherapy combinations, and autogenous reconstruction techniques, have become an essential part of the multidisciplinary clinic approach.


RESOURCE UTILIZATION IN CORONARY ARTERY BYPASS OPERATION: DOES SURGICAL RISK PREDICT COST?


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BACKGROUND: Current healthcare trends may render financial risk of cardiac operation a key component of clinical decision making. It has been suggested, based on large cohorts of patients stratified by clinical risk, that the cost of operation can be predicted from models of clinical risk since length of stay (LOS) is highly correlated to clinical risk, and LOS is correlated to hospital costs and charges. Direct correlation of actual surgical costs with surgical risk are lacking. METHODS: Variable direct costs, LOS, and The Society of Thoracic Surgeons predicted mortality risk [STS risk (%)] were collected and analyzed in 628 consecutive patients undergoing coronary artery bypass grafting (CABG) at our institution in 1997. RESULTS: Cost of CABG had a near-normal distribution, and cost in 21 outlier patients (cost > two standard deviations above the mean) was an average 5.3 times normal (median cost). For individual patients, cost was well correlated to LOS (R² = 0.48) but not with STS risk (R² = 0.12). LOS was also poorly predicted by STS risk (R² = 0.09). However, despite its poor prediction of cost, STS risk was an unbiased estimator over the entire population. A result manifested, when patients were grouped into similar risk (<1%, 1-2%, 2+-3%, 3+-5%, 5+-10%, and >10%) cohorts, by high correlation between cost and STS risk (R² = 0.99), cost and LOS risk (R² = 0.99), and LOS and STS risk (R² = 0.97). CONCLUSIONS: Our data demonstrated that, in large CABG cohorts, surgical risk models can accurately predict cost of CABG. However, despite a trend for increasing cost with increasing STS risk, surgical risk models based on preoperative data are poor predictors of cost in individual patients. Use of these models should be limited to analysis of cost trends in cardiac operation, but not for predicting financial risk in individual patients during clinical decision making.


INTRAOPERATIVE PHYSIOLOGIC VARIABLES AND OUTCOME IN CARDIAC SURGERY: PART I. IN-HOSPITAL MORTALITY.


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BACKGROUND: Risk stratification schemes have been developed to predict outcome of coronary artery bypass grafting (CABG) procedures, which are predominately based upon unalterable preoperative patient characteristics. The purpose of this study was to determine if minimum intraoperative hematocrit, maximum glucose concentration, mean arterial pressure on cardiopulmonary bypass, or duration of bypass influence risk-adjusted in-hospital mortality after CABG. METHODS: Outcome data from 2,862 CABG patients were merged with intraoperative physiologic data. A preoperative mortality risk index was calculated for each patient. Variables found significant (p<0.05) by univariate logistic regression were tested in a multiple variable model to determine risk-adjusted association with mortality. RESULTS: Overall mortality rate was 1.85%.
The preoperative risk index was significantly associated with mortality ($p = 0.0001$). No significant association was present between mortality and intraoperative variables. Preexisting hypertension was an independent predictor of mortality after controlling for risk index and bypass duration.

CONCLUSIONS: Preexisting hypertension proved to be an independent predictor of mortality in our patient population. This study found no evidence to support the hypothesis that mean arterial pressure less than 50 mm Hg, lower hematocrit, or elevated glucose while on bypass increases inhospital mortality.

(7) Coselli JS, LeMaire SA, Miller CC 3rd, Schmitting ZC, Koksoy C, Pagan J, Curling PE
MORTALITY AND PARAPLEgia AFTER THORACOABDOMINAL Aortic ANEURYSM REPAIR: A RISK FACTOR ANALYSIS.

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BACKGROUND: Recent recommendations regarding thoracoabdominal aortic aneurysm (TAAA) management have emphasized individualized treatment based on balancing a patient’s calculated risk of rupture with their anticipated risk of postoperative death or paraplegia. The purpose of this study was to enhance this risk-benefit decision by providing contemporary results and determining which preoperative risk factors currently predict mortality and paraplegia after TAAA surgery.

METHODS: Risk factor analyses based on data regarding 1,220 consecutive patients undergoing TAAA repair from 1986 through 1998 were performed using multiple logistic regression with stepwise model selection. RESULTS: The 30-day mortality rate was 4.8% (58 of 1,220) and the incidence of paraplegia was 4.6% (56 of 1,206). For elective cases, predictors of operative mortality included renal insufficiency ($p = 0.0001$), increasing age ($p = 0.0005$), symptomatic aneurysms ($p = 0.0059$), and extent II aneurysms ($p = 0.0054$). Extent II aneurysms ($p = 0.0023$) and diabetes ($p = 0.0402$) were predictors of paraplegia. CONCLUSIONS: These risk models may assist in decisions regarding elective TAAA operations. For patients who are acceptable candidates, contemporary surgical management provides favorable results.

MONITORING OF ANTIMICROBIAL PROPHYLAXIS IN GENERAL SURGERY.

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The incidence of infections in general surgery is related to different factors. Cost-benefit analysis of antimicrobial prophylaxis is positive, even though incorrect use may be even dangerous (development of resistance and/or superinfections, for instance). The authors report data on a study concerning a total of 316 patients divided into two series, who had antimicrobial prophylaxis before a surgical operation. 274 patients out of 316 (or 86.7%) had an ultra-short (one-shot-only) or short (<24 hours) prophylaxis, 42 (13.3%) standard (>24 hours). The operations performed were classified following class of contamination, i.e. I (clean), II (potentially contaminated), III (contaminated). Antibiotics used were ceftriaxone, cefepime, ceftriaxone, piperacillin and gentamicin in combination. A total of 16 postoperative infections was observed (5%); 11 of these 16 belonged to class III operations. Escherichia coli and Staphylococcus aureus were isolated in most of the infected wounds. The data confirm what is reported in the literature. The authors conclude that a preoperative single-shot 3rd or 4th generation cephalosporin reduces the incidence of wound infections in clean and clean-contaminated surgery.

(9) Silvestri L, Maffessanti M, Gregori D, Berlot G, Gullo A
USEFULNESS OF ROUTINE PRE-OPERATIVE CHEST RADIOGRAPHY FOR ANAESTHETIC MANAGEMENT: A PROSPECTIVE MULTICENTRE PILOT STUDY.

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A prospective multicentre pilot study was undertaken in 20 Italian hospitals to assess the influence of a routine pre-operative chest radiograph on anaesthetic management and to characterise which
patients might benefit from it. A total of 6111 patients undergoing elective surgery and submitted for routine pre-operative chest radiograph were enrolled. Abnormal preoperative chest radiographs were reported in 1116 patients (18.3%). Pre-operative chest radiograph altered the anaesthetic management (i.e. useful pre-operative chest radiograph) in 313 patients (5.1%). Male sex, age > 60 years, ASA classes > or = 3, respiratory diseases, and the presence of two or more co-existing diseases were significantly related to the probability of a useful pre-operative chest radiograph using multivariate analysis (P < 0.01). The classification of the surgical intervention and, of the co-existing diseases, the presence of cardiac disease had a very low influence when determining the probability that a pre-operative chest radiograph would be useful. A simple equation includes the effects of all the variables studied and allows calculation of the probability of a useful pre-operative chest radiograph. This study indicates that in healthy, female, < or = 60-year-old patients, submitted for standard surgery, the probability of a useful pre-operative chest radiograph ranges from 0.2% to 3.5% according to the hospital. The probability increases in male or elderly subjects, or in the presence of co-existing respiratory diseases, or in ASA classes > or = 3, but there is a wide variation between hospitals.

(10) Murdoch CJ, Murdoch DR, McIntyre P, Hosie H, Clark C

THE PRE-OPERATIVE ECG IN DAY SURGERY: A HABIT?

Anaesthesia 100 Sep; 54(9):907-908.

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As the population presenting for day-case surgery and anaesthesia increases, so does the challenge of adequate pre-operative assessment. Although an electrocardiogram is frequently performed, its value in day-case surgery remains unproven. One thousand, one hundred and eighty-five patients presenting for day-case surgery were assessed. One hundred and fifty-four (13%) were referred for electrocardiogram according to well-recognised criteria for the prediction of coronary artery disease. They were read independently by the anaesthetist responsible for the case and by an experienced cardiologist. A significant abnormality was noted in 26% of electrocardiograms, most frequently in patients referred with hypertension. There was a good correlation between the reports of the anaesthetist and cardiologist. Only 20% of those patients with an abnormal electrocardiogram had their surgery postponed. No adverse events occurred in patients proceeding to surgery despite the abnormalities. We conclude that a resting electrocardiogram is of limited value in risk stratification of patients undergoing day-case surgery.

(11) Nierman E, Zakrzewski K

RECOGNITION AND MANAGEMENT OF PREOPERATIVE RISK.


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Internists are frequently asked to do preoperative consultations and to manage perioperative complications. Realistic goals are to identify patient factors that increase the risk of surgery, to quantify this risk in order to make decisions about the appropriateness of and timing of the surgery, to provide recommendations on how to minimize the risk, to identify and manage coexisting medical conditions and their associated medication requirements, to monitor the patient for perioperative problems, and to make recommendations to deal with these problems when they occur. With few exceptions, nonselective imaging and laboratory screening tests have repeatedly been shown to be of little value when the history and physical do not suggest a problem. The risk associated with the planned surgery can be estimated, with the most common serious complications being cardiac events. Updated versions of Goldman's risk indices are particularly helpful for this. Clinical variables are optimally combined with selective stress testing to discern which patients will benefit from preoperative revascularization. This has been studied best in the setting of vascular surgery. A critical guiding principle is that the value of revascularization must be judged in terms of long term gains rather than just immediate perioperative benefit. Other interventions include the selective use of beta blockers, adequate analgesia for all, control of hypertension, and appropriate volume management, especially in the settings of preexisting CHF or valvular disease. It must also be recognized that perioperative ischemia and CHF often present atypically. An approach that combines aspects of both the ACC/AHA and the ACP guidelines seems optimal. A variety of
noncardiac issues must also be addressed. Postoperative pulmonary complications are common, especially with preexisting pulmonary disease, thoracic and upper abdominal surgery, and obesity. PFTs and ABGs are indicated in selected patients. Stopping smoking, incentive spirometry, and selective use of bronchodilators and antibiotics are helpful. Patients with rheumatologic diseases have specific concerns based on systemic manifestations of disease including anemia, thrombocytopenia, pulmonary fibrosis, pericarditis, and hypercoagulability: medication effects particularly from steroids and nonsteroidal anti-inflammatory drugs; and specific joint problems including contractures and atlantoaxial joint instability. Diabetes increases the risk of infection and cardiac complications. Prevention of ketoacidosis and glucose control are necessary and can be achieved through a variety of approaches, depending on whether the patient suffers from Type 1 or Type 2 diabetes. The threshold for transfusion has increased in recent years, as has the use of erythropoietin and autologous blood donation. There is no longer an absolute hemoglobin that requires transfusion, although most require transfusion for hemoglobins less than 8 mg/dL, especially in the setting of cardiac disease and bloody surgery. The elderly require surgery at an increased rate and often do not do as well as younger patients. The primary issues are, however, not their age but their increased frequency of underlying disease and diminished reserve. The latter makes them prone to postoperative delirium, sensitivity to medications, and cardiac and pulmonary problems. Despite the many diseases that patients often have and the stresses of surgery itself, modern anesthetic and surgical techniques allow almost all patients to undergo necessary procedures at acceptable risk. The internist plays a critical role in minimizing this risk even further.

(12) Chung F, Mezei G, Tong D
PRE-EXISTING MEDICAL CONDITIONS AS PREDICTORS OF ADVERSE EVENTS IN DAY-CASE SURGERY.

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We have developed mathematical models to estimate the risk of perioperative adverse events in patients with pre-existing conditions undergoing day-case surgery. We studied 17,638 consecutive day-case surgical patients in a prospective study. Preoperative, intraoperative and postoperative data were collected. Risk modelling was performed with backward stepwise multiple logistic regression and validated on a separate subset of our patients. Eighteen pre-existing conditions were entered into the model. We adjusted for age, sex, and duration and type of surgery. Seven associations between pre-existing medical conditions and perioperative adverse events were statistically significant. Hypertension predicted the occurrence of any intraoperative event and intraoperative cardiovascular events. Obesity predicted intraoperative and postoperative respiratory events, and smoking and asthma predicted postoperative respiratory events. Gastro-oesophageal reflux predicted intubation-related events. The presented models of risk estimation were validated internally and provided a useful tool for accurate risk estimation.

(13) Older P, Hall A, Hader R
CARDIOPULMONARY EXERCISE TESTING AS A SCREENING TEST FOR PERIOPERATIVE MANAGEMENT OF MAJOR SURGERY IN THE ELDERLY.

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STUDY OBJECTIVE: To develop an integrated strategy for the identification and subsequent management of high-risk patients in order to reduce both morbidity and mortality. DESIGN: Prospective consecutive series in which all patients underwent cardiopulmonary exercise (CPX) testing. SETTING: CPX laboratory and level 3 ICU and high-dependency unit (HDU) of a metropolitan teaching hospital. PATIENTS: Five hundred forty-eight patients >60 years of age (or younger with known cardiopulmonary disease) scheduled for major intra-abdominal surgery. INTERVENTIONS: The patients were assigned to one of three management strategies (ICU, HDU, or ward) based on the anaerobic threshold (deltaT) and ECG evidence of myocardial ischemia as determined by CPX testing that was performed as part of the presurgery evaluation, and by the expected oxygen demand stress of the surgical procedure. RESULTS: Overall mortality was 3.9%. Forty-three percent of deaths were attributed to poor cardiopulmonary function, as detected preoperatively. There were no deaths related to cardiopulmonary complications in any patient deemed fit for major abdominal surgery and ward management, as determined by CPX testing.
CONCLUSIONS: In elderly patients undergoing major intra-abdominal surgery, the AT, as determined by CPX testing, is an excellent predictor of mortality from cardiopulmonary causes in the postoperative period. Preoperative screening using CPX testing allowed the identification of high-risk patients and the appropriate selection of perioperative management.

(14) Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R
EUROPEAN SYSTEM FOR CARDIAC OPERATIVE RISK EVALUATION (EUROSCORE).

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OBJECTIVE: To construct a scoring system for the prediction of early mortality in cardiac surgical patients in Europe on the basis of objective risk factors. METHODS: The EuroSCORE database was divided into developmental and validation subsets. In the former, risk factors deemed to be objective, credible, obtainable and difficult to falsify were weighted on the basis of regression analysis. An additive score of predicted mortality was constructed. Its calibration and discrimination characteristics were assessed in the validation dataset. Thresholds were defined to distinguish low, moderate and high risk groups. RESULTS: The developmental dataset had 13,302 patients, calibration by Hosmer Lemeshow Chi square was $(8) = 8.26 (P < 0.40)$ and discrimination by area under ROC curve was 0.79. The validation dataset had 1479 patients, calibration Chi square $(10) = 7.5, P < 0.68$ and the area under the ROC curve was 0.76. The scoring system identified three groups of risk factors with their weights (additive % predicted mortality) in brackets. Patient-related factors were age over 60 (one per 5 years or part thereof), female (1), chronic pulmonary disease (1), extracardiac arteriopathy (2), neurological dysfunction (2), previous cardiac surgery (3), serum creatinine $>$200 micromol/l (2), active endocarditis (3) and critical preoperative state (3). Cardiac factors were unstable angina on intravenous nitrates (2), reduced left ventricular ejection fraction (30-50%: 1, <30%: 3), recent (<90 days) myocardial infarction (2) and pulmonary systolic pressure $>$60 mmHg (2). Operation-related factors were emergency (2), other than isolated coronary surgery (2), thoracic aorta surgery (3) and surgery for postinfarct septal rupture (4). The scoring system was then applied to three risk groups. The low risk group (EuroSCORE 1-2) had 4529 patients with 36 deaths (0.8%), observed mortality (0.56-1.10) and for expected mortality (1.27-1.29). The medium risk group (EuroSCORE 3-5) had 5977 patients with 182 deaths (3%), observed mortality (2.62-3.51), predicted (2.90-2.94). The high risk group (EuroSCORE 6 plus) had 4293 patients with 480 deaths (11.2%) observed mortality (10.25-12.16), predicted (10.93-11.54). Overall, there were 698 deaths in 14,799 patients (4.7%), observed mortality (4.37-5.06), predicted (4.72-4.95). CONCLUSION: EuroSCORE is a simple, objective and up-to-date system for assessing heart surgery, soundly based on one of the largest, most complete and accurate databases in European cardiac surgical history. We recommend its widespread use.

(15) Doyle RL
ASSESSING AND MODIFYING THE RISK OF POSTOPERATIVE PULMONARY COMPLICATIONS.
Chest 1999 May;115(5 Suppl):77S-81S.

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Preoperative pulmonary evaluation and preparation involve first identifying patients at risk for complications and then attempting to modify that risk. For most patients without underlying lung disease, a thorough history and physical examination and preoperative instruction in the use of incentive spirometry is sufficient. In patients with known or suspected lung disease, preoperative pulmonary function tests, while unproven as prognostic tools, may reduce risk by aiding in medical management, and in the case of the lung resection candidate, by helping determine very directly his or her viability for the procedure.

(16) Ferguson MK
PREOPERATIVE ASSESSMENT OF PULMONARY RISK.
Chest 1999 May;115(5 Suppl):58S-63S.
STUDY OBJECTIVES: A summary of current modalities for and the utility of preoperative assessment of pulmonary risk. DESIGN: Review of recent literature published in the English language. SETTING: Not applicable. PATIENTS OR PARTICIPANTS: Patients who undergo elective cardiothoracic or abdominal operations. INTERVENTIONS: Not applicable. MEASUREMENTS AND RESULTS: Postoperative pulmonary complications occur after 25 to 50% of major surgical procedures. The accuracy of the preoperative assessment of the risk of such complications is only fair. The routine assessment for all preoperative patients includes age, general physiologic status, and the nature of the planned operation. Specific tests such as measurement of spirometric values and diffusing capacity are indicated routinely only for patients who are candidates for major lung resection or esophagectomy. CONCLUSIONS: Pulmonary complications are an important form of postoperative morbidity after major cardiothoracic and abdominal operations. The appropriate preoperative assessment of the risk of such complications is well defined for lung resection and esophagectomy operations, but it requires refinement for general surgical and cardiovascular operations.

(17) Miller KH, Grindel CG, Patsdaughter CA
RISK CLASSIFICATION, CLINICAL OUTCOMES, AND THE USE OF NURSING RESOURCES FOR CARDIAC SURGERY PATIENTS.
Northeastern University, Boston, Mass., USA.
Several studies have used risk classification models to examine the effect of preoperative risk factors on operative morbidity and mortality. However, previous research has not linked risk classification models to factors such as frequency of postoperative complications, length of intensive care unit stay, mortality, and the use of nursing resources. This article reports on significant differences in clinical outcomes and hours of nursing care by risk classifications.

(18) Janvier G
[PREOPERATIVE EVALUATION OF HEMORRHAGIC RISK]. [ARTICLE IN FRENCH]
Ann Fr Anesth Reanim 1998;17 Suppl 1:2s-5s
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Evaluation of bleeding risk before surgery requires both precise knowledge of epidemiological data relating to haemostasis disorders and a true clinical approach to help guide the diagnosis. The patient's individual and familial history is recovered during both the interview with the anaesthesiologist and the clinical examination. Preoperative haemorrhage risk prevalence is 1/40,000 patients in patients with asymptomatic congenital haemostasis disorders with low bleeding and 1/2,000 patients for acquired asymptomatic haemostasis disorders. Deficits in haemostasis factors, i.e., congenital disorders with haemorrhage potential, have an overall prevalence of 1/6,500 patients. Whatever the clinical case, haemorrhage disorders will arise in patients with either congenital or acquired bleeding abnormalities without symptoms. To work in close collaboration with haemobiologists and to request appropriate biological screening tests, it is therefore important to take into account prevalence data according to the surgical environment from which the patient will benefit.

2. Preoperative Risks Anesthesiological Considerations

(1) Vilarasau Farre J, Martin-Baranera M, Oliva G.
[SURVEY ON THE PREOPERATIVE EVALUATION IN CATALONIAN SURGICAL CENTERS. I. WHAT IS THE PREOPERATIVE ROUTINE]? [ARTICLE IN SPANISH]
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OBJECTIVE: To describe the preoperative assessment procedures currently used in hospitals in Catalonia (Spain). SUBJECTS AND METHODS: The study population consisted of all heads of departments of anesthesiology, general and gastrointestinal surgery, orthopedic surgery and traumatology of hospitals and clinics in Catalonia with active operating theaters. Information was obtained by self-administered questionnaire prepared by an interdisciplinary team. RESULTS: Of the 227 questionnaires sent, 139 (61%) were answered and returned. A preoperative assessment visit was programmed according to 112 (81%) of the respondents and 123 (89.8%) reported following a protocol that included ordering preoperative tests. The same tests were ordered for all patients by 25% of the respondents. A chest film and an ECG were always ordered according to 61 and 65%, respectively, and always when the patient was over a certain age according to 36 and 32%, respectively. Coagulation and blood sugar tests and a complete blood workup were always ordered according to 94%, 95% and 89%, respectively. Tests were considered valid for less than six months by most. CONCLUSIONS: This survey provides evidence of widespread use of preoperative assessment, although application falls short of including all scheduled patients. According to these results, selective protocols for ordering complementary preoperative tests are rarely applied.


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OBJECTIVE: Previous studies have provided evidence of the existence of differences in preoperative assessment practices and have questioned the usefulness of generalized testing for all patients. The objective of this study was to determine the attitudes and opinions of anesthesiologists and surgeons about their application of preoperative assessment procedures and their knowledge of the scientific principles underlying their practice. SUBJECTS AND METHODS: A questionnaire was mailed to 227 specialists in anesthesiology and postoperative intensive care, general and gastrointestinal surgery, orthopedic surgery and traumatology of all hospitals in Catalonia (Spain) with active operating theaters. RESULTS: The overall response rate was 61% of the surveyed population, with 86% of the Catalan hospitals represented. The medical literature supports the routine performance of a chest x-ray and an ECG in the opinion of 17 and 26% of the respondents, respectively. Those two procedures are always ordered by 43 and 37%, respectively, even if they believe that the medical literature does not support generalized application. Legal protection was given as the reason for routine ordering of preoperative tests in asymptomatic patients, and 89% believed that a protocol for selective preoperative assessment procedures would improve efficiency. CONCLUSIONS: This study reveals a discrepancy between the opinions of professionals involved in preoperative assessment and their real practice in Catalan hospitals, probably influenced by perceived need for legal protection.


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The pre-operative anaesthetic records of 195 patients were analysed for the presence of 12 agreed core items of pre-operative assessment. This study showed that anaesthetists recorded 26.8 per cent of this information. In up to one-third of patients the following were recorded: smoking history, family history, gastro-oesophageal reflux, airway assessment, dental assessment, chest examination, heart-sounds and blood pressure. Previous anaesthesia, drug history and allergies were recorded in one to two-thirds of patients. Past medical history was recorded in over two-thirds of patients. With a view to improving the level of record-keeping, a formatted, pre-printed pre-operative assessment record was introduced into practice and two months later the audit was repeated. A small but non-significant improvement in record keeping was observed. An argument is made for the introduction of an interdisciplinary, unified anaesthetic pre-operative record.
(4) Knape JT
PREOPERATIVE SCREENING AND PREOPERATIVE MEDICINE: A NEW CHALLENGE FOR ANESTHESIOLOGY AND INTERNAL MEDICINE.

(5) Ejima Y, Satoh S, Hoshi K, Hasegawa R, Matsukawa S, Hashimoto Y
[ANESTHETIC MANAGEMENT OF A PATIENT WITH HEMOPHILIA A FOR LEFT MODIFIED BLALOCK-TAUSSIG SHUNT]. [ARTICLE IN JAPANESE]
Masui 2000 Jan;49(1):30-32.
Department of Intensive Care Unit, Tohoku University Medical Hospital, Sendai.
We gave anesthesia to a patient with hemophilia A for left modified Blalock-Taussig shunt. The patient was a twenty-five-day-old boy with pulmonary atresia. We performed the bolus injection test of factor VIII concentrate in the preoperative period. His factor VIII activity increased from 9.3 to 113.3% after a bolus injection of 165 units. To keep his factor VIII activity above 80% in the perioperative period, a bolus of 125 units of recombinant factor VIII concentrate was injected at anesthesia induction, 125 units 2 hours after the start of the operation, and 125 units 6 hours after the end of the operation. Factor VIII activity 2 hours after anesthesia induction increased only 37.8%, and we had to infuse recombinant factor VIII concentrate additionally. We measured factor VIII activity during the operation, and he finally received total of 415 units of factor VIII concentrate. Hydroxyethyl starch infusion, blood transfusion and bleeding in the perioperative period might have caused the factor VIII activity to decrease beyond our expectation. We should infuse factor VIII concentrate properly measuring the factor VIII activity during this operation.

(6) Mangano DT
ASSESSMENT OF THE PATIENT WITH CARDIAC DISEASE: AN ANESTHESIOLOGIST'S PARADIGM.
Anesthesiology 1999 Nov;91(5):1521-1526.
San Francisco Veterans Affairs Medical Center, California 94121, USA.
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(7) Shaw A, Boscoe MJ
ANAESTHETIC ASSESSMENT AND MANAGEMENT OF CARDIAC PATIENTS FOR NON-CARDIAC SURGERY. PART 2: MANAGEMENT.
Department of Anaesthetics, Harefield Hospital, Middlesex, UK.
In an earlier article in this journal (June 1999) we discussed the risk that the presence of cardiac disease poses to patients undergoing non-cardiac surgery. We outlined factors in the patient's medical history, examination findings and the value of various tests in arriving at an overall assessment of risk for any given patient. In this article we concentrate on the management of these patients as they undergo surgery itself. We shall consider what measures may usefully be employed in order to minimise the risk of an adverse cardiac event occurring in the perioperative period.

(8) Keller C
THE OBESE PATIENT AS A SURGICAL RISK.
Semin Perioper Nurs 1999 Jul;8(3):109-117
Department of Family Nursing Care, University of Texas Health Science Center at San Antonio 78284-7951, USA.
Obesity has become a serious problem in the United States. The increasing prevalence of obesity makes the likelihood of clinicians caring for these individuals high. Several considerations for the preoperative care of these patients include appropriate assessment, particularly of the cardiopulmonary systems, and a thorough clinical examination. Intraoperative concerns include
appropriate equipment, medication, positioning, and cardiopulmonary monitoring. Postoperative care for the obese patient requires special concern regarding oxygenation and wound healing.

(9) Koch CG, Estafanous FG
ANESTHESIA FOR CORONARY ARTERY SURGERY.
Cleveland Clinic Foundation, Ohio.
Anesthesia for coronary artery bypass graft surgery continues to evolve in concert with changing epidemiology, advances in technology and pharmacology, and refinement in technique. The profile of the cardiac surgical patient is increasingly characterized by factors such as advanced age, reoperation, combination procedures, complications of acute intervention, and more complex disease. Preoperative risk factor assessment offers a means of strategic planning and intervention. Choice of anesthetic agents, muscle relaxants, and anti-ischemic medications affects both perioperative management and long-term outcome. Transesophageal echocardiography and ST segment monitoring are being applied more broadly. Advances have been made in managing postoperative blood loss. As in other areas of medicine, economic issues have become important considerations in anesthesia for the cardiac surgical patient.

3. Preoperative Risk Analysis in Gastrointestinal Surgery

(1) Strobel O, Uhl W, Scholz T, Buchler MW
[UNTITLED GERD-PREOPERATIVE EVALUATION] [ARTICLE IN GERMAN]
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Gastroesophageal reflux disease (GERD) has a high prevalence of 40% in Western countries. A dysfunction of the lower esophageal sphincter of unknown origin is the main etiology. Less common pathophysiological reasons are disorders of esophageal motility, delayed gastric emptying, gastric acid hypersecretion and bile reflux. As causal surgical therapy for these disorders fundoplication has been developed 50 years ago. This technique uses a wrap of gastric fundus around the distal esophagus as reflux barrier. Because of severe postoperative complications (dysphagia, gas bloat syndrome, gastric ulcer) and recurrence after fundoplication, medical therapy became the treatment of choice with the development of H2-receptor antagonists and proton pump inhibitors in the 1970s. However, after improvement of surgical technique and introduction of laparoscopic fundoplication in 1991 surgery offers a secure and effective causal therapy. Randomized controlled trials proof the superiority of fundoplication versus medical therapy in regard of long term results, recurrence and cost effectiveness as well as the superiority of laparoscopic versus conventional open fundoplication in regard of recovery and cost effectiveness with equal long term results. Therefore, laparoscopic fundoplication by an experienced laparoscopic surgeon is the surgical therapy of choice. However the high prevalence of GERD requires careful selection of patients for surgery. A thorough preoperative evaluation including upper gastrointestinal endoscopy with biopsy, esophageal manometry and 24 h-pH monitoring as well as upper gastrointestinal contrast study is essential. Today the indication for fundoplication is seen in young symptomatic patients, requiring a long-term medical therapy, in hiatal hernia with threatening complications as well as in complications of severe GERD, especially Barrett-esophagus. At present the advantages of total (Nissen) or partial (Toupet) wrap as well as the benefit of dissection of the short gastric vessels for total fundoplication are still unclear, especially concerning long-term results. To answer these technical questions further randomized controlled trials with long-term follow-up have to be performed.

(2) Place RJ, Coloma M, White PF, Huber PJ, Van Vlymen J, Simmang CL
KETOROLAC IMPROVES RECOVERY AFTER OUTPATIENT ANORECTAL SURGERY.
Department of Surgery, University of Texas Southwestern School of Medicine, Dallas, USA.
PURPOSE: The purpose of this study was to evaluate the effectiveness of ketorolac combined with local anesthetics for anorectal surgery. METHODS: From June 1998 through March 1999, 123 outpatients undergoing anorectal surgery were entered into a prospective, randomized, double-blinded study involving three treatment groups. All patients received intravenous sedation consisting of fentanyl and a propofol infusion, with a local anesthesia mixture of lidocaine, bupivacaine, and bicarbonate. Group A (41 patients) received placebo (saline) injections. Group B (41 patients) received 60 mg of intravenous ketorolac at the onset of the procedure, and Group C (41 patients) received 60 mg of ketorolac mixed with the local anesthetic. Data were analyzed using analysis of variance and chi-squared tests. RESULTS: All groups had similar demographic characteristics and operative procedures. Twenty-nine of the 123 patients were human immunodeficiency virus-positive. There was no difference in operative or anesthesia time. Anesthesia and fluids given were similar in across groups. A significantly higher percentage of Group A patients had pain (34 percent) and required additional oral analgesia (20 percent) in the Day Surgery Unit. Only 5 percent of Group B and Group C patients complained of pain, with oral analgesics given to 2 percent of Group B and none in Group C. Voiding difficulties were more common in Group A patients, one patient requiring catheterization. CONCLUSION: The addition of ketorolac (60 mg), either intravenous or injected with local anesthetics, reduces voiding problems and significantly decreases postoperative analgesic requirements in outpatients undergoing anorectal surgery.

(3) Plank LD, Hill GL
USE OF BIOIMPEDANCE SPECTROSCOPY TO ASSESS EFFECTS OF PERIOPERATIVE TREATMENT WITH GROWTH HORMONE ON FLUID CHANGES IN PATIENTS UNDERGOING MAJOR SURGERY.
Ann N Y Acad Sci 2000 May;904:190-192
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(4) Tonelli F, Valanzano R, Messerini L, Ficari F
LONG-TERM TREATMENT WITH SULINDAC IN FAMILIAL ADENOMATOUS POLYPOSIS: IS THERE AN ACTUAL EFFICACY IN PREVENTION OF RECTAL CANCER?
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BACKGROUND AND OBJECTIVES: Ileorectal anastomosis (IRA) is still used in the treatment of familial adenomatous polyposis (FAP). Sulindac appears to induce regression of colorectal adenomas; however, its effects in long-term therapy and in preventing carcinoma remain unclear. METHODS: Fifteen FAP patients treated by IRA received sulindac (200 mg/day) for a mean period of 48.6 +/- 28.7 (range 12-124) months. Number, size, and type of rectal polyps were assessed by endoscopic and histological evaluation every 6 months. RESULTS: Significant regression of polyps was observed in all patients after 6 months (P < 0.02). However, after a mean of 48.6 +/- 28.7 months, both number and size of polyps increased again, showing no statistical difference with baseline values. Minute polyps appeared reddish, while the largest lesions were flat or slightly elevated. Endoscopic polypectomy was necessary in 9 patients and transanal surgical excision in 3. Two patients were submitted to restorative proctectomy because of a large polyp with severe dysplasia and a rectal cancer, respectively. CONCLUSIONS: Sulindac appears to influence the morphological appearance of polyps in FAP patients, inducing apparent regression. However, at a dose of 200 mg, it does not influence the progression of polyps toward a malignant pattern. Copyright 2000 Wiley-Liss, Inc.

(5) No Authors listed
EARLY MANAGEMENT OF BLEEDING OESOPHAGEAL VARICES.
Bleeding from oesophageal varices is a medical emergency with high mortality. In this article, we discuss its early management, focusing on the use of endoscopic therapy and drug treatment.
PREOPERATIVE ENDOSCOPIC ULTRASONOGRAPHY IN PATIENTS WITH GASTRIC CANCER.
Tumori 2000 Mar-Apr;86(2):139-141.

Centro Riferimento Oncologico della Basilicata, Rionero in Vulture PZ, Milan, Italy.
AIMS AND BACKGROUND: There is a need to assess the accuracy of endoscopic ultrasonography (EUS) in the diagnosis and staging of gastric cancer, especially in the early and very advanced stages of the disease when the therapeutic approach is still controversial. METHODS: A retrospective study was performed on 79 patients with gastric cancer in order to compare the stage defined by preoperative EUS with that assessed histopathologically. All patients underwent laparotomy for final diagnosis, staging, and eventually treatment. The results of EUS were correlated with the histologic findings of the resected specimens. RESULTS: In the uT1 group, which corresponds to early gastric cancer, the diagnosis was histologically confirmed in 85.7% of the cases. In patients with advanced tumors defined as uT3-uT4, i.e., tumors infiltrating the serosa or neighboring structures, the diagnostic concordance was 91.1%. In contrast, concordance for less advanced lesions confined to the muscular layer was only 31.2%. As regards the lymph nodes, they were defined metastatic in 31 patients and confirmed to be histologically involved in 77.4%. In contrast, when the lymph nodes were assessed as negative at EUS, they proved to be metastatic in more than half the cases.
CONCLUSIONS: From the data it appears that EUS has proven to be valuable in correctly staging most of the patients. EUS shows not only tumor depth and local spread but also the passage from a pathologic to a normal wall and lymph node metastasis. EUS appears to represent an important advance in the staging and follow-up of patients with gastric cancer. Instruments and techniques will continue to evolve, but the next level of research should be designed to show that the improved staging provided by EUS has clinical utility and can affect patient outcome. It is noteworthy that the highest accuracy of EUS has been shown in those conditions (uT1 and uT3-4) which currently are under consideration for a therapeutic approach that differs from the standard one.

(7) Bartels H, Stein HJ, Siewert
RISK ANALYSIS IN ESOPHAGEAL SURGERY.
Recent Results Cancer Res 2000;155:89-96.

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The postoperative mortality after esophagectomy still remains a major factor influencing the prognosis of esophageal cancer and largely depends on the patient's preoperative physiological status. A composite scoring system was developed to predict the risk of esophagectomy, based on quantitative assessment of preoperatively available physiological parameters. The scoring system was reviewed retrospectively on operated patients and evaluated prospectively in two subsequent patient groups. An initial retrospective multivariate analysis of 432 esophagectomy patients identified a compromised general status (p = 0.001) and poor cardiac (p < 0.001), hepatic (p < 0.05), and respiratory (p < 0.05) functions as independent predictors of a fatal postoperative course. Based on the relative risks associated with individual impaired organ functions—general status 3.6, cardiac function 2.8, hepatic function 2.1, pulmonary function 1.7—a composite risk score was established. A prospective study in 121 patients confirmed that this composite scoring system provides better identification of high-risk patients than does any of the individual parameters alone. Including this composite score into the process of patient selection and choice of procedure resulted in a decrease of postoperative mortality from 9.4% (52/553) to 1.2% (4/323) (p = 0.001). The risk of death after esophagectomy for esophageal cancer can be objectively assessed prior to surgery and quantified by a composite risk score. This score provides a useful tool in refining the criteria of patient selection for resection and choice of procedure, and markedly reduces postoperative mortality when applied prospectively.

RECURRENT AND SURVIVAL AFTER SURGICAL MANAGEMENT OF RECTAL CANCER.
Department of Surgical Services, Capital Health Region, and the Vancouver Island Cancer Centre, Victoria, British Columbia, Canada.

BACKGROUND: Reported local recurrence rates for rectal cancer are significantly reduced using a combination of superior surgical technique, in the form of total mesorectal excision, and routine radiotherapy. In an attempt to determine the effectiveness of current local management strategies, a review of Vancouver Island Cancer Centre patients with rectal cancer was performed and the overall local recurrence rate was identified. METHODS: We retrospectively reviewed the charts of 272 rectal cancer patients from 1988 to 1998. Two hundred and twenty-nine patients met inclusion criteria. Analysis of patient factors included age, gender, type of surgery, and adjuvant therapy. Tumors were assessed for level, stage, and grade. Local recurrence and distant metastases were also documented. Variables influencing local recurrence in this group were identified and disease-free and actuarial survival determined. RESULTS: Of 229 patients analyzed, 12.7% (29) had local recurrences. Variables influencing local recurrence were number of positive lymph nodes, vascular invasion, and neural invasion. There was no significant difference in local recurrence between patients having anterior resection and those having abdominoperineal resection. None of the patients who received preoperative radiotherapy had a local recurrence. Actuarial disease-free survival was 87% at 5 years. CONCLUSIONS: Limiting local recurrence is one of the most important goals in the treatment of rectal cancer. It is essential to identify those patients with "high risk” tumors as identified by endorectal ultrasound or pathologic features. These patients comprise the group most likely to benefit from a routine mesorectal excision combined with adjuvant radiotherapy.


(1) Calafiore AM, Gallina S, Di Mauro M, Gaeta F, Iaco AL, D'Alessandro S, Mazzei V, Di Giammarco G.

MITRAL VALVE PROCEDURE IN DILATED CARDIOMYOPATHY: REPAIR OR REPLACEMENT?


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BACKGROUND: Mitral valve (MV) procedure for dilated cardiomyopathy is becoming popular. We analyzed the indications to MV repair or replacement according to our 10-year experience. METHODS: From January 1990 to May 2000, 49 patients with dilated cardiomyopathy (12 idiopathic and 37 ischemic) underwent MV operation, 29 repair and 20 replacement. Preoperative evaluation included measurement of MV coaptation depth (CD) as a mirror of the abnormalities of MV apparatus leading to functional mitral regurgitation. RESULTS: Thirty-day mortality was 4.2% (2 patients). One-, 3-, 5-, and 10-year actuarial survival was, respectively, 90%, 87%, 78%, and 73%. The possibility of survival with at least one New York Heart Association functional class improvement was 88%, 76%, 71%, and 65%. Return of functional mitral regurgitation after MV repair was nearly inevitable; however, using a scale from 0 to 4, mean postoperative functional mitral regurgitation was 1.2+/-.0.8 when preoperative MVCD was 10 mm or less and 2.5+/-.0.7 when preoperative MVCD was 11 mm or higher (p < 0.05). Globally, functional results were not influenced by the strategy of treatment (MV repair or replacement). CONCLUSIONS: Mitral valve operation can give satisfying survival and good palliation of dilated cardiomyopathy. The MVCD can be helpful in the choice of the surgical strategy on the MV.

(2) Rohde LE, Polanczyk CA, Goldman L, Cook EF, Lee RT, Lee TH

USEFULNESS OF TRANSTHORACIC ECHOCARDIOGRAPHY AS A TOOL FOR RISK STRATIFICATION OF PATIENTS UNDERGOING MAJOR NONCARDIAC SURGERY

Am J Cardiol 2001 Mar 1;87(5):505-509.

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Transthoracic echocardiography (TTE) is frequently ordered before noncardiac surgery, although its ability to predict perioperative cardiac complications is uncertain. To evaluate the incremental
information provided by TTE after consideration of clinical data for prediction of cardiac complications after noncardiac surgery. 570 patients who underwent TTE before major noncardiac surgery at a university hospital were studied. Preoperative clinical data and clinical outcomes were collected prospectively according to a structured protocol. TTE data included left ventricular (LV) function, hypertrophy indexes, and Doppler-derived measurements. In univariate analyses, preoperative systolic dysfunction was associated with postoperative myocardial infarction (odds ratio [OR] 2.8, 95% confidence interval [CI] 1.1 to 7.0), cardiogenic pulmonary edema (OR 3.2, 95% CI 1.4 to 7.0), and major cardiac complications (OR 2.4, 95% CI 1.3 to 4.5). Moderate to severe LV hypertrophy, moderate to severe mitral regurgitation, and increased aortic valve gradient were also associated with major cardiac events (OR 2.3, 95% CI 1.2 to 4.6; OR 2.2, 95% CI 1.1 to 4.3; OR 2.1, 95% CI 1.0 to 4.5, respectively). In logistic regression analysis, models with echocardiographic variables predicted major cardiac complications significantly better than those that included only clinical variables (c statistic 0.73 vs 0.68; p <0.05). Echocardiographic data added significant information for patients at increased risk for cardiac complications by clinical criteria, but not in otherwise low-risk patients. In conclusion, preoperative TTE before noncardiac surgery can provide independent information about the risk of postoperative cardiac complications in selected patients.


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The aim of the PERISCOP study was to evaluate the predictive value of cardiological investigations performed after recent coronary bypass surgery with regards to cardiac event and mortality at one year. The treatment of lipid abnormalities was also analysed. This first article describes the methodology and patient characteristics at inclusion. This prospective national multicenter trial included 2065 patients (86% men) with an average age of 63.1 +/- 9.9 years. The number of diseased vessels was 2.6 +/- 0.6. Preoperative left ventricular function was normal (ejection fraction 60 +/- 13%). Revascularisation was complete in 73% of cases (22% of arterial grafts). The cardiological investigations were performed at Day 20 +/- 10 after surgery. The duration of exercise on stress testing was 429 +/- 170 seconds. It was positive or doubtful in 9% of cases. Ventricular arrhythmias were observed in 6.5% of cases. The blood pressure response was abnormal in 6% of cases. Holter monitoring showed a median number of ventricular extrasystoles over 24 hours of 44. Three per cent of patients had one episode of ventricular tachycardia and 7% had ischaemic episodes. The echocardiographic index of segmental contractility was on average 1.75 (ejection fraction: 52.6%). The lipid analysis performed at one month, under lipid therapy in 34% of cases, showed a total cholesterol level at 1.91 +/- 0.10 g/l, an LDL-cholesterol of 1.27 +/- 0.08 g/l. The therapeutic target (LDL-cholesterol < 1 g/l) was attained in 46% of cases with treatment and in 18% of cases without treatment.

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BACKGROUND: HDL cholesterol (HDL-C) is an important independent predictor of atherosclerosis, yet the role that HDL-C may play in the prediction of long-term survival after CABG remains unclear. The risk associated with a low HDL-C level in post-CABG men has not been delineated in relation to traditional surgical variables such as the use of arterial conduits, left ventricular function, and extent of disease. METHODS AND RESULTS: We performed a prospective, observational study of 432 men who underwent CABG between 1978 and 1979 in whom preoperative HDL-C values were available. Baseline lipid and lipoprotein values, history of diabetes
mellitus and hypertension, left ventricular ejection fraction, extent of disease, and use of internal thoracic arteries were recorded. Hazard ratios (HRs) were determined in the patients with and without a low HDL-C level, which was defined as the lowest HDL-C quartile (HDL-C $\leq$ 35 mg/dL). After adjustment for age, as well as for baseline metabolic parameters and surgical variables just noted, HDL-C corresponded to both overall (HR 0.40, CI 0.20 to 0.83, P=0.01) and event-free (HR 0.41, CI 0.24 to 0.70, P=0.001) survival. Patients with a high HDL-C level (>35 mg/dL) were 50% more likely to survive at 15 years than were patients with low HDL-C level (HDL-C $\leq$ 35 mg/dL) (74% versus 57% adjusted survival, respectively; HR 1.72, P=0.005). In addition, HDL-C showed a strong effect on time-to-event survival such that patients with an HDL-C level of >35 mg/dL were 50% more likely to survive without a subsequent myocardial infarction or revascularization (HR 1.42, P=0.02).

**CONCLUSIONS:** HDL-C is an important predictor of survival in post-CABG patients. In this study of >8500 patient-years of follow-up, HDL-C was the most important metabolic predictor of post-CABG survival. One third fewer patients survive at 15 years if their HDL-C levels are $\leq$ 35 mg/dL at the time of CABG. The measurement of HDL-C provides a compelling strategy for the identification of high-risk subsets of patients who undergo CABG.

(5) Sundt TM, Bailey MS, Moon MR, Mendeloff EN, Huddleston CB, Pasque MK, Barner HB, Gay WA Jr.

**QUALITY OF LIFE AFTER AORTIC VALVE REPLACEMENT AT THE AGE OF >80 YEARS.**


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**BACKGROUND:** The optimal management of aortic valve disease in patients >80 years old depends on functional outcome as well as operative risks and late survival. **METHODS AND RESULTS:** We retrospectively identified 133 patients (62 men, 71 women) aged 80 to 91 years (mean 84+/-3 years) who underwent aortic valve replacement alone or in combination with another procedure between January 1, 1993, and April 31, 1998. Demographics included hypertension 68%, diabetes mellitus 17%, and history of stroke 11%. Operative (30 day) mortality rate was 11%. Urgent or emergent surgery, aortic insufficiency, and perioperative stroke or renal dysfunction were risk factors for operative death by multivariable analysis. Intensive care unit and total hospital length of stay were prolonged at 6.2 and 14.7 days, respectively. Late follow-up between July 1, 1998, and November 1, 1999, was 98% complete. Actuarial survival at 1 and 5 years was 80% and 55%, respectively. Predictors of late mortality were preoperative or perioperative stroke, chronic obstructive pulmonary disease, aortic stenosis, and postoperative renal dysfunction. The mean New York Heart Association functional class for 65 long-term survivors improved from 3.1 to 1.7. Quality of life assessed with the Medical Outcomes Study Short Form-36 was comparable to that predicted for the general population >75 years old. **CONCLUSIONS:** Functional outcome after aortic valve replacement in patients >80 years old is excellent, the operative risk is acceptable, and the late survival rate is good. Surgery should not be withheld from the elderly on the basis of age alone.

(6) Das MK, Pellikka PA, Mahoney DW, Roger VL, Oh JK, McCully RB, Seward JB

**ASSESSMENT OF CARDIAC RISK BEFORE NONVASCULAR SURGERY: DOBUTAMINE STRESS ECHOCARDIOGRAPHY IN 530 PATIENTS.**

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**OBJECTIVE:** This study evaluated the incremental value of dobutamine stress echocardiography (DSE) for assessment of cardiac risk before nonvascular surgery. **BACKGROUND:** Limited information exists regarding the preoperative assessment of cardiac risk in patients with known or suspected coronary artery disease who are to undergo nonvascular surgery. **METHODS:** All patients (303 men, 227 women) who underwent DSE before nonvascular surgery and did not sustain an intervening event (coronary revascularization or cardiac event) were studied. Clinical, electrocardiographic and rest and stress echocardiographic variables were evaluated to identify predictors of postoperative cardiac events. **RESULTS:** Events occurred in 6% of patients: 1 cardiac death and 31 nonfatal myocardial infarctions. All of these patients had inducible ischemia on DSE (sensitivity 100%, specificity 63%). Multivariate predictors of postoperative events in patients with
ischemia were history of congestive heart failure (p = 0.006; odds ratio = 4.66; confidence interval 1.55 to 14.02) and ischemic threshold less than 60% of age-predicted maximal heart rate (p = 0.0001; odds ratio 7.002; confidence interval 2.79 to 17.61). Clinical variables of Eagle's index identified 21% of patients as low, 68% as intermediate and 11% as high risk preoperatively; the postoperative event rates were 3%, 6%, and 14%, respectively. Dobutamine stress echocardiography identified 60% of patients as low (no ischemia), 32% as intermediate (ischemic threshold 60% or more) and 8% as high risk (ischemic threshold < 60%); postoperative event rates were 0%, 9% and 43%, respectively. CONCLUSIONS: In this population of patients with known or suspected coronary artery disease evaluated before nonvascular surgery, DSE had incremental value over clinical, electrocardiographic and rest echocardiographic variables for identifying patients at low, intermediate and high risk for postoperative cardiac events. Ischemia occurring at less than 60% of age-predicted maximal heart rate identified patients at highest risk.

(7) Samain E, Farah E, Leseche G, Marty J
GUIDELINES FOR PERIOPERATIVE CARDIAC EVALUATION FROM THE AMERICAN COLLEGE OF CARDIOLOGY/AMERICAN HEART ASSOCIATION TASK FORCE ARE EFFECTIVE FOR STRATIFYING CARDIAC RISK BEFORE AORTIC SURGERY.
J Vasc Surg 2000 May;31(5):971-979
Department of Anesthesiology, Beaujon Hospital, University Xavier Bichat, Clichy, France.
PURPOSE: We assessed whether the American College of Cardiology/American Heart Association (ACC/AHA) task force guidelines for perioperative cardiac evaluation could reliably stratify cardiac risk before aortic surgery. METHODS: We retrospectively applied the guidelines to a closed database, set up prospectively. The setting was a referral center in an institutional practice with hospitalized patients. The closed database included 133 patients who had a routine cardiac examination, which comprised an estimation of functional capacity and noninvasive testing, before aortic surgery. This cardiac evaluation led to the proposal of coronary angiography in 23 patients and to treating an underlying coronary artery disease in 21 patients (including three myocardial revascularizations). One patient died after myocardial revascularization, and two patients died of cardiac causes after aortic surgery. The algorithm of the ACC/AHA guidelines was applied independently by two investigators to each patient's file that was included in the existing database. The main outcome measure was a comparison between cardiac risk stratification with the ACC/AHA guidelines and the results of the routine cardiac evaluation. RESULTS: The ACC/AHA guidelines were successfully applied to all 133 files by the two investigators. After applying the algorithm, 73 patients were stratified as low cardiac risk, and 60 patients were stratified as high risk. The 21 patients who had undergone a preoperative coronary artery disease optimization were stratified as high risk by means of the ACC/AHA guidelines. The patients who died from cardiac causes were stratified as high risk by means of the ACC/AHA guidelines, whereas none of the patients stratified as low risk died during hospitalization. CONCLUSION: The ACC/AHA guidelines were effective in stratifying cardiac risk by using clinical predictors and an estimate of the physical capacity of the patient. Their use may allow a reduction in unnecessary noninvasive testing in patients stratified as being at low risk, while permitting the selection of all patients likely to benefit from preoperative coronary artery disease optimization.

(8) Ferreira MJ
THE ROLE OF NUCLEAR CARDIOLOGY FOR PREOPERATIVE RISK ASSESSMENT PRIOR TO NONCARDIAC SURGERY.
Department of Cardiology, Coimbra University Hospital, Portugal.
Preoperative risk assessment, before noncardiac surgery, aims to reduce mortality and morbidity, during the perioperative period. Cardiac risk could be minimised through treatment and stabilisation of the underlying disease, careful monitoring and prophylactic medications. However, cardiac complications, especially, ischemic events are still frequent causes of death during surgery and hospital recovery. A teamwork approach that involves cardiologist, anaesthesiologist and surgeon is required for optimal risk assessment and monitoring in the perioperative period. The incidence of coronary artery disease increases with age and with the presence of risk factors such as
diabetes or hypertension. There is also a strong relation between coronary and vascular disease as they are part of the same pathophysiology and have common risk factors. Careful cardiac evaluation is essential when vascular surgery is planned. Clinical evaluation is the first step of preoperative risk assessment and allows the identification of low and high-risk patients. If there is absent or low cardiac risk, surgery may be carried out. In the presence of high-risk markers and if the surgery is elective, coronary arteriography should be considered before non-cardiac surgery. The information provided by non-invasive diagnostic testing is essential in those patients with an intermediate clinical risk for cardiac events. Concerning coronary artery disease, myocardial function and ischemic burden are strong prognostic markers and in this particular setting, nuclear cardiology can play an important role. The extent and localisation of ischemia is well defined by myocardial perfusion scintigraphy and ventricular function can be evaluated by radionuclide ventriculography or by gated perfusion studies.


**CORONARY AND MAJOR VASCULAR DISEASE: AGGRESSIVE SCREENING AND PRIORITY-BASED THERAPY.**


Department of Cardiac Surgery, University of Milano, Italy.

It is well known that atherosclerosis can simultaneously affect different vascular subsystems, and patients with diffuse atherosclerosis can be a major management problem both for preoperative evaluation and for intraoperative management. The authors have conducted a prospective study to evaluate the prevalence of coronary artery disease in arteriopathic patients, and vice versa, to assess the effectiveness of aggressive screening together with a priority-based approach. Study 1 consisted of 1,000 consecutive non-emergent patients who were affected by abdominal aortic or carotid disease and were screened for the presence of coronary artery disease before surgery with a newly developed clinical risk assessment. They were stratified into three risk categories with different preoperative evaluation strategies. When coronary artery disease was concomitantly demonstrated in these patients, the choice of surgical method was based on priorities, and the use of combined surgical procedures as required. In study 2, 1,000 consecutive patients that required coronary angiography for suspected coronary artery disease were screened for the presence of carotid or abdominal aortic pathology, directly in the cardiac catheter laboratory during coronary angiography, by obtaining views of the aortic arch and abdominal aorta. Surgical approaches paralleled those of study 1. The results for study 1 showed that 720 patients (72%) were affected by abdominal aortic disease, 238 (24%) by carotid disease and 42 (4%) by both pathologies. Significant coronary artery disease was found in 152 patients (15%), of these 123 (81.5%) were affected by abdominal aortic disease and 29 (18.5%) by carotid artery disease. Abdominal aortic surgery was performed directly or after myocardial revascularization, with an overall mortality rate of 4/718 (0.6%), and a perioperative myocardial infarction rate of 10/718 (1.4%). For patients with carotid artery disease, the completed screening and possible therapy for coronary artery disease resulted in an in-hospital mortality rate of 2/238 (0.8%), and a perioperative myocardial infarction rate of 2/238 (0.8%). There were no significant differences in these rates between patients with or without coronary artery disease. Results for study 2 showed that of the 1000 consecutive patients enrolled for suspicion of coronary artery disease, 767 (77%) were affected by significant coronary artery disease. Among these, 38 (4.9%) had a surgically correctable aortic disease and 31 (4%) a surgically correctable carotid disease, which was monolateral and bilateral in 22 (74%) and nine (26%) patients, respectively, and four (0.5%) were diagnosed with both pathologies. These arteriopathic patients were treated for their coronary and vascular disease with no in-hospital mortality nor perioperative myocardial infarction. In patients with multiple vascular involvement, both coronary and vascular surgery can be performed with low risk when aggressive screening and priority-based therapy are adopted.

(10) Busch T, Sirbu H, Aleksic I, Friedrich M, Dalichau H

**IMPORTANCE OF CARDIOVASCULAR INTERVENTIONS BEFORE SURGERY FOR ABDOMINAL AORTIC ANEURYSMS.**


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Preoperative screening, and **interventional and surgical therapy of cardiovascular diseases** are of pivotal importance for successful outcome after **abdominal aortic aneurysm surgery**. In a retrospective study, all patients who underwent surgery for **abdominal aortic aneurysm** were reevaluated by **preoperative diagnostic and therapeutic interventions** for cardiovascular disease. Two study periods (1980-1989 and 1990-1996) were compared. Of 603 patients operated upon for **abdominal aortic aneurysm** between 1980 and 1996, 449 had surgery on an elective basis and 154 as an emergency. **Preoperative diagnostic studies for coronary artery disease** were performed on elective patients and were positive in 76.8% (1980-1989, 76.1%, 1990-1996, 77.5%). **Coronary angiography** was performed in 108 patients (29.6%). **Medical therapy of coronary artery disease** declined by 2.3%, and interventional procedures by 18.8%. In contrast, **myocardial revascularization with subsequent aneurysm resection** increased by 26.6% and 12 patients (16%) required urgent simultaneous cardiac and aortic surgery. **Early mortality** after **abdominal aortic aneurysm surgery** decreased from 4.2 to 2.9%, and the frequency of **primary cardiac failure** as the cause of death was reduced from 33.3 to 22.2% (P < 0.05). It was concluded that 42.6% more cardiac surgical procedures were performed before **abdominal aortic aneurysm surgery** since 1990 compared with the period 1980-1989. In contrast, the number of interventional procedures fell by 18.8%. **Surgical therapy of cardiac disease reduces early mortality** after elective abdominal aortic aneurysm surgery.

(11) Yau TM, Fedak PW, Weisel RD, Teng C, Ivanov J

**PREDICTORS OF OPERATIVE RISK FOR CORONARY BYPASS OPERATIONS IN PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION.**


Division of Cardiovascular Surgery, Toronto General Hospital, Ontario, Canada.

OBJECTIVES: The prevalence of ventricular dysfunction in patients undergoing coronary operations, as well as the prevalence of other risk factors in these patients, has been increasing. We identified the predictors of mortality and morbidity in patients with ventricular dysfunction to permit more accurate evaluation of risk and to direct future strategies to improve outcomes.

METHODS: Demographic, intraoperative, and outcome data were collected prospectively on 20,614 patients undergoing isolated coronary operations at our institution from 1982-1997. Multivariable regression analyses were used to identify the independent predictors of mortality and low-output syndrome. RESULTS: Moderate ventricular dysfunction (ejection fraction, 20%-40%) was noted in 4107 (19.9%) patients, and severe dysfunction (ejection fraction, <20%) was noted in 680 (3.3%) patients. Patients with worse ventricular function had an increasing prevalence of other risk factors with time. Mortality decreased between the 1982-1986 and 1987-1991 cohorts but did not decrease further. Low-output syndrome was less common in the 1992-1997 cohort than in previous years. The predictors of mortality were ventricular dysfunction, age, reoperation, year of operation, urgency, female sex, and left main stenosis. Low-output syndrome was predicted by ventricular dysfunction, reoperation, year of operation, female sex, urgency, extensive coronary disease, age, left main stenosis, and symptom class. CONCLUSIONS: Despite the increasing prevalence and risk profile of patients with ventricular dysfunction, mortality rates and incidence of low-output syndrome declined with time. Patients with severe dysfunction were at greatest risk when facing reoperation or urgent operation. Earlier intervention and more aggressive preoperative optimization may improve outcomes in these high-risk patients.

(12) Rossi E

**CARDIAC RISK STRATIFICATION OF PATIENTS UNDERGOING PERIPHERAL VASCULAR SURGERY.**


Istituto di Cardiologia, Universita Cattolica del Sacro Cuore, Roma.

Approximately 50% of patients with peripheral vascular disease have severe coronary artery disease. Several ways of predicting the postoperative risk of major cardiac events in peripheral vascular patients have been suggested. Among preoperative tests, **echocardiography is now receiving greater favor** for risk stratification.
THE ADDITIVE VALUES OF LEFT VENTRICULAR FUNCTION AND EXTENT OF MYOCARDIUM AT RISK TO DIPYRIDAMOLE PERFUSION IMAGING FOR OPTIMAL RISK STRATIFICATION PRIOR TO VASCULAR SURGERY.


Although the increased risk of cardiac complications in surgical patients with diminished left ventricular ejection fraction (LVEF) is well-established, this method has been supplanted in recent years by assessment of ischaemic burden using myocardial perfusion imaging (MPI). This study was conducted to determine if MPI and LVEF determination provide complementary or redundant information in preoperative evaluation of vascular surgery patients. A total of 101 patients were studied with dipyridamole MPI and radionuclide ventriculography before surgery. Single photon emission tomographic MPI images were scored for defect severity and categorized as either fixed or reflecting ischaemia. Resting left ventricular cavity was also categorized as normal or dilated. LVEF was subdivided into normal (≥50%) and abnormal (<50%). Seventeen patients had cardiac events. Events were more frequent in patients with ischaemia, in patients with a LVEF <50% and in those with dilated left ventricular chambers. The mean number of ischaemic segments was also higher in the cardiac event group. Higher event rates were seen when a combination of these factors was present. A history of myocardial infarct, congestive heart failure or coronary artery disease was also a significant predictor of subsequent events. Thus, both abnormal left ventricular function and extent of ischaemic myocardium have independent and complementary predictive power for cardiac events in vascular surgery patients.

PREOPERATIVE CARDIAC PREPARATION.

Chest 1999 May;115(5 Suppl):82S-95S

Preoperative preparation of the cardiac patient is based on matching the cardiac reserve to the blood flow demands imposed by surgical stress and the underlying disease state. Evaluation must include functional assessment of any coronary artery disease or other organic cardiac disease that may place myocardial tissue at risk of ischemia as demand for cardiac output increases. Monitoring should be individualized based on anticipated problems and the risk assessment of the patient. Preoperative therapy should include maneuvers that reduce congestive heart failure, optimize volume status, and provide adequate cardiac output to deliver oxygen sufficient to meet or exceed demand. Underlying electrical and metabolic abnormalities should be corrected and controlled in the perioperative period. Long-term therapy should be evaluated and modified in the context of the anesthetic and surgical plan. Preventive interventions such as fluid loading and low-dose dopamine should be considered prior to surgery.

THE ROLE OF ECHOCARDIOGRAPHY IN PREOPERATIVE DIAGNOSIS OF CARDIAC RISK IN PATIENTS BEFORE NON-CARDIAC SURGICAL INTERVENTIONS). [ARTICLE IN GERMAN]


Echocardiography is a noninvasive method for cardiac evaluation. A review of the current literature shows that the routine use of echocardiography for assessing perioperative cardiac risk in patients undergoing noncardiac surgery can not be supported. Only patients with suspected relevant heart valve diseases, acute heart failure, cardiomyopathy or condition after heart or heart-lung transplantation may benefit from preoperative echocardiography. In patients with suspected or proven coronary artery disease stress echocardiography offers the most relevant additional information for the anaesthesiologist. However, because of the high financial and personal
implications it should be reserved to transthoracic echocardiography doesn't offer sufficient information or is not possible transesophageal echocardiography plays only a minor role in preoperative cardiac evaluation.

(16) Bohm M

[ECHOCARDIOGRAPHY. ITS ROLE IN PREOPERATIVE DIAGNOSIS OF CARDIAC RISK PATIENTS BEFORE NON-CARDIAC SURGICAL INTerventions]. [ARTICLE IN GERMAN]


PREOPERATIVE RISK MODELS FOR MINIMALLY INVASIVE CORONARY BYPASS: A PRELIMINARY STUDY.


Division of Cardiothoracic Surgery, University of Pittsburgh Medical Center, PA 15213-2582, USA.

OBJECTIVE: Available risk assessment models are designed for standard coronary artery bypass grafting. We hypothesized that minimally invasive coronary bypass could improve on predicted outcome in extremely high-risk patients (Parsonnet score > 20%) by the current risk models.

METHODS: From September 1996 to September 1997, 27 consecutive extremely high-risk patients underwent minimally invasive coronary bypass. Seventeen patients were male; age was 73 +/- 12 years, and 63% of patients were older than 75 years. Left ventricular ejection fraction was 33.7% +/- 15% and 63% had an ejection fraction of less than 35%. The predicted 30-day mortality according to the System 97 model was 25.6% +/- 11.3%. The Parsonnet risk score was 36.2% +/- 11%; the predicted length of stay in the hospital was 15.3 +/- 3 days. The predicted risk of stroke according to the Multicenter Perioperative Stroke Risk Index was 22.3% +/- 11.7%. RESULTS: Minimally invasive coronary bypass was isolated in 20 patients and integrated with angioplasty and stenting in 7 patients. The observed 30-day mortality was 0% (P < .01 vs predicted); at an average follow-up of 10.8 +/- 4.1 months, 26 patients (96.3%) are alive without angina; one patient with acquired immunodeficiency syndrome died on postoperative day 40 of acute pancreatitis. No patient had a stroke or neurologic deficit (P < .01 vs predicted). Patency of internal thoracic artery anastomosis was confirmed by angiography in all 27 patients. No patient required reoperation. Eighteen patients (67%) were extubated in the operating room. The observed length of hospital stay after minimally invasive coronary bypass was 3.8 +/- 2.6 days (P < .01 vs predicted). CONCLUSION: On the basis of our results on a relatively small series of patients, we suggest that risk models geared for standard coronary bypass grafting may not be appropriate for minimally invasive coronary bypass.

5. Preoperative Risk Management of Orthopedic Patients

(1) Gallus AS

APPLYING RISK ASSESSMENT MODELS IN ORTHOPAEDIC SURGERY: OVERVIEW OF OUR CLINICAL EXPERIENCE.


Flinders Medical Centre, Department of Haematology, Flinders University School of Medicine, Bedford Park, SA, Australia

those patients who are not able to perform a normal stress test. Besides in patients in whom. alexander.gallus@flinders.edu.au

Major joint surgery (elective hip or knee replacement, or hip fracture) carries a high risk of postoperative deep vein thrombosis (DVT) and pulmonary embolism. DVT prophylaxis has become an essential part of routine management, since several preventive methods, including low-molecular-weight heparins (LMWHs) and oral anticoagulants, are effective and safe in major joint surgery. Clinically important questions remain about the best way to use LMWHs for DVT prevention. The need for preoperative dosing, whether to give LMWHs once or twice daily, and the most suitable duration of prophylaxis remain issues of debate. Reports of local bleeding after spinal or epidural anaesthesia/analgesia in orthopaedic surgery patients given LMWH may make anaesthetists more...
reluctant to combine regional anaesthesia with LMWH prophylaxis, especially if a preoperative dose is required. The worldwide trend towards early transfer of postoperative patients from hospital to a convalescent facility or home has increased the need for formal recommendations about the optimal duration of prophylaxis. Ever shorter hospital admissions after elective surgery mean that prophylaxis given only in hospital may not be sufficient.

(2) Nierman E, Zakrzewski K
RECOGNITION AND MANAGEMENT OF PREOPERATIVE RISK.

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Internists are frequently asked to do preoperative consultations and to manage perioperative complications. Realistic goals are to identify patient factors that increase the risk of surgery, to quantify this risk in order to make decisions about the appropriateness of and timing of the surgery, to provide recommendations on how to minimize the risk, to identify and manage coexisting medical conditions and their associated medication requirements, to monitor the patient for perioperative problems, and to make recommendations to deal with these problems when they occur. With few exceptions, nonselective imaging and laboratory screening tests have repeatedly been shown to be of little value when the history and physical do not suggest a problem. The risk associated with the planned surgery can be estimated, with the most common serious complications being cardiac events. Updated versions of Goldman’s risk indices are particularly helpful for this. Clinical variables are optimally combined with selective stress testing to discern which patients will benefit from preoperative revascularization. This has been studied best in the setting of vascular surgery. A critical guiding principle is that the value of revascularization must be judged in terms of long term gains rather than just immediate perioperative benefit. Other interventions include the selective use of beta blockers, adequate analgesia for all, control of hypertension, and appropriate volume management, especially in the settings of preexisting CHF or valvular disease. It must also be recognized that perioperative ischemia and CHF often present atypically. An approach that combines aspects of both the ACC/AHA and the ACP guidelines seems optimal. A variety of noncardiac issues must also be addressed. Postoperative pulmonary complications are common, especially with preexisting pulmonary disease, thoracic and upper abdominal surgery, and obesity. PFTs and ABGs are indicated in selected patients. Stopping smoking, incentive spirometry, and selective use of bronchodilators and antibiotics are helpful. Patients with rheumatologic diseases have specific concerns based on systemic manifestations of disease including anemia, thrombocytopenia, pulmonary fibrosis, pericarditis, and hypercoagulability; medication effects particularly from steroids and nonsteroidal anti-inflammatory drugs; and specific joint problems including contractures and atlantoaxial joint instability. Diabetes increases the risk of infection and cardiac complications. Prevention of ketoacidosis and glucose control are necessary and can be achieved through a variety of approaches, depending on whether the patient suffers from Type 1 or Type 2 diabetes. The threshold for transfusion has increased in recent years, as has the use of erythropoietin and autologous blood donation. There is no longer an absolute hemoglobin that requires transfusion, although most require transfusion for hemoglobins less than 8 mg/dL, especially in the setting of cardiac disease and bloody surgery. The elderly require surgery at an increased rate and often do not do as well as younger patients. The primary issues are, however, not their age but their increased frequency of underlying disease and diminished reserve. The latter makes them prone to postoperative delirium, sensitivity to medications, and cardiac and pulmonary problems. Despite the many diseases that patients often have and the stresses of surgery itself, modern anesthetic and surgical techniques allow almost all patients to undergo necessary procedures at acceptable risk. The internist plays a critical role in minimizing this risk even further.

(3) Vitale MG, Stazzone EJ, Gelijns AC, Moskowitz AJ, Roye DP Jr
THE EFFECTIVENESS OF PREOPERATIVE ERYTHROPOIETIN IN AVERTING ALLOGENIC BLOOD TRANSFUSION AMONG CHILDREN UNDERGOING SCOLIOSIS SURGERY.

New York Orthopaedic Hospital, New York, USA.
Concerns about the transmission of the human immunodeficiency virus (HIV) have driven the evolution of surgical transfusion practices including the use of preoperative erythropoietin (rhEPO). Although there is significant experience documenting the efficacy of preoperative rhEPO in reducing transfusion requirements for adult patients, there is little experience in the pediatric population. With 178 pediatric patients who underwent surgery for spinal deformity, a retrospective cohort study was performed using patient charts, administrative records, and blood bank computer data. Of these patients, 44% received erythropoietin and 55% did not. From the entire population, 17.5% were in the rhEPO treatment group that received homologous blood transfusion compared with 30.6% in the untreated group (p < 0.05). Among the children with idiopathic scoliosis, this effect was more pronounced, with 3.9% of rhEPO patients receiving blood transfusion compared with 23.5% of nontreated patients (p = 0.006). Additionally, rhEPO treatment was associated with a significantly decreased length of stay only for patients in the idiopathic group (9.3 vs. 6.7, p = 0.02). Use of preoperative erythropoietin in pediatric patients undergoing scoliosis surgery resulted in higher preoperative hematocrit levels. Significantly lower rates of transfusion were noted only in the idiopathic group, however. Although there is a possibility of erythropoietin "resistance" in the neuromuscular and congenital patients, alternative explanations for the lack of effect on transfusion rates may include underdosing and biases existent in this nonrandomized retrospective study.

6. Preoperative Risk Management of Gynecologic Patients


USE OF PREOPERATIVE MR IMAGING IN THE MANAGEMENT OF ENDOMETRIAL CARCINOMA: COST ANALYSIS.


Department of Radiology, Magee Women's Hospital, University of Pittsburgh, 300 Halket St, Pittsburgh, PA 15213. From the 1998 RSNA scientific assembly. Received December 2, 1998.

PURPOSE: To compare the cost of magnetic resonance (MR) imaging and its ability to direct the use of lymph node dissection with the cost and ability of conventional surgery for the staging of endometrial carcinoma. MATERIALS AND METHODS: Preoperative MR images of 25 patients who underwent hysterectomy for endometrial carcinoma were retrospectively evaluated. MR imaging results were compared with those of intraoperative gross dissection of the uterus and final histopathologic examination. Medicare reimbursements for two scenarios were compared in each patient. In the MR imaging scenario, the necessity for lymph node dissection was based on MR imaging results and histologic findings at biopsy. In the actual scenario, lymph node dissection was performed at the surgeon's discretion on the basis of findings at gross dissection of the uterus and histologic examination at biopsy. RESULTS: The cost of the MR imaging scenario, as defined by Medicare reimbursements, was 1% ($1,265/$148,500) less than that of the actual scenario. In the MR imaging scenario, all patients who required lymph node dissection received it, and 86% of the lymph node dissections performed were necessary. In the actual scenario, one necessary lymph node dissection was not performed, and only 31% of the lymph node dissections performed were necessary. CONCLUSION: Staging with MR imaging has costs and accuracy similar to those of the current method of staging with intraoperative gross dissection of the uterus. In addition, MR imaging decreases the number of unnecessary lymph node dissections.

(2) Seto A, Fukuyama H, Niijima K, Takenaka I, Kadoya T

[ANESTHETIC MANAGEMENT OF A PATIENT WITH DEEP VENOUS THROMBOSIS USING TEMPORARY INFERIOR VENA CAVA FILTER]. [ARTICLE IN JAPANESE]

Department of Anesthesia, Nippon Steel Yawata Memorial Hospital, Kitakyushu.

Masui 2000 Mar;49(3):302-304

A patient with deep venous thrombosis caused by a huge uterine leiomyoma underwent abdominal hysterectomy. To prevent pulmonary thromboembolism, the patient received anticoagulant therapy until 6 hr before surgery and temporary inferior vena cava filter was placed. A combination of preoperative anticoagulant therapy and the filter placement during perioperative period enabled this patient to be successfully-managed.
(3) Rodolakis A, Diakomanolis E, Haidopoulos D, Voulgaris Z, Protopapas A, Makris N, Michalas S

**HOW TO AVOID SUBOPTIMAL MANAGEMENT OF CERVICAL CARCINOMA BY SIMPLE HYSTERECTOMY.**

Eur J Gynecol Oncol 1999;20(5-6):418-422.

1st Department of Obstetrics and Gynecology, Athens University, Alexandra Hospital, Gynecologic Oncology Unit, Greece.

OBJECTIVE: To determine the reasons leading to an inappropriate simple hysterectomy in the presence of carcinoma of the cervix and to evaluate factors related to survival. METHODS: All preoperative information was abstracted from 63 cervical cancer patients cleared by simple hysterectomy from 1980-1993. Cervical cancer screening history as well as the indication for hysterectomy were analyzed. The 5-year survival was calculated and correlated with the tumour histological subtype and presumed stage of disease. RESULTS: The most common preoperative symptom was abnormal uterine bleeding (73%). The absence of preoperative cytology, an inadequately evaluated abnormal Pap smear and the failure to differentiate from endometrial carcinoma were the main causes leading to an inappropriate simple hysterectomy. The cumulative 5-year survival was 63.5% and was correlated with the presumed stage of disease and the histological subtype. CONCLUSION: Only with close adherence to the cervical cancer screening guidelines and appropriate evaluation of presenting symptoms can we avoid inappropriate management of cervical carcinoma with simple hysterectomy.

(4) Donato DM

**SURGICAL MANAGEMENT OF STAGE IB-IIA CERVICAL CARCINOMA.**


Gynecologic Oncology, University of Virginia, Roanoke, USA.

The standard surgical approach to Stage IB and IIA cervical cancer consists of a radical hysterectomy, lower peri-aortic lymphadenectomy, and complete bilateral pelvic lymphadenectomy. This approach offers 5-year survival rates of 75% to 90% in most large series, which is equivalent to the radiotherapeutic treatment of this disease. Over the last 50 years, this classic surgical approach has undergone only minor modifications. The present day complication rate remains low, and is comparable to that of radiotherapy. This article will summarize the current indications, pre-, intra-, and post-operative management of this disease.


**WERTHEIM'S HYSTERECTOMY AFTER NEOADJUVANT CARBOPLATIN-BASED CHEMOTHERAPY IN PATIENTS WITH CERVICAL CANCER STAGE IIB AND IIIB.**


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BACKGROUND: To improve local response and survival, a prospective study was designed to determine the effects of neoadjuvant chemotherapy in the management of cervical carcinoma stage IIB and IIIB. PATIENTS AND METHODS: Fourteen patients were treated with preoperative neoadjuvant chemotherapy. Three courses of carboplatin were administered in combination with ifosfamide in 11/14 patients, whereas 3 patients received three courses of carboplatin and paclitaxel. RESULTS: After neoadjuvant chemotherapy, there were 8/14 clinical responses while 6/14 patients had no change. In 8 cases, Wertheim's hysterectomy was possible after neoadjuvant chemotherapy. Six of these 8 patients are still alive after a duration of 32 months median follow-up, 2 patients died of metastatic disease. In 6 cases with no change after chemotherapy, Wertheim's hysterectomy was impossible. In this subgroup, the median survival time was 15.5 months, and 4/6 patients died of metastatic disease. CONCLUSIONS: Neoadjuvant chemotherapy with carboplatin/ifosfamide or carboplatin/paclitaxel is safe, well-tolerated, effective and useful to enable Wertheim's hysterectomy.
(6) Maleemonkol S, Chareoniam V, Isariyodom P, Chaiyapan S

**COMPARISON OF SHORT VERSUS LONG DURATION OF AMPICILLIN AND GENTAMICIN FOR RADICAL HYSTERECTOMY.**


Department of Obstetrics and Gynecology, Faculty of Medicine, Chiang Mai University, Thailand.

Prophylactic antibiotic therapy for radical hysterectomy is still controversial. Although the efficacy of antibiotics have been demonstrated, there remains the question of duration of administration. In this study, we retrospectively reviewed 95 patients who underwent radical hysterectomy and pelvic lymphadenectomy for cervical cancer at our institute. The management was uniform except for the duration of antibiotic administration. Group I (34 cases) had ampicillin and gentamicin for 3 days while group II (61 cases) had the same regimen for 7 days. No significant difference was found in terms of postoperative infection (2.9% in group I and 1.6% in group II) or febrile morbidity (32.4% versus 50.8%). Other factors such as the patients' age, body weight, preoperative hemoglobin level, amount of blood loss and blood transfused, operative time, duration of retroperitoneal drain and duration of suprapubic cystostomy. Only operative time had a significant influence on febrile morbidity regardless of the duration of antibiotics administered. In conclusion, the antibiotic administration gave a radical hysterectomy and pelvic lymphadenectomy a very low incidence of postoperative infection. Longer duration of treatment did not appear to lessen postoperative infection nor febrile morbidity. Shorter duration of antibiotic administration needs further evaluation.

(7) Goldberg JM, Piver MS, Hempling RE, Aiduk C, Blumenson L, Recio FO

**IMPROVEMENTS IN PELVIC EXENTERATION: FACTORS RESPONSIBLE FOR REDUCING MORBIDITY AND MORTALITY.**


Department of Gynecologic Oncology, Roswell Park Cancer Institute, Buffalo, New York, USA.

BACKGROUND: Since pelvic exenteration for the treatment of recurrent gynecologic malignancy first was described, reported rates of morbidity and mortality have declined steadily. However, the factors responsible for this decline have never been clearly delineated. METHODS: We reviewed the charts of 154 patients who underwent pelvic exenteration for gynecologic malignancy between 1954 and 1994. Charts were abstracted for details of the surgical procedure, pathologic findings, postoperative management, short- and long-term complications, time to recurrence, and overall survival. RESULTS: Seventy-two patients (47%) experienced 95 identifiable postoperative complications, resulting in death in 22 patients (14%). The rate of infectious complications declined to a statistically significant degree between the first two decades and latter two decades of the study (odds ratio [OR] 0.28, 95% CI 0.11-0.69). The use of routine prophylactic antibiotics was associated with this decline in infectious complications (OR 0.25, 95% CI 0.07-0.83). The use of preoperative subcutaneous heparin was associated with a reduction in thrombotic complications from 5 of 100 patients to 0 of 54 patients (P = .11), as well as a significant reduction in overall risk of complications (OR 0.53, 95% CI 0.33-0.85) and risk of postoperative mortality (OR 0.19, 95% CI 0.05-0.80). There was a significant reduction in overall risk of postoperative complications with both intensive care unit monitoring postoperatively (OR 0.65, 95% CI 0.43-0.99) and routine postoperative monitoring with a pulmonary artery catheter (OR 0.61, 95% CI 0.38-0.98). CONCLUSIONS: Routine use of prophylactic antibiotics, prophylactic subcutaneous heparin, and intensive postoperative monitoring appear to have reduced morbidity from pelvic exenteration.

(8) Faridi A, Schroder W, Rath W

**[CURRENT TRENDS IN THE SURGICAL MANAGEMENT OF OVARIAN CANCER]. [ARTICLE IN GERMAN]**


Universitatsfrauenklinik der Med. Fakultat der RWTH Aachen.
Ovarian cancer is the leading cause of death from gynaecological malignancies in western countries, it is diagnosed at an advanced stage in approximately 75% of patients. The current standard treatment for ovarian cancer consists of maximum cytoreductive surgery to reduce tumor residuum to a minimum, followed by platin-based chemotherapy. If an unsuspected ovarian cancer is detected at diagnostic laparoscopy, staging and debulking by laparotomy should be undertaken without delay. For apparently early stages (I or II), appropriate surgical staging is extremely important and will result in the upstaging of about one-third of patients (usually to Stage III). Several retrospective clinical trials show that successful cytoreduction and systemic lymphonodectomy result in an improved survival, but prospective randomized studies have not been performed to evaluate this benefit. Patients who cannot be cytoreduced to an optimal stage should be considered candidates for interval cytoreduction after chemotherapy. Repeated surgical debulking in relapsed patients will probably only benefit a small subset of selected patients (e.g. disease-free interval > 2 years). Surgery may also be important for palliation, such as for the treatment of bowel obstruction to improve the patients quality of life. The question still remains whether the observed improved survival rates for patients with ovarian cancer are an effect of primary cytoreductive surgery or tumor biology.

(9) Monahan EG
MEDICAL CLEARANCE FOR GYNECOLOGIC SURGERY.

Department of Obstetrics and Gynecology, University of North Carolina, Chapel Hill School of Medicine, Raleigh 27610-1255, USA.

Physicians are charged to "foremost do no harm." Thus, before doing any surgical procedure, surgeons must convince themselves that the risk to the patient does not outweigh the benefit. The patient with multiple medical problems has additional risk factors for elective surgery. In the past, that patient would be sent to their general practitioner for "medical clearance." With gynecologists now assuming that role for the patient, it is increasingly important for us to understand what comprises medical clearance to better assess hazards. Studies concerning medical clearance for surgery obtained in a MEDLINE search through March 1997 were reviewed; the recent advances that apply to gynecologic surgery are covered in this article.

(10) Russell AH, Shingleton HM, Jones WB, Stewart AK, Fremgen A, Winchester DP, Clive R, Chimiel JS
TRENDS IN THE USE OF RADIATION AND CHEMOTHERAPY IN THE INITIAL MANAGEMENT OF PATIENTS WITH CARCINOMA OF THE UTERINE CERVIX.

Radiological Associates of Sacramento, CA, USA.

PURPOSE: The Commission on Cancer of the American College of Surgeons conducts Patient Care Evaluation studies to describe practice patterns and trends in disease management. This report surveys changing strategies in the initial treatment of patients with invasive cancer of the uterine cervix. METHODS AND MATERIALS: Using a standard data collection form designed by a multidisciplinary committee of specialists, cancer registrars at 703 hospitals submitted anonymous data on 11,721 total cervical cancer patients diagnosed in 1984 and 1990. RESULTS: Between the two study years, the use of radiation as all, or a component, of the initial course of therapy declined from 70 to 60.3%, coincident with a 32.3% increase in the use of hysterectomy alone and a 33.7% reduction in the use of radiation alone. The percentage of all patients receiving combined hysterectomy and radiation (preoperative or postoperative) remained virtually unchanged—10.2% in 1984, and 9.3% in 1990. However, women who were treated by hysterectomy in 1990 were less likely to receive radiation as part of their treatment than patients treated by hysterectomy in 1984. Among patients treated by radiation without hysterectomy, the use of intracavitary brachytherapy techniques substantially exceeded interstitial brachytherapy techniques in both study years. Among patients treated by local radiation without hysterectomy, the frequency of adjunctive chemotherapy used increased from 6.9% in 1984 to 24.8% in 1990, with chemotherapy and radiation increasingly administered concurrently rather than sequentially. Although differences based on age, histology, race/ethnicity, and insurance status were observed, these general management trends were seen in all groups. CONCLUSIONS: Changes in the utilization of radiation and surgery may reflect the increasing surgical involvement of gynecologic oncologists in the management of early stage cervical
cancer, rather than significant alterations in the demographics of the disease. Although brachytherapy is recognized as an important component of radiation treatment, some patients may not receive the potential benefit of this modality. Despite controversy concerning its efficacy, the use of adjuvant systemic chemotherapy to supplement local treatment modalities appears to be increasing rapidly.


[RATIONALIZATION OF THE USE OF PREOPERATIVE THORACIC RADIOGRAPHY IN OBSTETRICS AND GYNECOLOGY]. [ARTICLE IN ITALIAN]

Istituto di Radiologia, Universita di Pavia.

INTRODUCTION: Rationalizing preoperative chest radiography remains a problem in our Country. Therefore, we tried to use preoperative chest films rationally in obstetrics and gynecology to assess their impact on anesthesia planning and patient management and their use in early postoperative complications. MATERIAL AND METHODS: We examined two groups of patients: group A consisted of 570 women (mean age: 31 years) scheduled to be submitted to cesarean section but with no preoperative chest radiography; group B consisted of 471 patients (homogeneous in age to group A patients) submitted to nononcologic gynecologic surgery and with a single-projection preoperative chest radiograph. Anesthesiologic assessment, preoperative biochemical tests and EKG were performed in all patients. All patients underwent abdominal surgery under general anesthesia. The first 24 postoperative hours were monitored for possible anesthesia-related complications. The anesthesiologist need of chest radiography based on clinical findings was investigated in group A patients, as well as the importance of chest film findings in possible anesthesia-related complications. RESULTS: Group A and group B were homogeneous by mean patient age and anesthesia duration; clinical findings never suggested the need of chest radiography in group A patients. Three cardiorespiratory complications occurred (two respiratory arrests in group A and a gas embolism in group B), but the (un)availability of chest film findings made no difference in treatment.

DISCUSSION: The availability of the preoperative chest radiographs of a group of healthy women of 31 years mean age does not make any difference in anesthesia planning and type. In our series, the most severe cardiorespiratory complications were homogeneous in the two groups, which confirms their random character, and the (un)availability of preoperative chest film findings made no real difference, even though the lack of radiographic evidence made patient management more demanding for anesthesiologists.

(12) Dorsey JH, Steinberg EP, Holtz PM

CLINICAL INDICATIONS FOR HYSTERECTOMY ROUTE: PATIENT CHARACTERISTICS OR PHYSICIAN PREFERENCE?

Department of Gynecology, Greater Baltimore Medical Center, MD 21204, USA.

OBJECTIVES: Our purpose was to compare the indications, characteristics, surgical management, and outcomes of patients undergoing total abdominal hysterectomy, total vaginal hysterectomy, and laparoscopically assisted vaginal hysterectomy and to assess whether patients who underwent abdominal hysterectomy might have been candidates for laparoscopically assisted vaginal hysterectomy and whether patients who underwent total abdominal hysterectomy or laparoscopically assisted vaginal hysterectomy might have been candidates for total vaginal hysterectomy. STUDY DESIGN: The hospital charts of 502 women who underwent elective inpatient hysterectomy at a single large general hospital between January 1992 and November 1993 were abstracted retrospectively by use of a structured data abstraction instrument. The study included patients operated on by 16 different experienced gynecologists. Data were collected regarding patient demographic characteristics, clinical history and preoperative physical examination, indications for surgery, route of hysterectomy, intraoperative findings, pathologic study results, and outcomes in the immediate postoperative hospitalization period. RESULTS: Patient age, race, weight, parity, and previous surgical history were significantly associated with hysterectomy type. Although no nulliparous patients and no patients with a uterine size estimated preoperatively to be > 12 weeks of gestation underwent total vaginal hysterectomy, 16.6% and 30.6% of laparoscopically assisted vaginal hysterectomy patients had these characteristics, respectively. A total of 6.6% of total abdominal hysterectomy cases and 16.7% of laparoscopically assisted vaginal hysterectomy cases
lacked an obvious justification for an abdominal procedure. On average, surgical time was 23 minutes longer for laparoscopically assisted vaginal hysterectomy than for total abdominal hysterectomy and 30 minutes longer for total abdominal hysterectomy than for total vaginal hysterectomy. When uterine size or configuration impaired access to uterine vessels, laparoscopically assisted vaginal hysterectomy was difficult to perform. Postoperative morbidity was similar across the three procedures, but average length of hospital stay was 2.8 days, 3.5 days, and 4.4 days for laparoscopically assisted vaginal hysterectomy, total vaginal hysterectomy, and total abdominal hysterectomy, respectively. CONCLUSIONS: Although there are some consistent and statistically significant differences in the characteristics of patients undergoing total abdominal hysterectomy versus laparoscopically assisted vaginal hysterectomy versus total vaginal hysterectomy, laparoscopically assisted vaginal hysterectomy is enabling many patients to avoid total abdominal hysterectomy. However, many patients undergoing total abdominal hysterectomy and laparoscopically assisted vaginal hysterectomy could probably undergo total vaginal hysterectomy instead. Clinical outcomes were similar regardless of type of hysterectomy performed. Practice style and personal preference of the surgeon thus may be playing a significant role in selection of hysterectomy type. Laparoscopically assisted vaginal hysterectomy becomes technically difficult and conversion to total abdominal hysterectomy is more frequent when uterine size or configuration impairs access to uterine vessels.


7. Preoperative Risk Management in Pulmonary Surgery


IDENTIFICATION OF PROGNOSTIC FACTORS DETERMINING RISK GROUPS FOR LUNG RESECTION.


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BACKGROUND: Pulmonary resection belongs to a group of surgical procedures with significant morbidity and mortality. The aims of this study were to classify postoperative complications and to identify prognostic factors determining risk group. METHODS: In a prospective study 500 patients undergoing lung resection (wedge resection, n = 141; lobectomies, n = 245; bilobectomies, n = 12; and pneumonectomies, n = 102) were included. In 178 patients (36%) pulmonary resections were extended to structures or thoracic organs. Sleeve resection of the bronchus to preserve lung parenchyma was performed in 22 patients. RESULTS: Classification of postoperative complications fell into four categories: patients without postoperative complications; patients with moderate complications (n = 137); patients with severe complications (n = 38); and death (n = 33). Factors adversely affecting postoperative complications by multivariate analysis included pulmonary pathology, bronchoplastic technique, forced expiratory volume in 1 second (FEV1), extended resection, type of lung resection, comorbidity indices, and preoperative chemotherapy. Four risk groups were determined. Risk group I (n = 60) with the best prognosis included patients with FEV1 greater than or equal to 80% undergoing wedge resection for a benign lesion or metastasis. Risk group II (n = 161) included patients with FEV1 greater than or equal to 80% undergoing major pulmonary resection for a benign lesion or metastasis or lung cancer, or patients with FEV1 less than 80% undergoing wedge resection for benign lesion or metastasis. Risk group III (n = 233) with a fair prognosis included patients with comorbidity indices less than 4 and FEV1 greater than or equal to 80% undergoing extended pulmonary resection for a benign lesion or metastasis or lung cancer, or patients with FEV1 less than 80% and emphysema. Risk group IV (n = 46) with the worst prognosis included patients with FEV1 less than 80% undergoing an extended lung resection or bronchoplastic procedures for a benign lesion or metastasis or lung cancer, or patients with comorbidity indices greater than or equal to 4 undergoing extended lung resection for lung cancer. CONCLUSIONS: In a prospective study, based on these prognostic factors, a practical, easy-to-use risk group system of lung resection is proposed as a tool to aid the decision to perform lung resection.

B. Introduction Articles
(1) Hutchinson AB, Fergusson D, Graham ID, Laupacis A, Herrin J, Hillyer CD. **UTILIZATION OF TECHNOLOGIES TO REDUCE ALLOGENEIC BLOOD TRANSFUSION IN THE UNITED STATES.**


Joint PhD Program in Public Policy, Georgia Institute of Technology and Georgia State University, Atlanta GA, USA. Loeb Health Research Institute, University of Ottawa, Ottawa, Canada. Institute for Clinical Evaluative Sciences, Toronto, Canada. National Institute of Public Health, Olso, Norway. Emory University School of Medicine, Atlanta, GA, USA.

Concern over safety of the blood supply has led to the use of technologies to reduce allogeneic blood transfusion. The objective of this research was to determine the utilization of these technologies in the United States. We evaluated the following techniques: preoperative autologous donation (PAD), cell salvage (CS) and acute normovolemic haemodilution (ANH); and the following pharmaceuticals: aprotinin (APR), epsilon-aminocaproic acid (EACA), tranexamic acid (TXA), desmopressin (DDAVP) and recombinant human erythropoietin (EPO). In 1997, we conducted a cross-sectional mail survey of service chiefs at 1000 US hospitals randomly selected and stratified by status as a provider of open-heart surgery, geographical location and hospital bed size. Sixty-nine per cent (690) of hospitals responded to at least one of the four surveys sent to each hospital. Hospitals reported use of techniques more than pharmaceuticals (P < 0.001); PAD (83%, n = 206) and CS (82% n = 420) were used most frequently. Lack of familiarity was the most common reason cited for infrequent use of pharmaceuticals. Organizational characteristics (e.g. provision of open-heart surgery, size, geographical location, teaching status and type of hospital) were differentially associated with technology use. There is greater use of techniques than pharmaceuticals in US hospitals to reduce the need for allogeneic blood in the peri-operative setting. Providing open-heart surgery is strongly associated with the utilization of these technologies.

(2) Rosencher N, Woimant G, Ozier Y, Conseiller C. **[PREOPERATIVE STRATEGY FOR HOMOLOGOUS BLOOD SALVAGE AND PERI-OPERATIVE ERYTHROPOIETIN]. [ARTICLE IN FRENCH]**


Departement d'anesthesie-reanimation, Hopital Cochin-Saint-Vincent-de-Paul, Paris, France.

The amount of transfused blood is related to blood loss calculated for the specific type of surgical procedure, transfusion hematocrit trigger and patient's red blood cell mass on the day before surgery. To optimise the benefit/cost and benefit/risk ratios of blood transfusion, a correct prescription must be done in accordance with the patient's red blood cell mass and surgical blood loss. Indeed, there is a clear need to define the appropriate uses of blood management methods and to seek new methods of improving perioperative blood management. The number of moderately anaemic patients undergoing surgery is currently thought to be 20%. Where transfusion requirements are estimated at two to three blood units, as for instance in the most common types of orthopaedic surgery, preoperative haemoglobin is the key factor governing transfusion needs. In this case, the simplest approach is to prescribe Epoetin Alfa subcutaneous at a dose of 600 IU/kg/week starting three weeks before the surgery. In addition, it is important in all cases to give concomitant iron supplements. Concomitant use of other methods to decrease allogeneic blood requirements is of no value. Obviously, the higher the haematocrit the day prior to surgery, the higher the patient's RBC mass and the greater the patient's permitted blood loss, decreasing the transfusion trigger. In this way, allogeneic blood loss is reduced, but without the need for the patient to attend the blood transfusion center and to undergo laboratory screening and testing of donated blood, and without the risk of inducing preoperative anaemia compared with sequential autologous blood donation. But, to optimise the benefit/cost ratio, we try to define precisely the patient populations likely to benefit from preoperative erythropoietin. Using different examples, management is proposed with algorithms.
(3) Trovarelli T, Kahn B, Vernon S
TRANSFUSION-FREE SURGERY IS A TREATMENT PLAN FOR ALL PATIENTS.
_AORN J_ 1998 Nov;68(5):773-8, 780-4
Ortho Biotech, Cliffside Park, NJ, USA.
Due to the increased risks associated with _allogenic blood transfusion_, blood management in surgical procedures, especially in orthopedic settings, should include reduction of _perioperative blood loss_. Preoperative nursing assessment will help define patients at increased risk for transfusion. Both _nonpharmacologic_ and _pharmacologic techniques_ can help minimize _allogenic transfusion_ by reducing _blood loss_. One such method of managing _anemia_ and reducing patient exposure to _allogenic transfusion_ is the _perioperative use of recombinant human erythropoietin—erythropoietin alfa_—an innovative surgical blood management tool. Increased awareness by perioperative nurses of the use of erythropoietin alfa and patient implications can contribute to the overall _blood conservation goal_.

(4) Rosengart TK, et al.
OPEN HEART OPERATIONS WITHOUT TRANSFUSION USING A MULTIMODALITY BLOOD CONSERVATION STRATEGY IN 50 JEHOVAH'S WITNESS PATIENTS: IMPLICATIONS FOR A "BLOODLESS" SURGICAL TECHNIQUE.
Blood transfusion persists as an important _risk_ of _open heart operations_ despite the recent introduction of a variety of _new pharmacologic agents_ and _blood conservation techniques_ as Independent therapies. A multimodality blood conservation program was developed to minimize this risk. The blood conservation program used for these patients included the use of:
1) High-dose erythropoietin (800 U/kg load, 500 U/kg every other day),
2) Aprotinin (6 million U total dose full Hammersmith regimen),
3) "Maximal" volume intraoperative autologous blood donation
4) Intraoperative cell salvage,
5) Continuous shed blood reinfusion, and
6) Drawing as few blood specimens as possible.
RESULTS: The overall in-hospital mortality for the group was 4 percent. The chest tube output in group 1 patients was less than 40 percent of that for group 2 patients at all points measured after operation (p < 0.01).
CONCLUSIONS: These results suggest that even _complex open heart operations_ can be performed without homologous transfusion _by optimally applying available blood conservation techniques_. More generalized application of these measures may increasingly allow "bloodless" operations in all patients.

(5) Kunz J, et al.
MANAGEMENT OF SEVERE BLOOD LOSS AFTER TUMOR RESECTION IN A JEHOVAH'S WITNESS.
This report describes the peri- and postoperative management of a patient with _thalassemia minor_ and a _carcinoma colli uteri_(FIGO IIIB). As a consequence of the surgical intervention her hemoglobin dropped to 22 g/l.
The patient refused autologous and homologous blood transfusions for religious reasons (Jehovah’s Witness).
During surgery _hemodilution_ and _cell salvage_ were used. Postoperatively she developed a coagulopathy and hemorrhage with the lowest hemoglobin value of 22 g/l.
The patient recovered under a therapy regimen of _recombinant human erythropoietin_ and _parenteral iron_ (Ferrum Hausman intravenously 100 mg Fe(III) per week.
Klinik für Anasthesiologie, Universität Graz, Österreich.

After rapid changes in transfusion practice over the past few years, blood conservation techniques have become standard in modern perioperative management. As a result, the amount of homologous blood products transfused has been markedly reduced in some types of surgical procedures. Provided that skillful surgical technique is applied and the use of blood products is restricted, autologous transfusion techniques (predonation of autologous blood, preoperative plasmapheresis, acute normovolaemic haemodilution, and intra- and postoperative blood salvage) can be performed with an acceptable risk for patients.

In addition, stimulation of erythropoiesis with recombinant human erythropoietin, supplemental iron therapy, and improving haemostasis by aprotinin may further reduce homologous blood requirements. All patients undergoing elective surgery have to be informed about the side effects of transfusion of homologous blood products and the possibility of blood-saving methods. An individual blood conservation plan, based on the patient's status and surgery, the equipment available, and personal experience should be worked out by the responsible anaesthesiologist, whereby a combination of different methods may be most effective.

Although blood conservation programs are time-consuming and more expensive, they reduce the various risks of using homologous blood products.


(7) Akingbola O.A et al.

MANAGEMENT OF SEVERE ANEMIA WITHOUT TRANSFUSION IN A PEDIATRIC JEHOVAH’S WITNESS PATIENT.

Critical Care Med :1994;Vol:22,No:3,pp.524-8,

The patient a 12-yr-old male with glomerulonephritis and renal failure requiring peritoneal dialysis since the age of 9 years. He had bilateral nephrectomy and an unsuccessful renal transplant from his father, he also had Hypertension and hypothyreoidism. He had a new transplant from his mother and was admitted to the pediatric intensive care unit (ICU). Initially Hemoglobin(Hb) Concentration of 8g/dL(80g/l), Hematocrit of 24%, Blood Urea Nitrogen was 17mg/dL(6.1 mmol/L),and Creatinine was 2.6 mg/dL(230umol/L). On postoperative day 4 there was proteinuria(4+ protein on dipstick) and a deteroriated kidney function, he was clinically stable and was taken to the operating room for an open Renal biopsy. On postoperative day 7, his Hematocrit was 10%,the next day his clinical status deteriorated. He refused blood transfusion; his parents also signed a written statement upholding that decision. He had a heart rate of 80 to 90 beats/min respiratory rate was 26 breaths/min and Blood pressure was 108/65mmHg, The pulse was bounding and an active precordium was found on palpation, with a leftward displacement of the apical impulse. On auscultation, he had a grade 3/6 systolic ejection murmur along the lower left sternal border, with an S3 gallop. Hemoglobin was 2.1g/dL and Hematocrit had fallen to 6%.

Treatment consisted of the following measures: __________________________________________________________

a) He was intubated and mechanically ventilated.
b) Hypothermia was induced by surface cooling to maintain rectal temperature at 34 o to 35 oC.
   "Mild Hypothermia"
c) Pentobarbital coma were used as an adjunctive therapy. Loading dose 4 mg/kg followed by a
   continuous infusion at 2 mg /kg/hr .
d) Neuromuscular blockade was maintained with Pancourium bromide at 0.1 mg/kg/hr.
e) Monitoring: End-tidal CO2 was monitored and maintained at 30 torr(4.0 kPa), the arterial oxygen
   satturation was kept at >95% . Arterial blood gas measurements showed a pH of 7.48,Pa O2 of 143
torr(9.0kPa). Pa CO2 of 26 torr (3.5 kPa) with 100% arterial oxygen satturation. Oxygen
   consumption (OC) and resting energy expenditure (REE) were measured daily. OC at baseline was
   148mL/min(5.3mL/min/kg)REE was 1048 kcal/24 hrs.
f) Blood sampling: was limited to 1 to 3ml daily for Blood Urea, Nitrogen ,Creatinine, Hemoglobin
   (Hb) and Hematocrit measurements.
g) Recombinant human Erythropoietin(EPO)10.000 units subcutanously twice daily was begun.
h) Intravenous Iron (100mg) was administered daily. (IRON DEXTRAN).

i) Anabolic steroids: Methyltestosterone (25mg) was administered.

j) Intravenous hyperalimentation 1800 kcal/day, with a protein intake of 2g/kg/day.

The OC and REE decreased to 94mL/min (3mL/min/kg) and 649kcal/24hrs respectively by the institution of hypothermia (35°C), pentobarbital coma and muscle paralysis. Similarly, CO2 production decreased from 132mL/min (4.7 mL/min/kg) at a baseline to 78mL/min (2.8 mL/min/kg). Pentobarbital therapy was discontinued on the fourth day.

After gradual surface rewarming to a body temperature of 36 to 37°C, neuromuscular blockade was discontinued. The patient was extubated and maintained on oxygen by face mask. Hematocrit was 10% and the serum Creatinine concentration was 1.5 mg/dL (132.6 umol/L). On the 14th day of pediatric ICU admission, his Hb had increased to 7 g/dL (72.6 g/L) and Hematocrit of 22%. He continued to receive EPO and oral iron therapy. He was discharged home with a Hb concentration of 8.6 g/dL (86 g/L) and a Hematocrit of 26.6%. He remains in good health at follow-up, with good allograft function.

(8) J. MERVYN THOMAS

THE WORLDWIDE NEED FOR EDUCATION IN NONBLOOD MANAGEMENT IN OBSTETRICS AND GYNECOLOGY

Journal SOGC 1994:16:1483-7:

What does nonblood management in obstetrics and gynecology require of the surgical team? A: First, demonstrate professional respect for the informed choice of a patient who refuses only one form of medical treatment.

Second, take a fresh approach to the application of present knowledge of nonsolid management in obstetrics and gynecology, recognizing the need to:

1) PLAN in advance for possible haemorrhage.
2) Use every indicated, available, and patient accepted Method to limit blood loss.
3) Promptly institute measures to stop the bleeding. (Restrict intravenous fluids for arterial bleeding. "A Bucket with a hole in it cannot be filled").
4) Use every indicated, available, and patient accepted treatment to improve her haemological status rapidly.

The solution to GAPS in our medical knowledge has always been, and always will be, EDUCATION; and perhaps it is TIME that classes in these matters were introduced to the undergraduate medical curriculum and training programs for residents WORLD-WIDE, and that sessions were mounted in continuing medical education courses.

(9) KEMKES BM.

HEMOSTATIC FAILURES AND HEART-LUNG TRANSPLANTATION: ASSESSING THE CURRENT SITUATION.

J Heart Lung Transplant: 1993:Jan/Feb:12:S3-S6

Most routine heart surgery procedures and heart transplantations currently can be performed without exposure to homologous blood or blood products. Cooly et al(Am J Surg:1966:112:743), first reported a successful transplantation without blood transfusion in 1966, subsequently several groups duplicated this feat when transplanting hearts in patients who were Jehovah's Witnesses. (CORNX et al:J Heart Transplant:1986:5:175)

Which future perspectives and therapies will contribute to "Blood-free" cardiac surgery? A first aim must be to use methods that will conserve the patient's blood, in combination with both EPO therapy and normovolemic hemodilution. Besides these procedures, blood-saving methods are available that use NEW CELL SAVERS with advanced technology. Among the new technology are a hemofiltration system and heparin-coated circuits and oxygenators that cause less trauma. Another approach to blood saving involves pharmacologic agents. In the context of pharmacologic intervention, an optimization of heparin/protamin monitoring is also mandatory. Finally, every surgeon should keep in mind that persistent operative bleeding despite APROTININ application is not a medical problem. The patient should be returned to the operating room for a second look.
(10) KITCHENS CS.

**ARE TRANSFUSIONS OVERRATED?**

**SURGICAL OUTCOME OF JEHOVAH'S WITNESSES**


Data obtained from 16 reports of surgical outcome of a series of patients of the Jehovah 's Witnesses faith who were not given transfusion for operations during which transfusion is typically given. Analysis of these data supports the concept that approximately 0.5 % to 1.5 % of such operations are complicated by anemia resulting in death. The risks of not transfusing patients must be weighed against the risks of transfusing. Now of the 1,404 patients 20% avoided complications of transfusion.

(11) MANN MC, et al.

**MANAGEMENT OF SEVERELY ANEMIC PATIENTS WHO REFUSES TRANSFUSION:**

**LESSONS LEARNED DURING THE CARE OF A JEHOVAH'S WITNESS.**


Proper management of the severely anemic patient refusing blood therapy requires an astute clinician who understands the patient's philosophy and appreciates the often conflicting medicolegal and ethical aspects of their care, as well as the therapeutic options that are currently available. One must be aware of the many alternative therapeutic options that can maximize oxygen delivery and minimize oxygen consumption. The insights gained from this review are applicable to any severely anemic patient who refuses blood transfusion.

(12) SPENCE RK, et al.

**IS HEMOGLOBIN LEVEL ALONE A RELIABLE PREDICTOR OF OUTCOME IN SEVERELY ANEMIC SURGICAL PATIENTS ?**


The relationship between outcome and hemoglobin (HgB), Oxygen extraction ratio (ER),... and active bleeding was analyzed in 47 patients with severe anaemia (HgB<7.0 gm/dl,mean= 4.6 ± -2 gm/dl) to evaluate the effect of HgB on survival and look for other predictors of outcome. Active bleeding was a predictor for levels of HgB below 4.0 gm/dl. HgB level alone was a significant predictor only at levels below 3 gm/dl (P<0.05). Extraction ratio interacted with HgB only below 3 gm/dl (P<0.05).

Multiple independent factors influence outcome in the severely anemic patient the strongest being SEPSIS and ACTIVE BLEEDING. Prevention of sepsis and EARLY intervention to stop bleeding should improve survival in the patient who refuses transfusion.

(13) SPENCE RK, et al.

**TRANSFUSION GUIDLINES FOR CARDIOVASCULAR SURGERY:**

**LESSON LEARNED FROM OPERATIONS IN JEHOVAH'S WITNESSES.**


Patients undergoing cardiovascular surgery are among the top users of homologous blood transfusion (HBT). Estimated bloodloss averaged 870 ml, but one third to one half of losses were replaced by Intraoperative AutoTransfusion (IAT).

Three of 59 patients died (5.1%), but only one died of operative bleeding complications. Maximum blood-ordering schedule guidelines for HBT in major Cardiovascular operations can be reduced to near zero by the use of intraoperative autotransfusion and acceptance of a postoperative hemoglobin nadir of 7.0 gm/dl.

(14) LEWIS CTP, et al.

**RISK FACTORS FOR CARDIAC OPERATIONS IN ADULT JEHOVAH'S WITNESSES**


The early mortality rate of patients who had operation between January 1986 and March 1989, was 7 %. Blood loss was the cause of death in 3 patients (2.935%). In the other 3 patients, blood loss was a major contributor to death.

Only the last 12 months, the CELL SAVER was used. One to two units of blood is usually recovered in this way. SINCE the introduction of this technique, NO PATIENT HAS DIED SECONDARY TO
BLOOD LOSS or ANEMIA.
DEXTRAN and HETASTARCH were avoided because of their known adverse effects on coagulation in HEMODILUTED patients. On postoperative day 1, a hemoglobin level lower than 80 g/L was strongly associated with an increased risk of early death \( p=0.001 \). The average hemoglobin level at the time of death was 40 g/L he preoperative ejection fraction averaged 0.49 in the patients who survived and 0.37 in the 6 patients who died, ejection fraction of less than 0.35 was associated with a significantly increased risk of early death \( p<0.01 \). In the patients undergoing repeat DOUBLE-VALVE PROCEDURES, the average ejection fraction was 0.30. Tree of the 5 having a repeat procedure died. Two of the 6 patients who died had major wound complications necessitating sternal revision, and each death occurred early after second operation. TWO of the 6 patients who died early had undergone DIALYSIS for renal failure.

(15) TRENT B.
JEHOVAH'S WITNESSES AND THE TRANSFUSION DEBATE:
"WE ARE NOT ASKING FOR THE RIGHT TO DIE"
The protocol calls for doctors to:
1) Pursue Non Blood Medical Management and treat the patient without using homologous blood.
2) CONSULT with other doctors experienced in nonblood management.
3) CONTACT the Witnesses's local medical liaison committee to locate experienced and cooperative doctors at other facilities for consultation on medical care.
"The problem we've run into in all such cases is that the doctor is programmed to go in a certain way and then, when something different comes up, it's difficult to make the transition.” Today it is unacceptable to use blood routinely during surgery.
Our message to the doctors is simple: "We want to work with them and we're not out to get them,. We need them.”

(16) BRIMACOMBE J, et al.
ACUTE ANAEMIA TO HAEMOGLOBIN OF 14 G/L WITH SURVIVAL
It was felt that the bleeding problem was a combination of factors including surgical hemorrhage, fibrinolysis secondary to a placental abruption and a dilutional coagulopathy. "A CELL SAVER" would have prevented such a severe fall in haemoglobin concentration, but was not available at this hospital. An FiO2 was maintained for three days and allowed high pa O2 levels to be achieved. Cardiac output was held at ten liters with Noradrenaline infusion support. Serum Albumin fell to 8 g.l-1 and contributed to development of pulmonary and peripheral edema. The pulmonary edema was treated with ventilation, PEEP and FUROSEMIDE.

(17) SPENCE RK, et al.
ELECTIVE SURGERY WITHOUT TRANSFUSION:
INFLUENCE OF PREOPERATIVE HEMOGLOBIN LEVEL AND BLOOD LOSS ON MORTALITY
Mortality for preoperative hemoglobin levels greater than 10 g/dl was 3 of 93(3.2%). For preoperative hemoglobin levels between 6 to 10 g/dl, mortality was 1:20 or 5%. There was no mortality if estimated blood loss was LESS THAN 500 ML, regardless of the preoperative hemoglobin level. We conclude that:
1) Mortality in elective surgery appears to depend more on estimated blood loss than on preoperative hemoglobin levels.
2) Elective surgery can be done safely in patients with a preoperative hemoglobin level as low as 6 g/dl if estimated blood loss is kept below 500 ml.

(18) Garcia F, et al.
ANEMIA AND ANESTHESIA
Today, it is unacceptable to use blood routinely during surgery.
Positively, the patient with the low hemoglobin has a decrease in blood viscosity, a shift in the oxyhemoglobin dissociation curve to the right, an increased oxygen extraction by various organs, and
increased cardiac output. But an increase in cardiac output is only possible if the patient is hemodiluted to normovolemia. Techniques of blood less surgery are presented.

A. IMPROVE HEMOSTASIS

Stop, a good time in advance, using COUMARIN, ASPIRIN, DIPYRIDAMOLE or other medicaments which could act on the blood coagulation, at least 2 weeks before the operation. These drugs cause a lowered level of clotting factors or a disturbed THROMBOCYTE-FUNCTION, with impaired coagulation and give a tendency to bleed as the result. (5-13-fold increase)

I. ANTICOAGULATION A short Review of Methods

A. Prevalence of Pulmonary Embolism (PE) in High Risk Patients

(1) Heit JA, Minor TA, Andrews JC, Larson DR, Li H, Nichols WL
DETERMINANTS OF PLASMA FIBRIN D-DIMER SENSITIVITY FOR ACUTE PULMONARY EMBOLISM AS DEFINED BY PULMONARY ANGIOGRAPHY.
Arch Pathol Lab Med 1999 Mar;123(3):235-40

Department of Medicine, Mayo Clinic and Foundation, Rochester, Minn. 55905, USA.

BACKGROUND: The reported operating characteristics of the plasma fibrin D-dimer level for the diagnosis of acute pulmonary embolism vary widely. OBJECTIVE: To determine the sensitivity, specificity, predictive value, and clinical utility of the D-dimer for the diagnosis of pulmonary embolism, and to describe the effect of D-dimer assay method (enzyme-linked immunosorbent assay [ELISA], latex agglutination, membrane ELISA) and discriminate level, patient location at onset, comorbid disease, duration and intensity of concurrent heparin administration, and duration of symptoms on these operating characteristics. DESIGN: Prospective laboratory investigation. SETTING: Community and tertiary care teaching hospital. PATIENTS: Consecutive patients with suspected acute pulmonary embolism referred for pulmonary angiography from April 1993 through March 1996. MEASUREMENTS: Baseline characteristics, the duration and intensity of heparin anticoagulation, the time interval between symptom onset and plasma D-dimer testing, pulmonary angiography, and the D-dimer level on the day of pulmonary angiography. RESULTS: Of 105 consenting patients, 33 (31%) had a positive pulmonary angiogram. The D-dimer sensitivity/ negative predictive value for the ELISA, latex agglutination (American Bioproducts Co/Diagnostica Stago and Biopool International), and membrane ELISA were 100%/100%, 94%/94%, 100%/100%, and 97%/96%, respectively, at a discriminate level of 250 microg/L or less. The clinical utility, defined as the prevalence of a negative test, ranged from 17% to 33%. D-dimer sensitivity was unaffected by patient location at onset, comorbid disease, or heparin therapy but was inversely related to the duration of symptoms. CONCLUSIONS: The sensitivity of the plasma fibrin D-dimer for the diagnosis of pulmonary embolism depends on the assay method, the assay-specific discriminate level, and the duration of symptoms. At the appropriate discriminate level, the plasma D-dimer is a sensitive but nonspecific test for the diagnosis of pulmonary embolism.

(2) Gorman TE, Arcot AN, Baker P, Prior TW, Brandt JT
PREVALENCE OF THE FACTOR VLEIDEN MUTATION AMONG AUTOPSY PATIENTS WITH PULMONARY THROMBOEMBOLIC DISEASE USING AN IMPROVED METHOD FOR FACTOR VLEIDEN DETECTION.
Am J Clin Pathol 1999 Mar;111(3):413-7
Activated protein C resistance caused by factor VLeiden mutation is the most common inherited predisposing cause of venous thromboembolism, including pulmonary embolism (PE). We studied whether the incidence of factor VLeiden is higher among patients with PE evident at autopsy than in the general population. Paraffin-embedded fixed tissue blocks from all autopsy patients with diagnosed pulmonary thromboembolic disease during a 4-year period were collected for DNA extraction. Extraction and molecular analysis of the DNA was performed with an improved technique with an internal control to determine the presence of factor VLeiden mutation. Analysis of 82 autopsy cases with PE yielded 5 patients who were heterozygotes. Seventy-seven of the 82 patients analyzed were normal, and no homozygotes for factor VLeiden mutation were identified. This yielded a positive rate of 6% overall and 7% among white patients, which is similar to the incidence of heterozygotes in the white population. This study indicates that routine determination of factor VLeiden mutation is not warranted for patients with PE diagnosed at autopsy.

ACCURACY OF CLINICAL ASSESSMENT IN THE DIAGNOSIS OF PULMONARY EMBOLISM.
Am J Respir Crit Care Med 1999 Mar;159(3):864-71

Istituto di Fisiologia Clinica del Consiglio Nazionale delle Ricerche (CNR), Pisa, Italy.
To provide clinical diagnostic criteria for pulmonary embolism (PE), we evaluated 750 consecutive patients with suspected PE who were enrolled in the Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis (PISA-PED). Prior to perfusion lung scanning, patients were examined independently by six pulmonologists according to a standardized diagnostic protocol. Study design required pulmonary angiography in all patients with abnormal scans. Patients are reported as two distinct groups: a first group of 500, whose data were analyzed to derive a clinical diagnostic algorithm for PE, and a second group of 250 in whom the diagnostic algorithm was validated. PE was diagnosed by angiography in 202 (40%) of the 500 patients in the first group. A diagnostic algorithm was developed that includes the identification of three symptoms (sudden onset dyspnea, chest pain, and fainting) and their association with one or more of the following abnormalities: electrocardiographic signs of right ventricular overload, radiographic signs of oligemia, amputation of hilar artery, and pulmonary consolidations compatible with infarction. The above three symptoms (singly or in some combination) were associated with at least one of the above electrocardiographic and radiographic abnormalities in 164 (81%) of 202 patients with confirmed PE and in only 22 (7%) of 298 patients without PE. The rate of correct clinical classification was 88% (440/500). In the validation group of 250 patients the prevalence of PE was 42% (104/250). In this group, the sensitivity and specificity of the clinical diagnostic algorithm for PE were 84% (95% CI: 77 to 91%) and 95% (95% CI: 91 to 99%), respectively. The rate of correct clinical classification was 90% (225/250). Combining clinical estimates of PE, derived from the diagnostic algorithm, with independent interpretation of perfusion lung scans helps restrict the need for angiography to a minority of patients with suspected PE.

(4) Wroblewski BM, Siney PD, Fleming PA
FATAL PULMONARY EMBOLISM AFTER TOTAL HIP ARTHROPLASTY: DIURNAL VARIATIONS.
Orthopedics 1998 Dec;21(12):1269-71

John Charnley Research Institute, Wrightington Hospital, Lancashire, United Kingdom.
From 1970 through 1986, a total of 18,104 Charnley low-friction arthroplasties were performed; of these, 122 deaths occurred from pulmonary embolism within 1 year of surgery. Diagnosis was confirmed by postmortem examination in 71% of cases. The exact time of the onset of the complication was recorded in 90 cases. In 74 (82%) cases, the time of collapse occurred during the 7-hour period from 9:00 AM to 4:00 PM, and in 16 (18%) cases, it occurred in the 17-hour period from 4:00 PM to 9:00 AM. The patient's activity at the time of collapse was recorded in 73 cases. Sixty (82%) were mobile, 3 were in the bathroom, and 10 (14%) were in bed. Sixty-six (70.2%) patients died within 1 hour of the onset of symptoms.
FIVE-YEAR FOLLOW-UP OF PROPHYLACTIC VENA CAVA FILTERS IN HIGH-RISK TRAUMA PATIENTS.

Arch Surg 1998 Apr;133(4):406-11; discussion 412

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OBJECTIVE: To assess the short- and long-term outcomes of vena cava filter (VCF) placement for prophylaxis against pulmonary embolism in patients at high risk due to trauma.

DESIGN AND SETTING: Case series at a level I trauma center. PATIENTS: Patients were considered for prophylactic VCF placement if they met 1 of the injury criteria—spinal cord injuries with neurologic deficit, severe fractures of the pelvis or long bone (or both), and severe head injury—and had a contraindication to anticoagulation. INTERVENTION: Vena cava filters were placed percutaneously by the interventional radiologists when the acute trauma condition was stabilized following admission. MAIN OUTCOME MEASURES: Filter tilt of 14 degrees or more, strut malposition, insertion-related deep vein thrombosis, pulmonary embolism, or inferior vena cava patency.

RESULTS: There were 132 prophylactic VCFs placed. A 3.1% rate of insertion-related deep vein thrombosis occurred, all of which were asymptomatic. Filter tilt occurred in 5.5% of patients and strut malposition in 38%. Three cases of pulmonary embolism (1 fatal) occurred in a prophylactic VCF, and all patients had either filter tilt or strut malposition. The risk of pulmonary embolism developing was higher in those patients with filter tilt or strut malposition than in those who did not have these complications (6.3% vs 0%; P=0.05; Fisher exact test). The 1-, 2-, and 3-year inferior vena cava patency rates (+/-SD) were 97%+/-3%.

CONCLUSIONS: Prophylactic VCF can be placed safely with an acceptable rate of insertion-related deep vein thrombosis and long-term inferior vena cava patency. Patients with prophylactic VCF remain at risk for pulmonary embolism if the filter is tilted 14 degrees or more or has strut malposition. In such patients, consideration should be given to placing a second filter.

B. Anticoagulation in Trauma Patients for Low Risk Patients

THE NATURAL HISTORY OF EXTREMITY VENOUS REPAIR PERFORMED FOR TRAUMA.

Am Surg 1999 Feb;65(2):116-20

Surgical repair of extremity venous injuries remains controversial. Literature supports both ligation and repair when analyzed for functional recovery. However, few studies review the natural history of venous repair for trauma. Twenty patients were prospectively enrolled in a protocol of immediate repair of major extremity veins. Simple venorrhaphy and complex reconstructions were performed at the discretion of the operative team. Patients were studied by contrast venogram on postoperative day 3 and 6 weeks after surgery. Patients with occluded repairs at 3 days received a 5-day course of intravenous anticoagulation and were discharged. Overall, patency at 3 days was 55 per cent and increased to 88 per cent at 6 weeks (P < 0.02). Lateral venorrhaphy and direct reapproximation had higher patency rates than complex repairs at 6 weeks (92% versus 50%; P < 0.05). All veins that were patent at 3 days remained patent (correlation coefficient 1.0). Repair of traumatized extremity veins carries minimal morbidity and has a high rate of early and eventual patency. Long-term anticoagulation in the face of early thrombosis is unnecessary.

DELAYED CORTICAL BLINDNESS AND RECURRENT QUADRIPEGIA AFTER CERVICAL TRAUMA.


Department of Orthopaedic Surgery and the Rothman Institute, Philadelphia, Pennsylvania, USA.
In a retrospective, single-patient case report, we report on a 56-year-old woman with delayed cortical blindness and recurrent quadriplegia after a comminuted C1 burst fracture and a type II odontoid fracture. The vertebral artery is susceptible to injury during trauma to the cervical spine. The resulting vascular compromise may be responsible for a variety of neurologic outcomes. The patient was followed up through personal examination and chart review from initial presentation to 6 months after the injury. Three months after cervical fusion and anticoagulation therapy, the patient was noted to have marked improvement of her visual acuity with almost complete return of strength, as well as normalization of vertebral vessel size. Because of the proximity of the vertebral artery to the atlantoaxial complex, it is susceptible to injury during trauma to the cervical spine. Injury to the vasculature supplying the brain may result in both immediate and delayed neurologic consequences.

(3) Eeachempati SR, Vaslef SN, Sebastian MW, Reed RL 2nd
BLUNT VASCULAR INJURIES OF THE HEAD AND NECK: IS HEPARINIZATION NECESSARY?
Trauma 1998 Dec;45(6):997-1004

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BACKGROUND: Blunt vascular injuries to the head and neck (BHVI) represent some of the most devastating and morbid injuries seen by a trauma surgeon. This series reviewed the experience of a single institution to determine if diagnostic and therapeutic guidelines can be established for these uncommon injuries. In particular, the utility of anticoagulation in the treatment of these injuries is examined. METHODS: The institutional trauma registry of a single state-designated Level I trauma center was examined for patients with BHVI. Patients were identified and their charts reviewed individually with regard to multiple data points including the type of injury, its presentation, the treatment of the injury, and the functional outcome of the patient. RESULTS: Twenty-nine BHVI in 23 patients were reviewed from 1989 to 1997. No mortalities were noted. Among the injuries noted were 14 internal carotid artery dissections and 8 carotid artery tears. Thirteen patients had accompanying closed head injuries. Ten patients were diagnosed after an abnormal neurologic examination, and eight others were diagnosed after having carotid canal fractures. Heparin was started within 48 hours of injury in 4 patients (17%) and was used in a total of 12 patients (52%). No patient worsened neurologically after diagnosis independent of the use of heparin. Thirteen patients (57%) had no or minimal deficits upon discharge. CONCLUSION: BHVI represent a serious cause of morbidity in the patient with multiple injuries. Patients with closed head injuries and carotid canal fractures appear most at risk. A multicenter, randomized trial involving antiplatelet therapy, full systemic anticoagulation, or observation with a long-term functional assessment is indicated to determine the optimal management of these injuries.

THE UNRECOGNIZED EPIDEMIC OF BLUNT CAROTID ARTERIAL INJURIES: EARLY DIAGNOSIS IMPROVES NEUROLOGIC OUTCOME.

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OBJECTIVE: To determine the benefit of screening for blunt carotid arterial injuries (BCI) in patients who are asymptomatic. SUMMARY BACKGROUND DATA: Blunt carotid arterial injuries have the potential for devastating complications. Published studies report 23% to 28% mortality rates, with 48% to 58% of survivors having permanent severe neurologic deficits. Most patients have neurologic deficits when the injury is diagnosed. The authors hypothesized that screening patients who are asymptomatic and instituting early therapy would improve neurologic outcome. METHODS: The Trauma Registry of the author's Level I Trauma Center identified patients with BCI from 1990 through 1997. Beginning in August 1996, the authors implemented a screening for BCI. Arteriography was used for diagnosis. Patients without specific contraindications were anticoagulated. Endovascular stents were deployed in the setting of pseudoaneurysms. RESULTS: Thirty-seven patients with BCI were identified among 15,331 blunt-trauma victims (0.24%). During the screening period, 25 patients were diagnosed with BCI among 2902 admissions (0.86%); 13 (52%) were asymptomatic. Overall, eight patients died, and seven of the survivors had permanent severe neurologic deficits. Excluding those dying of massive brain injury...
and patients admitted with coma and brain injury, mortality associated with BCI was 15%, with severe neurologic morbidity in 16% of survivors. The patients who were asymptomatic at diagnosis had a better neurologic outcome than those who were symptomatic. Symptomatic patients who were anticoagulated showed a trend toward greater neurologic improvement at the time of discharge than those who were not anticoagulated. CONCLUSIONS: Screening allows the identification of asymptomatic BCI and thereby facilitates early systemic anticoagulation, which is associated with improved neurologic outcome. The role of endovascular stents in the treatment of blunt traumatic pseudoaneurysms remains to be defined.

BILATERAL THROMBOSIS OF THE INTERNAL CAROTID ARTERIES AFTER A CLOSED TRAUMA. ADVANTAGES OF MAGNETIC RESONANCE IMAGING AND REVIEW OF THE LITERATURE.

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Bilateral traumatic dissection of an internal carotid artery (BTDIC) after a closed injury is very rare. We report a case of bilateral thrombosis caused by internal carotid artery dissection due to a closed injury. The 22 cases documented in the literature are also reviewed. Six of the patients (26%) were asymptomatic at the initial examination, but all developed secondary symptoms, during the first 48 hours. Sixteen patients (69%) had associated traumatic lesions. Six patients died during the week after the accident, all of them had initial neurological symptoms. Magnetic resonance imaging (MRI) provided more items of information than angiography, showing a dissection on an occluded artery and a clearer picture of the length of the dissection, directly visualizing the wall hematoma and a residual signal that showed the persistence or arrest of blood flow. Treatment of BTDIC is based on early anticoagulation therapy.

(6) Anglen JO, Goss K, Edwards J, Huckfeldt RE
FOOT PUMP PROPHYLAXIS FOR DEEP VENOUS THROMBOSIS: THE RATE OF EFFECTIVE USAGE IN TRAUMA PATIENTS.

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Trauma patients are at risk for deep venous thrombosis (DVT) but often cannot receive systemic anticoagulation therapy. The major reason for failure of mechanical methods of DVT prophylaxis is ineffective usage. It has been postulated that foot pumps may have a better compliance rate than do other devices. One thousand observations were performed on trauma patients in both the intensive care unit (ICU) and on the surgical ward. Foot pumps were applied properly and functioning correctly 59% of the time. Patients in the ICU had significantly better compliance than did patients on the surgical ward. These rates are not better than published rates for other devices for DVT prophylaxis.

(7) Ferrera PC, Pauze DR, Chan L
SAGITTAL SINUS THROMBOSIS AFTER CLOSED HEAD INJURY.

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Superior sagittal sinus thrombosis (SSST) is an unusual disorder, most often attributed to hematological abnormalities, oral contraceptive use, or association with the puerperium. Although SSST secondary to trauma has been reported, it still remains an extremely rare entity. Antemortem diagnosis of SSST is made by findings on computed tomographic scanning, cerebral angiography, or magnetic resonance imaging. Prognosis is variable and spontaneous resolution has been reported. Successful treatment options of spontaneous cases include systemic anticoagulation and thrombolytic therapy along with supportive measures. There are currently no guidelines for the management of SSST associated with traumatic brain injury. This report describes a case of SSST in a man who sustained a closed head injury.
Identification of blunt carotid injury prior to the development of ischemic symptoms requires aggressive screening of patients at risk. The treatment of these lesions has centered around long-term anticoagulation therapy. However, studies have revealed that many of these lesions persist despite medical treatment, as does the risk of distal embolization. The authors present a series of six patients who were successfully treated by means of endovascular stent placement for nonpenetrating carotid injuries. In the authors' experience this treatment requires only temporary anticoagulation therapy, results in immediate reconstruction of the injured vessel, obliterates pseudoaneurysms, and prevents distal embolization.

**Blunt injury of the internal carotid artery (ICA) is a rare entity that should be considered by Maxillofacial surgeons in patients with facial fractures.** Its recognition is often delayed because of the common association with other severe multi-system injuries. Early diagnosis is the key to successful management; the arteriography plays a confirmatory role on the diagnosis and determines whether surgical management of the injury is feasible. Therapeutic alternatives vary from one center to another; they include observation, conservative treatment, anticoagulation, ligation of the carotid artery with or without extracranial-intracranial bypass, and arterial reconstruction.

**Complications of anticoagulation for pulmonary embolism in low risk trauma patients.**

Trauma patients are at significant risk for deep venous thrombosis (DVT) and pulmonary embolism (PE). Anticoagulation is standard therapy for DVT/PE, but may cause severe complications. We reviewed the course of 70 trauma ICU patients treated over a 28-month period. Thirty-six patients (51.4 percent) were treated by continuous IV heparin and/or oral warfarin. Of these, 13 patients (36 percent) developed complications requiring termination of anticoagulation. These included recurrent PE (four), subdural hematomas (three), hemothorax (two), heparin-induced thrombocytopenia (one), hemorrhagic pericardial effusion (one), retroperitoneal hematoma (one), and sudden unexplained drop in hemoglobin and shock (one). All patients with subdural hematomas had no prior evidence of head injury on brain computed tomography. All patients with recurrent PE received adequate anticoagulation therapy. Age > 55 was associated with increased risk of complications (8 of 13; p = .02; chi 2). Thirty-four other patients (48.6 percent) received inferior vena caval filters with no related complications or deaths. Anticoagulation for DVT/PE should be used selectively in trauma patients and avoided in elderly patients. Such patients should undergo early caval filter placement.
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The thrombophilias are conditions characterized by an increased tendency to thrombosis. This paper aims at presenting the actual guidelines concerning the preventive attitudes in the thrombophilias that mainly expose to venous thromboembolism. The identification of these thrombophilias resides on one hand on the patients' and their family's history of venous thrombosis, and on the other hand on the diagnosis of disorders known to be associated with an increased risk of venous thrombosis. Heparin-associated thrombocytopenia of type II is a still too often underdiagnosed syndrome in which the prevention of thrombosis requires a specific approach. The authors discuss thoroughly the preventive attitudes for patients that do not require a long-term anticoagulation, for patients in whom a long-term anticoagulation is generally recommended, and for patients in whom it is sometimes recommended. The practical use of anticoagulation is described. Lastly, a special attention is paid to situations in which the thrombotic risk is increased, such as prolonged immobilization, surgery, traumas, pregnancy and postpartum, contraception and oestrogen.

C. Prevalence of Deep Venous Thrombosis in ICU patients

(1) Kollef MH, Zahid M, Eisenberg PR

PREDICTIVE VALUE OF A RAPID SEMIQUANTITATIVE D-DIMER ASSAY IN CRITICALLY ILL PATIENTS WITH SUSPECTED VENOUS THROMBOEMBOLIC DISEASE.


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OBJECTIVE: To evaluate the performance of a new, rapid semi-quantitative assay for the detection of circulating D-dimer in whole blood from critically ill patients with suspected venous thromboembolic disease. DESIGN: Prospective, blinded, single-center study. SETTING: Medical intensive care unit (ICU) of Barnes-Jewish Hospital, St. Louis, MO, a university-affiliated urban teaching hospital. PATIENTS: Two hundred thirty-nine adult patients with clinical suspicion of venous thromboembolic disease admitted to a medical ICU. INTERVENTIONS: Collection of blood samples within 24 hrs of clinical suspicion of venous thromboembolic disease. MEASUREMENTS AND MAIN RESULTS: The main outcome measures evaluated included the occurrence of venous thromboembolic disease (i.e., lower extremity venous thrombosis, pulmonary embolism, catheter-associated venous thrombosis) and hospital mortality. Fifty-seven patients (23.8%) were classified as having venous thromboembolic disease during their ICU stays (pulmonary embolism, 21 patients; lower extremity thrombosis, 44 patients; line-associated venous thrombosis, 3 patients). The semi quantitative whole-blood assay for circulating D-dimer had a 96.4% sensitivity and a negative predictive value of 92.1% for identifying patients with venous thromboembolic disease. The specificity of this assay was 19.7%, and its positive predictive value was 26.9%. There was a strong correlation between the semi quantitative assay for circulating D-dimer and the quantitative measurement of circulating D-dimer using an enzyme immunoassay (Spearman’s correlation coefficient, 0.8643; p<.001). We also identified a strong correlation between both the quantitative and semi quantitative measurements of circulating D-dimer with the sepsis classification proposed by the American College of Chest Physicians/Society of Critical Care Medicine (i.e., systemic inflammatory response syndrome, sepsis, severe sepsis, septic shock) for patients without venous thromboembolic disease (n = 182; quantitative measure: Spearman’s correlation coefficient, 0.207; p = .002; semi quantitative measure: Spearman’s correlation coefficient, 0.3519; p<.001). CONCLUSIONS: These preliminary findings suggest that a rapid whole-blood assay for the semi quantitative detection of circulating D-dimer may be a useful diagnostic tool for the exclusion of venous thromboembolic disease among critically ill patients.

Comment in: Crit Care Med 2000 Feb;28(2):583-4

(2) Joynt GM, Kew J, Gomersall CD, Leung VY, Liu EK

DEEP VENOUS THROMBOSIS CAUSED BY FEMORAL VENOUS CATHETERS IN CRITICALLY ILL ADULT PATIENTS.


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STUDY OBJECTIVES: To determine the frequency of and potential risk factors for catheter-related deep venous thrombosis (DVT) in critically ill adult patients. DESIGN: Prospective, controlled, observational cohort study. SETTING: A mixed medical and surgical ICU in a university hospital. PATIENTS: All adult patients undergoing femoral vein catheterization. INTERVENTIONS: None. MEASUREMENTS: ICU diagnosis, underlying disease, demographic data, type of catheter, complications during cannulation, use of anticoagulants, coagulation status, medications infused, and duration of catheterization were recorded. Compression and duplex Doppler ultrasound studies of both femoral veins were performed prior to insertion, at 12 h after insertion, and daily until catheter removal. Follow-up investigation was performed at 24 h and 1 week after removal. RESULTS: Of 140 cases entered into the study, 124 were evaluated. Fourteen patients developed iliofemoral vein DVTs. Two were clinically obvious. Twelve (9.6%) were line related (uncannulated leg normal) and two (1.6%) occurred only in the uncannulated leg (p = 0.011; relative risk, 6.0; confidence interval, 1.5 to 23.5). Line-related DVT can occur any time from the day after insertion to 1 week after removal. The incidence of catheter-related DVT was unrelated to number of insertion attempts, arterial puncture or hematoma, duration of catheterization, coagulation status, or type of infused medications. No other predisposing or protective factors were identified. Three of the 12 patients with catheter-related DVT died. In no patient was clinical pulmonary embolus suspected. CONCLUSION: Although the femoral route is convenient and has potential advantages, the use of femoral lines increases the risk of iliofemoral DVT. Catheter-related DVT may occur as soon as 1 day after cannulation and is usually asymptomatic. This increased risk should be carefully considered when the femoral route of cannulation is chosen.

(3) Martin C, Viviand X, Saux P, Gouin F

UPPER-EXTREMITY DEEP VEIN THROMBOSIS AFTER CENTRAL VENOUS CATHETERIZATION VIA THE AXILLARY VEIN.


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OBJECTIVE: To determine the frequency of central venous catheter-induced thrombosis of the axillary vein. DESIGN: Prospective, controlled study. SETTING: Tertiary care university center. PATIENTS: Sixty patients in a medical-surgical intensive care unit who required central venous catheterization via the axillary vein. INTERVENTIONS: Single-lumen, silicone elastomer or polyurethane catheters were inserted for a mean duration of 14.7+/−7.4 days (range, 4-33 days). On catheter removal, bilateral upper-extremity phlebographic examination was performed in each patient. The incidence of deep vein thrombosis in catheterized arms was compared with that in uncatheterized arms. MEASUREMENTS AND MAIN RESULTS: Of the 60 patients who underwent axillary vein cannulation, one patient had clinical signs of arm vein thrombosis, but no patient had clinical sign of pulmonary embolism. There were 35 patients (58.3%) who developed positive phlebographic examinations homolateral to the catheter. Fibrin sleeves that developed around the catheters were observed in 28 patients (47%). Five patients (8.3%) had phlebographic signs of partial axillary vein thrombosis: nonobstructive clots adherent to the vessel wall and/or the catheter. Two patients (3.3%) had phlebographic signs of complete axillary vein thrombosis. No thrombosis was observed in patients with catheterizations lasting < or =6 days, two cases were observed for duration of 7-14 days, and five cases were observed for duration of > or =15 days (p < .01). In the seven patients with axillary vein thrombosis, the vessel was cannulated with fewer than three puncture attempts, and the mean duration for catheter insertion (10+/−2.5 min) was not different from that of patients with no axillary vein thrombosis (14+/−9 min). CONCLUSIONS: Based on the data from the present study, we conclude that axillary vein catheterization is associated with a 11.6% frequency of upper-extremity deep vein thrombosis. This rate of vein thrombosis is similar to that observed after internal jugular or subclavian vein cannulation. Given the acceptable rate of this clinically important complication, axillary vein cannulation offers an attractive alternative site for catheter insertion to the internal jugular or subclavian vein in the critically ill. Because thrombosis is rare or absent in catheterizations lasting <15 days, it seems wise to withdraw axillary catheters after a maximum of 2 wks.

Comment in: Crit Care Med 1999 Dec;27(12):2827-9
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The objective of this study was to determine the feasibility, cost-effectiveness, and complications of bedside placement of inferior vena cava (IVC) filters in the intensive care unit (ICU) in the trauma patient. A prospective trial involving 25 trauma patients admitted to Memorial Regional Hospital (Hollywood, Florida), a Level I trauma center, from April 1997 to April 1998, meeting the criteria for insertion of a prophylactic IVC filter according to Eastern Association for the Surgery of Trauma trauma practice guidelines was conducted. IVC filters were placed in the ICU with the use of a digital C-arm (Siemens) and strict adherence to sterile technique. Renal vein anatomy and size of the IVC were documented for every case. Charges for equipment and supplies were analyzed and compared with those placed in the radiology suite and the operating room. Of 810 patients admitted as trauma alerts during the study period, 25 had an IVC filter placed at the bedside in the ICU. The indications for filter placement included a contraindication to anticoagulation and one of the following: severe pelvic fracture and/or associated long-bone fracture (32%); bilateral lower extremity fractures (28%); spinal cord injury with para- or quadriplegia (16%); femoral vein thrombosis (16%); and severe brain injury (8%). There were no intraoperative nor postoperative complications; overall mortality was 20 per cent, unrelated to the IVC filter placement. Average time for insertion was 47 minutes for the series and 20 minutes for the last five cases. Savings of $1844 or $2245 per filter are obtained when IVC filters are placed in the ICU when compared with the operating room or radiology suite, respectively. Bedside placement of IVC filters in the ICU is a safe, cost-effective method that can be performed without compromising the patient and avoids the potential disasters involved in transporting critically ill patients.

Discussion: Am Surg 1999 Sep;65(9)837-838.

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Venous thromboembolic disease has emerged as a significant cause of morbidity and mortality in hospitalized patients. This article reviews the salient features of venous thromboembolism as they pertain to the critically ill. Emphasis is placed on identifying risk factors, diagnostic strategies, prophylaxis, and treatment of this disorder. Deep venous thrombosis and pulmonary embolism, both being manifestations of the same disease processes, are considered together in this discussion of venous thromboembolism.

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Long recognized to be a major source of morbidity in the adult population, venous thromboembolism is being increasingly recognized in the pediatric age group. Pediatric intensive care unit patients are exposed to multiple risk factors for venous thromboembolism. Prothrombotic tendencies may be inherited or acquired, secondary to either the underlying disease or selected therapeutic interventions. In children in whom venous thromboembolism is diagnosed, the most commonly identified risk factor is the presence of a central venous catheter. Many cases are not diagnosed until autopsy. Because current treatment recommendations are extrapolated from adult studies, further
investigation is needed to define the optimal treatment and prophylaxis regimens in critically ill children.

(7) Shorr AF, Trotta RF, Alkins SA, Hanzel GS, Diehl LF

D-DIMER ASSAY PREDICTS MORTALITY IN CRITICALLY ILL PATIENTS WITHOUT DISSEMINATED INTRAVASCULAR COAGULATION OR VENOUS THROMBOEMBOLIC DISEASE.


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OBJECTIVE: To determine if D-dimer predicts outcomes in critically ill patients. DESIGN: Observational, cohort study. SETTING: Medical intensive care unit (MICU) of a tertiary care hospital. PATIENTS AND PARTICIPANTS: Seventy-four patients consecutively admitted to the MICU. INTERVENTIONS: D-dimer was measured by latex agglutination within 12 h of admission to the MICU. MEASUREMENTS AND RESULTS: Of the study population, 43.2% had positive D-dimers. The in-hospital mortality rate in D-dimer positive patients was 28.1% as compared to 7.1% in D-dimer negative subjects (p = 0.024). D-dimer positive patients had significantly greater frequencies of venous thromboses (21.9% vs 4.8%, p = 0.035). CONCLUSIONS: The D-dimer assay identifies patients at increased risk for mortality and may be a more sensitive test to determine the presence of underlying microvascular pathology in critically ill patients. A positive D-dimer at admission to the MICU is associated with an increased risk for the later development of a venous thromboembolic event (VTE).

(8) Lindahl TL, Lundahl TH, Nilsson L, Andersson CA

APC-RESISTANCE IS A RISK FACTOR FOR POSTOPERATIVE THROMBOEMBOLISM IN ELECTIVE REPLACEMENT OF THE HIP OR KNEE--A PROSPECTIVE STUDY.


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Postoperative venous thromboembolic complications are commonly seen after total replacement of the hip or knee. Recently, an inherited defect with resistance to the anticoagulant activity of activated protein C (APC-resistance) has been detected. APC-resistance seems to be a common risk factor, especially in Sweden, and it increases the propensity for venous thrombosis. This study assesses the prevalence of APC-resistance in a general population and its clinical significance for patients undergoing surgery associated with a high risk of thromboembolic complications. In a prospective cohort study, we analysed for APC-resistance in 645 consecutive patients before elective replacement of the hip or knee at 3 hospitals in southern Sweden. Thromboprophylaxis with LMWH-heparin was given to all patients throughout the hospitalisation period. We recorded events of clinical thromboembolism for 3 months postoperatively. Venography, ultrasonography or pulmonary scintigraphy was requested by the clinicians according to the existing routines, i.e. only patients with symptoms of thromboembolism were examined. A thromboembolic complication was registered in 20 (3.1%) patients. Fifty per cent of the venous thrombi had a proximal location. Only 0.3% of the patients had verified pulmonary embolism. APC-resistance was found in 14.1% of the patients, of whom 9.9% had experienced postoperative thromboembolism compared with 2.0% of the patients without APC-resistance (p<0.0007). We conclude that APC-resistance is a frequent risk factor for symptomatic postoperative deep venous thrombosis with an estimated relative risk of 5.0 (95% confidence interval: from 1.9 to 12.9) in elective replacement of the hip or knee.

(9) Turpie AG, Kher A

PREVENTION OF VENOUS THROMBOSIS AFTER ELECTIVE HIP SURGERY.

Orthopedics 1998 Dec;21(12):1275-81

McMaster University and Hamilton Health Sciences Corporation, General Division, Ontario, Canada
(10) Andre E, Siguret V, Alhenc-Gelas M, Saint-Jean O, Gaussem P

VENOUS THROMBOSIS IN OLDER PEOPLE: PREVALENCE OF THE FACTOR V GENE MUTATION Q506.


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OBJECTIVES: Old age is usually considered to be a risk factor for venous thromboembolism, in conjunction with other factors such as heart failure, major surgery, cancer, long-term immobilization, and antiphospholipid antibodies. Genetic risk factors, especially inherited deficiencies in coagulation inhibitors, also play a role in the pathogenesis of thrombosis, but these are usually diagnosed in thrombophilic patients before the age of 50. The factor V Q506 mutation, responsible for activated protein C resistance, was recently linked to thromboembolic disease. We therefore investigated the prevalence of biological risk factors in older hospital patients with venous thromboembolism.

DESIGN: A 2-year study period.

SETTING: Ivry sur Seine (Paris), France.

PARTICIPANTS: Seventy-nine geriatric patients (60 women and 19 men, mean age 83 +/- 6.8 years, range 70-102 years) who had had at least one proven episode of venous thromboembolism were enrolled over a 2-year period.

MEASUREMENTS: Lupus anticoagulant and antithrombin (AT), protein C (PC), and protein S (PS) levels were determined in plasma. The factor V Q506 mutation was detected on genomic DNA.

RESULTS: Lupus anticoagulant was detected in two women, one of whom also had a high level of anticardiolipin IgG, leading to the diagnosis of an antiphospholipid syndrome. No hereditary deficiency in AT, PC, or PS was found, but one patient had an acquired AT deficiency. Interestingly, nine of the 79 patients (11.4%, six women and three men) were heterozygous for the factor V Q506 mutation, although none were homozygous. The only major risk factor for thrombosis identified in these patients was prolonged immobilization in four cases. Four of the nine patients who were heterozygous for the factor V Q506 mutation had recurrent thromboembolism, and two of these patients had been immobilized for long periods.

CONCLUSIONS: This study confirms that hereditary deficiencies in coagulation inhibitors, and the lupus anticoagulant, are rarely involved in the pathogenesis of venous thromboembolism in older subjects. In contrast, the factor V Q506 mutation was frequently associated with thrombosis (11.4% of our patients) and should, therefore, be considered an important risk factor in the older people.

(11) Cyrkowicz A, Fiala J, Kacalski J, Jackowski P, Bielaszka K, Smida A

[PREVENTION OF DEEP VEIN THROMBOSIS (DVT) WITH THE LOW MOLECULAR WEIGHT HEPARIN (LMWH) AND EPIDURAL/SPINAL ANESTHESIA. THE EFFICACY VIEWPOINT]. [ARTICLE IN POLISH]


Oddzialu Ginekologiczno-Polozniczego WSZ im. prof. E. Szczeklika w Tarnowie.

OBJECTIVES: To compare the frequency of DVT and PE (pulmonary embolism) events in patients who had undergone gynecological operations under epidural/spinal anaesthesia without LMWH prophylaxis with patients receiving LMWH prophylaxis. DESIGN: Retrospective, hospital record based study. MATERIALS AND METHODS: The majority of patients had undergone vaginal operations. 441 consecutive, unselected patients without LMWH prophylaxis vs. 463 ones treated with LMWH. The patients were given Fraxiparine a 7,500 ICU s.c. 2 h before operation. The same doses were repeated every 24 h during 5-7 days or to the regaining by the patient sufficient physical activity. DVT diagnosis was based on the clinical signs and ultrasound techniques. PE was stated on clinical symptoms, ECG chest x-ray characteristics and gasometric data. RESULTS: Among the patients without LMWH prophylaxis 2 cases of PE occurred (0.45%), one of these was fatal. 1 case of proximal DVT (0.23%) and 3 distal DVT complications (0.68%) were stated. In the LMWH group 1 proximal DVT (0.22%) and 2 distal DVT (0.43%) developed. CONCLUSIONS: Perioperative LMWH prevention proved to be efficient. The clinically expressed incidence of DVT expressively diminished: 8 cases-(1.66%) vs. 3 cases-(0.53%). The pulmonary embolism was avoided.

(12) Strekerud F, Johansen AM, Abildgaard U

[VENOUS THROMBOEMBOLISM--INCIDENCE AND RISK FACTORS IN OSLO] [ARTICLE IN NORWEGIAN].

*Tidsskr Nor Laegeforen* 1998 Oct 20;118(25):3934-8
Over a period of three years, 378 patients with objectively verified venous thromboembolism were treated at Aker University Hospital. Below the age of 60, men and women had about the same incidence of venous thromboembolism, but that age the incidence was significantly higher among men than among women. Incidence increased exponentially with age, from about 1:10,000 at age 20 to about 1:1,000 at age 50. The incidence found here is lower than in earlier Nordic studies.

The great majority of the patients (93%) had deep venous thrombosis in the lower extremities, 11% had symptomatic and verified pulmonary embolism, and 1% had their thrombus in an inner organ vein. 23% of patients were previously treated for venous thromboembolism, and 22% had cancer. Seven women were on oral contraception, and 22 used postmenopausal hormone substitution. An obvious temporary precipitating factor was present in 42% of the patients, while 36% had a spontaneous venous thromboembolism. Hereditary thrombophilic disorder was found in 32% of patients below the age of 60.

(13) Lewis MA

THE EPIDEMIOLOGY OF ORAL CONTRACEPTIVE USE: A CRITICAL REVIEW OF THE STUDIES ON ORAL CONTRACEPTIVES AND THE HEALTH OF YOUNG WOMEN.


EPES Epidemiology, Pharmacoepidemiology and Systems Research, Berlin, Germany.

Recent observational studies show a slightly increased risk of venous thromboembolism among users of newer combined oral contraceptives with odds ratios between 0.8 and 2.3 when compared with users of older oral contraceptives. The controversy regarding the newer oral contraceptives is reviewed by analyzing the recent studies with epidemiologic methods. Key studies on venous thromboembolism may be subject to bias related to prescribing criteria, diagnostics, hospital referral, cohort effects, and residual confounding, resulting in an overestimate of the risk of venous thromboembolism associated with the newer oral contraceptives. The studies on stroke showed no difference between newer and older oral contraceptives, and studies on myocardial infarction show that newer oral contraceptives carry no risk of this event. Newer-generation oral contraceptives are unlikely to constitute a significant hazard to the user population with regard to venous thromboembolism. The results for other disease entities also need to be taken into account when the results on venous thromboembolism are assessed on a population basis.

(14) Warwick D, Harrison J, Glew D, Mitchelmore A, Peters TJ, Donovan J

COMPARISON OF THE USE OF A FOOT PUMP WITH THE USE OF LOW-MOLECULAR-WEIGHT HEPARIN FOR THE PREVENTION OF DEEP-VEIN THROMBOSIS AFTER TOTAL HIP REPLACEMENT. A PROSPECTIVE, RANDOMIZED TRIAL.


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We conducted a prospective, randomized trial to compare the safety and effectiveness of the A-V Impulse System foot pump with that of low-molecular-weight heparin for reducing the prevalence of deep-vein thrombosis after total hip replacement. Of 290 patients who were to have a primary total hip replacement, 143 were randomized to receive enoxaparin (forty milligrams daily) for seven days after the operation and 147, to use the foot pump for seven days. The primary outcome measure was the prevalence of deep-vein thrombosis, as determined by venography on the sixth, seventh, or eighth postoperative day. Secondary outcome measures included transfusion requirements, intraoperative blood loss, postoperative drainage, blood-loss index, appearance of the site of the wound according to a subjective visual-analog scale, and swelling of the thigh. The patients' compliance with the regimen for use of the foot pump was monitored with an internal timing device, and their acceptance of the device was assessed with a questionnaire. Symptoms consistent with pulmonary embolism were investigated with ventilation-perfusion scanning. The patients were contacted later for detection of symptoms of venous thromboembolism that may have occurred during the first three months after discharge from the hospital. Venography was performed on 274 patients: 136 who used the foot pump and 138 who received enoxaparin. Deep-vein thrombosis was detected in twenty-four (18 per
(15) Cafferata HT, Morrison S, Duer C, Depalma RG

VENOUS THROMBOEMBOLISM IN TRAUMA PATIENTS: STANDARDIZED RISK FACTORS


Department of Surgery, University of Nevada School of Medicine, Reno, USA.

PURPOSE: This study was done to evaluate the use of published standardized risk factors for venous thromboembolism (VTE) in patients admitted to a trauma intensive care unit (ICU) and to derive guidelines for the use of low molecular weight heparin (LMWH) and surveillance venous Doppler ultrasound scanning (VDUS). METHODS: Patients were admitted to a regional trauma center ICU. Two periods were studied. Period 1 was a retrospective analysis of documented cases of VTE in the trauma registry from 1993 to 1995 (n=39). The period was also a review of all patients admitted to a trauma ICU in 1994 without VTE who met the following criteria: age greater than 11 years, ICU stay of more than 36 hours, and survival of more than 72 hours (n=227). Period 2 was a concurrent analysis of 1996 documented cases of VTE and similarly selected ICU admissions (VTE, n=10; no VTE, n=224). Risk factor scores (R1, admitting; R2, total) were calculated from the International Society for Cardiovascular Surgery/Society for Vascular Surgery reporting standards. The scores were cumulative by category and over time. The suitability of such standards was determined in period 1. The resulting therapeutic and surveillance guidelines were evaluated in period 2. RESULTS: Period 1 risk factor scores, R1 and R2, were correlated with the occurrence of VTE from chi2 test (P < .05 and P < .01, respectively). Risk categories were grouped as low, moderate, and high. VTE was not observed in the low-risk group (0 to 2). Among all VTE (n=49), 11 cases occurred in patients with moderate-risk scores and 38 in patients with high-risk scores. In 1994 and 1996, the selected groups were analyzed and the incidence rate of VTE was 4.7% in both years for the moderate-risk group and 2.5% and 4.8% for the high-risk group, respectively. Most VTE cases (78%) received some form of prophylaxis (PRx), and 26% of cases had multiple methods of prophylaxis (MPRx). This included 80% of the cases that received unfractionated heparin. In period 2, no pulmonary embolism (PE) occurred, in contrast to period 1, in which 16 of 39 cases of VTE (41%) were first seen with PE. In period 2, no patient receiving MPRx, including compression and LMWH, had VTE develop. Surveillance VDUS discovered 60% of 1996 cases in period 2. No PE were seen in period 2.

CONCLUSION: Standard risk factors were easily applied to the trauma patient at the bedside. Patients at low risk needed no PRx. Patients at high risk did best with both compression devices and LMWH. VDUS was recommended selectively in patients at high risk in whom multiple-method PRx could not be achieved. Patients at moderate risk required further study to define optimal PRx and need for surveillance VDUS. Intracaval devices were used prophylactically only twice.
(16) Hirsch DR, Ingenito EP, Goldhaber SZ
PREVALENCE OF DEEP VENOUS THROMBOSIS AMONG PATIENTS IN MEDICAL INTENSIVE CARE.
JAMA 1995 Jul 26;274(4):335-7

Department of Medicine, Brigham and Women's Hospital, Boston, MA 02115, USA.
OBJECTIVE--To determine the frequency of deep venous thrombosis (DVT) in medical intensive care unit (MICU) patients. DESIGN--Prospective ultrasound case series. SETTING--An MICU in a large tertiary care hospital in Boston, Mass. SUBJECTS--Patients older than 18 years of age admitted to the MICU with an anticipated stay of more than 48 hours. MAIN OUTCOME MEASURE--Deep venous thrombosis as detected by ultrasonography with color Doppler imaging performed twice weekly in the MICU and once within 1 week of discharge from the MICU. RESULTS--Deep venous thrombosis was detected in 33% (95% confidence interval, 24% to 43%) of 100 eligible patients during the 8-month study period. Forty-eight percent (16/33) were proximal lower extremity DVT, and 15% (5/33) were upper extremity DVT associated with central venous catheters, with one patient having both upper and proximal lower extremity DVT. Ultrasound examination results led to inferior vena cava filter placement in three patients, initiation of full-dose anticoagulation in four patients, initiation or continuation of low-dose subcutaneous heparin in 10 patients, follow-up ultrasound studies in three patients, central line removal in one patient, and no intervention in 10 patients due to active bleeding, prior filter, or heparin-induced thrombocytopenia. Two patients remained anticoagulated for other reasons. In this series, there was no difference in age, gender, body mass index, diagnosis of cancer, recent surgery, duration of hospitalization prior to DVT detection, and DVT prophylaxis between patients with DVT and those without. CONCLUSIONS--An unexpectedly high rate of DVT was detected by ultrasound in these MICU patients despite prophylaxis in 61%. Traditionally recognized DVT risk factors failed to identify patients who developed DVT. Routine ultrasound surveillance or more intensive prophylaxis regimens may be warranted in this patient population if these DVT rates are confirmed in other settings.

D. Anticardiolipin Antibodies a Sign of imminent Thrombosis

(1) Schulman S, Svenungsson E, Granqvist S
ANTICARDIOLIPIN ANTIBODIES PREDICT EARLY RECURRENT OF THROMBOEMBOLISM AND DEATH AMONG PATIENTS WITH VENOUS THROMBOEMBOLISM FOLLOWING ANTICOAGULANT THERAPY. DURATION OF ANTICOAGULATION STUDY GROUP.

Department of Medicine, Karolinska Hospital, Stockholm, Sweden.
PURPOSE: To compare the risk of recurrent venous thromboembolism in patients with and without antiphospholipid antibodies. PATIENTS AND METHODS: Anticardiolipin antibodies were tested 6 months after a first or second episode of venous thromboembolism. Of the patients with a first episode of venous thromboembolism only the 412 who received 6 months of anticoagulation were studied. Two hundred and eleven patients with a second episode received oral anticoagulation for 6 months or indefinitely. The therapy was targeted at an international normalized ratio (INR) of 2.0 to 2.85. All patients were followed up for 4 years after enrollment. RESULTS: Among the 412 patients with a first episode of venous thromboembolism the risk of recurrence was 29% in patients with anticardiolipin antibodies and 14% in those without antibodies (P = 0.0013). In those with antibodies, there was an increased risk during the first 6 months after cessation of anticoagulation. The risk of recurrence increased with the titer of the antibodies. Four-year mortality rate was 15% in those with antibodies and 6% in those without (P = 0.01). Among 34 patients with a second event of venous thromboembolism and anticardiolipin antibodies, there were no recurrences during anticoagulant therapy versus 20% in those who received only 6 months of treatment (P = 0.08). CONCLUSIONS: The presence of elevated titers of anticardiolipin antibodies 6 months after an episode of venous thromboembolism is a predictor for an increased risk of recurrence and of death. Patients with anticardiolipin antibodies and venous thromboembolism seem to benefit from prolonged oral anticoagulation.

E. Anticoagulation and Antiplatelet Treatments General Aspects
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Background: While atrial fibrillation (AF) increases the risk of cardioembolic stroke, some ischemic strokes in AF patients are noncardioembolic. Objectives: To assess ischemic stroke mechanisms in AF and to compare their responses to antithrombotic therapies. Methods: On-therapy analyses of ischemic strokes occurring in 3,950 participants in the Stroke Prevention in Atrial Fibrillation I-III clinical trials. Strokes were classified by presumed mechanism according to specified neurologic features by neurologists unaware of antithrombotic therapy. Results: Of 217 ischemic strokes, 52% were classified as probably cardioembolic, 24% as noncardioembolic, and 24% as of uncertain cause (i.e., 68% of classifiable infarcts were deemed cardioembolic). Compared to those receiving placebo or no antithrombotic therapy, the proportion of cardioembolic stroke was lower in patients taking adjusted-dose warfarin (p = 0.02), while the proportion of noncardioembolic stroke was lower in those taking aspirin (p = 0.06). Most (56%) ischemic strokes occurring in AF patients taking adjusted-dose warfarin were noncardioembolic vs. 16% of strokes in those taking aspirin. Adjusted-dose warfarin reduced cardioembolic strokes by 83% (p < 0.001) relative to aspirin. Cardioembolic strokes were particularly disabling (p = 0.05). Conclusions: Most ischemic strokes in AF patients appear to primarily reduce noncardioembolic strokes. AF patients at highest risk for stroke have the highest rates of cardioembolic stroke and have the greatest reduction in stroke by warfarin. Copyright 2000 S. Karger AG, Basel

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This pilot study was designed to determine whether the low molecular weight heparin, enoxaparin, could be used for elective percutaneous coronary intervention (PCI) to provide antithrombotic effects without the full systemic anticoagulation that occurs with the use of unfractionated heparin. Sixty patients were randomized to receive intravenous enoxaparin (1 mg/kg bolus dose) or unfractionated heparin at the time of coronary intervention. Laboratory testing was performed at baseline, 5 minutes, and 4 hours after study drug to test if a single bolus dose of intravenous enoxaparin can consistently achieve therapeutic antithrombotic effect, thus eliminating the need for multiple doses of heparin and closely monitoring levels of anticoagulation during PCI. Thirty percent of patients who received unfractionated heparin required a second bolus of intravenous heparin to achieve the target-activated clotting time of 300 seconds before PCI. Enoxaparin showed antithrombotic properties comparable to that of unfractionated heparin as measured by anti-Xa levels, with less inhibition of thrombin (factor IIa) at the time points measured (p <0.0001). Angioplasty success rates, in-hospital ischemia, bleeding, and vascular complications were similar in both groups. Thus, intravenous enoxaparin has predictable and effective antithrombotic effects during elective PCI. Although the level of anticoagulation attained with enoxaparin is significantly lower than that after unfractionated heparin, no increase in ischemic complications were noted. The use of a single bolus of intravenous enoxaparin, without the need for measuring the activated clotting time or titrating heparin anticoagulation, has the potential for simplifying the performance and perhaps enhancing the safety of PCI.
(3) Gruberg L, Dangas G, Leon MB

**CORONARY ARTERY STENTS: APPROPRIATE USE OF ADJUNCTIVE PHARMACOTHERAPY TO PREVENT STENT THROMBOSIS.**

*Drugs Aging* 1999 Nov;15(5):341-8

Cardiovascular Research Foundation, Washington Hospital Center, Washington, DC 20010, USA.

In 1986, the first metallic stent was implanted inside a human coronary artery in order to reduce the incidence of abrupt vessel occlusion and restenosis after percutaneous coronary balloon angioplasty. Little was known at that time regarding the adequate anticoagulation regimen needed and the initial enthusiasm was soon marred by a high rate of thrombotic stent closure that usually occurred 2 days to 4 weeks after stent implantation. Antithrombotic drugs such as heparin, aspirin (acetylsalicylic acid), low molecular weight heparins, dextran, dipyridamole and warfarin (coumadin) were incorporated in a series of trials which reduced the risk of stent thrombosis, but increased substantially the rate of bleeding complications and the length of hospitalisation. The greatest breakthrough came with the improvement in stent deployment techniques using intravascular ultrasound-guided, high-pressure balloon inflation inside the stent, and the understanding of the central role of platelet activation in stent thrombosis. These 2 factors have led to 'optimal stent deployment' with high-pressure ballooning after stent deployment and the simultaneous use of more potent antiplatelet agents in conjunction with aspirin. Newly developed selective inhibitors of the platelet glycoprotein IIb/IIIa receptor and new stent designs have also recently been integrated into clinical practice and are currently being evaluated in clinical trials.

(4) Collet JP, Montalescot G

**[ANTITHROMBOTICS AND INTERVENTIONAL CARDIOLOGY]. [ARTICLE IN FRENCH]**

*Arch Mal Coeur Vaiss* 1999 Nov;92(11 Suppl):1667-79

Service de cardiologie, groupe hospitalier La Pitie-La Salpetriere, Paris.

Angioplasty is a technique associated until recently with aspirin and heparin therapy, two classical molecules, for the prevention of thrombotic complications. The first therapeutic innovation has been the introduction of Reopro (abciximab, c7E3). The abciximab has been shown to be useful in the short term, sometimes in the medium (EPIC, EPILOG) and long term (EPIC) in all acute or stable coronary coronary syndromes requiring angioplasty with or without stenting. Other changes are awaited shortly with the arrival of low molecular weight heparin which some have shown to be effective in unstable angina. The association of antithrombotics will become the rule but the number of molecules should decrease to consist only of the most effective drugs and exclude the redundant ones. The risk of haemorrhage increases with the increased efficacy of the antithrombotic agent. Global evaluation of the clinical benefits should be advocated with a register of ischaemic and serious haemorrhagic events amongst the criteria of evaluation of the trials.

(5) Hirsh J, Weitz JI

**THROMBOSIS AND ANTICOAGULATION.**

*Semin Hematol* 1999 Oct;36(4 Suppl 7):118-32

Hamilton Civic Hospitals Research Centre, Ontario, Canada.

Most of the major advances in thrombosis research have occurred in the last 50 years, reflecting progress in biomedical sciences and clinical trials methodology. Improved understanding of the mechanisms of thrombogenesis has led to the discovery of a plethora of new antithrombotic agents that target many of the key steps in blood coagulation and platelet activation. Although most of these compounds are still under development, low-molecular-weight heparins (LMWH), glycoprotein (GP) IIb/IIIa receptor antagonists, and inhibitors of the adenosine diphosphate (ADP) receptor on platelets have already established their niche in the clinic. The vessel wall has emerged as a major player, both in protecting against and in promoting thrombosis, and as we approach the new millennium, compounds are being developed that have the potential to prevent and treat thrombosis by modulating vessel wall function.
(6) Anand SS, Kundi A, Eikelboom J, Yusuf S

LOW RATES OF PREVENTIVE PRACTICES IN PATIENTS WITH PERIPHERAL VASCULAR DISEASE.


Hamilton Civic Hospitals Research Centre, McMaster University, Hamilton, Canada.

**BACKGROUND:** Patients with peripheral vascular disease (PVD) have a three-fold increased risk of myocardial infarction, stroke and death. Recently, a number of therapies have been demonstrated to prevent morbidity or mortality in patients with PVD or other arterial disease. Given the scarcity of data on the preventive practice patterns of this high risk patient group, the in-hospital management of patients admitted to hospital for a peripheral vascular intervention was reviewed. **PATIENTS AND METHODS:** Charts of 195 patients with a diagnosis of peripheral arteriosclerotic disease (International Classification of Diseases, 9th revision, code 440.2) who were hospitalized at a tertiary care hospital in Ontario between June 1996 and June 1998 were reviewed. **RESULTS:** The average age of patients admitted was 70.6 years, and 39% of patients were women. The main reason for admission was peripheral artery bypass graft surgery in 88% (172 of 195) of patients had clinically apparent coronary or cerebrovascular disease, and 92% (180 of 195) of patients had at least one cardiovascular disease risk factor. Fewer than half of all patients (49%) were discharged on any antithrombotic therapy (antiplatelet agent or anticoagulant), and a small proportion of patients were treated with a beta-blocker (20%) and cholesterol-lowering medications (16%). **CONCLUSIONS:** The leading cause of morbidity and mortality in PVD patients is coronary and cerebrovascular disease. Despite this, the use of proven antithrombotic agents and other cardiac medications is suboptimal. Health professionals need to be aware of the high risk nature of the PVD population and to develop strategies to ensure that patient care is optimized.

(7) Eikelboom JW, Ginsberg JS

PREVENTING THROMBOEMBOLIC COMPLICATIONS IN OLDER ORTHOPAEDIC SURGERY PATIENTS: INTERVENTIONS AND OUTCOMES.


Preventive Cardiology and Therapeutics Program, McMaster University, Hamilton, Ontario, Canada.

The aging of the population in developed countries has been associated with a growing burden of degenerative joint disease and hip fracture, and this has contributed to a progressive increase in the utilisation of major hip and knee arthroplasty. In the absence of effective thromboprophylaxis, patients undergoing major orthopaedic surgery are at high risk of deep vein thrombosis, which may in turn lead to life-threatening complications such as pulmonary embolism, as well as long term sequelae including the post-thrombotic syndrome. However, increasing age is also associated with an increased risk of venous thromboembolism, and older orthopaedic patients are, therefore, at particularly high risk. Randomised trials have demonstrated that the risk of venous thromboembolism in these patients, as demonstrated by venography, can be reduced by more than 50% with the use of effective thromboprophylaxis. However, antithrombotic agents such as low molecular weight heparin and warfarin, which are widely used for the prevention of venous thromboembolism, are also associated with an increased risk of bleeding complications, and selection of the most appropriate strategy should, therefore, involve consideration of the potential risks as well as benefits of the currently available interventions.

(8) Verstraete M

8TH SEAH CHENG SIANG MEMORIAL LECTURE: NEW ANTITHROMBOTIC AGENTS.


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For the long-term prevention of thromboembolic events in patients with atherosclerotic vascular disease, aspirin is the preferred antiplatelet drug. Only clopidogrel was shown to be more effective and at least as safe than medium-dose aspirin in direct comparative large-scale trials. Aspirin
inhibits the cyclooxygenase dependent pathway of platelet aggregation while ticlopidine and clopidogrel selectively bind to adenosine diphosphate (ADP) receptors on the platelet surface. Compounds which inhibit the synthesis of thromboxane synthase, block the thromboxane receptor or have the dual activity were effective in experimental thrombosis models in animals but not predictive of results in humans. Activation of the platelet glycoprotein (GPIIb/IIIa) receptor on the platelet surface is the final pathway of platelet aggregation, regardless of the initiating stimulus. Inhibitors of GPIIb/IIIa receptors include monoclonal antibodies (abciximab) against this receptor and peptidic as well as non-peptidic synthetic specific receptor blockers. Abciximab exchanges between and binds to platelets for as long as two weeks whereas synthetic GPIIb/IIIa inhibitors inhibit ex vivo platelet aggregation for only a few hours after the end of infusion but have the advantage of being also orally active. In the secondary prevention of atherothrombosis, large scale trials were successfully conducted with aspirin, dipyridamole and clopidogrel. In the first large-scale trials with GPIIb/IIIa inhibitors with abciximab was investigated. In aggregate, this class of platelet inhibitors, combined with aspirin and heparin, was shown to reduce ischaemic events in patients with high- and low-risk coronary intervention, stents, unstable angina and non-Q-wave infarction with long-term preservation of the initial benefit. With synthetic GPIIb/IIIa inhibitors there is no suppression of clinical evident restenosis 6 months after the end of treatment. With the doses presently used, bleeding occurs more often with the synthetic GPIIb/IIIa inhibitors (used for 3 days) than with abciximab (used for 12 hours) but there are no direct comparisons between these drugs.

(9) Ridker PM, O'Donnell CJ, Hennekens CH
DIRECT COMPARISON OF ASPIRIN PLUS HIRUDIN, ASPIRIN PLUS HEPARIN, AND ASPIRIN ALONE AMONG 12,000 PATIENTS WITH ACUTE MYOCARDIAL INFARCTION NOT RECEIVING THROMBOLYSIS: RATIONALE AND DESIGN OF THE FIRST AMERICAN STUDY OF INFARCT SURVIVAL (ASIS-1).

I. Antiplatelet Agents
A. Aspirin (ASA)
A. Function and Fields of Use
1. General aspects of ASA

**[ANTIAGGREGANTS, ASPIRIN, MYOCARDIAL INFARCTION AND CORONARY DEATHS IN THE HAUTE-GARONNE AREA].**  
Arch Mal Coeur Vaiss 1995 Apr;88(4):459-463  
Inserm U-326, ORSMIP, CHU Purpan, Toulouse. [Article in French]  
The aim of this study was to determine changes in treatment of myocardial infarction between 1986 and 1989 in the Haute-Garonne region and, in particular, to assess the role of aspirin and antiaggregant therapy. The cases of 416 patients admitted to hospital for myocardial infarction. During this period the prescription of acetylsalicylic acid during the acute phase of myocardial infarction increased threefold and fivefold when associated with fibrinolytics, coronary bypass or angioplasty. Similarly, the prescription of aspirin at the time of hospital discharge doubled (from 32.6 to 69.5%; p < 0.001). The dosage of aspirin decreased from 500 mg and more per day in 1986 to a dosage of 250 mg or 100 mg per day in 1989. The most commonly prescribed preparation is lysine acetylsalicylate. The hospital mortality in the Haute-Garonne between 1985 and 1989 has decreased as observed in the Haute-garonne centre of the MONICA project. The changes observed during this period of observation are in perfect accord with results already published of therapeutic trials of antithrombotic agents in the acute phase or the post-infarction period (ISIS 2).

2. ASA and Ticlopidine and their Combinations

(1) Kaplan S, Kaplan A, Marcoe K, Sauvage LR  
**TICLOPIDINE, ALKA-SELTZER, OR A COMBINATION OF CITRIC ACID WITH ASPIRIN: EFFECTS ON PLATELET AGGREGATION IN INDIVIDUALS WITH AN INSUFFICIENT RESPONSE TO ASPIRIN ALONE.**  
The Hope Heart Institute, Seattle, Washington 98122, USA. kaplana@prodigy.net  
Aspirin (ASA) does not effectively lower platelet aggregation in all people. The platelet aggregation (PA) score is an easily used clinical method for measuring the effect in individuals of antiplatelet medications. Fifteen apparently healthy subjects (2 men and 13 women), selected for their resistance to ASA’s antiaggregation effect, completed a sequential trial of ticlopidine, Alka-Seltzer, and ASA + citric acid (CTA). Ticlopidine was the strongest aggregation inhibitor and the ASA + CTA combination was more inhibitory than Alka-Seltzer. It was determined that measuring antiaggregation effects of a particular agent in an individual prior to usage would optimize treatment. The PA score methodology provides a means for testing patients prior to antiplatelet therapy for prevention and treatment of the thrombotic complications of vascular disease.

(2) Reimann JD, Modi NB, Novotny W.  
**PHARMACOKINETICS AND PHARMACODYNAMICS OF SIBRAFIBAN, AN ORALLY ADMINISTERED GP IIb/IIIa ANTAGONIST, FOLLOWING COADMINISTRATION OF ASPIRIN AND HEPARIN.**  
Department of Medical Affairs, Genentech, Inc., South San Francisco, CA 94080, USA.  
Sibrafiban is a double prodrug that is converted to the inactive single prodrug and to the active GP IIb/IIIa antagonist after oral administration. This clinical investigation evaluated whether coadministration of oral aspirin or intravenous heparin would alter the pharmacokinetics or pharmacodynamics of oral sibrafiban. Twenty-four adult subjects received two of the following four combinations: sibrafiban alone, sibrafiban with ASA, sibrafiban with heparin, and sibrafiban with ASA and heparin, separated by a 2-week washout period. Concentration profiles of active drug in citrate and EDTA plasma were unchanged with coadministration of ASA or heparin. No pharmacodynamic interaction was seen with coadministration of heparin. Inhibition of platelet aggregation increased 4% to 55%, and Ivy bleeding time increased 58% to 87% with coadministration of sibrafiban and ASA. The combined pharmacodynamic effect of sibrafiban and
ASA may indicate a potentially greater therapeutic effect but an increased risk of bleeding when these drugs are used in combination.

(3) Rupprecht HJ, Darius H, Borkowski U, et al.

COMPARISON OF ANTIPLATELET EFFECTS OF ASPIRIN, TICLOPIDINE, OR THEIR COMBINATION AFTER STENT IMPLANTATION.


Department of Medicine II, Johannes Gutenberg University, Mainz, Germany.

BACKGROUND: This study was performed to analyze the influence of either aspirin, ticlopidine, or their combination on platelet activation and aggregation parameters after stent implantation. METHODS AND RESULTS: Sixty-one patients with successful implantation of a single Palmaz-Schatz stent in a native coronary artery were randomly assigned to either group A (aspirin 300 mg/d + ticlopidine 2X250 mg/d), group B (ticlopidine 2X250 mg/d), or group C (aspirin 300 mg/d). The ADP-induced aggregation declined significantly in group A (74.7+/−1.4% versus 55.3+/−2.6%), whereas a delayed reduction was seen in group B (72.0+/−3.0% versus 52.6+/−4.2%) and no change was seen in group C (P=0.0017). The CD62p expression declined significantly in groups A (68.2+/−2.7% versus 41.3+/−2.7%) and B (64.8+/−2.9% versus 39.3+/−3.5%) but not in group C (P<0.0001). Moreover, the fibrinogen binding decreased significantly in group A (61.0+/−4.3% versus 36.3+/−4.2%) and with delay in group B (58.3+/−2.2% versus 39.4+/−3.0%), whereas no alterations were seen in group C (P=.012). CONCLUSIONS: Our results demonstrate synergistic and accelerated platelet inhibitory effects of ticlopidine plus aspirin in patients after stent implantation compared with a monotherapy with either ticlopidine or aspirin alone.

(4) Facchini M, Muntwyler J et al.

[INFLUENCE OF VARIOUS ANTITHROMBOTIC THERAPY METHODS ON THE INCIDENCE OF SUBACUTE CORONARY STENT OCCLUSIONS, HEMORRHAGIC COMPLICATIONS AND LENGTH OF HOSPITALIZATION].


Abteilung Kardiologie, Universitatsklinik Zürich. [Article in German]

BACKGROUND: The clinical benefit of coronary stenting is reduced by the risk of thrombotic stent occlusion as well as hemorrhagic complications of intensive antithrombotic therapy. We compared the influence of different antithrombotic therapies on the incidence of post-interventional complications and inhospital stay duration. METHODS: After successful placement of a coronary stent, 334 consecutive patients were given different antithrombotic treatments in addition to aspirin 100 mg/d indefinitely: (1) phenprocoumon for 3 months (n = 47), (2) low molecular weight heparin 2 x 100 U/kg/d s.c. for 4 weeks (n = 90), (3) ticlopidine 2 x 250 mg/d and low molecular weight heparin 2 x 100 U/kg/d s.c. for 4 weeks (n = 72), and (4) ticlopidine 2 x 250 mg/d for 4 weeks (n = 125). RESULTS: Major events were subacute stent thrombosis in 17 patients (5%), and severe hemorrhagic complication in 20 patients (5.9%). CONCLUSIONS: These results confirm that anti-thrombotic therapy with aspirin and ticlopidine combines low rates of subacute stent occlusion and hemorrhagic complications. Treatment with phenprocoumon and low molecular weight heparin does not improve the rate of subacute stent occlusion but increases hemorrhagic complications. Very low rates of stent occlusion permit short in-hospital stays with concomitant reduction in cost.

3. ASA versus Cilostazol

(1) Kunishima T, Musha H, Eto F, Iwasaki T,

A RANDOMIZED TRIAL OF ASPIRIN VERSUS CILOSTAZOL THERAPY AFTER SUCCESSFUL CORONARY STENT IMPLANTATION.

Clin Ther 1997 Sep;19(5):1058-1066

Department of Cardiology, Yokohama City Seibu Hospital, St. Marianna University School of Medicine, Japan.

From November 1995 to March 1997, the usefulness of cilostazol versus aspirin in preventing subacute thrombosis and restenosis was studied in 70 patients (55 men and 15 women; 82 total lesions) who had undergone successful elective Palmaz-Schatz stent implantation. Patients were randomly allocated to...
receive aspirin 81 mg/d (40 patients with 45 lesions) or cilostazol 200 mg/d (30 patients with 37 lesions) alone. Cilostazol selectively inhibits the 3'5'-cyclic-nucleotide phosphodiesterase (PDE) III (cyclic guanosine monophosphate-inhibited PDE) of the cyclic adenosine monophosphate PDE family; it also has antithrombotic and vasodilating effects, as well as an inhibitory effect on vascular smooth muscle cell proliferation through PDE III inhibition. There was no difference in patients or angiographic characteristics between these groups. No subacute thrombosis, acute complications (ie, death, emergent coronary artery bypass grafting, or hemorrhagic complications), or drug side effects were found in the cilostazol group. The restenosis rate was 26.8% in the aspirin group, compared with 8.6% in the cilostazol group; this difference was statistically significant. Administration of cilostazol alone after the implantation of intracoronary Palmaz-Schatz stents was useful for the prevention of subacute thrombosis and restenosis.

4. ASA and Coumarin

(1) Meschengieser SS, Fondevila CG, LOW-INTENSITY ORAL ANTICOAGULATION PLUS LOW-DOSE ASPIRIN VERSUS HIGH-INTENSITY ORAL ANTICOAGULATION ALONE: A RANDOMIZED TRIAL IN PATIENTS WITH MECHANICAL PROSTHETIC HEART VALVES. J Thorac Cardiovasc Surg 1997 May;113(5):910-916

Departamento de Hemostasia y Trombosis, Instituto de Investigaciones Hematologicas Mariano R. Castex, Academia Nacional de Medicina, Buenos Aires, Argentina.

BACKGROUND. Aspirin has proved useful in further reducing thromboembolic events when added to oral anticoagulants. However, increased (gastrointestinal) bleeding was observed at the doses previously tested for this combination in heart valve prostheses. METHODS: We performed a prospective randomized trial to compare the combination of low-intensity oral anticoagulants (international normalized ratio 2.5 to 3.5) plus aspirin (100 mg/day) (arm A) versus high-intensity oral anticoagulants alone (arm B) (international normalized ratio 3.5 to 4.5). RESULTS: The outcomes of the study were embolism, valve thrombosis, and major hemorrhage. The median follow-up was 23 months. The two treatments offered similar antithrombotic protection. The incidence of embolic episodes was 1.32 per 100 patient-years for arm A and 1.48 per 100 patient-years for arm B. Major hemorrhage occurred in 1.13 per 100 patient-years for arm A and 2.33 per 100 patient-years for arm B. Gastrointestinal bleeding was not increased by this combined reduced dose of aspirin and coumarin.

5. ASA and new Antithrombotic Regimen


Department of Cardiology, Hospital Universitario, Valladolid, Spain.

METHODS. We studied 110 consecutive patients (121 lesions) who underwent elective Palmaz-Schatz stenting. Intravenous heparin was given only during the procedure. After stenting, patients took aspirin, dipyridamole, dextran, warfarin and low molecular weight heparin (enoxaparin, 40 mg subcutaneously daily, stopped when an international normalized ratio of 2 to 3 was achieved). Only two patients (0.32% to 7%) developed bleeding. CONCLUSIONS. After coronary stenting with optimal angiographic results, this new antithrombotic regimen prevented subacute stent occlusion and bleeding, with a brief hospital stay. No detrimental effect on the previously reported restenosis rate was observed.

(2) Schersten F, Grip L, Emanuelsson H [ANTITHROMBOTIC TREATMENT IN CONNECTION WITH PTCA. NEW SUBSTANCES AND REGIMES ARE COMING]. Lakartidningen 1996 Jun 26;93(26-27):2499-2502
Kardiologdivisionen, Sahlgrenska sjukhuset, Göteborg. [Article in Swedish]

(3) Cappelleri JC, Fiore LD, Brophy MT, et al.  
EFFICACY AND SAFETY OF COMBINED ANTICOAGULANT AND ANTIPLATELET THERAPY VERSUS ANTICOAGULANT MONOTHERAPY AFTER MECHANICAL HEART-VALVE REPLACEMENT: A METAANALYSIS.  
*Am Heart J* 1995 Sep;130(3 Pt 1):547-552

New England Medical Center, Boston, MA 02111, USA.  
We performed a metaanalysis of five randomized controlled trials to compare the efficacy and safety of combined oral anticoagulant and antiplatelet therapy versus oral anticoagulants alone after prosthetic heart-valve replacement. The combined regimen reduced embolism and overall mortality by approximately 67%, but increased the risk of hemorrhage by approximately 65% and of major gastrointestinal hemorrhage by approximately 250%. It is estimated that for every 1.6 patients who had their stroke prevented by combination therapy, there was an excess of one major gastrointestinal bleed.  
**CONCLUSION.** This metaanalysis suggests that the benefits derived from the enhanced antithrombotic potential of combined therapy outweigh the toxic effects resulting from the enhanced anticoagulant potential of this regimen.

6. Low Dose ASA and Warfarin effect on Factor VII

EFFECT OF TREATMENT WITH LOW-DOSE WARFARIN-ASPIRIN ON ACTIVATED FACTOR VII.  
*Blood* 1995 Jun 1;85(11):3034-3039

Department of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City 73190, USA.  
Factor VII is an independent risk factor for ischemic heart disease. We performed a prospective study to evaluate the effect of combined low-dose warfarin-aspirin on activated factor VII (factor VIIa) and to determine if abruptly stopping this treatment is associated with a rebound in the level of factor VIIa. Thirty-three patients with clinically stable coronary artery disease were treated with combined 3 mg warfarin and 80 mg aspirin daily for 8 weeks. The mean percent level of factor VIIa on-treatment was 74% (P < .001). Factor VIIa is reduced by 26% on average during treatment. This finding provides further rationale for the antithrombotic effect of low-dose warfarin. The results suggest a rebound in the factor VIIa level may occur after treatment is stopped. The potential rebound and its clinical importance should be evaluated by further studies.

(2) van der Meer J, et al.  
EFFECTS OF LOW DOSE ASPIRIN (50 MG/DAY), LOW DOSE ASPIRIN PLUS DIPYRIDAMOLE, AND ORAL ANTICOAGULANT AGENTS AFTER INTERNAL MAMMARY ARTERY BYPASS GRAFTING: PATENCY AND CLINICAL OUTCOME AT 1 YEAR. CABADAS RESEARCH GROUP OF THE INTERUNIVERSITY CARDIOLOGY INSTITUTE OF THE NETHERLANDS. PREVENTION OF CORONARY ARTERY BYPASS GRAFT OCCLUSION BY ASPIRIN, DIPYRIDAMOLE AND ACENOCOUMAROL/PHENPROCOCUMON STUDY.  
*J Am Coll Cardiol* 1994 Nov 1;24(5):1181-1188

Department of Cardiology, University Hospital, Groningen, The Netherlands.  
OBJECTIVES. This study in 948 patients was performed to compare the efficacy and safety of aspirin, aspirin plus dipyridamole, and oral anticoagulant agents in the prevention of internal mammary artery graft occlusion. The design was double-blind for both aspirin groups and open for oral anticoagulant treatment. Dipyridamole (5 mg/kg body weight per 24 h intravenously, followed by 200 mg twice daily) and oral anticoagulant agents were started before operation, and low dose aspirin (50 mg/day) after operation. Clinical outcome was assessed by the incidence of myocardial infarction, thrombosis, major bleeding or death.  
**RESULTS.** Occlusion rates of distal anastomoses were 4.6% in the aspirin plus dipyridamole group and
6.8% in the oral anticoagulant group versus 5.3% in the aspirin group (p = NS). Overall clinical event rates were 23.3% and 13.3% in the aspirin plus dipyridamole group and the aspirin group, and 17.1% in the oral anticoagulant group.

**CONCLUSIONS.** Internal mammary artery graft patency at 1 year is not improved by aspirin plus dipyridamole or oral anticoagulant agents over that obtained with low dose aspirin alone. However, there is evidence that the overall clinical event rate increases if dipyridamole is added to aspirin.

(3) Magnani B, Semprini F

[LOW-DOSE ASPIRIN IN THE LONG-TERM TREATMENT OF THE PATIENT WITH ISCHEMIC HEART DISEASE].


Istituto di Malattie dell'Apparato Cardiovascolare, Universita degli Studi, Bologna. [Article in Italian]

Coronary atherosclerosis is the process when ulcer or fissure in the fibrous cap of the atheroma occur, platelet adhesion to subendothelium, aggregation and further platelet recruitment culminate in thrombus formation. Inside platelets, aspirin blocks the synthesis of thromboxane A2 by irreversibly inhibiting cyclooxygenase. Aspirin, alone or in combination with dipyridamole, prevents early and late occlusion of aortocoronary vein grafts. Higher daily doses (900-1500 mg) are not more effective than lower doses (75-325 mg). Other antiplatelet drugs are not more effective than aspirin, which has the best risk-to-benefit and cost-to-benefit ratios. Ticlopidine is a reasonable alternative for use in preventing vascular events among patients intolerant to aspirin. Warfarin is an effective antithrombotic alternative to aspirin for secondary prevention after a myocardial infarction. However aspirin is easier to administer and follow-up when compared with warfarin. Warfarin should be preferred in high risk patients with left ventricular dysfunction with or without a mural thrombus, and those with associated atrial fibrillation.

7. ASA for Kawasaki Disease

(1) Kim NS, Menahem S

SERIOUS SEQUELS OF KAWASAKI DISEASE.

*Cardiol Young* 1998 Jul;8(3):386-9

Department of Cardiology, Royal Children's Hospital, Parkville, Victoria, Australia.

A male infant, aged 2 month, with Kawasaki disease had a myocardial infarction despite intravenous infusions of gamma globulin and aspirin at high dosage. He developed progressively a thin walled, dilated aneurysm of the apex of the left ventricle which became lined with thrombus despite treatment with warfarin. Another boy, aged 6 years, was noted on the 10th day of the evolution of Kawasaki disease to have developed a giant aneurysm of the main stem of the left coronary artery. Despite infusion of gamma globulin, the aneurysm remained unaltered and developed a thrombus. The thrombus resolved following treatment with warfarin, though the giant aneurysm has persisted. These two cases illustrate the serious consequences that can follow Kawasaki disease despite management optimal by current standards.

(2) Saphyakhajon P, Greene GR

DO WE NEED HIGH-DOSE ACETYLSALICYLIC ACID (ASA) IN KAWASAKI DISEASE?


Comment on: J Pediatr 1996 May;128(5 Pt 1):701-3

(3) Rubin B, Cotton DM

KAWASAKI DISEASE: A DANGEROUS ACUTE CHILDHOOD ILLNESS.

*Nurse Pract* 1998 Feb;23(2):34, 37-8, 44-8

Husson College, Bangor, Maine, USA.

Kawasaki disease is an acute febrile illness most commonly seen in children under the age of 5. It is characterized by fever, rash, cervical lymphadenopathy, bilateral nonexudative conjunctivitis,
oropharyngeal mucosal changes, and erythema of the hands and feet followed by desquamation. However, a child with Kawasaki disease may not exhibit all of these symptoms. The disease resembles many other childhood illnesses, such as measles and scarlet fever, and misdiagnosis is common. Left untreated, Kawasaki disease has potential life-threatening consequences; 20% to 25% of children develop coronary artery aneurysms as a result. Although no specific laboratory tests exist that identify Kawasaki disease definitively, there are clinical and laboratory findings that guide diagnosis and treatment. Treatment includes the hospitalization of the child and subsequent administration of high doses of aspirin and intravenous immunoglobulin. With recovery, aspirin doses are reduced and the child may be monitored at home with outpatient follow-up. It is imperative that the health care provider be aware of the symptoms of Kawasaki disease in order to make the diagnosis and treat the child before cardiac sequelae ensue.

(4) Durongpisitkul K, Gururaj VJ, Park JM, Martin CF
THE PREVENTION OF CORONARY ARTERY ANEURYSM IN KAWASAKI DISEASE: A META-ANALYSIS ON THE EFFICACY OF ASPIRIN AND IMMUNOGLOBULIN TREATMENT.
Pediatrics 1995 Dec;96(6):1057-61

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OBJECTIVE. Varying observations have been made concerning the use of aspirin (ASA) and/or intravenous immunoglobulin (IVIG) in the prevention of coronary artery aneurysm (CAA) in children with Kawasaki disease. A meta-analysis of published articles on the subject was conducted to evaluate the reported efficacy of these therapies. METHODS. All published studies in all languages from 1967 through 1993 obtained from MEDLINE and EMBASE were considered, and a defined set of inclusion and exclusion criteria selected the studies for analysis. These studies were grouped based on whether the children in the studies received: (1) ASA alone, (2) low IVIG (< or = 1 g/kg) and ASA, (3) high IVIG (> 1 g/kg) and ASA, (4) single IVIG (> 1 g/kg) and ASA, (5) high IVIG and low ASA (< or = 80 mg/kg), or (6) high IVIG and high ASA (> 80 mg/kg). Studies that satisfied the test for homogeneity were subjected to further analysis. The best estimate of the true proportion of CAA as well as the 95% confidence interval for each group were calculated at 30 and 60 days. Hypothesis testing was conducted to determine the statistical significance of the calculated difference in each compared treatment group. RESULTS. The best estimate of true proportion of CAA and the 95% confidence interval in each group at 30 and 60 days were: (1) ASA group, 30 days, 22.8% (20.6%, 25%); 60 days, 17.1% (13.6%, 20.7%); (2) low-IVIG group, 30 days, 17.3% (14.3%, 20.2%); 60 days, 11.1% (8.7%, 13.6%); (3) high-IVIG group, 30 days, 10.3% (8.3%, 12.3%); 60 days, 4.4% (2.8%, 6%); (4) single-IVIG group, 30 days, 2.3% (0.5%, 4.2%); 60 days, 2.4% (0.5%, 4.2%); (5) high-IVIG-low-ASA group, 30 days, 13% (9%, 17%); 60 days, 4.8% (2.3%, 7.4%); and (6) high-IVIG-high-ASA group, 30 days, 9.1% (6.9%, 11.4%); 60 days, 4% (2%, 6.1%). CONCLUSION. The incidence of CAA both at 30 and 60 days was significantly lower in low-IVIG than in ASA and in high-IVIG than in low-IVIG groups. Also, the incidence was lower in the single-IVIG than in the high-IVIG group, but this was noted at 30 days and not at 60 days. There was no statistically significant difference in the incidence of CAA both at 30 and 60 days between the high-IVIG-low-ASA and high-IVIG-high-ASA groups.

(5) Terai M, Shulman ST
PREVALENCE OF CORONARY ARTERY ABNORMALITIES IN KAWASAKI DISEASE IS HIGHLY DEPENDENT ON GAMMA GLOBULIN DOSE BUT INDEPENDENT OF SALICYLATE DOSE.
J Pediatr 1997 Dec;131(6):888-93

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The efficacy of intravenous gamma globulin (IVGG) for treatment of Kawasaki disease (KD) is clearly established. In a metaanalysis, we reviewed U.S. and Japanese multicenter, randomized controlled studies regarding the effect of various doses of IVGG with aspirin administered within the first 7 to 10 days of illness on the prevalence of coronary artery abnormalities in KD. We studied 1629 patients with acute KD from the six reported studies that included blinded echocardiographic assessments. In 868 Japanese patients treated with moderate-dose aspirin (30 to 50 mg/kg per day), the prevalence of
coronary abnormalities at the subacute stage (illness day 30) was 26.8% with aspirin alone, 18.1% with total IVGG dose < 1 gm/kg, 17.3% with total IVGG of 1.0 to 1.2 gm/kg, and 5.3% with total IVGG of 2 gm/kg; the corresponding prevalence at the convalescent stage of illness (illness day 60) was 17.5%, 13.5%, 9.8%, and 3.5%, respectively. In 761 U.S. patients treated with high-dose aspirin (80 to 120 mg/kg per day), the prevalence of coronary abnormalities at the subacute stage (2 to 3 weeks after enrollment) was 23.0% with aspirin alone, 9.0% with total IVGG of 1.0 gm/kg, 8.6% with total IVGG of 1.6 gm/kg, and 4.8% with total IVGG of 2.0 gm/kg; corresponding prevalence at the convalescent stage (6 to 8 weeks after enrollment) was 17.7%, 9.0%, 6.3%, and 3.8%, respectively. When all data for the 1629 patients were combined, the prevalence at the subacute stage was 25.8% with aspirin alone, 18.1% with IVGG < 1 gm/kg, 15.7% with IVGG of 1 to 1.2 gm/kg, 8.6% with IVGG of 1.6 gm/kg, and 4.8% with IVGG of 2 gm/kg (adjusted R2 = 0.966, p = 0.0017); corresponding prevalence at the convalescent stage was 17.6%, 13.5%, 9.7%, 6.3%, and 3.8%, respectively (adjusted R2 = 0.993, p = 0.0602). The prevalence of coronary abnormalities was inversely related to the total dose of IVGG and was independent of the aspirin dose. We conclude that 2 gm/kg IVGG combined with at least 30 to 50 mg/kg per day aspirin provides maximum protection against development of coronary abnormalities after KD.


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OBJECTIVES: A comprehensive description of clinical data, cardiological complications, evolution and treatment of patients who were diagnosed with Kawasaki disease in our hospital is presented.

MATERIAL AND METHODS: A retrospective study of clinical and cardiological data, as well as laboratory tests collected from 23 patients who suffered from Kawasaki disease and were treated between January 1989 and December 1995 was performed. RESULTS: The mean age of the patients was 3 years and 6 months of age, ranging from 5 months to 6 years old. The ratio male/female was 1.5/1. Clinical features were typical of the disease: persistent fever (100%), bilateral conjunctivitis (87%), changes in lips and oropharynx (100%), rash (91%), periungual desquamation (83%) and laterocervical adenopathy (74%). The diagnosis was delayed in 7 cases due to some symptoms that appeared as the beginning of the illness: hydrops of the gallbladder (one case), adenophlegmon (two cases), aseptic meningitis (two cases), diarrhoea (one case) and “sunburn-like” skin rash (one case). Five patients (22%) showed cardiological sequelae, three of them also had coronary artery aneurysms. One of these, whose diameter measured more than 8 mm, was several times complicated with coronary thrombus. Every patient was treated with salicylates and 19 of them were also treated with intravenous gamma globulins. As of December 1995, no deaths had been reported. CONCLUSIONS: Whenever the first symptoms and the evolution of the disease are not classical, it is more difficult to diagnose the disease.

8. ASA at Low Dose for Fetal loss caused by Anticardiolipin Antibodies


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OBJECTIVE: To assess maternal and fetal outcomes in 15 patients with antiphospholipid syndrome (19 pregnancies) treated with intravenous immunoglobulin (IV Ig) during pregnancy. METHODS: Monthly IV Ig therapy was initiated in the first or early second trimester of all pregnancies except two. Additional therapy consisted of low-dose aspirin and subcutaneous heparin. Six patients also received steroid therapy. Serial anticardiolipin IgG levels were measured in eight pregnancies. RESULTS: The live-birth rate was 84% (16 of 19 live births), and there were three pregnancy losses. There were no cases of fetal growth restriction (FGR). Preeclampsia and nonreassuring fetal status were each diagnosed in 25% of the pregnancies. Seventy-five percent of the infants were delivered at 34 weeks' gestation or later.
Anticardiolipin IgG decreased throughout the course of therapy in seven pregnancies. Placental pathology was minimal. CONCLUSION: Pregnancy complications appear to be minimized with the use of IV Ig. Definitive recommendations regarding the use of IV Ig in pregnancy await the conclusion of randomized trials. If the combination of IV Ig, aspirin, and heparin significantly decreases the incidences of FGR and prematurity, it may be a cost-effective primary therapy for pregnancies complicated by the antiphospholipid syndrome.

(2) Amigo MC, Khamashta MA, Hughes GR
ANTIPHOSPHOLIPID SYNDROME IN SLE.

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The antiphospholipid syndrome, initially described in systemic lupus erythematosus (SLE), occurs in 20-35% of patients with this condition. Its clinical manifestations may precede, be concurrent with, or follow clinical features of SLE. There are no major differences between the primary antiphospholipid syndrome and the secondary form that associates with SLE. Several studies suggest that the presence of an antiphospholipid syndrome in patients with SLE conveys a worse prognosis.

To prevent recurrence of thrombotic events (particularly arterial events), oral anticoagulation with an international normalized ratio (INR) close to 3 is recommended. Treatment of recurrent fetal loss is with aspirin, or with aspirin plus heparin. Controlled studies are underway to determine optimal treatment in patients with cerebral ischaemia as well as the optimal treatment in women with recurrent pregnancy loss.

[ABORTIONS CAUSED BY ANTICARDIOLIPIN ANTIBODIES: PREVENTION BY LOW-DOSE ACETYLSALICYLIC ACID]. [ARTICLE IN SPANISH]
*Sangre (Barc)* 1997 Jun;42(3):179-82

Servicio de Hematologia y Hemoterapia, Hospital Virgen del Rocio, Sevilla.

BACKGROUND: It is a very well-known fact the relationship between pregnancy with history of fetal losses and positive aCL, and many treatments have been tried in order to prevent it. We present a study about the treatment of these pregnant women with ASA at low doses. PATIENTS AND METHODS: We have followed-up a group of 28 women with previous abortions and positive aCL. They were treated with ASA (50 mg/day) since beginning until end of pregnancy. We measured aCL levels monthly. RESULTS: 24 cases of pregnancy (86%) were successfully, 3 cases were fetal losses and 1 case was a fetal malformation. IgG aCL were positive in 16 patients before treatment, and IgM aCL in 11 cases. One patient had both of them. 18 patients became negative after pregnancy. We have not found any relationship between the level of aCL and fetal losses. CONCLUSIONS: In our study, ASA at low doses (50 mg/day) is a safe and effective treatment in achieving successful pregnancies, and reducing aCL levels in patients with history of fetal losses.

9. ASA for Antiphospholipid Syndrome in Combinations

(1) Cowchock S
TREATMENT OF ANTIPHOSPHOLIPID SYNDROME IN PREGNANCY.
*Lupus* 1998;7 Suppl 2:S95-7

Department of Obstetrics and Gynecology, New York University Medical Center, New York 10016, USA.

Women with antiphospholipid antibodies (aPL = IgG anticardiolipin and/or lupus anticoagulants) and a history of either prior thrombotic events or pregnancy loss are at high risk during pregnancy for either another fetal death or thrombosis. The treatment of choice is anticoagulation with heparin. Both standard unfractionated heparin and low-molecular-weight heparin (LMWH) are used for prophylactic anticoagulation during pregnancy. The half-lives of either standard heparin, or low-molecular-weight heparin (LMWH), and the peak values for each after subcutaneous injection, are lower than those in nonpregnant patients. Doses and injection intervals need to be adjusted when
treating a pregnant woman. Clotting tests such as the activated partial thromboplastin time (aPTT) vary greatly during pregnancy, and the aPTT is often not even prolonged when antithrombotic levels of heparin are achieved. The aPTT is not a useful test when the patient has a lupus anticoagulant. Levels of plasma heparin are therefore needed to best care for pregnant women who need anticoagulation even for prophylaxis. Low-dose aspirin is often added empirically to heparin for treatment of aPL during pregnancy, but its efficacy has not been evaluated. Intravenous infusions of gamma globulins (IVGG) have been used as additional therapy when prior treatment with heparin during pregnancy failed to save the fetus, when severe and early onset preeclampsia has complicated a prior pregnancy (in such cases efficacy is unproven), or when there is an additional medical complication (such as immune thrombocytopenia) for which IVGG is an appropriate treatment. There are some situations in which treatment with corticosteroids is the best, or the only choice. However, corticosteroids should not be combined with heparin for long-term treatment during pregnancy because the risk for vertebral fracture is so high.

(2) Rojas-Poceros G, Ramirez Peredo J, Hernandez Andrade E, Bustos Lopez HH
[RECURRENT FETAL DEATH AND ANTIPHOSPHOLIPID ANTIBODY SYNDROME. A CASE REPORT]. [ARTICLE IN SPANISH]
Ginecol Obstet Mex 1997 Dec;65:523-8

Departamento de Esterilidad e Infertilidad, Instituto Nacional de Perinatologia, Mexico D.F.

Antiphospholipid Antibodies has been associated with severe maternal and fetal sequel, like recurrent miscarriage, death, intrauterine growth retardation, pregnancy-induced hypertensive disease, thromboembolic phenomena and thrombocytopenia. Pathogenesis has been explained reporting that IgG from women with antiphospholipid antibodies increases placenta thromboxane production without affecting prostacyclin production, which conducts to thrombosis of placenta uterus junction. In 1982, it was suggested for the first time low doses of aspirin and prednisone for treatment of recurrent fetal death associated to this syndrome. Heparin therapy was reported in 1984, recommended a doses of 15,000 U/day during first pregnancy trimester and 20,000 U/day posteriorly. The objective of this report, is the description a clinic case of a patient with recurrent fetal death and antiphospholipid antibodies syndrome, discussing a prenatal and obstetric treatment model, including diagnosis and final therapeutic, which includes the participation of some other specialists, the national experience in diagnosis and treatment is initial, and also because it has been reported a rate of fetal death in those patient with no treatment, almost of 90%. The importance of identify this syndrome is not based on its prevalence but on its maternal complications and that it is a cause of fetal death potentially treatable.

(3) Derksen RH, Christiaens GC, Kater L
[IMMUNOLOGY IN MEDICAL PRACTICE. II. ANTIPHOSPHOLIPID ANTIBODIES IN PREGNANCY] [ARTICLE IN DUTCH].
Ned Tijdschr Geneeskd 1997 Sep 13;141(37):1769-73


Antibodies against phospholipids are a risk factor for thrombotic disorders, but also for foetal death, pre-eclampsia, foetal distress and dysmaturity. This group of antibodies (aPLab) includes lupus anticoagulant (LAC) and anticardiolipin antibodies (aCL). These antibodies are encountered in patients with systemic lupus erythematosus (SLE), but also in patients with lupus-like disease and in women with (a history of) symptoms compatible with the antiphospholipid syndrome. Screening for aPLab is advisable in these patients when they want to conceive and in women with recurrent foetal death after the 12th week of pregnancy. It is not clear if the antibodies exert a direct noxious action or are an accompanying phenomenon. Secondary prevention is possible with acetylsalicilcylic acid (80 mg/day), if desired in combination with subcutaneous heparin (5000-12,000 units twice daily). The thrombosis prophylaxis should be continued for 6 weeks after delivery.

(4) Rai R, Regan L
ANTIPHOSPHOLIPID ANTIBODIES, INFERTILITY AND RECURRENT MISCARRIAGE.
Antiphospholipid antibodies are found in 15% of women with recurrent miscarriage. These women have only a 10% live birth rate in subsequent pregnancies in which no pharmacological treatment is given. Pregnancy loss is often attributable to uteroplacental insufficiency subsequent to placental thrombosis. Treatment with low dose aspirin improves the live birth rate amongst women with antiphospholipid antibodies to 40% but this is further and significantly increased to 70% when they are treated with aspirin together with low-dose heparin.

10. ASA for Stroke, "Dosing differences" North America vs Western Europe

(1) Masuhr F, Busch M, Einhaupl KM

**DIFFERENCES IN MEDICAL AND SURGICAL THERAPY FOR STROKE PREVENTION BETWEEN LEADING EXPERTS IN NORTH AMERICA AND WESTERN EUROPE.**

*Stroke* 1998 Feb;29(2):339-45

University Department of Neurology, Charite Medical School, Berlin, Germany.

**BACKGROUND AND PURPOSE:** Large multicenter trials have evaluated the benefit of different medical and surgical therapies to prevent stroke. However, the application of trial results to clinical practice remains uncertain for some areas of stroke prevention and has been discussed passionately among international experts. As part of a worldwide survey, the purpose of this analysis was to provide an informative and comparative view of the current practice of leading experts in North America (NA) and Western Europe (WE), where most of the large prevention trials have been performed. METHODS: The survey was performed worldwide among 185 neurologists who are currently leading the discussions of stroke prevention practices. It contained questions on the use of antiplatelet agents, oral anticoagulation, and surgery for the prevention of ischemic stroke. The population of this present analysis is the two groups of experts from WE (n=73) and NA (n=48) exclusively. RESULTS: Of each group, >90% responded to the survey. Nearly all respondents reported prescribing aspirin in patients at risk of atherothrombotic stroke, but significant differences between NA and WE are shown by the recommended doses (P<.0001): aspirin doses of >500 mg daily are given exclusively by American participants (36%), whereas doses <200 mg are recommended only in Europe (51%). Eighty-six percent of American versus 59% of European respondents reported using ticlopidine as their second choice (P<.005), and 23% of respondents from WE used warfarin compared with 5% from NA (P<.05). The reported use of anticoagulants in patients with atrial fibrillation increased in accordance with the patient's individual risk of stroke, but respondents from WE were more reluctant to use anticoagulants in patients older than 75 years. Relatively higher target international normalized ratio values were reported by European respondents. Nearly all participants recommend carotid endarterectomy in patients with symptomatic carotid stenosis. The use of carotid endarterectomy in asymptomatic patients was significantly more common among responding experts from NA (48% versus 28%; P<.05), particularly in patients with >95% stenosis (89% versus 53%; P<.0005). CONCLUSIONS: This analysis shows significant differences in several areas of stroke prevention practices between leading experts from NA and WE. These differences may be explained partly by divergent results of trials from the two continents, but in some areas of controversy currently available trial data are not sufficient to form an international consensus to guide daily clinical practice.

11. ASA for Cerebral Thromboses and Prevention.

(1) De Schryver EL

**DESIGN OF ESPRIT: AN INTERNATIONAL RANDOMIZED TRIAL FOR SECONDARY PREVENTION AFTER NON-DISABLING CEREBRAL ISCHAEMIA OF ARTERIAL ORIGIN. EUROPEAN/AUSTRAILIAN STROKE PREVENTION IN REVERSIBLE ISCHAEMIA TRIAL (ESPRIT) GROUP.**


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The ESPRIT trial addresses the problem that aspirin, the standard therapy for secondary prevention of vascular complications after a transient ischaemic attack (TIA) or ischaemic stroke of arterial origin, reduces the risk of serious vascular events by only about 13%. Anticoagulants may be an alternative, as these have proved highly efficacious in trials after myocardial infarction and after cerebral ischaemia with atrial fibrillation. After cerebral ischaemia of presumed arterial origin, high-intensity anticoagulation (INR 3.0-4.5) is not safe, but the value of anticoagulation with an INR between 2.0 and 3.0 is still unknown. Secondly, a recent, large trial showed that the combination of aspirin and dipyridamole prevents more major vascular events than aspirin alone, but several earlier trials did not find such an advantage. In ESPRIT, patients with a TIA or minor ischaemic stroke (Rankin grade \( \leq 3 \)) will be randomized between oral anticoagulation (INR 2.0-3.0), the combination of dipyridamole (400 mg daily) plus aspirin (in any dose between 30 and 325 mg daily) and aspirin only. Primary outcome is the composite event 'death from all vascular causes, non-fatal stroke, non-fatal myocardial infarction or major bleeding complication', whichever occurs first. Outcome assessment will be blinded. The recruitment of a total of 4,500 patients from more than 10 countries is planned; the mean follow-up will be 3 years. Copyright 2000 S. Karger AG, Basel.

(2) Crassard I, Niclot P, Bousser MG
[ASPIRIN AND CEREBRAL ISCHEMIC ACCIDENTS]. [ARTICLE IN FRENCH]

Service de neurologie, hopital Lariboisiere, Paris, France.

At the acute phase of cerebral infarction, two recent large studies found that the use of aspirin reduces both mortality and the risk of the recurrence of stroke. In primary prevention, aspirin nearly halves the risk of myocardial infarction but does not reduce that of stroke. Concerning the secondary prevention of atherothrombotic brain infarcts, aspirin has been the most extensively studied drug, and is efficient between 50 mg and 1.3 g. In spite of the efficacy of other antiplatelets in this indication—ticlopidine (500 mg), clopidogrel (75 mg) and dipyridamole (400 mg)—aspirin remains the most cost-effective, doses between 100 and 300 mg being the most widely used. Cardiac diseases with a high embolic risk require the use of oral anticoagulation. In nonvalvular atrial fibrillation, the choice of antithrombotic drugs depends on risk stratification: oral anticoagulants are indicated in high-risk subjects, whereas aspirin is recommended in low-risk subjects and when oral anticoagulants are contraindicated. Studies with associations of aspirin and other antiplatelets are required to increase the yield of this medication in high-risk subjects, in parallel with efforts to detect and to treat the vascular risk factors.

(3) Mosso M, Baumgartner RW
[TRANSIENT ISCHEMIC ATTACKS AND PROLONGED REVERSIBLE ISCHEMIC NEUROLOGIC DEFICIT. DIAGNOSIS, DIFFERENTIAL DIAGNOSIS AND TREATMENT]. [ARTICLE IN GERMAN]

Neurologische Klinik, UniversitätsSpital, Zurich.

Cerebral and ocular ischemic events are classified according to their duration and localisation in transient (< 24 hours) or permanent (\( > = 24 \) hours) cerebral (transient ischemic attack (TIA), cerebral infarct) and ocular (amaurosis fugax, retinal infarct) deficits. The terms "Prolonged Reversible Ischemic Neurological Deficit" (PRIND, \( > = 24 \) hours to \( < = 7 \) days) and "Reversible Ischemic Neurological Deficit" (RIND, \( > = 24 \) hours to \( < = 3 \) days) are no longer used. The differential diagnosis of TIs and ischemic strokes is discussed. Ischemic strokes are an emergency and should be referred within five hours at the latest to a centre, which offers around the clock acute therapies such as fibrinolysis and an organised stroke management. Secondary stroke prevention after TIA or stroke encompasses the treatment of vascular risk factors, carotid endarterectomy, anticoagulation in the presence of cardiac embolism (target international normalised ratio, 2.5; range 2.0-3.0) and the administration of platelet inhibitors. Carotid endarterectomy is indicated, when luminal narrowing is at least 70%, and not indicated when it is less than 50%. The benefit of endarterectomy in 50-69% stenoses decreases, and individual predictors of the operation risk are useful for choosing the appropriate treatment. Patients without indication for carotid endarterectomy or oral anticoagulation are treated with platelet inhibitors. We use the combination dipyridamole-aspirin as first choice drug, because it has been shown to be superior to aspirin and dipyridamole alone. In the presence of adverse effects or contraindications for dipyridamole we
prescribe aspirin (100-300 mg daily). We administer clopidogrel (75 mg daily) if dipyridamole and aspirin are not indicated, have caused adverse effects, or did not prevent ocular or cerebral ischemic events.

(4) Hankey GJ, Warlow CP
TREATMENT AND SECONDARY PREVENTION OF STROKE: EVIDENCE, COSTS, AND EFFECTS ON INDIVIDUALS AND POPULATIONS.
Royal Perth Hospital, and Department of Medicine, University of Western Australia.
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This review of the effectiveness of treatment for acute stroke and methods of secondary prevention shows that the highest priority for providers of a stroke service must be to establish a stroke unit and multidisciplinary team that delivers organised stroke care. Acute ischaemic stroke patients should be immediately started on aspirin 300 mg daily, and, if possible, many of them should be entered into further trials of thrombolysis and other promising treatments. After the acute phase, aspirin should be continued in a lower dose, 75 mg daily; smoking should be discouraged; high blood pressure treated initially with a diuretic; and fibrillating ischaemic stroke/transient ischaemic attack survivors anticoagulated long-term with warfarin or given aspirin if anticoagulation is not sensible. Statins are probably indicated in patients who already have symptomatic coronary heart disease. Adding dipyridamole to aspirin, substituting clopidogrel for aspirin, and carotid endarterectomy are all expensive interventions to prevent stroke, but if ways could be found to focus them on those patients at especially high risk, they would become more affordable.
Comment in: Lancet 2000 Jan 22;355(9200):319-20; discussion 320-1
Comment in: Lancet 2000 Jan 22;355(9200):320; discussion 320-1
Comment in: Lancet 2000 Jan 22;355(9200):321

(5) Leys D
[PREVENTION OF CEREBRAL ISCHEMIA: ANTI-PLATELET AGENTS]. [ARTICLE IN FRENCH]
Rev Neurol(Paris) 1999;155(9):688-693.
Service de neurologie et pathologie neurovasculaire, Centre Hospitalier et Universitaire de Lille. dleys@chru-lille.fr
Besides the optimal management of risk factors for stroke and carotid surgery, antiplatelet agents are the cornerstone for prevention of cerebral ischaemia. The aim of this overview is to determine their role in the prevention of cerebral ischaemia, from available literature. In primary prevention, the benefit of aspirin has been established only for patients with non-valvular atrial fibrillation and a low risk of cardioembolism, or as an alternative choice of warfarin, and in subjects at high risk of atherosclerosis. In secondary prevention, antiplatelet agents are effective to reduce the risk in patients with ischaemic stroke due to atherosclerosis: aspirin (50 to 1300 mg), ticlopidine (500 mg), clopidogrel (75 mg) and dipyridamole (400 mg) are effective, but the higher levels of risk reduction are obtained with clopidogrel, ticlopidine and the association aspirin–dipyridamole. Aspirin is recommended in most other causes of cerebral ischaemia, except in high risk cardiopathies when anticoagulation is possible. Other domains should still be explored: are antiplatelet agents also effective to reduce the risk of cerebral ischaemia in patients with other causes, especially lipohyalinosis of the deep perforators leading to lacunar infarcts? In daily practice, does prescription follow recommendations? Will it be possible to reproduce the results of the European Stroke Prevention Study (ESPS)? Are antiplatelet agents other than aspirin effective in non-valvular atrial fibrillation? Are other associations of antiplatelet agents more effective than these agents alone? Finally, what will be the role of new antiplatelet agents in the future?
(6) Gorter JW, De Schryver EL, Algra A

[SECONDARY PREVENTION AFTER ISCHEMIC CEREBRAL INFARCT. THE ESPRIT STUDY: LOW DOSE ANTICOAGULATION, COMBINED THERAPY WITH ACETYLSALICYLIC ACID/DIPYRIDAMOLE OR MONOTHERAPY WITH ACETYLSALICYLIC ACID]? [ARTICLE IN GERMAN]


Trial Bureau Neurologie, Universitatsklinikum Utrecht, Niederlande.

The European and Australian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT) is a randomised clinical trial in which patients with cerebral ischaemia of arterial origin will be randomised between oral anticoagulation (international normalized ratio (INR): 2.0-3.0), the combination of acetylsalicylic acid (in any dose between 30 and 325 mg per day) plus dipyridamole (400 mg daily) and acetylsalicylic acid only (in any dose between 30 and 325 mg per day). It is planned to enroll 4500 patients with a mean follow-up of three years. Primary outcome is the composite event of vascular death, stroke, myocardial infarction, or major bleeding complication; outcome assessment will be blinded. ESPRIT is an international, multi-center study in which 60-80 hospitals in the Netherlands and other countries in Europe and Australia will participate.

(7) Gorter JW, De Schryver EL, Algra A

[PREVENTION OF VASCULAR COMPLICATIONS FOLLOWING CEREBRAL ISCHEMIA OF ARTERIAL ORIGIN; THE ESPRIT TRIAL: MILD ANTICOAGULANT THERAPY, COMBINATION TREATMENT WITH ACETYLSALICYLIC ACID PLUS DIPYRIDAMOLE OR TREATMENT WITH ACETYLSALICYLIC ACID ALONE]? [ARTICLE IN DUTCH]


Academisch Ziekenhuis, afd. Neurologie (Trial Bureau), Utrecht.

The European and Australian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT) is a randomised clinical trial in which patients with cerebral ischaemia of arterial origin will be randomised between oral anticoagulation (international normalized ratio (INR): 2.0-3.0), the combination of acetylsalicylic acid (in any dose between 30 and 325 mg per day) plus dipyridamole (400 mg daily) and acetylsalicylic acid only (in any dose between 30 and 325 mg per day). It is planned to enroll 4500 patients with a mean follow-up of three years. Primary outcome is the composite event of vascular death, stroke, myocardial infarction, or major bleeding complication; outcome assessment will be blinded. ESPRIT is an international, multicentre study in which 60-80 hospitals in the Netherlands and other countries in Europe and Australia will participate.

(8) Algra A, Koudstaal PJ, van Gijn J

[SECONDARY PREVENTION FOLLOWING CEREBRAL ISCHEMIA: IS MONOTHERAPY WITH ACETYLSALICYLIC ACID STILL FIRST CHOICE]? [ARTICLE IN DUTCH]


Acetylsalicylic acid (ASA) alone (at least 30 mg per day) in post-cerebral ischaemia patients reduces the relative risk of further vascular events by 13% compared with placebo. A meta-analysis of all studies shows that the combination of ASA with dipyridamole reduces the relative risk by 16% (95% confidence interval: 5-26%) compared with ASA alone, but confirmation by a major trial appears desirable, because of discrepant results of a recent trial and 4 previous ones. Clopidogrel might reduce the risk by 7% compared with ASA alone, but this drug is expected to be expensive. Anticoagulation therapy with an international normalized ratio (INR) of 2.0-4.0 is particularly efficacious for secondary prevention in patients with atrial fibrillation, but anticoagulation therapy with an INR of 3.0-4.5 is not safe in secondary prevention of cerebral ischaemia of presumed arterial origin. Finally, not all atherosclerotic vascular diseases are identical from the therapeutic point of view; the effect of treatment depends in part on the clinical manifestation form.

Published erratum appears in Ned Tijdschr Geneeskd 1998 Mar 7;142(10):552
(9) Matchar DB, McCrory DC, Barnett HJ, Feussner JR

MEDICAL TREATMENT FOR STROKE PREVENTION.

Center for Health Policy Research and Education, Duke University, Durham, NC 27708.
PURPOSE: To review the effectiveness of medical treatments for stroke prevention in patients at elevated risk for stroke. DATA SOURCES: English-language articles published after 1977 and indexed in MEDLINE under the following Medical Subject Heading terms: anticoagulants, aspirin, dipyridamole, ticlopidine, or sulfinpyrazone, combined with cerebrovascular disorders. STUDY SELECTION: Randomized controlled trials of anticoagulant or platelet antiaggregant treatment reporting subsequent stroke and myocardial infarction, death, or complications in persons with asymptomatic carotid stenosis or bruit, transient ischemic attack (TIA), previous stroke, nonvalvular atrial fibrillation, or other vascular diseases. DATA EXTRACTION: Of 900 articles identified, 33 were selected by two independent reviewers and abstracted for outcome events and person-years of follow-up. RESULTS: In patients with nonvalvular atrial fibrillation, warfarin is highly effective in reducing stroke and death but may result in more complications. Aspirin appears to be less effective and less risky than anticoagulation. In patients with TIA or minor stroke, both aspirin and ticlopidine reduce the risk for stroke. In patients who have had myocardial infarction, warfarin is effective but had high complication rates in the reviewed studies. Aspirin slightly reduces the risk for stroke. CONCLUSIONS: Warfarin is strongly recommended for persons with nonvalvular atrial fibrillation who are older than 60 years or who have additional risk factors for stroke. Aspirin is recommended for persons at elevated risk for bleeding while receiving anticoagulants. For persons with TIA or minor stroke, aspirin should be used first. Patients who do not respond to or tolerate aspirin or who have had a major stroke are reasonable candidates for ticlopidine. For patients who have had myocardial infarction, aspirin is recommended for the prevention of secondary myocardial infarction but not of stroke.

Comment in: ACP J Club 1994 Nov-Dec;121(3):60

(10) Kollegger H, Oder W, Zeiler K, Deecke L

[CLINICAL ASPECTS OF TREATMENT AND PREVENTIVE TREATMENT WITH THROMBOCYTE AGGREGATION INHIBITORS IN CEREBROVASCULAR DISEASES]. [ARTICLE IN GERMAN]

Neurologischen Universitatsklinik, Wien.
Inhibitors of thrombocyte aggregation are generally accepted in the therapy and prophylaxis of ischemic cerebrovascular disease. The frequency of re-infarction, morbidity and mortality after TIA, PRIND and minor stroke is influenced favourably. There are controversial opinions, however, about the usefulness for patients suffering from completed strokes. In patients with progressive stroke, cerebral embolism of cardiac source, or non-infective thrombosis of sinuses or cerebral veins, inhibitors of thrombocyte aggregation are used if anticoagulation therapy is not possible. Additionally, they are applied in cases of infective thrombosis of sinuses or cerebral veins, after termination of anticoagulation therapy, after cardiac valve replacement, and after surgical reconstructions of craniocervical vessels. Acetylsalicylic acid is the clinically best examined substance; its effect—especially in males—was proven by numerous prospective trials. A combined treatment with dipyridamole, sulfinpyrazone or other drugs seems to be unnecessary. A daily dose of not more than 300 to 325 mg acetylsalicylic acid is recommended for prophylaxis after ischemic cerebral events; in connection with that dose severe gastrointestinal side effects are hardly to be expected. Whether even lower doses would yield the same prophylactic effects will have to be clarified by further studies.

B. ASA induced Adverse Effects

1. ASA and its Prothrombotic Properties at 8-10 days after administration
(1) Li N, Wallen NH, Hjemdahl P

EVIDENCE FOR PROTHROMBOTIC EFFECTS OF EXERCISE AND LIMITED PROTECTION BY ASPIRIN.

_Circulation_ 1999 Sep 28;100(13):1374-9

Department of Laboratory Medicine, Division of Clinical Pharmacology, Karolinska Hospital, Stockholm, Sweden.

BACKGROUND: Exercise may activate platelets and leukocytes and promote thrombosis. The effects of aspirin treatment on the prothrombotic effects of exercise have not been established.

METHODS AND RESULTS: A total of 15 healthy men performed exhaustive exercise without and with 1 week of pretreatment with aspirin (500 mg/day). Before and immediately after exercise, platelet aggregability ex vivo was measured by filtragometry, and venous blood samples were obtained. Whole-blood flow cytometry was used to determine platelet and leukocyte activation and platelet-leukocyte aggregates. Exercise increased platelet P-selectin expression, CD11b expression in neutrophils and lymphocytes, and platelet and leukocyte responses to thrombin, ADP, platelet activating factor, and N-formyl-methionyl-leucyl-phenylalanine (fMLP) in vitro. Consistent with enhanced platelet and leukocyte activation, more circulating platelet-platelet and platelet-leukocyte aggregates were detected after exercise (P<0.001 for both). Filtragometry readings were shortened, and plasma soluble P-selectin and prothrombin fragment 1+2 were elevated. Aspirin markedly reduced the urinary excretion of 11-dehydrothromboxane B(2), decreased P-selectin expression in single platelets at rest (P<0.05), and inhibited fMLP-induced neutrophil CD11b expression, but it did not attenuate exercise-induced increases in platelet aggregability, platelet P-selectin expression, leukocyte CD11b expression, platelet-leukocyte aggregate formation, soluble P-selectin, or prothrombin fragment 1+2. CONCLUSIONS: Exercise induced platelet and leukocyte activation and platelet-leukocyte aggregation in vivo, and it increased platelet and leukocyte responsiveness to in vitro stimulation. Aspirin treatment attenuated certain signs of platelet activity in vivo at rest and fMLP-induced neutrophil activation in vitro, but it did not attenuate the prothrombotic effects of exercise.

(2) Valles J, Santos MT, Aznar J, Osa A, Lago A, Cosin J, Sanchez E, Broekman MJ, Marcus AJ

ERYTHROCYTE PROMOTION OF PLATELET REACTIVITY DECREASES THE EFFECTIVENESS OF ASPIRIN AS AN ANTITHROMBOTIC THERAPEUTIC MODALITY: THE EFFECT OF LOW-DOSE ASPIRIN IS LESS THAN OPTIMAL IN PATIENTS WITH VASCULAR DISEASE DUE TO PROTHROMBOTIC EFFECTS OF ERYTHROCYTES ON PLATELET REACTIVITY.


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BACKGROUND: Aspirin (acetylsalicylic acid, ASA) is widely used for secondary prevention of ischemic vascular events, although its protection only occurs in 25% of patients. We previously demonstrated that platelet reactivity is enhanced by a prothrombotic effect of erythrocytes in a thromboxane-independent manner. This diminishes the antithrombotic therapeutic potential of ASA. Recent data from our laboratory indicate that the prothrombotic effect of erythrocytes also contains an ASA-sensitive component. In accordance with this observation, intermittent treatment with high-dose ASA reduced the prothrombotic effects of erythrocytes ex vivo in healthy volunteers. In the present study, the effects of platelet-erythrocyte interactions were evaluated ex vivo in 82 patients with vascular disease: 62 patients with ischemic heart disease treated with 200 mg ASA/d and 20 patients with ischemic stroke treated with 300 mg ASA/d. METHODS AND RESULTS: Platelet activation (release reaction) and platelet recruitment (fluid-phase proaggregatory activity of cell-free releasates from activated platelets) were assessed after collagen stimulation (1 microg/mL) of platelets, platelet-erythrocyte mixtures, or whole blood. Platelet thromboxane A2 synthesis was inhibited by >94% by ASA administration in all patients. Importantly, platelet recruitment followed one of three distinct patterns. In group A (n=32; 39%), platelet recruitment was blocked by ASA both in the presence and absence of erythrocytes. In group B (n=37; 45%), recruitment was abolished when platelets were evaluated alone but continued in the presence of erythrocytes, indicating a suboptimal effect of ASA on erythrocytes of this patient group. In group C (n= 13; 16%), detectable recruitment in stimulated platelets alone persisted and was markedly enhanced by the
presence of erythrocytes. CONCLUSIONS: In two thirds of a group of patients with vascular disease, 200 to 300 mg ASA was insufficient to block platelet reactivity in the presence of erythrocytes despite abolishing thromboxane A2 synthesis. Platelet activation in the presence of erythrocytes can induce the release reaction and generate biologically active products that recruit additional platelets into a developing thrombus. Insufficient blockade of this proaggregatory property of erythrocytes can lead to development of additional ischemic complications.

(3) Aguejouf O, Belougne-Malfatti E, Doutremepuich F, Belon P, Doutremepuich C

THROMBOEMBOLIC COMPLICATIONS SEVERAL DAYS AFTER A SINGLE-DOSE ADMINISTRATION OF ASPIRIN.

Res 1998 Feb 1;89(3):123-7

Laboratoire d'Hematologie, Faculte de Pharmacie, Universite de Bordeaux II, France.

The antithrombotic properties of acetyl salicylic acid (ASA) used at current doses are largely demonstrated. However, our previous study showed unexpected thrombotic potencies associated with the use of this drug. In this study we investigate the effect of aspirin on an experimental thrombosis induced by laser beams, according to its in vivo plasma concentration. Experiments were done on nine groups of seven Wistar male rats. The groups are defined by the delay between aspirin administration time and the laser-induced thrombosis time. Results from this study showed an enhancement of thromboembolic complications when thrombosis was induced 8 or 10 days after aspirin administration; the number of emboli and the duration of embolization are increased, compared to the control group. The prothrombotic properties of ASA demonstrated in this study, might limit its therapeutic benefit and might explain thromboembolic complications observed in some ASA-treated patients. These results also suggest a biological monitoring several days after aspirin administration to patients.

(4) Valles J, Santos MT, Aznar J, Osa A, Lago A, Cosin J, Sanchez E, Broekman MJ, Marcus AJ

ERYTHROCYTE PROMOTION OF PLATELET REACTIVITY DECREASES THE EFFECTIVENESS OF ASPIRIN AS AN ANTITHROMBOTIC THERAPEUTIC MODALITY: THE EFFECT OF LOW-DOSE ASPIRIN IS LESS THAN OPTIMAL IN PATIENTS WITH VASCULAR DISEASE DUE TO PROTHROMBOTIC EFFECTS OF ERYTHROCYTES ON PLATELET REACTIVITY.


Research Center, University Hospital La Fe, Valencia, Spain. mteresas@san.gva.es

BACKGROUND: Aspirin (acetylsalicylic acid, ASA) is widely used for secondary prevention of ischemic vascular events, although its protection only occurs in 25% of patients. We previously demonstrated that platelet reactivity is enhanced by a prothrombotic effect of erythrocytes in a thromboxane-independent manner. This diminishes the antithrombotic therapeutic potential of ASA. Recent data from our laboratory indicate that the prothrombotic effect of erythrocytes also contains an ASA-sensitive component. In accordance with this observation, intermittent treatment with high-dose ASA reduced the prothrombotic effects of erythrocytes ex vivo in healthy volunteers. In the present study, the effects of platelet-erythrocyte interactions were evaluated ex vivo in 82 patients with vascular disease: 62 patients with ischemic heart disease treated with 200 mg ASA/d and 20 patients with ischemic stroke treated with 300 mg ASA/d. METHODS AND RESULTS: Platelet activation (release reaction) and platelet recruitment (fluid-phase proaggregatory activity of cell-free releasates from activated platelets) were assessed after collagen stimulation (1 microg/mL) of platelets, platelet-erythrocyte mixtures, or whole blood. Platelet thromboxane A2 synthesis was inhibited by >94% by ASA administration in all patients. Importantly, platelet recruitment followed one of three distinct patterns. In group A (n=32; 39%), platelet recruitment was blocked by ASA both in the presence and absence of erythrocytes. In group B (n=37; 45%), recruitment was abolished when platelets were evaluated alone but continued in the presence of erythrocytes, indicating a suboptimal effect of ASA on erythrocytes of this patient group. In group C (n=13; 16%), detectable recruitment in stimulated platelets alone persisted and was markedly enhanced by the presence of erythrocytes. CONCLUSIONS: In two thirds of a group of patients with vascular disease, 200 to 300 mg ASA was insufficient to block platelet reactivity in the presence of erythrocytes despite abolishing thromboxane A2 synthesis. Platelet activation in the presence of erythrocytes can induce the release reaction and generate biologically active products
that recruit additional platelets into a developing thrombus. Insufficient blockade of this proaggregatory property of erythrocytes can lead to development of additional ischemic complications.

ERYTHROCYTES METABOLICALLY ENHANCE COLLAGEN-INDUCED PLATELET RESPONSIVENESS VIA INCREASED THROMBOXANE PRODUCTION, ADENOSINE DIPHOSPHATE RELEASE, AND RECRUITMENT.

_Blood_ 1991 Jul 1;78(1):154-62

Hospital La Fe, Valencia, Spain.

Erythrocytes promoted platelet reactivity in a plasma medium, as demonstrated in an in vitro system that independently evaluated the biochemistry of platelet activation and recruitment. The prothrombotic erythrocyte effects were metabolically regulated, as evidenced by lack of activity of ATP-depleted or glutaraldehyde-fixed erythrocytes. They occurred in the absence of cell lysis as verified by lactate dehydrogenase assays, and had an absolute requirement for platelet activation. The presence of erythrocytes induced a twofold increase in platelet thromboxane B2 (TXB2) synthesis upon collagen stimulation, indicating that erythrocytes modulated platelet eicosanoid formation. Cell-free releasates from stimulated platelet-erythrocyte suspensions, which exhibited increased recruiting capacity, contained 6.9-fold more ADP and 4.9-fold more ATP than releasates from stimulated platelets alone. Following aspirin ingestion, TXB2 formation was blocked, but erythrocyte promotion of platelet reactivity persisted at those doses of collagen that reinduced platelet activation. Moreover, when platelet mixtures consisted of as little as 10% obtained before aspirin plus 90% obtained post-aspirin ingestion, significant erythrocyte enhancement of platelet reactivity occurred, even at low agonist concentrations. These erythrocyte effects would decrease the therapeutic potential of inhibition of platelet cyclooxygenase by aspirin. The erythrocyte-induced modulation of platelet biochemistry and function emphasizes the importance of cell-cell interactions in stimulus-response coupling.

2. ASA induced Asthma and Allergy

(1) Stevenson DD, Simon RA, Mathison DA, Christiansen SC
MONTELUKAST IS ONLY PARTIALLY EFFECTIVE IN INHIBITING ASPIRIN RESPONSES IN ASPIRIN-SENSITIVE ASTHMATS.


Division of Allergy, Asthma & Immunology, Scripps Clinic and The Scripps Research Institute, La Jolla, California, USA.

BACKGROUND: Leukotrienes have been implicated as major mediators of ASA-induced respiratory reactions. In several prior studies, pretreatment of ASA-sensitive respiratory disease (ASRD) patients with leukotriene modifiers have sometimes allowed subjects to tolerate previously established provoking doses of oral ASA or inhalation ASA-lysine, without respiratory reactions. OBJECTIVE: The purpose of this study was to examine whether ASA-provoked respiratory reactions would be blocked or attenuated by pretreatment with a cystLT1 receptor antagonist, montelukast, particularly if ASA doses were increased above their threshold doses. METHODS: Baseline ASA oral challenges were performed. Eight to 12 days later, following pretreatment with montelukast 10 mg daily, threshold and then escalating doses of ASA were used during repeat oral ASA challenges. The differences in responses between baseline and montelukast protected ASA oral challenges were then compared. RESULTS: Nine of 10 patients, despite pretreatment with montelukast, experienced at least naso-ocular reactions during their second oral ASA challenges. In four of nine patients, asthmatic reactions also occurred. In comparing baseline and montelukast protected ASA challenges, there were no statistically significant differences in their responses. CONCLUSIONS: Pretreatment with montelukast allowed only one patient to proceed through all challenge doses of ASA without any reactions. The remaining nine patients enjoyed only partial protection from respiratory reactions. Montelukast pretreatment was generally not effective in altering upper airway reactions and only partly effective in altering lower airway reactions.
(2) Casadevall J, Ventura PJ, Mullol J, Picado C.

**INTRANASAL CHALLENGE WITH ASPIRIN IN THE DIAGNOSIS OF ASPIRIN INTOLERANT ASTHMA: EVALUATION OF NASAL RESPONSE BY ACOUSTIC RHINOMETRY**


Servei de Pneumologia Hospital General, Vic, Spain.

BACKGROUND: Nasal provocation tests with lysine-aspirin have recently been introduced for assessment of aspirin intolerant asthma. A study was undertaken to evaluate the usefulness of acoustic rhinometry, a new non-invasive technique, in the diagnosis of aspirin intolerant asthma/rhinitis. METHODS: Fifteen patients with aspirin intolerant asthma/rhinitis (nine women, mean (SD) age 54.7 (14) years), eight patients with aspirin tolerant asthma/rhinitis (three women, mean (SD) age 52.6 (7.8) years), and eight healthy subjects (two women, mean (SD) age 32.5 (9.7) years) were studied. All subjects were challenged with saline (0.9% NaCl) and 25 mg lysine acetylsalicylic acid (L-ASA) instilled into each nostril of the nose on two separate days. The clinical response was evaluated based on nasal symptoms (sneezes, itching, secretion and blockage). The nasal response was measured by acoustic rhinometry. Symptoms and rhinometry curves were recorded at 10 minute intervals for three hours, one hour before challenge and two hours after challenge. RESULTS: L-ASA challenge induced a significant increase in symptoms in patients with aspirin intolerant asthma/rhinitis. No differences in the clinical response were detected in those with aspirin tolerant asthma/rhinitis or healthy subjects. L-ASA challenge induced a significant decrease in nasal volume measured by acoustic rhinometry in aspirin intolerant patients. No differences were detected between the challenges in aspirin tolerant patients. If a 25% decrease in nasal volume is taken as the cut off point, the specificity of the test was 94% and the sensitivity reached 73%. The nasal challenge was well tolerated by all subjects. CONCLUSION: Acoustic rhinometry may be used to study the nasal response to L-ASA. Nasal challenge with L-ASA is safe and can be used as a diagnostic test even in asthmatic patients with severe bronchial obstruction.

(3) Nizankowska E, Bestynska-Krypel A, Cmiel A, Szczeklik A

**ORAL AND BRONCHIAL PROVOCATION TESTS WITH ASPIRIN FOR DIAGNOSIS OF ASPRIN-INDUCED ASTHMA.**


Jagiellonian University School of Medicine, Dept of Medicine, Cracow, Poland

In 35 asthmatic patients with acetylsalicylic acid (aspirin; ASA) intolerance (AIA) and 15 asthmatics tolerating ASA well, the authors compared the diagnostic value of the placebo-controlled oral ASA versus inhaled L-lysine (L) ASA challenges. All AIA subjects gave a history of asthmatic attacks following ingestion of ASA and in all of them the intolerance was confirmed by oral challenge test over the past 10 yrs. Doses of ASA increasing in geometric progression were used in oral tests 10-312 mg (cumulative dose 500 mg); in bronchial tests 0.18-115 mg (cumulative dose 182 mg). Either challenge was considered as positive, if forced expiratory volume in one second (FEV1) dropped at least 20% from the baseline value and/or strong extrabronchial symptoms of intolerance occurred. Urinary leukotriene E4 excretion was determined at baseline and following the challenges. In 24 out of 35 patients the oral test was positive, based on a 20% decrease in FEV1. When including extrabronchial symptoms this was positive in 31 cases. Bronchial L-ASA challenge led to > or =20% fall FEV1 in 21 out of 35 cases, and in 27 cases when including extrabronchial symptoms. No correlation was observed between ASA provocative dose causing a 20% fall in FEV1, determined by the oral route compared to the inhalation route. Urinary LTE4 increased after both challenges the rise being higher following oral as compared to inhalation provocation (p=0.0001). It is concluded that both tests had similar specificity whilst the oral test showed a tendency to higher sensitivity for the clinical diagnosis of acetylsalicylic acid intolerance. The inclusion of extrabronchial symptoms into the criteria of test positivity enhanced the diagnostic value of both procedures. In both tests the highest leukotriene E4 increases were found in the presence of extrabronchial symptoms, suggesting the participation of tissues other than the lung in aspirin induced leukotriene E4 release to urine.
(4) Wong JT, Nagy CS, Krinzman SJ, Maclean JA, Bloch KJ

RAPID ORAL CHALLENGE-DESENSITIZATION FOR PATIENTS WITH ASPIRIN-RELATED URTICARIA-ANGIOEDEMA.


Clinical Immunology and Allergy Units, Massachusetts General Hospital, Boston, MA 02114, USA.

BACKGROUND: Acetylsalicylic acid (ASA), commonly known as aspirin, is indicated in the treatment of coronary artery disease (CAD). Many patients are denied treatment with ASA because of a history of ASA or nonsteroidal anti-inflammatory drug (NSAID)-induced urticaria or angioedema. OBJECTIVE: We sought to develop a safe and practical protocol to allow the administration of ASA to patients with a history of ASA- or NSAID-induced urticaria-angioedema. METHODS: Eleven subjects with a history of ASA- or NSAID-induced urticaria-angioedema were challenged-desensitized by oral protocols based on rapidly escalating doses of ASA. Most had CAD, one had a history of pulmonary embolism, and one had refractory chronic sinusitis and asthma. Starting doses ranged from 0.1 to 10 mg and were administered at intervals of 10 to 30 minutes. Dosing was individualized for each patient but followed this general sequence (in milligrams): 0.1, 0.3, 1, 3, 10, 20, 40, 81, 162, 325. RESULTS: Nine patients tolerated the procedure without adverse effects and continued taking ASA for periods ranging from 1 to 24 months, without development of urticaria or angioedema. A patient who had a history of chronic idiopathic urticaria in addition to aspirin-induced urticaria had chest tightness during the protocol. Another patient who had continuing urticaria and angioedema associated with antithyroid antibodies developed angioedema several hours after completing the protocol. CONCLUSION: In patients with historical ASA- or NSAID-induced urticaria-angioedema reactions but who did not have urticaria and angioedema independent of ASA/NSAID, rapid oral challenge-desensitization to ASA was performed safely and permitted patients with CAD and other diseases to receive treatment with ASA.

(5) Park HS, Nahm DH, Park K, Suh KS, Yim HE

IMMUNOHISTOCHEMICAL CHARACTERIZATION OF CELLULAR INFILTRATE IN NASAL POLYP FROM ASPIRIN-SENSITIVE ASTHMATIC PATIENTS.


Department of Allergy and Clinical Immunology, Ajou University School of Medicine, Suwon, Korea.

BACKGROUND: The immunopathologic mechanism of nasal polyp in aspirin-sensitive asthma remains to be further defined. OBJECTIVE: To characterize the features of the inflammatory cellular infiltrate in the nasal polyp tissue from aspirin-sensitive asthmatic patients. METHODS: We have taken nasal polyp tissue during nasal polyp resection from 13 aspirin-sensitive asthma, 6 allergic, and 12 non-allergic subjects. Immunohistochemistry was employed to stain and enumerate the individual inflammatory cell types using monoclonal antibodies against tryptase (AA1) to identify mast cells, against secreted forms of eosinophil cationic protein (EG2), to identify activated eosinophils, against neutrophil elastase (NE) for neutrophils and against T cell surface markers (CD3) to identify total T cells. RESULTS: There were no significant differences in AA1+ cells among three groups (P>.05). EG2+ cells tended to be higher in ASA-sensitive asthma than in allergic and non-allergic subjects, but no statistical significance was observed. NE+ cells were found in most subjects of the three groups (P>.05). Some patients had CD3+ cells with no statistical significance among the three groups. Significant correlation was found in numbers between NE+ cell and AA1+ cell (r=.44, P=.01), and between NE+ cell and EG2+ cell (r=.40, P=.02). CONCLUSION: These findings suggested that major effector cells such as mast cells and eosinophils might be placed in the center of the inflammatory response of nasal polyps, regardless of their association with aspirin sensitivity.

(6) Dahlen B, Melillo G

INHALATION CHALLENGE IN ASA-INDUCED ASTHMA.

Respir Med 1998 Mar;92(3):378-84

Karolinska Institutet, Division of Respiratory Medicine, Thoracic Clinics, Karolinska Hospital, Stockholm, Sweden.
ENHANCED EXPRESSION OF CYCLO-OXYGENASE ISOENZYME 2 (COX-2) IN ASTHMATIC AIRWAYS AND ITS CELLULAR DISTRIBUTION IN ASPIRIN-SENSITIVE ASTHMA.


Department of Allergy and Respiratory Medicine, UMDS, Guy's Hospital, London, UK.

BACKGROUND: There are two isoforms of cyclo-oxygenase (COX), namely COX-1 and COX-2. COX-1 is constitutively expressed in most tissues and in blood platelets. The metabolites derived from COX-1 are probably involved in cellular housekeeping functions. COX-2 is expressed only following cellular activation by inflammatory stimuli and is thought to be involved in inflammation.

METHODS: The expression of COX-1 and COX-2 isoenzymes has been studied in the bronchial mucosa of 10 normal and 18 asthmatic subjects, 11 of whom had aspirin-sensitive asthma (ASA) and seven had non-aspirin-sensitive asthma (NASA)

RESULTS: There was a significant fourfold and 14-fold increase, respectively, in the epithelial and submucosal cellular expression of COX-2, but not of COX-1, in asthmatic patients. There was no significant difference in the total number of cells staining for either COX-1 or COX-2 between subjects with ASA and NASA, but the number and percentage of mast cells that expressed COX-2 was significantly increased sixfold and twofold, respectively, in individuals with ASA. There was a mean fourfold increase in the percentage of COX-2 expressing cells that were mast cells in subjects with ASA and the number of eosinophils expressing COX-2 was increased 2.5-fold in these subjects.

CONCLUSION: COX-2-derived metabolites may play an essential part in the inflammatory processes present in asthmatic airways and development of drugs targeted at this isoenzyme may have therapeutic potential in the treatment of asthma. Mast cells and eosinophils may also have a central role in the pathology of aspirin-sensitive asthma.


3. ASA Reye's Syndrome

(1) Vinas-Machin PL, Nunez-Diaz BC
[REYE SYNDROME: A CASE STUDY IN A CUBAN PROVINCIAL HOSPITAL FROM 1990 TO 1996]. [ARTICLE IN SPANISH]

Rev Neurol 1999 May 16-31;28(10):959-61

Hospital Provincial Pediatrico Docente Pepe Portilla, Pinar del Rio, Cuba.

INTRODUCTION: Reye's syndrome is a metabolic encephalopathy of infancy which is often fatal. Epidemiological studies have shown associated factors including having taken Aspirin for viral illness. Some patients with this disorder may have preexisting organic acidemia such as dicarboxylic aciduria. OBJECTIVE: To study the behavior of Reye's syndrome in a group of patients during the years 1990-1996 in a provincial paediatric hospital and review variables such as age, sex, race, prodromal illness, previous consumption of Aspirin, hospital stay, mortality, diagnosis of dicarboxylic aciduria, etc. PATIENTS AND METHODS: We selected patients with Reye's syndrome seen during the period mentioned and considered the above variables. RESULTS: All 10 patients seen with Reye's syndrome were boys. Their ages were between 3 months and 2 years. Most (nine) of the patients were Caucasian. All patients had influenza as the prodromal illness, and all took Aspirin as an antipyretic. There was considerable variation in the length of their stay in the hospital. In our series there was a high mortality and only two patients survived. One boy had dicarboxylic aciduria. CONCLUSIONS: The fatal character of Reye's syndrome has been shown, as has its relation to the use of Aspirin. In our environment there seems to be a tendency for Caucasian boys to be affected.

(2) Bray PF
ARE WE STILL ABUSING ASPIRIN?

(3) Butterworth RF
ANTIPYRETICS AND REYE'S SYNDROME.
Reye's syndrome (RS) is a biphasic illness that occurs predominantly in children and adolescents. A prodromal viral illness (frequently influenza A or B or chicken pox) is followed by protracted vomiting and neurologic changes that start 3 to 5 days later, just when the child seems to be recovering. Aspirin has been identified as one factor contributing to the metabolic disorder that occurs. Since 1986 the FDA has required labels on all aspirin products warning about the association of aspirin use and RS. Media messages heightened public awareness regarding the alternatives to aspirin for analgesia and antipyretic use. Since 1988, the incidence of RS has decreased dramatically. RS is now more prevalent in older adolescents who may self-medicate. Because early recognition of the disease is associated with decreased morbidity and mortality, it is important for health care providers to recognize the symptoms of RS. Unexpected vomiting and disturbed brain functioning following a viral illness are symptoms of RS in children and adolescents. In infants, the symptoms of RS may be more subtle, including diarrhea, respiratory disturbances, and seizures.

Reye's syndrome is most frequently seen in children but has also been described in adults. This syndrome is usually associated with ingestion of 5-aminosalicylates (ASA) or infection with influenza A, influenza B, or varicella virus. A case of Reye's syndrome in a 47 year old, previously healthy woman precipitated by ingestion of ASA and acute hepatitis A virus infection is described. Reye's syndrome was diagnosed on the basis of her clinical course, and the presence of hepatic microvesicular steatosis and characteristic electron microscopic changes in the hepatocyte mitochondria. The diagnosis of hepatitis A was based on higher amino-transferase values than would be expected in Reye's syndrome alone, viral serology including the presence of hepatitis A IgM and the demonstration of hepatitis A virus RNA on liver biopsy by in situ hybridisation. Mitochondrial injury has been demonstrated in acute hepatitis A which, in addition to ASA, may have precipitated Reye's syndrome in this patient. The association between hepatitis A and Reye's syndrome has not been reported before. As hepatitis A virus infection is not sought routinely in patients with Reye's syndrome, the frequency of this association is unknown.

4. ASA induced Mitochondrial Dysfunction

Tomoda T, Takeda K, Kurashige T, Enzan H, Miyahara M

Acetylsalicylate (ASA)-induced mitochondrial dysfunction and its potentiation by Ca2+. Liver 1994 Apr;14(2):103-8
Although it has been suggested that acetylsalicylate (ASA)-induced mitochondrial dysfunction plays an important role in the pathogenesis of Reye's syndrome, administration of ASA alone does not cause this syndrome in therapeutic doses. We noted, however, that Ca\(^{2+}\) plays important roles in the regulation of cellular functions. ASA at concentrations of 250 microM or less, which had little effect on succinate-linked respiration, impaired Ca\(^{2+}\) accumulation in liver mitochondria by causing an increase in Ca\(^{2+}\) release. ASA plus Ca\(^{2+}\), which in concentrations of 150 microM or less alone had little effect on mitochondrial respiration, inhibited state 3 respiration and dinitrophenol-induced uncoupling of respiration. In addition, ASA plus Ca\(^{2+}\) increased state 4 respiration and ATPase activity. These results indicate that ASA plus Ca\(^{2+}\) impaired mitochondrial ATP synthesis, and suggest that ASA and ASA-induced Ca\(^{2+}\) increases in cytosol form a vicious circle of effects. Furthermore, oral administration of ASA (150 mg/kg for 5 days running) to rats did not affect mitochondrial structure or liver function, but resulted in aberrations of mitochondrial respiration. These results suggest that even therapeutic doses of ASA may induce alteration in mitochondrial function.

5. ASA effect on Intracerebral Bleeding - No Primary Risk!!

(1) Thrift AG, McNeil JJ, Forbes A, Donnan GA

**RISK OF PRIMARY INTRACEREBRAL HAEMORRHAGE ASSOCIATED WITH ASPIRIN AND NON-STEROIDAL ANTI-INFLAMMATORY DRUGS: CASE-CONTROL STUDY.**

*BMJ* 1999 Mar 20;318(7186):759-764

Department of Epidemiology and Preventive Medicine, Monash Medical School, Alfred Hospital, Prahran 3181, Australia.

Objective: To examine the association between use of aspirin or other non-steroidal anti-inflammatory drugs and intracerebral haemorrhage. Design: Case-control study. Setting: 13 major city hospitals in the Melbourne and metropolitan area. Subjects: 331 consecutive cases of stroke verified by computed tomography or postmortem examination, and 331 age (+/- 5 years) and sex matched controls who were community based neighbours. Interventions: Questionnaire administered to all subjects either directly or by proxy with the next of kin. Drug use was validated by reviewing prescribing records held by the participants' doctors. Main outcome measures: Previous use of aspirin or other non-steroidal anti-inflammatory drugs. Results: Univariate analysis showed no increased risk of intracerebral haemorrhage with low dose aspirin use in the preceding 2 weeks. Using multiple logistic regression to control for possible confounding factors, the odds ratio associated with the use of aspirin was 1.00 (95% confidence interval 0.60 to 1.66, P=0.998) and the odds ratio associated with the use of other non-steroidal anti-inflammatory drugs was 0.85 (0.45 to 1.61, P=0.611) compared with respective non-users in the preceding fortnight. Moderate to high doses of aspirin (>1225 mg/week spread over at least three doses) yielded an odds ratio of 3.05 (1.02 to 9.14, P=0.047). There was no evidence of an
increased risk among subgroups defined by age, sex, blood pressure status, alcohol intake, smoking, and the presence or absence of previous cardiovascular disease. Conclusions: No increase in risk of intracerebral haemorrhage was found among aspirin users overall or among those who took low doses of the drug or other non-steroidal anti-inflammatory drugs. These data provide evidence that doses of aspirin usually used for prophylaxis against vascular disease produce no substantial increase in risk of intracerebral haemorrhage.

6. ASA and Streptokinase "Increased Risk" for Intracerebral Bleeding

(1) Ciccone A, Motto C, Aritzu E, Piana A, Candelise L
NEGATIVE INTERACTION OF ASPIRIN AND STREPTOKINASE IN ACUTE ISCHEMIC STROKE: FURTHER ANALYSIS OF THE MULTICENTER ACUTE STROKE TRIAL-ITALY.
Cerebrovasc Dis 2000 Jan;10(1):61-64

Istituto di Clinica Neurologica, IRCCS Ospedale Maggiore-Policlinico, Universita degli Studi di Milano, Milano, Italia.

Background: Thrombolytic therapy improves the functional outcome in acute ischemic stroke, but the risk of death and cerebral hemorrhage remains high. Aspirin given together with a thrombolytic agent may worsen the risk-to-benefit ratio. We performed a further Multicenter Acute Stroke Trial-Italy (MAST-I) which is the only randomized, controlled trial that has tested the effect of this combination to evaluate the risk of aspirin use plus streptokinase. Patients and Methods: We made a post hoc analysis of the MAST-I results comparing streptokinase plus aspirin (156 patients) with streptokinase alone (157 patients). We evaluated the risk of death and cerebral hemorrhage. Results: The combined regimen significantly increased early case fatality from day 3-10 (53 vs. 30; OR 2.1; CI 1.2-3.6). The death excess was solely due to treatments and was not explained by the main prognostic predictors (multifactorial analysis). The cause of death in the combination group was mainly cerebral (42 vs. 24; OR 2.0; CI 1.3-3.7) and associated with hemorrhagic transformation (22 vs. 11; OR 2.2; CI 1.0-5.0). The rate of stroke reoccurrence was not increased in patients treated with streptokinase alone (15 vs. 11; OR 1.4; CI 0.6-3.4). Conclusions: Stroke patients treated with streptokinase plus aspirin have an increased risk of early death, probably due to cerebral hemorrhagic complications. Whenever thrombolytics are chosen for acute stroke treatment, aspirin and other antiplatelet agents should be avoided. Copyright 2000 S. Karger AG, Basel

7. ASA Interactions

a) ASA with Enalapril

(1) Guazzi M
HEMODYNAMIC INTERACTION OF ASPIRIN WITH ENALAPRIL.
Circulation 1999 Dec 21;100(25):e141-2

(2) Nawarskas JJ, Townsend RR, Cirigliano MD, Spinler SA
EFFECT OF ASPIRIN ON BLOOD PRESSURE IN HYPERTENSIVE PATIENTS TAKING ENALAPRIL OR LOSARTAN.

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The ability of angiotensin converting enzyme (ACE) inhibitors to lower blood pressure may in part be due to the formation of vasodilatory prostaglandins. Inhibition of prostaglandin synthesis with aspirin may therefore theoretically attenuate the antihypertensive effect of ACE inhibitors. This trial studied the interaction between aspirin (ASA) and enalapril, an ACE inhibitor, and ASA and losartan, an angiotensin subtype 1 receptor antagonist. Seventeen essential hypertensive patients were studied, maintained on a stable dose of either enalapril (n = 7) or losartan (n = 10) monotherapy for > or =12 weeks before and throughout the study. Each patient received a 2-week course of placebo, 81 mg/day ASA, and 325 mg/day ASA, each treatment separated by a 2-week washout
period. Blood pressure (BP) and serum thromboxane B2 (TXB2) samples were obtained at the end of each treatment period. Placebo was compared with each dose of ASA for each group. In both the enalapril and losartan groups, mean, systolic, and diastolic BP were unchanged with the addition of ASA. Concentrations of TXB2 were suppressed to <10% in both groups with ASA. This study demonstrates that 81 to 325 mg/day ASA exerts no significant effect on BP in essential hypertensives taking enalapril or losartan.

(3) Guazzi M, Pontone G, Agostoni P

**ASPIRIN WORSENS EXERCISE PERFORMANCE AND PULMONARY GAS EXCHANGE IN PATIENTS WITH HEART FAILURE WHO ARE TAKING ANGIOTENSIN-CONVERTING ENZYME INHIBITORS.**

*Am Heart J* 1999 Aug;138(2 Pt 1):254-60

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BACKGROUND: Pulmonary function abnormalities participate in causing exercise disability in patients with congestive heart failure (CHF). Impaired pulmonary gas transfer is one of these abnormalities. Angiotensin-converting enzyme (ACE) inhibitors improve diffusion for carbon monoxide and exercise capacity, an effect that is seemingly mediated through prostaglandin activation because it is inhibited by cyclooxygenase blockade with aspirin. This suggests the possibility that aspirin may disturb the pulmonary function and exercise ability in CHF, at least in those patients who are taking ACE inhibitors. This study was aimed at probing this hypothesis.

METHODS: A dose of 325 mg aspirin was given daily for 8 weeks to 26 consecutive patients with primary dilated cardiomyopathy (New York Heart Association class II or III) whose current outpatient antifailure therapy included (group 1, 18 cases) or did not include (group 2, 8 cases) an ACE inhibitor in addition to digoxin and furosemide. During the study ACE inhibition was continued in group 1 by giving enalapril 20 mg daily. RESULTS: Tests repeated at 8 weeks proved that aspirin was deleterious in group 1. Compared with run-in, rest carbon dioxide, peak exercise oxygen uptake (peak VO₂), and tidal volume levels were diminished in this group; the ratio of exercise minute ventilation to carbon dioxide production (VE/VCO₂) was augmented and its variations were inversely related to those of peak VO₂. Similar results were not observed in group 2; however, once this part of the study was completed and enalapril was included in the current therapeutic regimen, an inhibitory effect of aspirin on carbon dioxide, peak VO₂, peak tidal volume, and VE/VCO₂ at 1 L levels became evident and was similar to that observed in group 1. CONCLUSIONS: Aspirin does not affect ventilation efficiency and peak VO₂ in patients with CHF who are on a regimen that does not include an ACE inhibitor, but it worsens the pulmonary diffusion for carbon monoxide, VO₂, and the ventilatory response to exercise in the presence of ACE inhibition. This may be relevant in patients with CHF from ischemic heart disease. Whether the same may be true of smaller aspirin doses was not investigated in this study.


(4) Teerlink JR, Massie BM

**THE INTERACTION OF ACE INHIBITORS AND ASPIRIN IN HEART FAILURE: TORN BETWEEN TWO LOVERS.**

*Am Heart J* 1999 Aug;138(2 Pt 1):193-7

Comment on: *Am Heart J* 1999 Aug;138(2 Pt 1):254-60

(5) Katz SD, Radin M, Graves T, Hauck C, Block A, LeJemtel TH

**EFFECT OF ASPIRIN AND IFEPROBAN ON SKELETAL MUSCLE BLOOD FLOW IN PATIENTS WITH CONGESTIVE HEART FAILURE TREATED WITH ENALAPRIL.**

**IFEPROBAN STUDY GROUP.**

*J Am Coll Cardiol* 1999 Jul;34(1):170-6

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OBJECTIVES: The purpose of this study was to determine the acute and chronic effects of cyclooxygenase inhibition with aspirin and thromboxane A2 receptor blockade with ifetroban on the chronic vasodilating effects of enalapril in the skeletal muscle circulation of patients with heart failure. BACKGROUND: Angiotensin-converting enzyme inhibition and antiplatelet therapy with aspirin independently reduce the risk for subsequent nonfatal coronary events in survivors of myocardial infarction. The safety of the combined administration of angiotensin-converting enzyme inhibitors and aspirin has been questioned due to their divergent effects on the vascular synthesis of vasodilating prostaglandins. METHODS: Forearm blood flow (ml/min/100 ml) at rest and during rhythmic handgrip exercise and after transient arterial occlusion was determined by strain gauge plethysmography before and 4 h and six weeks after combined administration of enalapril with either aspirin, ifetroban or placebo in a multicenter, double-blind, randomized trial of 62 patients with mild to moderate heart failure. RESULTS: Before randomization, forearm hemodynamics were similar in the three treatment groups except for increased resting forearm blood flow and decreased resting forearm vascular resistance in the aspirin group when compared with the placebo group. After combined administration of enalapril and study drug for 4 h and six weeks, changes from prerandomization values of mean arterial pressure, forearm blood flow and forearm vascular resistance at rest, during handgrip exercise and after transient arterial occlusion did not differ among the three treatment groups. CONCLUSIONS: These findings demonstrate that the vasodilating effects of enalapril in the skeletal muscle circulation of patients with heart failure are not critically dependent on prostaglandin pathways.

ASPIRIN AND MORTALITY IN PATIENTS TREATED WITH ANGIOTENSIN-CONVERTING ENZYME INHIBITORS: A COHORT STUDY OF 11,575 PATIENTS WITH CORONARY ARTERY DISEASE.

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OBJECTIVES: The purpose of this study was to investigate the significance of the possible negative interaction between aspirin and angiotensin-converting enzyme (ACE) inhibitors. BACKGROUND: Several provocative reports have recently suggested that aspirin is unsafe in patients with heart failure and has negative interaction with ACE inhibitors that might attenuate their beneficial effects upon survival. METHODS: We analyzed mortality data of 11,575 patients with coronary artery disease screened for the Bezafibrate Infarction Prevention trial. A total of 1,247 patients (11%) were treated with ACE inhibitors. Of them, 618 patients (50%) used aspirin. RESULTS: Five-year mortality was lower among patients on ACE inhibitors and aspirin than patients on ACE inhibitors without aspirin (19% vs. 27%; p < 0.001). After adjusting for confounders, treatment with aspirin and ACE inhibitors remained associated with lower mortality risk than using ACE inhibitors only (relative risk [RR] = 0.71; 95% confidence interval [CI] = 0.56 to 0.91). Subgroup analysis of 464 patients with congestive heart failure treated with ACE inhibitors revealed 221 patients (48%) on aspirin and 243 patients not on aspirin. Although clinical characteristics and therapy were similar, patients taking aspirin experienced lower mortality than patients who did not (24% vs. 34%; p = 0.001). After adjustment, treatment with aspirin was still associated with lower mortality (RR = 0.70; 95% CI = 0.49 to 0.99). CONCLUSIONS: Among coronary artery disease patients with and without heart failure who are treated with ACE inhibitors, the use of aspirin was associated with lower mortality than treatment without aspirin. Our findings contradict the claim that aspirin attenuates the beneficial effect of ACE inhibitors and supports its use in patients with coronary artery disease treated with ACE inhibitors.

(7) Song KH, Fedyk R, Hoover R
INTERACTION OF ACE INHIBITORS AND ASPIRIN IN PATIENTS WITH CONGESTIVE HEART FAILURE.

Roche Laboratories, Inc., Nutley, NJ 07110, USA.

The beneficial effects of aspirin and ACE inhibitors in CHF have been well established; however, the clinical relevance of the drug interaction between these agents remains controversial. The exact
mechanism of this interaction is not known, but the proposed theory involves the opposing effects of aspirin and ACE inhibitors on prostaglandins. The medical literature does not provide a clear picture of the clinical significance of concomitant aspirin and ACE inhibitor therapy. Some studies suggest that the dose of aspirin may influence the clinical relevance of this interaction. Short-term use of aspirin > or = 300 mg was found to attenuate enalapril's effect on hemodynamic variables. However, short-term use of low-dose aspirin (236 mg) produced no effect on blood pressure. Patients with CHF who require therapy with both aspirin and ACE inhibitors may want to consider low doses of aspirin with active monitoring of hemodynamic parameters. However, chronic aspirin therapy in patients with CHF on concomitant ACE inhibitors has not been adequately studied at this time. Data concerning a possible interaction between angiotensin II receptor antagonists and aspirin are not available. However, because angiotensin II receptor antagonists do not interfere with kininase II activity, it would seem unlikely that aspirin would interact similarly with an angiotensin II receptor antagonist. Further studies are needed to examine the exact mechanism of the interaction between aspirin and ACE inhibitors. These studies should focus on the effects of different doses of aspirin given concomitantly with ACE inhibitors in patients with CHF. Prospective, randomized studies are also needed to determine the long-term effects of aspirin and ACE inhibitor therapy on mortality in patients with CHF.

(8) Bays HE, Dujovne CA
DRUG INTERACTIONS OF LIPID-ALTERING DRUGS.

Louisville Metabolic and Atherosclerosis Research Center, Audubon Regional Medical Center, Kentucky, USA.

The use of lipid-altering drugs has been shown to reduce the progression of atherosclerotic lesions and reduce the risk of atherosclerotic events (such as myocardial infarction and stroke). In general, these lipid-altering drugs are well tolerated but there is the potential for drug interactions. For example, HMG-CoA reductase inhibitors may interact with macrolides, azalides, azole antifungals and cyclosporin. Resins (such as cholestyramine and colestipol) may impair the absorption of many concurrent medications. Fibrates have potential drug interactions with warfarin, furosemide (frusemide), oral hypoglycaemics and probenecid. Nicotinic acid (niacin) may have potential drug interactions with warfarin, furosemide (frusemide), oral hypoglycaemics and probenecid. Nicotinic acid (niacin) may have potential drug interactions with high dose aspirin (acetylsalicylic acid), uricosuric agents (such as sulfapyrazine) and alcohol (ethanol). Finally, probucol may have potential drug interactions with antidiabetic medicines, tricyclic antidepressants and phenothiazines. In addition, lipid-altering drugs, used in combination, may have the potential for drug interactions, enhancing some of the risks of adverse effects, such as myositis and hepatotoxicity. Therefore, in order to use lipid-altering drugs in the most effective, and safest manner, it is important for the clinician to have an understanding of the mechanisms of potential drug interactions, which drug interactions may theoretically occur, and specifically, which specific drug interactions have already been described.

B. Ticlopidine

A. Function and Fields of Use

1. Ticlopidine metabolic effects

a) Ticlopidine Antioxidant Properties

(1) Lapenna D, de Gioia S, Ciofani G, Bruno C, Porreca E, Pierdomenico SD, Cuccurullo F
ANTIOXIDANT PROPERTIES OF TICLOPIDINE ON HUMAN LOW DENSITY LP PROTEIN OXIDATION.

Dipartimento di Medicina e Scienze dell'Invecchiamento, Universita degli Studi G. d'Annunzio, Facolta di Medicina e Chirurgia, Chieti, Italy.

We found that ticlopidine, at therapeutically relevant concentrations (2.5-10 microM), but not aspirin nor salicylate, significantly counteracted copper-driven human LDL oxidation. Ticlopidine, at
5 and 10 microM, was also antioxidant on peroxyl radical-induced LDL oxidation; yet it was ineffectual on thiol and ascorbate oxidation mediated by peroxyl radicals themselves, suggesting that drug antioxidant capacity is somehow related to the lipoprotein nature of the oxidizable substrate, but not to radical scavenging. The drug could not indeed react with the stable free radical 1,1-diphenyl-2-pycrylhydrazyl, nor had apparent metal complexing-inactivating activity. Thus, ticlopidine has antioxidant effects on LDL oxidation, which, together with its anti-platelet activity, could confer peculiar antiatherogenic properties to the drug in vivo.

b) Ticlopidine Effect on the Platelet Inhibitory Capacity


**TICLOPIDINE ENHANCES THE PLATELET INHIBITORY CAPACITY OF ABCIXIMAB IN VITRO.**


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Ticlopidine and abciximab are two antiplatelet agents that are frequently administered during percutaneous coronary interventions. Although they have different mechanisms of action and pharmacological profiles, the two agents are often concomitantly used in complicated stent placements. The purpose of the study was to evaluate the effect of ticlopidine therapy on the capacity of abciximab to inhibit platelet aggregation, in vitro. Blood samples from 13 ticlopidine-treated stent placement patients and 8 patients undergoing PTCA who did not receive ticlopidine were obtained prior to, 12-36 hours and 7-10 days after initiating ticlopidine treatment. For each patient, the minimal ADP and the thrombin receptor activating peptide (TRAP) concentrations that elicited maximal platelet aggregation responses at baseline were used to measure the extent of platelet aggregation and the abciximab concentration that gave a 50% decrease in aggregation (IC(50)) for both agonists at the three time points. The ticlopidine group baseline and 12-36 hour mean ADP aggregation responses were equivalent, but decreased by 34% (P = 0.009) at 7-10 days. The control group ADP and TRAP, as well as the ticlopidine group TRAP aggregation responses, were equivalent at all time points. The ticlopidine group baseline and 12-36 hour abciximab IC(50) values for ADP were comparable (1.58 +/- 1.1 ng/mL vs. 1.23 +/- 0.5 ng/mL; P = 0.266), but decreased to 1.00 +/- 0.6 ng/mL (36%; P = 0.004) at 7-10 days. In contrast, the abciximab IC(50) for TRAP increased from 1.48 +/- 1.0 ng/mL to 1.85 +/- 1.1 ng/mL (25%; P = 0.033) at 12-36 hours, but returned to baseline at 7-10 days (1.40 +/- 0.8; P = 0.975). The control group IC(50) abciximab values for ADP and TRAP were comparable throughout the monitoring period. The results demonstrate that ticlopidine elicits subtle potentiation of the platelet-inhibitory capacity of abciximab to the agonist ADP, but not TRAP, at 1 week after initiation of treatment.

2. Ticlopidine and Nitric Oxide Generation

(1) de Lorgeril M, Bordet JC, Salen P, Durbin S, Defreyn G, Delaye J, Boissonnat P

**TICLOPIDINE INCREASES NITRIC OXIDE GENERATION IN HEART-TRANSPLANT RECIPIENTS: A POSSIBLE NOVEL PROPERTY OF TICLOPIDINE.**


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The objective of this study was to evaluate the effects of ticlopidine on the generation of eicosanoids and nitric oxide in heart-transplant recipients. In a randomized double-blind study, we studied the urinary excretion of the stable metabolites of thromboxane, prostacyclin, and nitric oxide before and after ticlopidine (250 mg/day). Platelet aggregation was significantly reduced in ticlopidine-treated patients [from 40.2 +/- 24.2% of maximal aggregation to 14.7 +/- 8.2% in response to adenosine diphosphate (ADP); p < 0.001] but not in the placebo group, confirming the efficacy of the drug with that dosage in these specific patients. The 24-h urinary excretion of prostacyclin metabolites was not modified by
ticlopidine (1,865 +/- 833 ng/24 h at day 14 and 1,664 +/- 425 ng/24 h at day 0), whereas the excretion of thromboxane B2 tended to increase in the ticlopidine group (from 3,854 +/- 1,163 ng/24 h at day 0 to 5,014 +/- 2,914 ng/24 h at day 14), although not significantly. The excretion of nitric oxide metabolites (although not different from that of healthy nonimmunosuppressed subjects) was significantly (p < 0.005) increased in the ticlopidine group (from 3,082 +/- 1,683 micromol/24 h at day 0 to 4,133 +/- 2,262 micromol/24 h at day 14), but not in controls. Thus ticlopidine does not reduce prostacyclin but increases the systemic generation of nitric oxide, both substances having major antiplatelet and vasodilator properties. Further studies are warranted to examine whether ticlopidine could reduce the incidence of thromboembolic complications in these patients and whether this possible novel property of ticlopidine is restricted to immunosuppressed heart-transplant recipients.

3. Ticlopidine in Cardiac Disease and Stent thrombosis Prevention

a) Aspirin and Ticlopidine for stented patients (FANTASTIC)


RANDOMIZED EVALUATION OF ANTICOAGULATION VERSUS ANTIPLATELET THERAPY AFTER CORONARY STENT IMPLANTATION IN HIGH-RISK PATIENTS: THE MULTICENTER ASPIRIN AND TICLOPIDINE TRIAL AFTER INTRACORONARY STENTING (MATTIS).

*Circulation* 1998 Nov 17;98(20):2126-2132

Department of Cardiology; La Tour Hospital, Geneve, Switzerland (P.U.); Hospital Clinico San Carlos, Madrid, Spain (C.M.); Klinikum der Johannes-Gutenberg-Universitat, Mainz, Germany (H.-J.R.); Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands (F.K.); Sahlgrensk Hospital, Gothenburg, Sweden (H.E.); Ospedale S. Maria della Misericordia, Udine, Italy (A.F.); Herzzentrum Bodensee, Kreuzlingen, Switzerland (M.P.); Sanofi Recherche, Paris, France (T.W.); and Sanofi, Paris, France (L.S.). Correspondence to Philip Urban, MD, Department of Cardiology, La Tour Hospital, 1 Ave JD Maillard, 1217 Meyrin-Geneva, Switzerland.

Background—Although the association of ticlopidine and aspirin has been shown to be superior to anti-vitamin K agents and aspirin after coronary stent implantation in low-risk patients, the latter combination has remained an unproven reference regimen for high-risk patients until recently.

Methods and Results—We randomized 350 high-risk patients within 6 hours after stent implantation to receive during 30 days either aspirin 250 mg and ticlopidine 500 mg/d (A+T group) or aspirin 250 mg/d and oral anticoagulation (A+OAC group) targeted at an international normalized ratio of 2.5 to 3. The primary composite end point was defined as the occurrence of cardiovascular death, myocardial infarction, or repeated revascularization at 30 days. Patients were eligible if (1) the stent(s) were implanted to treat abrupt closure after PTCA; (2) the angiographic result after implantation was suboptimal; (3) a long segment was stented (>45 mm and/or >/=3 stents); or (4) the largest balloon inflated in the stent had a nominal diameter of </=2.5 mm. The primary cardiac end point was reached for 10 patients (5.6%) in the A+T group and 19 (11%) in the A+OAC group (relative risk [RR], 1.9; 95% CI, 0.9 to 4.1; P=0.07). Major vascular and bleeding complications were less frequent in the A+T group (3 patients, 1.7%) than in the A+OAC group (12 patients, 6.9%) (RR, 4.1; 95% CI, 1.2 to 14.3; P=0.02).

Conclusions—High-risk patients should be treated with A+T rather than A+OAC after coronary stenting because the bleeding and vascular complications are significantly reduced and there is a marked trend suggesting a decrease in cardiac events.

(2) Jain SP, Ramee SR, White CJ, Mehra MR, Ventura HO, Zhang S, Jenkins JS, Collins TJ

CORONARY STENTING IN CARDIAC ALLOGRAFT VASCULOPATHY.


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OBJECTIVE: The purpose of this study was to evaluate acute angiographic success, in-hospital complications and long-term outcome after intracoronary stenting in patients with cardiac allograft vasculopathy. BACKGROUND: The application of conventional interventional modalities to treat discrete
lesions in patients with cardiac allograft vasculopathy is associated with higher procedural morbidity, mortality and higher restenosis compared to atherosclerotic coronary artery disease. Elective coronary stenting has been shown to lower restenosis rates and improve long-term outcome in selected patients with native coronary artery disease; however, its safety and efficacy in reducing restenosis in patients with cardiac allograft vasculopathy is unknown. METHODS: Ten patients with 19 discrete lesions in a major coronary artery without diffuse distal disease underwent intracoronary stenting using Palmaz-Schatz stents. The average stent size was 3.4 mm, and the stent/artery ratio was 0.99 +/- 0.07. Eight of ten (80%) patients received antiplatelet therapy (aspirin plus ticlopidine) only. RESULTS: Procedural success was 100% with no in-hospital stent thrombosis, Q-wave myocardial infarction or death. Minimal luminal diameter increased from 0.83 +/- 0.38 mm to 3.23 +/- 0.49 mm after stenting. Diameter stenosis decreased from 74.91 +/- 11.52% to 5.90 +/- 4.09% after stenting. Follow-up angiography was performed in 8 of 10 (80%) patients and 16 of 19 (84%) lesions. Target lesion revascularization was required in 2 of 10 (20%) patients and 3 of 16 (19%) lesions. Allograft survival was 7 of 10 (70%) at the end of 22 +/- 11 months follow-up. CONCLUSIONS: Intracoronary stenting can be performed safely with excellent angiographic success in selected patients with cardiac allograft vasculopathy. The restenosis rate appears to be low despite the aggressive nature of the disease. A multicenter study with a larger number of patients is required to assess its efficacy in reducing restenosis and improving allograft survival. 

(3) Stein PD, Dalen JE, Goldman S, Theroux P

ANTITHROMBOTIC THERAPY IN PATIENTS WITH SAPHENOUS VEIN AND INTERNAL MAMMARY ARTERY BYPASS GRAFTS.


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Aspirin (325 and 900 mg/d) is effective for a period of 1 year in reducing the frequency of saphenous vein bypass graft occlusion when begun 1 day before operation or on the day of operation. Aspirin in combination with dipyridamole is not more effective than aspirin alone in the prevention of saphenous vein graft occlusion. Bleeding is higher among patients treated with aspirin (325 mg/d) than among controls if aspirin is started 1 day before operation. Bleeding in one trial was greater than controls if aspirin (300 mg/d) was started the day of operation, and in one trial there was no difference when aspirin (325 mg/d) was started the day of operation. Ticlopidine (500 mg/d), started 2 days after operation, was effective in maintaining graft patency. Oral anticoagulants were inconsistent in the maintenance of saphenous vein graft patency. The continued use of aspirin for 2 additional years after an initial year of aspirin therapy for the prevention of saphenous vein bypass graft occlusion showed no additional long-term benefit on graft patency at the end of the third year. Antithrombotic agents given to patients with internal mammary artery bypass grafts showed no benefit in comparison to placebo because patency on placebo was high.


RANDOMIZED MULTICENTER COMPARISON OF CONVENTIONAL ANTICOAGULATION Versus Antiplatelet Therapy IN UNPLANNED AND ELECTIVE CORONARY STENTING : THE FULL ANTICOAGULATION Versus Aspirin AND Ticlopidine (FANTASTIC) STUDY.

Circulation 1998 Oct 20;98(16):1597-603

Background-Dual therapy with ticlopidine and aspirin has been shown to be as effective as or more effective than conventional anticoagulation in patients with an optimal result after implantation of intracoronary metallic stents. However, the safety and efficacy of antiplatelet therapy alone in an unselected population has not been evaluated. Methods-Patients were randomized to conventional anticoagulation or to treatment with antiplatelet therapy alone. Indications for stenting were classified as elective (decided before the procedure) or unplanned (to salvage failed angioplasty or to optimize the results of balloon angioplasty). After stenting, patients received aspirin and either ticlopidine or conventional anticoagulation (heparin or oral anticoagulant). The primary end point was the occurrence of bleeding or peripheral vascular complications; secondary end points were cardiac events (death, infarction, or stent occlusion) and duration of hospitalization. Results-In 13 centers, 236 patients were randomized to anticoagulation and 249 to antiplatelet therapy. Stenting was elective in
58% of patients and unplanned in 42%. **Stent implantation** was successfully achieved in 99% of patients. A primary end point occurred in 33 patients (13.5%) in the antiplatelet group and 48 patients (21%) in the anticoagulation group (odds ratio=0.6 [95% CI 0.36 to 0.98], P=0.03). Major cardiac-related events in electively stented patients were less common (odds ratio=0.23 [95% CI 0.05 to 0.91], P=0.01) in the antiplatelet group (3 of 123, 2.4%) than the anticoagulation group (11 of 111, 9.9%). Hospital stay was significantly shorter in the antiplatelet group (4.3+/−3.6 versus 6.4+/−3.7 days, P=0.0001). Conclusions—Antiplatelet therapy after coronary stenting significantly reduced rates of bleeding and subacute stent occlusion compared with conventional anticoagulation.

(5) Hsieh IC, Chang HJ, Chern MS, Hung KC, Lin FC, Wu D

**LATE CORONARY ARTERY STENTING IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION.**

*Am Heart J* 1998 Oct;136(4 Pt 1):606-12

Department of Medicine, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taipei, Taiwan, Republic of China.

**BACKGROUND:** The safety and efficacy of late coronary artery stenting of the infarct-related artery after **acute infarction** has not been evaluated previously. **METHODS AND RESULTS:** Coronary artery stenting was performed in 117 consecutive patients with **acute infarction** who were receiving ticlopidine/aspirin regimen **without coumarin**. There were 97 men and 18 women, aged 58+/−11 (mean +/− SD) years. A total of 136 Palmaz-Schatz stents were successfully implanted in 130 lesions 15+/−8 days after acute myocardial infarction (median 9 days) in 115 of 117 (98%) patients. The minimal luminal diameter (MLD) increased from 0.66+/−0.46 to 3.14+/−0.53 mm (P< .001), with an acute gain of 2.49+/−0.61 mm. One patient had **acute thrombosis** requiring further stenting and another patient received emergency bypass surgery. There was no subacute thrombosis or other complications. During a follow-up duration of 14+/−3 months, 2 patients had **angina pectoris** develop and 1 died suddenly. Sixty-two patients underwent a follow-up coronary angiography 195+/−36 days after stenting. Restenosis was noted in 8 patients (13%); the MLD was 2.19+/−0.73 mm, the late loss was 0.96+/−0.65 mm (P<.001), the loss index was 0.39+/−0.28, and the net gain was 1.56+/−0.79 mm (P<.001). The angiographic left ventricular ejection fraction increased from 47%+−12% to 55%+−12% (P< .001).

**CONCLUSIONS:** Late coronary stenting of the infarct-related artery in patients with acute myocardial infarction is a safe and effective late reperfusion therapy and may be beneficial to the patients.

(6) Bossavy JP, Thalamas C, Sagnard L, Barret A, Sakariassen K, Boneu B, Cadroy Y

**A DOUBLE-BLIND RANDOMIZED COMPARISON OF COMBINED ASPIRIN AND TICLOPIDINE THERAPY VERSUS ASPIRIN OR TICLOPIDINE ALONE ON EXPERIMENTAL ARTERIAL THROMBOGENESIS IN HUMANS.**

1998 Sep 1;92(5):1518-25

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No randomized study comparing the effect of **combined ticlopidine and aspirin therapy** versus each drug alone in reducing poststenting thrombotic complications has been performed. To compare these three antiplatelet regimens versus placebo, we conducted a double-blind randomized study using an ex vivo model of thrombosis. **Sixteen healthy male volunteers were assigned to receive for 8 days the following four regimens separated by a 1-month period:** aspirin 325 mg/d, ticlopidine 500 mg/d, aspirin 325 mg/d + ticlopidine 500 mg/d, and placebo. At the end of each treatment period, native nonanticoagulated blood was drawn directly from an antecubital vein over collagen- or **tissue factor (TF)-coated coverslips** positioned in a parallel-plate perfusion chamber at an arterial wall shear rate (2, 600 s−1 ) for 3 minutes. Thrombus, which formed on collagen in volunteers treated by placebo, were rich in platelets and poor in fibrin. As compared with placebo, **aspirin and ticlopidine alone** reduced **platelet thrombus formation** by only 29% and 15%, respectively (P > .2). In contrast, platelet thrombus formation was blocked by more than 90% in volunteers treated by aspirin + ticlopidine (P < .01 v placebo or each treatment alone). Furthermore, the effect of the drug combination therapy was significantly larger than the sum of the two active treatments (P < .05). **Thrombus,** which formed on TF-coated coverslips in volunteers treated by placebo, were rich in fibrin and platelets. Neither of the three antiplatelet treatments significantly inhibited fibrin deposition and platelet thrombus formation on this surface (P > .2). Thus, the present study shows that **combined aspirin and ticlopidine therapy** dramatically potentiates the
antithrombotic effect of each drug alone, but that the antithrombotic effect of the combined treatment depends on the nature of the thrombogenic surface.

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(7) Sharis PJ, Cannon CP, Loscalzo J
THE ANTIPLATELET EFFECTS OF TICLOPIDINE AND CLOPIDOGREL.
Ann Intern Med 1998 Sep 1;129(5):394-405

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Ticlopidine and clopidogrel achieve antiplatelet effects by inhibiting the binding of adenosine 5'-diphosphate to its platelet receptor. Ticlopidine was first shown to decrease major events compared with placebo or aspirin in patients with stroke or recent transient ischemic attack. Randomized studies in patients undergoing coronary artery stenting have shown that ticlopidine reduces the risk for subacute stent thrombosis compared with warfarin-based regimens. Smaller studies have also shown this drug to have benefit during follow-up in patients with unstable angina, peripheral arterial disease, saphenous vein coronary bypass grafts, and diabetic retinopathy. Clopidogrel was recently approved by the U.S. Food and Drug Administration for the reduction of ischemic events in patients with recent myocardial infarction, stroke, or peripheral arterial disease (incidence, 5.32% per year compared with 5.83% per year for aspirin; P = 0.043) with no added risk for neutropenia. The combination of clopidogrel and aspirin, as well as the utility of clopidogrel in other patient populations and in stenting, requires further study. Ticlopidine and clopidogrel seem to have beneficial effects compared with aspirin (the current standard) in a broad range of patients. These observations highlight the importance of antiplatelet therapy in cardiovascular disease.

(8) Facchini M, Muntwyler J, Schuiki E, Rickli H, Kiowski W, Amann FW
[INFLUENCE OF VARIOUS ANTITHROMBOTIC THERAPY METHODS ON THE INCIDENCE OF SUBACUTE CORONARY STENT OCCLUSIONS, HEMORRHAGIC COMPLICATIONS AND LENGTH OF HOSPITALIZATION].
[ARTICLE IN GERMAN]

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BACKGROUND: The clinical benefit of coronary stenting is reduced by the risk of thrombotic stent occlusion as well as hemorrhagic complications of intensive antithrombotic therapy. We compared the influence of different antithrombotic therapies on the incidence of post-interventional complications and in-hospital stay duration. METHODS: After successful placement of a coronary stent, 334 consecutive patients were given different antithrombotic treatments in addition to aspirin 100 mg/d indefinitely: (1) phenprocoumon for 3 months (n = 47), (2) low molecular weight heparin 2 x 100 U/kg/d s.c. for 4 weeks (n = 90), (3) ticlopidine 2 x 250 mg/d and low molecular weight heparin 2 x 100 U/kg/d s.c. for 4 weeks (n = 72) and (4) ticlopidine 2 x 250 mg/d for 4 weeks (n = 125). RESULTS: Major events were subacute stent thrombosis in 17 patients (5%), and severe hemorrhagic complication in 20 patients (5.9%). The incidence of subacute stent thrombosis in groups 1 to 4 was 10.6%, 11%, 1.4% and 0.8% respectively. The use of ticlopidine was associated with a significant lowering of stent occlusions in univariate and multivariate analysis (p = 0.0013). Additional univariate predictors were stent placement as a "bail-out" procedure (p = 0.033) and in patients with acute coronary syndrome (p = 0.049). Anticoagulant therapy was associated with a higher incidence of severe hemorrhagic complications (p < 0.01) and a prolonged in-hospital stay (p = 0.01). CONCLUSIONS: These results confirm that antithrombotic therapy with aspirin and ticlopidine combines low rates of subacute stent occlusion and hemorrhagic complications. Treatment with phenprocoumon and low molecular weight heparin does not improve the rate of subacute stent occlusion but increases hemorrhagic complications. Very low rates of stent occlusion permit short in-hospital stays with concomitant reduction in cost.
INTRACORONARY STENT IMPLANTATION WITHOUT ULTRASOUND GUIDANCE AND WITH REPLACEMENT OF CONVENTIONAL ANTICOAGULATION BY ANTIPLATELET THERAPY. 30-DAY CLINICAL OUTCOME OF THE FRENCH MULTICENTER REGISTRY.

Circulation 1996 Oct 1;94(7):1519-27

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BACKGROUND: Stenting reduces both acute complications of coronary angioplasty and restenosis rates but increases subacute thrombosis rates and hemorrhagic complications when used with coumadin anticoagulation. METHODS AND RESULTS: To simplify postcoronary stenting treatment and to reduce these drawbacks, we evaluated the 1-month outcome of a prospective registry of 2900 patients in whom successful coronary artery stenting was performed without coumadin anticoagulation. Patients received 100 mg/d aspirin and 250 mg/d ticlopidine for 1 month. Low-molecular-weight heparin (LMWH) treatment was progressively reduced in four consecutive stages, from 1-month treatment to none. Event-free outcome at 1 month was achieved in 2816 patients (97.1%). Major stent-related cardiac events were subacute closure in 51 patients (1.8%), including death in 12 (0.5%), acute myocardial infarction in 17 (0.6%), and coronary artery bypass graft surgery in 9 (0.3%). Stent thrombosis was more frequent with balloon size of < 3.0 mm (< or = 2.5 mm, 10%; 3.0 mm, 2.3%; > or = 3.5 mm, 1.0%; P < .001), bail-out situations (6.67% versus 1.38%, P < .001), and patients with unstable angina or acute myocardial infarction (2.2% versus 1.12%, P = .02). Bleeding complications that required transfusion, surgical repair, or both occurred in 55 patients (1.9%). Bleeding complications were related to female gender (4.0% versus 1.51%, P < .001), duration of LMWH treatment (3.83% in phase II/III versus 0.69% in phase IV/V, P < .001), sheath size (6F, 0.52%; 7F, 1.04%; > or = 8F, 4.23%; P < .001), bail-out situations (4.76% versus 1.67%, P < .01), and saphenous graft stenting (4.38% versus 1.75%, P = .04). CONCLUSIONS: These results suggest that poststenting treatment by ticlopidine/aspirin is an effective alternative to coumadin anticoagulation, achieving low rates of subacute closure and bleeding complications. LMWH treatment does not improve subacute reocclusion rates but increases bleeding complications. Furthermore, as bleeding complications were independently related to sheath size, we suggest that stenting with 6F guiding catheters may prevent local complications. Furthermore, the ticlopidine/aspirin combination allows a low-cost stenting strategy without ultrasound assessment of stent deployment and permits short inhospital stay.

b) Antiplatelet Therapy in Elderly Stent Patients

Tisdale JE

ANTIPATELET THERAPY IN CORONARY ARTERY DISEASE: REVIEW AND UPDATE OF EFFICACY STUDIES.


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The mechanisms of action of currently available and newer antiplatelet agents and evidence of the efficacy of antiplatelet agents for primary and secondary prevention of coronary artery disease are reviewed. Available data do not support the widespread use of aspirin for primary prevention of cardiovascular disease. Patients over the age of 50 years with at least one additional risk factor for coronary artery disease may benefit, although possibly at an increased risk of hemorrhagic stroke. Aspirin is recommended for secondary prevention of vascular disease in patients with stable or unstable angina, clinical or laboratory evidence of coronary artery disease, history of myocardial infarction, or history of stroke or transient ischemic attack. There are no data supporting a role for dipyridamole for primary or secondary prevention of ischemic heart disease. Abciximab has been shown to reduce the risk of cardiovascular complications at 30 days after percutaneous transluminal coronary angioplasty in patients with refractory unstable angina. Studies with other glycoprotein IIb/IIIa-receptor antagonists, including eptifibatide, tirofiban, and lamifiban, have yielded promising results.
Ticlopidine may be used for secondary prevention of cardiovascular disease in patients with unstable angina who are allergic to or intolerant of aspirin. Clopidogrel has been shown to be safe and effective for secondary prevention of vascular events. Aspirin has a role in secondary prevention of coronary artery disease; among patients who are allergic to or intolerant of aspirin, ticlopidine has a role in patients with unstable angina and clopidogrel has a potential role in patients with ischemic heart or vascular disease.

(2) Lefevre T, Morice MC, Eltchaninoff H, Chabrillat Y, Amor M, Juliard JM, Gommeaux A, Cattan S, Dumas P, Benveniste E
ONE-MONTH RESULTS OF CORONARY STENTING IN PATIENTS > OR = 75 YEARS OF AGE.
Am J Cardiol 1998 Jul 1;82(1):17-21

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Coronary artery bypass operations are associated with increased morbidity and mortality in the elderly. Similarly, it has been shown that coronary angioplasty is associated with a higher risk of complications in the elderly than in younger patients. The purpose of this study was to evaluate the 1-month outcome of elderly patients (>75 years old) who were included in the Stenting without Coumadin French Registry. From December 1992 to March 1995, 2,900 patients (mean age 61 +/- 11 years) were included in this registry. All patients were treated with ticlopidine (250 to 500 mg/day) for 1 month from the day of percutaneous transluminal angioplasty, aspirin (100 to 250 mg/day) for >6 months, and low-molecular-weight heparin (antiXa 0.5 to 1 IU/ml) for 1 month in phase II, 15 days in phase III, and 7 days in phase IV. No heparin was given in phase V. The study group included 233 patients (8.0%) > 75 years old (mean age 79 +/- 4), 44 (18%) of whom were women. All patients underwent dilatation of a native coronary vessel. One hundred seventeen had unstable angina (50.2%), 20 had postmyocardial infarction ischemia (8.6%), and 6 had acute myocardial infarction (2.6%).

Indications for stenting were de novo lesion in 63 patients (27.0%), restenosis in 38 (16.3%), suboptimal result in 48 (20.6%), nonocclusive dissection in 56 (24.0%), and occlusive dissection in 28 (12.0%), respectively. Stented coronary arteries were the left anterior descending in 109 (46.8%), the right in 80 (34.3%), the left circumflex in 40 (17.2%), and the left main in 4 (1.7%). Palmaz-Schatz stents were used in 228 patients (82.0%), AVE microstents in 38 (13.7%), and other stents in 12 (4.3%). More than 1 stent was used in 48 patients (17.3%). The mean diameter of the balloon used for stenting was 3.31 +/- 0.38 mm and maximal inflation pressure was 12.2 +/- 2.9 atm. At one-month follow-up, vascular complications occurred in 5 patients, requiring surgery in 2 (1.3%), acute closure occurred in 1 (0.4%), subacute closure in 3 (1.3%), emergency or planned coronary artery bypass graft surgery in none, acute myocardial infarction in 4 (1.7%), stroke in 1 (0.4%), and death in 8 (3.4%). The composite end point of a major cardiac event was observed in 13 cases (5.6%). Coronary stenting using ticlopidine and aspirin appears to be a particularly safe approach in this high-risk subset.

c) Ticlopidine and Cilostazol for Coronary Stenting
(1) Yoon Y, Shim WH, Lee DH, Pyun WB, Kim IJ, Jang Y, Cho SY
USEFULNESS OF CILOSTAZOL VERSUS TICLOPIDINE IN CORONARY ARTERY STENTING.
Am J Cardiol 1999 Dec 15;84(12):1375-80

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A combination of ticlopidine and aspirin has been accepted as the standard antithrombotic regimen after coronary stenting. However, ticlopidine poses serious side effects such as neutropenia or thrombocytopenia. Cilostazol, a cyclic adenosine monophosphate phosphodiesterase inhibitor, is a novel antiplatelet agent with vasodilatory properties. We compared the efficacy and safety of cilostazol plus aspirin (C+A) with ticlopidine plus aspirin (T+A) in elective coronary stenting. Three hundred patients were randomly assigned to receive C+A or T+A 2 days before stenting. The primary end point was a composite of angiographic stent thrombosis, or major cardiac events (death, myocardial infarction, bypass surgery, repeat intervention) at 30 days. The secondary end points were bleeding vascular complications, neutropenia, thrombocytopenia, or side effects requiring discontinuation of the drugs at 30 days. The primary end point was reached in 1.4% in the C+A
group and 2.0% in the T+A group (p = 1.0). The rate of bleeding vascular complications was 1.4% in the C+A group and 2.0% in the T+A group (p = 1.0). The rate of drug-related side effects was not statistically different between the 2 groups but slightly higher in the T+A group than in the C+A group (2.7% vs 0.7%, p = 0.37). However, neutropenia was seen in 2 patients only in the T+A group. As a poststenting antithrombotic, C+A is as effective as T+A in preventing major cardiac events including stent thrombosis, and safer in that it does not cause neutropenia despite the fact that there is no statistical difference in the incidence of adverse effects and complications.

4. Ticlopidine in AV Fistula Patency


EFFECTS OF TICLOPIDINE IN AV-FISTULA SURGERY IN UREMIA. FISTULA STUDY GROUP.


Department of Internal Medicine, Eskilstuna Central Hospital, Sweden.

Two hundred and fifty-eight patients with uremia who were offered surgery for placement of an arteriovenous fistula for hemodialysis were recruited in nine regional dialysis centers. The patients were randomized to receive the platelet aggregation inhibitory compound ticlopidine, 250 mg b.d., or matching placebo. Study medication was targeted at 7, minimum 3, days before scheduled surgery and continued for 28 days after surgery. The overall rate of occlusion was 41/260 evaluable operations (16%), 25/131 (19%) in the placebo group and 16/129 (12%) in the ticlopidine group. The risk of early occlusion was a non-significant 35% lower in the ticlopidine group. Limited risk factor analysis did not clearly identify any subgroup other than females at greater risk of early thrombosis nor any subgroup deriving particular benefit from ticlopidine treatment.

5. Ticlopidine in Ophthalmic Surgery

(1) Saitoh AK, Saitoh A, Taniguchi H, Amemiya T

ANTICOAGULATION THERAPY AND OCULAR SURGERY.


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BACKGROUND AND OBJECTIVE: It is not rare for patients receiving anticoagulant therapy to undergo ocular surgery; however, there are no clear guidelines with reference to the operative management of the eye. This study examines the complications in patients receiving anticoagulant therapy who undergo ocular operations and suggests a management regimen for these patients. RESULTS: Ticlopidine hydrochloride, an antiplatelet drug, was administered to 24 patients. Warfarin sodium was administered to 8 patients, heparin was administered to 8 patients, and other anticoagulants were administered to 20 patients. There were no significant differences in complications between the groups that stopped or reduced anticoagulant therapy and those that did not, but speech disturbance due to thrombotic complication occurred in 1 of 10 patients in whom ticlopidine hydrochloride was stopped or reduced. Hemorrhagic complications occurred in 50% of those who continued ticlopidine hydrochloride, but in none of those who discontinued it (P = .019). There was a significant difference in hemorrhagic complications after cataract surgery between the phacoemulsification, aspiration, and intraocular lens implantation (PEA + IOL) and the planned extracapsular cataract extraction and intraocular lens implantation (PECCE + IOL) groups that continued the drug (P = .0011). No patients showed visual acuity reduction due to hemorrhagic complications. CONCLUSIONS: To avoid life-threatening systemic complications, one need not always stop anticoagulant therapy before performing only cataract surgery. Cataract surgery in patients receiving ticlopidine hydrochloride should be performed with PEA + IOL via a small sclerocorneal or a corneal incision. In cataract surgery for patients receiving anticoagulant therapy, hemorrhagic complications are more frequent than in patients not receiving anticoagulant therapy.

6. Ticlopidine in Cerebrovascular Disease and Stroke Prevention
(1) Harbison JW

**Clinical Considerations in Selecting Antiplatelet Therapy in Cerebrovascular Disease.**


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Effective antiplatelet drugs—**aspirin**, **ticlopidine**, **dipyridamole**, and **clopidogrel**—are reviewed. **Aspirin** has remained the pharmacologic foundation of stroke prevention, primarily because of its low cost. It has been shown to provide a 22% relative risk reduction of stroke in high-risk patients. Its principal adverse effect is **gastrotoxicity**. **Ticlopidine** has been widely used in patients with a high risk of stroke who are sensitive to aspirin or in whom aspirin has failed. It has been associated with a median reduction in adenosine diphosphate-induced platelet aggregation of 70% in about 8-11 days. **Ticlopidine** has been shown to be superior to aspirin at three years in preventing stroke. The principal adverse effects are **diarrhea and rash**; there has been a **2.4% occurrence of neutropenia**. In a trial comparing aspirin, dipyridamole, and a combination of the two, the risk of stroke was **18% lower with aspirin**, **16% lower with dipyridamole**, and **37% lower with combination therapy** compared with placebo. The adverse-effect profile of dipyridamole has **proved to be less problematic than that of aspirin or ticlopidine**. In a trial comparing **clopidogrel** with aspirin, patients receiving **clopidogrel** had an annual **5.32% risk of ischemic stroke**, myocardial infarction, or vascular death compared with 5.83% for patients receiving aspirin. **Clopidogrel** has been associated with a small occurrence of rash and diarrhea, and gastrointestinal intolerance and hemorrhage were less frequent with clopidogrel than with aspirin. **Both aspirin and clopidogrel are associated with a low occurrence of neutropenia.** **Aspirin**, **ticlopidine**, **dipyridamole**, and **clopidogrel** have earned a role in stroke prevention; the different adverse-effect profiles of the drugs will influence the choice of agent.

(2) Schellinger PD, Orberk E, Hacke W

**[Antithrombotic Therapy After Cerebral Ischemia].**

*Fortschr Neurol Psychiatr* 1997 Sep;65(9):425-34

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Following cerebral ischaemia a recurrent stroke must be avoided in most patients by means of antithrombotic agents. Based on the results reviewed here of new therapy studies, we discuss the presently available antithrombotic treatment options for prophylaxis in ischaemic stroke. TASS (Ticlopidine Aspirin Stroke Study) and CATS (Canadian American Ticlopidine Study) are two multicentre studies investigating the effect of ticlopidine, a new antiplatelet agent of the thienopyridine family, compared to acetylsalicylic acid (ASA) respectively placebo, in the secondary prophylaxis of ischaemic stroke. A significant relative risk reduction of ticlopidine against ASA (21%) and against placebo (28.1%) was shown. CAPRIE (Clopidogrel vs. Aspirin in Patients with Risk of Ischemic Events) evaluated clopidogrel and ASA in the secondary prophylaxie of stroke, myocardial infarction and peripheral vascular occlusive disease. **Clopidogrel** has been shown to be as effective as ticlopidine compared to ASA in the secondary prevention of vascular disease but had the advantage of a far less severe side effect profile as ticlopidine. ESPS 2 (2nd European Stroke Prevention Study) compared dipyridamole and ASA alone and in combination against placebo in stroke prevention. The combination of agents showed a 24.4% relative risk reduction to suffer ischaemic stroke as opposed to placebo. The ranking of heparin and heparinoids in the secondary prevention of ischaemic stroke has not been completely established but seems to diminish according to recently published data from three major trials. The American TOAST study (Trial of Org 10172 in Acute Stroke Treatment) failed to prove any advantage of intravenous Orgaran compared to placebo. In IST (International Stroke Trial) and CAST (Chinese Acute Stroke Trial) the benefits of heparin are invalided by a higher bleeding rate of patients on intravenous heparin therapy. Furthermore, the results of IST have to be judged critically because of significant methodical inadequacies. When applying antithrombotic agents, therapeutic effect and presumed better outcome should be weighed against the risk of associated bleedings. The indication for an antithrombotic treatment should be reevaluated in regular control examinations and the possibility of a less aggressive treatment should be considered.
(3) Dewarrat A, Bogousslavsky J

**[ANTITHROMBOTIC AGENTS AND PREVENTION OF CEREBROVASCULAR ACCIDENTS]. [ARTICLE IN FRENCH]**


Prevention remains a major therapeutic approach of stroke. Inhibitors of platelet aggregation are the treatment of choice in the secondary prevention of an arterial embolism stroke. **Aspirin (200-300 mg/d)** is the most commonly used drug, **ticlopidine (500 mg/d)** is advised if aspirin is contraindicated or if a recurrent stroke of arterial embolism origin occurs in spite of treatment with aspirin. We are waiting with interest for the results of the clinical trial of clopidogrel, a derivative of ticlopidine. Till now, no studies have proved the benefit of antiplatelet treatment in the primary prevention of stroke. In non **rheumatic atrial fibrillation**, the unanimous results of recent studies confirmed the benefit of oral anticoagulation in the primary and secondary prevention of stroke. Although **coumadin is superior to aspirin in non rheumatic atrial fibrillation**, **aspirin is an efficient alternative when anticoagulation is contraindicated.**

7. **Ticlopidine Interactions with Enalapril**


**ACUTE HEMODYNAMIC INTERACTION OF ASPIRIN AND TICLOPIDINE WITH ENALAPRIL: RESULTS OF A DOUBLE-BLIND, RANDOMIZED COMPARATIVE TRIAL.**


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**BACKGROUND:** Coprescription of aspirin and ACE inhibitors is frequent in heart failure caused by coronary artery disease. **Negative interaction** between aspirin and enalapril has been reported, presumably through inhibition by aspirin of ACE inhibitor-induced prostaglandin synthesis. **Ticlopidine** is a potent antiplatelet agent without interaction with prostaglandin synthesis.

**METHODS AND RESULTS:** The objective of this study was to compare the influence of a coadministration of ticlopidine or aspirin on the hemodynamic effects of an ACE inhibitor (enalapril) in patients with chronic heart failure. Twenty patients with severe heart failure were enrolled in a double-blind comparative trial and allocated to ticlopidine (500 mg daily, 12 patients) or aspirin (325 mg daily, 8 patients). Hemodynamic evaluation was performed after 7 days of treatment, every hour for 4 hours after an oral administration of 10 mg of enalapril. **Significant reductions in systemic vascular resistance** were observed in the ticlopidine group, in contrast to no significant decrease in the aspirin group. A significant (P=0.03) time-by-treatment interaction indicated significant aspirin-enalapril drug interaction. **Total pulmonary resistance decreased significantly in both groups, with no difference between patients assigned to aspirin or ticlopidine.** **CONCLUSIONS:** Enalapril reduced systemic vascular resistance more effectively when given in combination with ticlopidine than with aspirin. In contrast, the reduction in total pulmonary resistance is similar when enalapril is administered in combination with aspirin or ticlopidine. Negative aspirin-enalapril interaction on prostaglandin synthesis presumably alters vasodilatation in systemic vessels, whereas prostaglandin-independent actions of ACE inhibition such as pulmonary arterial vasodilatation are maintained.

8. **Ticlopidine Platelet effect single or in combinations**

(1) Farrell TP, Hayes KB, Sobel BE, Schneider DJ

**THE LACK OF AUGMENTATION BY ASPIRIN OF INHIBITION OF PLATELET REACTIVITY BY TICLOPIDINE.**

*Am J Cardiol* 1999 Mar 1;83(5):770-4

Department of Medicine, The University of Vermont College of Medicine, Burlington, USA.

A decreased threshold for **platelet activation** apparently contributes to the **risk of cardiovascular events**, such as **acute myocardial infarction**. To evaluate the impact of specific agents, we
characterized platelet reactivity in 9 healthy subjects before and after 5 days of ingestion of 4 commonly prescribed regimens, 81 mg of aspirin daily, 325 mg of aspirin daily, ticlopidine 250 mg twice daily, and ticlopidine plus 325 mg of aspirin daily. Platelet reactivity was assessed with (1) aggregometry induced by 4 microM adenosine diphospate (ADP) and collagen (0.19 mg/ml) and performed in platelet-rich plasma; and (2) flow cytometric determination of ADP-induced (0.2, 0.8, and 1.5 microM) P-selectin expression in whole blood. Because anticoagulants alter platelet reactivity, results were obtained with 3 anticoagulants, citrate, enoxaparin, or corn trypsin inhibitor (CTI, a specific inhibitor of factor XIIa without effect on other coagulation factors). Ingestion of aspirin did not alter platelet activation as assessed with flow cytometry. Inhibition of the second phase of aggregation was seen with ADP-induced aggregation in platelet-rich plasma anticoagulated with citrate but not enoxaparin or CTI. Ingestion of ticlopidine led to inhibition of ADP-induced aggregation and P-selectin expression. Inhibition of platelet reactivity after the combination of aspirin and ticlopidine did not differ from ticlopidine alone. Marked interindividual variability in platelet reactivity was seen after ingestion of ticlopidine. The results indicate that assessment of effects of specific pharmacologic regimens with accurate and readily available assays of platelet reactivity may facilitate effective prophylaxis and treatment of high-risk subjects with antiplatelet regimens designed to optimally diminish platelet reactivity.

B. Ticlopidine Complications

1. Ticlopidine Induced Hepatic Complications!


   Gastroenterologische Abteilung, Stadtspital Waid, Zurich.

   We report a case of ticlopidine-induced cholestatic hepatitis. CASE SUMMARY: An 82-year-old man suffered a myocardial infarction in February 1998. Because of persistent angina pectoris a coronary stent was implanted in May 1998. At this time medication with 1 x 250 mg ticlopidine was started in addition to the preexistent medication of aspirin 1 x 100 per day, metoprolol fumarate 1 x 95 mg per day and isosorbide dinitrate 1 x 100 mg per day. Three weeks after starting ticlopidine the patient complained of itching, and on day 28 painless jaundice developed. At this time, the serum activities of alkaline phosphatase (923 U/l), gamma-GT (823 U/l) and total bilirubin concentration (129 mumol/l) were markedly elevated, whereas the activities of the transaminases (AST 131 U/l, ALT 194 U/l) were slightly increased. An extra- or intrahepatic biliary obstruction was ruled out, and there were no signs of a toxic, infectious or immunological cause for the hepatic injury. Liver biopsy showed centro-acinar cholestasis. After drug discontinuation the itching stopped after 4 weeks and jaundice disappeared after 2 weeks. Eight months after the onset of symptoms, the activities of alkaline phosphatase (226 U/l) and gamma-GT (213 U/l) were still elevated but the patient was asymptomatic. CONCLUSIONS: Ticlopidine-induced mild serum liver enzyme elevations have been observed in some studies (incidence 1-2%). The incidence of severe hepatitis has been estimated at 0.0013%. Only a few cases (in approximately 20 patients receiving ticlopidine) of a severe cholestatic pattern of injury have been reported. In all cases the jaundice resolved and serum liver enzyme concentrations normalised over a period of months. Characteristically, liver biopsies demonstrated centro-acinar cholestasis. Monitoring of serum liver enzyme concentrations is not recommended. When itching or jaundice occur in a patient taking ticlopidine, the possibility of toxic liver damage should be taken into account.

   (2) Zeolla MM, Carson JJ. SUCCESSFUL USE OF CLOPIDOGREL FOR CEREBROVASCULAR ACCIDENT IN A PATIENT WITH SUSPECTED TICLOPIDINE-INDUCED HEPATOTOXICITY. Ann Pharmacother 1999 Sep;33(9):939-41

   Albany College of Pharmacy, NY, USA.

   OBJECTIVE: To report a case of successful clopidogrel use in a patient who developed suspected ticlopidine-induced hepatotoxicity during therapy for a cerebrovascular accident. CASE REPORT:
A 79-year-old white woman with a history of hypertension, type 2 diabetes, Alzheimer disease, and coronary artery disease started receiving ticlopidine 250 mg twice daily three days after hospital admission for a cerebrovascular accident. Medications prior to admission included quinapril, furosemide, insulin, atorvastatin, conjugated estrogen, medroxyprogesterone, donepezil, and vitamin E. The estrogen, medroxyprogesterone, and donepezil were discontinued on admission. Laboratory tests on admission revealed that total bilirubin, alkaline phosphatase, and aspartate aminotransferase (AST) were within normal limits. On day 39 of hospitalization, laboratory tests showed marked increases in alkaline phosphatase, AST, alanine aminotransferase, gamma-glutamyltransferase, and 5’ nucleotidase. Physical examination revealed no signs of jaundice or hepatomegaly, and laboratory tests for viral hepatitis were negative. A presumptive diagnosis of ticlopidine-induced hepatotoxicity was made and ticlopidine was discontinued. The following day, clopidogrel 75 mg/d was initiated. Liver function tests returned to baseline over the following four months with ongoing clopidogrel therapy.

DISCUSSION: Ticlopidine-induced hepatotoxicity is well documented in the literature. In the present case, clopidogrel, a structurally similar thienopyridine, was substituted for ticlopidine following the development of presumptive ticlopidine-induced hepatotoxicity. Serum liver enzyme concentrations returned to baseline with continued clopidogrel therapy, suggesting that clopidogrel is a suitable alternative in patients who develop ticlopidine-induced hepatotoxicity.

CONCLUSIONS: Clopidogrel may be a suitable alternative for patients who develop ticlopidine-induced hepatotoxicity.

(3) Kubin CJ, Sherman O, Hussain KB, Feinman L
DELAYED-ONSET TICLOPIDINE-INDUCED CHOLESTATIC JAUNDICE.
Pharmacotherapy 1999 Aug;19(8):1006-10

Department of Pharmacy, Bronx VA Medical Center, New York 10468, USA.
An 86-year-old man experienced a rash approximately 2 weeks after starting ticlopidine therapy, necessitating discontinuation of the drug. About 1 month later, despite discontinuation, he developed jaundice and liver test abnormalities. These resolved gradually over the next few months. Based on case reports and the drug’s pharmacokinetic profile, a high index of suspicion for ticlopidine-induced jaundice is prudent in patients with recent exposure to the agent who have evidence of liver damage.

(4) Ruiz-Martinez J, Lopez De Munain A, Marti Masso JF
HEPATOTOXICITY DUE TO TICLOPIDINE.

(5) Ceylan C, Kirimli O, Akarsu M, Undar B, Guneri S
EARLY TICLOPIDINE-INDUCED HEPATIC DYSFUNCTION, DERMATITIS AND IRREVERSIBLE APLASTIC ANEMIA AFTER CORONARY ARTERY STENTING.

(6) Iqbal M, Goenka P, Young MF, Thomas E, Borthwick TR
TICLOPIDINE-INDUCED CHOLESTATIC HEPATITIS: REPORT OF THREE CASES AND REVIEW OF THE LITERATURE.

Department of Internal Medicine, East Tennessee State University, James H. Quillen College of Medicine, Johnson City Medical Center, USA.

(7) Grieco A, Vecchio FM, Greco AV, Gasbarrini G
CHOLESTATIC HEPATITIS DUE TO TICLOPIDINE: CLINICAL AND HISTOLOGICAL RECOVERY AFTER DRUG WITHDRAWAL. CASE REPORT AND REVIEW OF THE LITERATURE.

Istituto di Medicina Interna e Geriatria, Universita Cattolica Sacro Cuore, Rome, Italy.
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A 72-year-old housewife presented with clinical and laboratory signs of acute cholestatic hepatitis. Symptoms had appeared 6 months after she was started on ticlopidine 250 mg/day. Infectious aetiologies were excluded by serology and there was no history of alcohol abuse or use of other drugs. Clinical findings were confirmed by liver biopsy. The drug was discontinued and symptoms gradually subsided. A second biopsy obtained during this phase documented complete resolution of the hepatic damage. A review of the literature shows that the late onset of hepatic toxicity in this case is unique and this is the first report to include histological documentation during the acute phase and after recovery.

[GRANULOMATOUS HEPATITIS AND TICLOPIDINE]. [ARTICLE IN FRENCH]
Therapie 1997 Nov-Dec;52(6):610-1

2. Ticlopidine induced BM Adverse Effects

(1) Taher A, Ammash Z, Dabajah B, Nasrallah A, Mourad FH
TICLOPIDINE-INDUCED APLASTIC ANEMIA AND QUICK RECOVERY WITH G-CSF: CASE REPORT AND LITERATURE REVIEW.
Am J Hematol 2000 Feb;63(2):90-93
Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon.
We report here a case of ticlopidine-induced aplastic anemia that responded to G-CSF and review the literature. An 83-year-old woman was started on ticlopidine for coronary artery disease after an episode of upper gastrointestinal bleeding secondary to aspirin. She developed aplastic anemia seven weeks after initiation of ticlopidine. She was hospitalised and received empiric antibiotic therapy and granulocyte colony stimulating factor (G-CSF). Her bone marrow started to recover quickly, and white blood cell and platelet counts returned to normal within three weeks. A review of medical literature revealed 20 similar cases of ticlopidine-induced aplastic anemia resulting in death in seven cases. G-CSF has been used previously with variable success. Ticlopidine is associated with serious, sometimes fatal hematological side effects. This risk should be seriously taken into consideration when prescribing ticlopidine. G-CSF may be helpful in the treatment of ticlopidine-induced aplastic anemia. Copyright 2000 Wiley-Liss, Inc.

(2)

(3) Redlich K, Parschalk B, Ehringer H, Minar E
TICLOPIDINE INDUCED PROLONGED LEUCOPENIA IN A PATIENT WITH IMMUNOCYTOMA AND CHRONIC HEPATITIS C.
Vasa 1999 Nov;28(4):301-3
Department of Medical Angiology, Vienna General Hospital, University of Vienna Medical School, Austria.
Ticlopidine is increasingly used in the secondary prophylaxis in patients with arterial occlusive diseases. Neutropenia is a well known side effect of this drug. We report a case of a 73 year old woman who was admitted because of severe prolonged ticlopidine induced leucopenia. The past medical history included an immunocytoma of the IgM-kappa type diagnosed seven years ago with less than 10% infiltration of the bone marrow and a chronic hepatitis C. On admission the white cell count was 1000/microL. Ticlopidine was stopped. The white cell count did not increase within one week, thus filgastrim was applied on two consecutive days. The leucocyte count promptly increased to 6000/microL but consecutively dropped within the next fortnight again to levels below 500/microL forcing daily filgastrim application for another 9 days. Four months after the initiation of the therapy with filgastrim the patient had a white cell count of 4300/microL. We therefore conclude that in patients with a history of potentially bone marrow suppressing diseases the use of ticlopidine has to be carefully weighed against possible myelosuppressive effects.
Aplastic anemia is a rare side-effect associated with ticlopidine therapy. We report two cases of severe aplastic anemia developed after the use of ticlopidine. A 51-year-old woman took ticlopidine at 500 mg/day for 49 days to prevent a secondary stroke. She developed fever and dizziness within 49 days of initiating ticlopidine therapy. A 70-year-old woman was started on ticlopidine after coronary stent insertion. Fifty days after starting ticlopidine, she developed fever and dizziness. Both patients showed pancytopenia and were diagnosed as aplastic anemia which were confirmed by bone marrow examination. Both patients were hospitalized and received antibiotics, blood products and hematopoietic growth factors. Four and seven weeks after the withdrawal of ticlopidine, the hematologic parameters of each patient improved. A complete blood count should be monitored during ticlopidine therapy to check for cytopenia.

Serious hematologic complications associated with ticlopidine have been reported, including aplastic anemia. We report here an additional case of fatal aplastic anemia due to ticlopidine. A 66-year-old male patient developed fever and pancytopenia 2 months after ticlopidine was started. Despite the administration of granulocyte colony-stimulating factor (G-CSF) and broad-spectrum antibiotics, as well as aggressive red cell and platelet transfusions, the patient died 16 days after admission due to septic shock. Eighteen other cases of ticlopidine-induced aplastic anemia published in the English literature are also reviewed and presented here. Eight of the total 19 patients (including the one reported here) have died, mostly due to infection. Of the seven who received supportive treatment only, four had spontaneous recovery. Nine cases were treated with G-CSF or granulocyte-macrophage colony-stimulating factor (GM-CSF), and response was observed in only four of them. Several other cases were treated with high-dose corticosteroids or androgens; however, it was not possible to evaluate the efficacy of these treatments because of the limited number of cases. In the absence of satisfactory treatment for ticlopidine-induced aplastic anemia at present, it may be reasonable to try antilymphocyte globulin or cyclosporine. Also, great efforts should be made in the prevention and management of infection accompanying this disease.

3. Ticlopidine induced Thrombocytopenia
(1) Bennett CL, Davidson CJ, Raisch DW, Weinberg PD, Bennett RH, Feldman MD
THROMBOTIC THROMBOCYTOPENIC PURPURA ASSOCIATED WITH
TICLOPIDINE IN THE SETTING OF CORONARY ARTERY STENTS AND STROKE
PREVENTION.
Arch Intern Med 1999 Nov 22;159(21):2524-8

Institute for Health Services Research and Policy Studies, Robert H. Lurie Comprehensive
Cancer Center, Northwestern University, Chicago, Ill, USA. cbenne@nwu.edu

BACKGROUND: One of the most unusual causes of thrombotic thrombocytopenic purpura (TTP), a
life-threatening disease, is ticlopidine hydrochloride, an antiplatelet agent used to prevent strokes in
high-risk populations or following coronary artery stent placement. Recently, Hoffman-LaRoche
Pharmaceuticals, following reports of 20 deaths from ticlopidine-associated TTP, updated the
information about the hematologic adverse effects of the drug. OBJECTIVES: To review our recent
findings on ticlopidine-associated hematologic toxic effects, which served as the impetus for the
revised warnings, and to discuss the implications of these findings. METHODS: Data were obtained
from the Food and Drug Administration's MedWatch program, published phase 3 clinical trials and
case reports, hematologists, and plasmapheresis centers. RESULTS: No cases of TTP have been
reported in phase 3 ticlopidine trials. In contrast, postmarketing surveillance has identified serious
adverse drug reactions to ticlopidine, resulting in 259 deaths, with TTP accounting for 40 of these
deaths. Detailed information was available on 98 cases of ticlopidine-associated TTP. Compared with
42 patients in the coronary artery stent setting, 56 patients with ticlopidine-associated TTP in the
stroke prevention setting were more likely to be women (62.5% vs 28.6%; P = .01). Before the onset
of TTP in patients receiving stroke prevention therapy and patients with stent placement, ticlopidine
had been used for less than 2 weeks in 5.4% and 2.4%, between 2 and 3 weeks in 17.9% and 21.4%,
between 3 and 4 weeks in 30.4% and 38.1%, and between 4 and 12 weeks in 46.4% and 38.1%,
respectively. Death occurred in almost 60% of all patients not receiving plasmapheresis compared
with 21.9% of patients receiving plasmapheresis for stroke prevention and 14.3% of patients
receiving plasmapheresis in the stent setting. CONCLUSIONS: Use of ticlopidine requires frequent
physician visits and laboratory tests for at least 3 months in the stroke prevention setting, while, with
short-term use in the coronary artery stent setting, adverse events are less likely to occur. These
factors, as well as competition from clopidogrel bisulfate, a new antiplatelet agent, potentially limit
the feasibility of ticlopidine as a stroke prevention agent, while having less impact on its use following
coronary artery stent placement.

(2) Koornstra JJ, Loualidi A, de Vries CJ
TICLOPIDINE-INDUCED THROMBOCYTOPENIA.

Department of Internal Medicine, MCL-Zuid, Leeuwarden, The Netherlands.
A case is presented of a 58-year-old woman developing profound thrombocytopenia within one week
after starting treatment with ticlopidine. Ticlopidine was prescribed following coronary artery
stenting. The patient recovered rapidly after discontinuation of the drug, suggesting a possible
relationship between ticlopidine and thrombocytopenia. Haematological disorders associated with
ticlopidine, such as neutropenia, thrombocytopenia and bone marrow aplasia, are rare and usually
seen within the first three months of therapy. As the use of ticlopidine increases, clinicians should be
aware of haematological complications associated with its use and inform their patients
appropriately.

(3) Bennett CL, Kiss JE, Weinberg PD, Pinevich AJ, Green D, Kwaan HC, Feldman MD
THROMBOTIC THROMBOCYTOPENIC PURPURA AFTER STENTING AND
TICLOPIDINE.
Lancet 1998 Sep 26;352(9133):1036-7

(4) Bennett CL, Weinberg PD, Rozenberg-Benzor K, Yarnold PR, Kwaan HC, Green D
THROMBOTIC THROMBOCYTOPENIC PURPURA ASSOCIATED WITH
TICLOPIDINE. A REVIEW OF 60 CASES.
Ann Intern Med 1998 Apr 1;128(7):541-4
BACKGROUND: Thrombotic thrombocytopenic purpura, a life-threatening multisystem disease, has been infrequently associated with use of ticlopidine, a platelet anti-aggregating agent. PURPOSE: To review 60 cases of ticlopidine-associated thrombotic thrombocytopenic purpura. DATA SOURCES: Medical records, published case reports, and case reports submitted to the U.S. Food and Drug Administration. STUDY SELECTION: Instances of ticlopidine-associated thrombotic thrombocytopenic purpura were identified. Data Synthesis: Ticlopidine had been prescribed for less than 1 month in 80% of the patients, and normal platelet counts had been found within 2 weeks of the onset of thrombotic thrombocytopenic purpura in most patients. Mortality rates were higher among patients who were not treated with plasmapheresis than among those who underwent plasmapheresis (50% compared with 24%; P < 0.05). CONCLUSIONS: Ticlopidine use may be associated with the development of thrombotic thrombocytopenic purpura, usually within 1 month of initiation of therapy. The onset of ticlopidine-associated thrombotic thrombocytopenic purpura is difficult to predict, despite close monitoring of platelet counts.

4. Ticlopidine LymphocyticColitis


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Lymphocytic colitis is a clinico-pathological syndrome characterized by chronic diarrhea, normal endoscopy, diffuse colonic mucosal inflammatory changes. Collagenous colitis is defined by a thickening of the collagen plate. The etiology is unknown but immune disorders have been frequently associated with it and it has been linked with the taking of certain drugs such as nonsteroid anti-inflammatory drugs or veinotonics. We are reporting a case of microscopic colitis associating both lymphocytic and collagenous colitis, which induced chronic diarrhea in a 65-year-old man. It appeared after he had taken ticlopidine. Diarrhea stopped after he had discontinued ticlopidine, and recurred after he resumed taking the drug. Histological damages from lymphocytic colitis improved six month after he had stopped taking ticlopidine. Chronic diarrhea induced by ticlopidine might be caused by lymphocytic colitis.


Department of Gastroenterology, University Hospital Gasthuisberg, Leuven, Belgium.

BACKGROUND AND AIMS: It is not known whether lymphocytic colitis and collagenous colitis represent different clinical entities or constitute part of a spectrum of disease. METHODS: Detailed clinical features and histological findings were compared in a large series of patients with confirmed lymphocytic and collagenous colitis. RESULTS: Histological diagnosis was confirmed in 96 patients with collagenous colitis and 80 with lymphocytic colitis. Twenty eight per cent of patients with collagenous colitis and 26% of patients with lymphocytic colitis had overlapping but less pronounced histological features. Both groups were equal in terms of age, use of aspirin and non-steroidal anti-inflammatory drugs, associated autoimmune conditions, arthritis, diarrhoea, and abdominal pain. The male:female ratio was 27:73 for collagenous colitis and 45:55 for lymphocytic colitis (p=0.013). Twenty five per cent of patients with collagenous colitis compared with 14% of patients with lymphocytic colitis were active smokers; only 8.3% of patients with collagenous colitis had stopped smoking compared with 23% of patients with lymphocytic colitis (p=0.013). Drug induced disease was suspected for ticlopidine (two collagenous colitis, four lymphocytic colitis) and flutamide (four lymphocytic colitis). Mean duration of symptoms before diagnosis was two months for lymphocytic
colitis and four months for collagenous colitis. Overall prognosis was generally mild; 84% of patients with lymphocytic colitis and 74% of patients with collagenous colitis reported resolution or significant improvement (p=0.033). CONCLUSIONS: Collagenous and lymphocytic colitis are similar but not identical. Patients with lymphocytic colitis present somewhat earlier and are less likely to be active smokers. Symptoms are milder and more likely to disappear in lymphocytic colitis. Ticlopidine and flutamide should be added to the list of drugs inducing colitis.

5. Ticlopidine Interactions

a) Ticlopidine interaction with Phenytoin

(1) Donahue S, Flockhart DA, Abernethy DR
TICLOPIDINE INHIBITS PHENYTOIN CLEARANCE.
Division of Clinical Pharmacology, Georgetown University School of Medicine, Washington, DC, USA.
Because cases of phenytoin toxicity during concomitant ticlopidine therapy have been reported, we investigated the effects of multiple doses of ticlopidine on phenytoin pharmacokinetics in six patients receiving phenytoin monotherapy. Two steady-state dosing rate and serum phenytoin minimum concentration (Cmin) pairs were obtained for each patient administered oral phenytoin alone, then phenytoin plus 250 mg ticlopidine twice daily. All patients had serum Cmin ticlopidine values of 0.06 to 0.25 microg/mL when receiving ticlopidine. Individual pharmacokinetic parameters for phenytoin were calculated. The Michaelis-Menten constant (Km) was determined as the slope and maximum velocity (Vmax; equivalent to the maximal rate of elimination or the maximum daily dose that can be metabolized) as the y-intercept of the linear Michaelis-Menten plot. Mean phenytoin Km significantly increased from 5.8 to 12.3 during ticlopidine coadministration compared with administration of phenytoin alone (P = .02). Mean phenytoin Vmax was not significantly changed by the coadministration of ticlopidine. These data indicate that ticlopidine inhibits the clearance and alters the clinical pharmacokinetics of phenytoin so that dosage adjustment of phenytoin should be considered when ticlopidine is coadministered. The results are consistent with previous human liver microsome findings that ticlopidine is a potent inhibitor of CYP2C19, a P450 isozyme that is significantly responsible for phenytoin metabolism.

C. Clopidogrel

A. Function and Fields of Use

1. Clopidogrel General Aspects

a) Clopidogrel effect on Platelets

(1) Weber AA, Reimann S, Schror K
SPECIFIC INHIBITION OF ADP-INDUCED PLATELET AGGREGATION BY CLOPIDOGREL IN VITRO.
Pharmacol 1999 Jan;126(2):415-20
Institut fur Pharmakologie, Heinrich-Heine-Universitat Dusseldorf, Germany.
1. The thienopyridine clopidogrel is a specific inhibitor of ADP-induced platelet aggregation ex vivo. No direct effects of clopidogrel (< or = 100 microM) on platelet aggregation in vitro have been described so far. 2. Possible in vitro antiaggregatory effects (turbidimetry) of clopidogrel were studied in human platelet-rich plasma and in washed platelets. 3. Incubation of platelet-rich plasma with clopidogrel (< or = 100 microM) for up to 8 h did not result in any inhibition of ADP (6 microM)-induced platelet aggregation. 4. Incubation of washed platelets with clopidogrel resulted in a time- (maximum effects after 30 min) and concentration-dependent (IC50 1.9+/-.0.3 microM)
inhibition of ADP (6 microM)-induced platelet aggregation. Clopidogrel (30 microM) did not inhibit collagen (2.5 mcrog ml(-1))- or thrombin (0.1 u ml(-1))-induced platelet aggregation. The inhibition of ADP-induced aggregation by clopidogrel (30 microM) was insurmountable indicating a non-equilibrium antagonism of ADP actions. The R enantiomer SR 25989 C (30 microM) was significantly less active than clopidogrel (30 microM) in inhibiting platelet aggregation (32+/−5% vs 70+/−1% inhibition, P < 0.05, n = 5). 5. In washed platelets, clopidogrel (< or = 30 microM) did not significantly reverse the inhibition of prostaglandin E1 (1 microM)-induced platelet cyclic AMP formation by ADP (6 microM). 6. The antiaggregatory effects of clopidogrel were unchanged when the compound was removed from the platelet suspension. However, platelet inhibition by clopidogrel was completely abolished when albumin (350 mg ml(-1)) was present in the test buffer. 7. It is concluded that clopidogrel specifically inhibits ADP-induced aggregation of washed platelets in vitro without hepatic bioactivation. Inhibition of ADP-induced platelet aggregation by clopidogrel in vitro occurs in the absence of measurable effects on the reversal of PGE1-stimulated cyclic AMP by ADP.

(2) Sharis PJ, Cannon CP, Loscalzo J
THE ANTIPLATELET EFFECTS OF TICLOPIDINE AND CLOPIDOGREL.

Ann Intern Med 1998 Sep 1;129(5):394-405

Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115, USA.

Ticlopidine and clopidogrel achieve antiplatelet effects by inhibiting the binding of adenosine 5'-diphosphate to its platelet receptor. Ticlopidine was first shown to decrease major events compared with placebo or aspirin in stroke or recent transient ischemic attack. Randomized studies in patients undergoing coronary artery stenting have shown that ticlopidine reduces the risk for subacute stent thrombosis compared with warfarin-based regimens. Smaller studies have also shown this drug to have benefit during follow-up in patients with unstable angina, peripheral arterial disease, saphenous vein coronary bypass grafts, and diabetic retinopathy. Clopidogrel was recently approved by the U.S. Food and Drug Administration for the reduction of ischemic events in patients with recent myocardial infarction, stroke, or peripheral arterial disease (incidence, 5.32% per year compared with 5.83% per year for aspirin; P = 0.043) with no added risk for neutropenia. The combination of clopidogrel and aspirin, as well as the utility of clopidogrel in other patient populations and in stenting, requires further study. Ticlopidine and clopidogrel seem to have beneficial effects compared with aspirin (the current standard) in a broad range of patients. These observations highlight the importance of antiplatelet therapy in cardiovascular disease.

(3) Dormandy JA
RATIONALE FOR ANTIPLATELET THERAPY IN PATIENTS WITH ATHEROTHROMBOTIC DISEASE.


St George's Hospital Medical School, St George's Hospital, London, UK.

The most common cause of morbidity and mortality in developed countries results from atherosclerosis and superimposed thrombosis (atherothrombosis) leading to partial or complete vascular occlusion. Much evidence supports the idea that all atherothrombosis is similar, regardless of which vascular bed it occurs in. Thus, similar therapies may be used for patients with symptomatic cardiac, cerebral, or peripheral vascular disease. The types of agents that have shown efficacy in atherothrombosis include antihypertensives, lipid-lowering agents and antiplatelet agents. The focus of this article is on the antiplatelet agents, of which there are several subcategories, including ADP receptor antagonists, GpIIb/IIIa antagonists, cyclo-oxygenase inhibitors and prostacyclin analogues. Clinical testing of these agents is ongoing and the efficacy and safety of the various agents are being defined. To date, the ADP receptor antagonist, clopidogrel, appears to provide the best antithrombotic result with the fewest side effects. Further testing may reveal that combinations of the various forms of antiplatelet agents may provide even further improvements on safety and efficacy.

(4) Joseph JE, Machin SJ
NEW ANTIPLATELET DRUGS.

Antiplatelet drugs are used in a wide range of disorders, either as sole agents or as adjuncts to other therapies. Aspirin has been shown to be clinically effective in a number of ischaemic conditions and has been in use for many years. The newer agents, ticlopidine and clopidogrel (which are thought to inhibit ADP-mediated platelet reactions) are also effective and may prove to be superior to aspirin in certain indications. However, ticlopidine in particular has a different spectrum of side-effects, which may eventually limit its widespread use. The Gp IIb/IIIa antagonists have been most extensively investigated in the acute coronary syndromes, and shown to significantly improve outcome. Most of these studies have utilized agents which need to be given parenterally, and subsequently oral compounds are currently being developed. A number of other antiplatelet drugs such as prostacyclin and its analogues, as well as thromboxane inhibitors have been studied over the years, but overall they have failed to demonstrate any real clinical advantage.

b) Clopidogrel Vasomodulatory effect

(1) Yang LH, Hoppensteadt D, Fareed J
MODULATION OF VASOCONSTRICTION BY CLOPIDOGREL AND TICLOPIDINE.

Department of Pathology, Loyola University Medical Center, Maywood, Illinois 60153, USA.

Clopidogrel is an antiplatelet drug which has undergone extensive clinical trials in the management of stroke and other arterial disorders related to platelet activation. This agent is believed to produce the inhibition of ADP mediated direct and indirect actions leading to platelet adhesion/aggregation and other activation processes. Several other observed pharmacologic actions suggest that this drug may have additional sites of action. Ticlopidine also belongs to the same class of ADP receptor inhibitors and is extensively used for stroke prevention. To study the vasomodulatory action of clopidogrel and ticlopidine, the drugs were administered intravenously into canines at a dose of 10 mg/kg. Thirty minutes later femoral and pulmonary arteries were removed and taken for isolated tissue preparations. The intravenous injection of clopidogrel and ticlopidine caused significant vasomodulatory actions in both femoral and pulmonary ring preparations showing a marked desensitization to serotonin, endothelin-1, serum, and platelet rich plasma/arachidonic acid mixtures. In contrast, when the drugs were added directly to the organ bath containing femoral or pulmonary ring preparations from untreated animals, both clopidogrel and ticlopidine did not produce any effect on contractile response induced by serotonin, endothelin-1, serum, and platelet rich plasma/arachidonic acid mixtures. These data suggest that endogenous transformation of clopidogrel and ticlopidine plays an important role in producing their vasomodulatory actions. Furthermore, these observations indicate that both clopidogrel and ticlopidine also modulate the vascular sites which may be contributory to the observed clinical effects.

c) Clopidogrel effect on Platelet induced Tissue factor Expression

(1) Savi P, Bernat A, Dumas A, Ait-Chek L, Herbert JM
EFFECT OF ASPIRIN AND CLOPIDOGREL ON PLATELET-DEPENDENT TISSUE FACTOR EXPRESSION IN ENDOTHELIAL CELLS.

Sanofi Recherche, Toulouse, France.

Tissue factor is an ubiquitous membrane-anchored glycoprotein that initiates blood coagulation by forming a complex with circulating factors VII and VIIa. Under normal circumstances, endothelial cells do not express tissue factor but, in some pathological situations, when the endothelium or the monocytes are exposed to inflammatory mediators, they can acquire procoagulant properties. When rat platelets were incubated with cultured bovine aortic endothelial cells, a significant increase in tissue factor expression was obtained. When added simultaneously, thrombin or 2-methylthio-ADP, a stable analogue of ADP, potentiated in a time and dose-dependent manner the effect obtained with platelets alone. In order to determine if antiplatelet agents can modulate these effects, the activity of two compounds was evaluated. When administered orally at the dose of 25 mg/kg, clopidogrel, a potent and selective analogue of ticlopidine, was able to inhibit platelet-induced tissue factor expression whereas aspirin (100 mg/kg,
p.o.) was ineffective. These effects were closely correlated to their respective anti-aggregatory and antithrombotic activities showing that platelet activation which has already been shown to be mainly involved in arterial-type thrombosis could also play an important role in the initiation of venous thrombosis where tissue factor expression is thought to play a major role.

d) Clopidogrel Antithrombotic Activity versus Aspirin

[NO TITLE AVAILABLE]. [ARTICLE IN DUTCH]
*Ned Tijdschr Geneeskd* 1999 Dec 4;143(49):2479

Academisch Ziekenhuis, Julius Centrum voor Patientgebonden Onderzoek, Utrecht.

A number of Dutch medical journals recently carried an advertisement stating that clopidogrel treatment reduced the number of ischaemic complications with 26%, compared with aspirin treatment. This is a miscalculation: the actual reduction is 0.51% in absolute rates, and 8.7% in relative terms. The error by Sanofi-Synthelabo arose by comparison of the event rates for clopidogrel (5.32%) as well as for aspirin (5.83%) with that in an imaginary placebo group (7.77%), yielding a reduction of ischaemic complications of 2.45% and 1.94% respectively; erroneous comparison of these two numbers leads to a difference of 26%.

(2) Tan WA, Moliterno DJ
**ASPIRIN, TICLOPIDINE, AND CLOPIDOGREL IN ACUTE CORONARY SYNDROMES: UNDERUSED TREATMENTS COULD SAVE THOUSANDS OF LIVES.**

Section of Interventional Radiology, Pittsburgh Vascular Institute, University of Pittsburgh Medical Center-Shadyside, USA.

Aspirin is the cornerstone of therapy for unstable angina and acute myocardial infarction and the foundation on which other therapies are added, both in the short term and the long term. Yet, despite clear data, aspirin is woefully underused or is often used late. Prompt administration of aspirin could save thousands of lives each year. Ticlopidine and clopidogrel have a synergistic effect when used with aspirin, and can also have a role in treating patients who are aspirin-resistant or have diffuse atherosclerosis.

(3) Samama MM
[WHERE TO LOOK FOR PROGRESS IN ANTITHROMBOTIC TREATMENTS]? [ARTICLE IN FRENCH]
*Rev Prat* 1999 Oct 1;49(15):1664-8

Service d'hematologie biologique Hotel-Dieu, Paris.

Thrombosis is the most frequent cause of venous and arterial vascular events. Anticoagulants and antiplatelet agents are able to prevent both types of thrombotic episodes. However, available agents have limitations which justify the search for new antithrombotic drugs or at least the clinical investigation of combined treatment with already available drugs. Progress in the knowledge of the mechanism of thrombosis guides the search for new antithrombotic agents. Novel strategies should take into account the intensity of the thrombogenic stimulus involved in the occurrence of the thrombotic episodes. Among antiplatelet agents, the logic combination of aspirin and ticlopidine or clopidogrel is already challenging the anti-GP IIb/IIIa orally active compounds. Among anticoagulant agents a long list of competitors for the replacement of oral anticoagulants and heparins is already available. They target factors Xa, IIa or VIIa. A promising alternative is to increase the thromboresistance of the vascular wall.

(4) Castaigne A, Benacerraf S, Le Roux A
[INDICATIONS FOR ANTIPLATELET MEDICATIONS]. [ARTICLE IN FRENCH]
*Rev Prat* 1999 Oct 1;49(15):1635-9
Platelet active drugs are part of the antithrombotics. Their biological effect is not assessed in current practice. Their clinical efficacy has been firmly established in randomised controlled trials. Aspirin has been the most widely tested drug and is effective in various forms of coronary artery disease and in the secondary prevention after a first ischaemic stroke; in these settings, aspirin reduces the incidence of myocardial infarction, stroke and cardiac death; aspirin has been tested in various daily doses from 30 to 1300 mg: best evidence has been gathered for dosages between 75 and 300 mg; good clinical practice is to use the lowest effective dose. Ticlopidine and clopidogrel have been shown to be superior to aspirin in 2 trials where the incidence of myocardial infarction has been lowered by the new drugs; nevertheless the superiority is apparent only in patients with lower limb atherosclerosis and after stroke. The combination of dipyridamole and aspirin has been proven to be superior to aspirin in the secondary prevention of stroke in one trial contrasting with the other trials performed with other combinations of those two drugs. Glycoprotein GP IIb/IIIa antagonists have been tested in coronary angioplasty and in acute coronary syndromes and only in short intravenous administration; these drugs reduce the incidence of myocardial infarction without any effect on 6-month mortality.

(5) Lecompte T
[ANTIPLATELET AGENTS AND THEIR THERAPEUTIC USE].
[ARTICLE IN FRENCH]
Rev Prat 1999 Oct 1;49(15):1627-33
CHU de Nancy.
Antiplatelet agents have a well established effect against thrombosis complicating atherosclerosis. Drugs currently in use in France are: aspirin and flurbiprofen, inhibiting thromboxane synthesis; ticlopidine and clopidogrel, inhibiting platelet activation by adenosine diphosphate; dipyridamole, inhibiting platelet activation through adenosine; abciximab, acting on the mechanism of aggregation. Their molecular and cellular pharmacology is in agreement with the clinical effects and the guidelines for practical use. These drugs have in common that they carry a risk of hemorrhage, albeit low but difficult to cope with in case of invasive procedures. There is no antidote. They also have specific contraindications. No laboratory tests aimed at assessing their effect on primary haemostasis are proved of any clinical value.

(6) Harker LA, Boissel JP, Pilgrim AJ, Gent M
COMPARATIVE SAFETY AND TOLERABILITY OF CLOPIDOGREL AND ASPIRIN: RESULTS FROM CAPRIE. CAPRIE STEERING COMMITTEE AND INVESTIGATORS. CLOPIDOGREL VERSUS ASPIRIN IN PATIENTS AT RISK OF ISCHAEMIC EVENTS.
Department of Medicine, Emory University School of Medicine, Atlanta, Georgia, USA.
OBJECTIVE: The objective of this study was to provide a comprehensive comparison of the long term safety and tolerability of clopidogrel, a new adenosine diphosphate (ADP) receptor antagonist that inhibits platelet activation induced by ADP, and aspirin (acetylsalicylic acid). PATIENTS AND METHODS: The study population comprised 19,185 patients with symptomatic atherosclerosis manifested as recent ischaemic stroke, recent myocardial infarction or symptomatic peripheral arterial disease. Patients were randomised to receive clopidogrel 75 mg/day or aspirin 325 mg/day for a minimum of 1 year and a maximum of 3 years. RESULTS: Compared with aspirin, clopidogrel reduced the combined risk of ischaemic stroke, myocardial infarction or vascular death by 8.7% (p = 0.043). The incidence of early permanent discontinuations of the study drug due to adverse events was almost identical in both treatment groups (11.94% for clopidogrel vs 11.92% for aspirin). Reported neutropenia was similar in the clopidogrel and aspirin groups (0.10 vs 0.17%, respectively) with corresponding rates (0.05 vs 0.04%, respectively) for severe neutropenia. Thrombocytopenia was identical in the clopidogrel and aspirin groups (0.26%), with the rates of severe thrombocytopenia being 0.19 vs 0.10%, respectively. None of these observed differences was statistically significant. The overall incidence of haemorrhagic events did not differ statistically significantly between treatment groups (9.27% for clopidogrel vs 9.28% for aspirin; p = 0.98). There was a trend towards a lower incidence of intracranial haemorrhage in the clopidogrel group (0.31%) compared with the aspirin group (0.42%). Any reported gastrointestinal haemorrhage was
significantly less frequent with clopidogrel (1.99%) than with aspirin (2.66%) \(p < 0.002\). The corresponding data for severe gastrointestinal bleeding were 0.49 vs 0.71%; \(p < 0.05\). Overall, there were significantly fewer gastrointestinal adverse events with clopidogrel than with aspirin (27.1 vs 29.8%; \(p < 0.001\)), with less abdominal pain, dyspepsia, constipation, or peptic, gastric, or duodenal ulceration with clopidogrel. Diarrhoea was significantly more common in the clopidogrel group (4.46 vs 3.36%; \(p < 0.001\)), although the incidence of severe diarrhoea (0.23 vs 0.11%) was low and was not significantly different between groups. There were significantly more patients with rash in the clopidogrel group (6.0%) compared with the aspirin group (4.6%) \(p < 0.001\). However, these events were generally mild and transient in nature. CONCLUSION: Given the favourable benefit/risk ratio, clopidogrel represents a clinically important advance in the treatment of patients with manifest atherosclerotic disease.


EFFECTIVENESS OF ASPIRIN AND CLOPIDOGREL COMBINATION THERAPY IN CORONARY STENTING.

Am J Cardiol 1999 Sep 15;84(6):726-8, A8

Department of Cardiology, The New York Presbyterian Hospital, New York 10021, USA.

Two hundred fifty consecutive patients underwent coronary stenting and received a 2-week course of clopidogrel (75 mg orally each day after a loading dose of 150 mg) and aspirin. There was 1 (0.4%) in-hospital death, 1 (0.4%) acute stent thrombosis, and 2 (0.8%) subacute stent thromboses. There were no Q-wave myocardial infarctions, vascular complications, or repeat interventions at 30-day follow-up.


COMPARATIVE ARTERIAL ANTITHROMBOTIC ACTIVITY OF CLOPIDOGREL AND ACETYLATED SALICYLIC ACID IN THE PIG.


Department d'Anesthesie, Hopital Pitie, Paris, France.

We investigated the comparative antithrombotic properties of clopidogrel, an analogue of ticlopidine, and aspirin, using the Folts' model on femoral arteries in 22 pigs. On each animal, clopidogrel or aspirin were used to treat the thrombotic process on the left femoral artery and to prevent this process on the right femoral artery. Sequentially: an injury and stenosis were carried out on the left femoral artery and to prevent this process on the right femoral artery. The thrombotic process was monitored with a Doppler during a 30-min observation period for cyclic flow reductions or permanent cessation of flow; after the first cyclic flow reduction occurred, clopidogrel (5 mg kg\(^{-1}\)) or aspirin (2.5, 5, 100 mg kg\(^{-1}\)) were injected intravenously; if cyclic flow reductions were abolished, epinephrine (0.4 micrograms kg\(^{-1}\) min\(^{-1}\)) was injected to try to restore cyclic flow reductions and/or permanent cessation of flow; then injury and stenosis were applied on the right femoral artery. Before and after injection of clopidogrel or aspirin, ear immersion bleeding times and ex-vivo platelet aggregation were performed. Clopidogrel \((n = 7)\) abolished cyclic flow reductions were efficiently prevented, even for two injuries. Basal bleeding time (5 min 28) was lengthened (> 15 min, 30 min after clopidogrel and remained prolonged even after 24 h). ADP-induced platelet aggregation was inhibited (more than 78%). Comparatively, aspirin had a moderate and no dose-dependent effect. Aspirin 2.5 mg kg\(^{-1}\) \((n = 6)\) abolished cyclic flow reductions in 2 animals, CFR reoccurred spontaneously in one animal and epinephrine restored it in a second animal.

e) Clopidogrel and Drug interactions

(1) Forbes CD, Lowe GD, MacLaren M, Shaw BG, Dickinson JP, Kieffer G

CLOPIDOGREL COMPATIBILITY WITH CONCOMITANT CARDIAC CO-MEDICATIONS: A STUDY OF ITS INTERACTIONS WITH A BETA-BLOCKER AND A CALCIUM UPTAKE ANTAGONIST.

Semin Thromb Hemost 1999;25 Suppl 2:55-60

Department of Medicine, Ninewells Hospital and Medical School, Dundee, Scotland, UK.
The safety and pharmacodynamic compatibility of clopidogrel with medications commonly used in patients with atherosclerosis, such as, a beta-adrenergic receptor antagonist (atenolol) and a calcium uptake inhibitor (nifedipine) were assessed. Atenolol and nifedipine interactions with clopidogrel were studied in patients with peripheral arterial obstructive disease taking a well-established regimen of nifedipine (N group of 6 patients) and in patients with coronary artery disease taking a well-established regimen of either atenolol (A group of 8 patients) or of atenolol and nifedipine (AN group of 8 patients). The study was conducted as a double-blind, randomized, crossover comparison of clopidogrel, 75 mg once daily, and placebo treatment for 7 days, with a 14-day washout between treatments. Pharmacodynamic interactions between atenolol and nifedipine, either alone or in combination, and clopidogrel were assessed primarily on the clinical control of angina or hypertension and, secondarily, by comparing the extent of inhibition of ADP (5 microM)-induced platelet aggregation achieved between the 3 groups. The mean number of anginal episodes per patient during the placebo week was 1.50, 9.0 and 11.5 in the A, N and AN groups, respectively; during the week of clopidogrel treatment, it was 1.39, 7.3 and 9.0, respectively, indicating no change in occurrence. Likewise, review of the use of nitrates (long or short acting) did not suggest any major change in usage during any period of the study. ECGs did not change between the three recording times (at screening and at the end of each treatment period). Vital signs were also unchanged throughout. Percent inhibition of platelet aggregation on day 7 was 31% in the N group, 39% in the A group, 28% in the AN group, and 33% overall. In conclusion, the coadministration of clopidogrel did not interfere with the clinical control of hypertension or angina established with atenolol or nifedipine, or both. Clopidogrel retained its full antiplatelet effect, and there were no safety problems caused by the coadministration.

(2) Peeters PA, Crijns HJ, Tamminga WJ, Jonkman JH, Dickinson JP, Necciari J
CLOPIDOGREL, A NOVEL ANTIPLATELET AGENT, AND DIGOXIN: ABSENCE OF PHARMACODYNAMIC AND PHARMACOKINETIC INTERACTION.
Semin Thromb Hemost 1999;25 Suppl 2:51-4
N.V. Organon, Oss, The Netherlands.

The safety, and the pharmacodynamic and pharmacokinetic compatibility of clopidogrel, 75 mg daily, with the cardiac glycoside digoxin, were assessed in 12 healthy male subjects who took digoxin 0.25 mg once daily for 20 days and, in addition, clopidogrel 75 mg once daily from day 11 to day 20, so as to achieve steady-state conditions with both drugs. The drugs were taken after an overnight fast, and a standardized breakfast was served 30 minutes later. Blood samples for digoxin determination were drawn pre-dose on days 1, 8, 9, 10, 18, 19, and 20 of the schedule, and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16, and 24 hours post-dose on days 10 and 20. Urine samples were collected pre-dose and from 0-4, 4-8, 8-12, and 12-24 hours post-dose on days 10 and 20. Platelet aggregation studies were carried out using ADP at 5 micromol/L final concentration as an agonist. Establishment of steady-state plasma concentrations of digoxin on days 8-11 and 18-21 was confirmed by application of Dunnett's test on the trough plasma concentrations. The plasma pharmacokinetics and urinary excretions of digoxin for day 10 and day 20 were very similar: the day 20/day 10 ratios (90% CI) were 1.1 (0.99; 1.24) for Cmax, 1.0 (0.92; 1.08) for Cmin, 1.02 (0.96; 1.07) for AUC(0-24), and 0.99 (0.94; 104) for urinary excretion. Mean inhibition of ADP-induced platelet aggregation at the end of the clopidogrel treatment period was 34%. The clinical, cardiac, and biological evidence from the study indicated that clopidogrel administration does not enhance digoxin’s cardiac effects. Overall, the data indicated that there is no reason to anticipate an interaction when clopidogrel is added to digoxin for long-term management of patients with cardiac disease.

(3) Caplain H, Thebault JJ, Necciari J
CLOPIDOGREL DOES NOT AFFECT THE PHARMACOKINETICS OF THEOPHYLLINE.
Institut Aster, Hopital Cognacq-Jay, Paris, France.

The potential influence of clopidogrel on the pharmacokinetics of theophylline was evaluated in 15 healthy male subjects during the pharmacokinetic steady state of theophylline, after single and multiple doses. Theophylline was administered orally as one 300-mg capsule in the morning before breakfast and one in the evening before dinner for 13 days (day 1 through day 13), and one capsule on the morning of day 14. Clopidogrel was administered orally as one 75-mg tablet in the morning
before breakfast from day 5 through day 14. Plasma concentration of theophylline was determined at
the following times: before the morning dose on days, 1, 6-9, and 12; before administration, then at
0.5, 1.2, 3, 4, 5, 6, 7, 8, 10, and 12 hours after administration on days 4, 5, and 14. Tests of hemostasis
(ADP-induced platelet aggregation and bleeding time) were carried out 2 hours after clopidogrel
dosing on days 5, 7, 9, 11, and 14. The curves of the mean plasma concentration of theophylline over
12 hours post-morning dose on day 4 (drug alone), day 5 (after a single dose of clopidogrel), and day
14 (after 10 days of clopidogrel coadministration) were superimposable, indicating the absence of an
effect of clopidogrel on the steady-state pharmacokinetics of theophylline. There were no statistically
significant differences between the days of administration for the log-transformed values of
theophylline C(bt) (concentration before treatment) Cmax, AUC(0-12h), and Cmin; and the 90%
confidence intervals of the day 5/day 4, day 14/day 4, and day 14/day 5 ratios of the geometric means
of C(bt) all fell within the (0.80; 1.25) interval. These results show that the administration of
clopidogrel during steady state theophylline administration had no effect on the plasma
concentration of the latter drug. The average steady-state (days 11-14) percentage of inhibition of
ADP-induced platelet aggregation by clopidogrel with respect to day 1 was 46%. The geometric
mean of the bleeding time prolongation factor was about 2 at steady state. The latter results indicate
that the pharmacodynamics of clopidogrel were not affected by concomitant theophylline.

(4) Pierce CH, Houle JM, Dickinson JP, Kindermans M, Serre-Lacroix E, Kieffer G, Necciari J
CLOPIDOGREL AND DRUG METABOLISM: ABSENCE OF EFFECT ON HEPATIC
ENZYMES IN HEALTHY VOLUNTEERS.
Semin Thromb Hemost 1999;25 Suppl 2:35-9

MDS Harris, Lincoln, Nebraska, USA.
The influence of clopidogrel 75 mg, given once daily for 10 days on hepatic P-450 mixed function
oxidases, was examined by assessing its effect on the disposition of antipyrine, on urinary 6-
beta-hydroxycortisol (6beta-OHC) and on the plasma activity of gamma-glutamyl transpeptidase.
This double-blind, randomized, placebo-controlled study was conducted in two parallel groups of 10
healthy young volunteers. Subjects were required to fast for 12 hours before and for 4 hours after
dosing. Antipyrine 10 mg/kg was administered in the morning, two days before treatment (day -2)
and 24 hours after the last dose of clopidogrel or placebo. Plasma levels of antipyrine, and urinary
excretion of antipyrine, 3-hydroxymethyl-antipyrine and nor-antipyrine were measured over 36
hours post-drug for pharmacokinetic determinations. **Bleeding time** and **platelet aggregation** induced
by 5 microM of ADP were measured before treatment (baseline) and at regular intervals after dosing
during treatment. **Clopidogrel treatment** had a marked effect on platelet aggregation and bleeding
time. No significant change in the disposition of antipyrine was observed after the ingestion of
clopidogrel over 10 days: mean AUC ratio (+/-SEM) for plasma antipyrine was 1.021+/-0.023 for the
clopidogrel group versus 1.001+/-0.019 for the placebo group; mean day 10/day -2 t 1/2 ratios were
1.019+/-0.018 and 1.027+/-0.023, respectively. **Urinary excretions** of antipyrine and metabolites were
unchanged by clopidogrel compared to placebo. The changes in plasma cortisol concentrations,
6beta-OHC excretion and serum gamma-glutamyl transpeptidase activities observed at the end of
treatment were fully comparable between the two treatment groups. Thus, the different tests showed
no evidence of hepatic enzyme induction by clopidogrel in a pharmacologically effective dose
regimen.

2. Clopidogrel in Cardiologic Disease

a) Clopidogrel in Cardiology General Aspects

(1) Meyer BJ
ANTITHROMBOTIC DRUGS: INSIGHTS FROM CARDIOLOGY.

Division of Cardiology, Department of Medicine, University Hospital Inselspital, Bern,
Switzerland.
The primary purpose of this overview is to provide an update on the **newer antiplatelet drugs**
evaluated in clinical trials and introduced in clinical practice of modern cardiology. Despite the
remarkable clinical developments with the use of **new antiplatelet drugs**, several fundamental issues
remain unresolved. Some of the observed safety/efficacy problems in major clinical trials can be directly attributed to the lack of careful phase II studies where issues such as monitoring, pharmacological profiles, and individual response variations were not considered sufficiently. Nevertheless, none of the available antplatelet agents meet all the criteria of an ideal antplatelet agent. Aspirin has been the standard reference agent in cardiovascular disease. However, it is a weak and nonselective antplatelet compound and is unable to interfere substantially with the thrombogenic activity of a fresh mural thrombus of a stenosed vessel. The newer antplatelet drug classes such as the ADP receptor blockers (ticlopidine, clopidogrel) and the platelet glycoprotein IIb/IIIa receptor inhibitors produce their therapeutic effects by distinct mechanisms which differ from aspirin. Large clinical trials have documented their efficacy in acute coronary syndromes associated with intracoronary thrombus formation. The future challenge is to evaluate long-term treatment strategies which are equally safe but distinctly more effective than aspirin, e.g. a combination therapy with aspirin and clopidogrel or oral GP IIb/IIIa receptor antagonists.

(2) Ischinger TA

ANTITHROMBOTICS IN INTERVENTIONAL CARDIOLOGY: OPTIMIZING TREATMENT AND STRATEGIES.

Am J Cardiol 1998 Sep 10;82(5B):25L-28L

Kardiologie und Pneumologie Stadt Krankenhaus, Munchen-Bogenhausen, Germany.

Although the use of coronary stents has virtually abolished the threat of periprocedural obstructive dissection, subacute and acute intracoronary thrombosis and late restenosis remain a major problem with catheter-guided transluminal coronary interventions, despite significant technical advances over the last 10 years. Acute stent thrombosis emerged as a new problem with the introduction of metallic coronary prostheses (stents), which unfortunately represent an ideal stimulus for platelet deposition. Recently, dramatic progress has been achieved by focusing on the inhibition of thrombin and platelets, before and during interventional procedures. This has stimulated the search for powerful and well-tolerated antithrombotic agents-platelet inhibitors and antithrombins so that long-term (oral) administration may become possible, if necessary. The current roles of unfractionated and low-molecular-weight heparins (LMWHs), direct thrombin inhibitors (such as hirulog and hirudin), antplatelet agents (such as aspirin, clopidogrel, and ticlopidine) and the potential of the glycoprotein IIb/IIa receptor blockers are reviewed and put into perspective with respect to their acute and long-term clinical value.

b) Clopidogrel in Coronary Artery Disease

(1) David JL, Limet R

ANTIPLATELET ACTIVITY OF CLOPIDOGREL IN CORONARY ARTERY BYPASS GRAFT SURGERY PATIENTS.

Thromb Haemost 1999 Nov;82(5):1417-21

Thrombosis-Haemostasis Unit, University of Liege, Belgium.

Clopidogrel is a recently introduced platelet ADP receptor antagonist, belonging to the thienopyridine derivatives, like its analogue ticlopidine. Its potential advantage is to be safer than ticlopidine. At 75 mg/od clopidogrel significantly inhibits platelet aggregation in ambulatory patients with symptomatic atherosclerotic disease and it prevents the recurrence of ischemic events more efficiently than aspirin. Its adequate dose in more acute situations remained to be determined. Therefore, sixty two patients with coronary artery disease were randomly assigned in four groups treated, within 24 h after coronary artery bypass graft, by clopidogrel 50 mg/od, 75 mg/od or 100 mg/od or by ticlopidine 250 mg/bid which was considered as the reference. The tolerance of clopidogrel was fairly good during the whole period of the study. Bleeding time and ex-vivo platelet aggregation induced by ADP 2 microM and 5 microM were performed at day -1, +9 and +28 after surgery. Like ticlopidine, the three dose levels of clopidogrel significantly inhibited ex-vivo platelet activity and prolonged the bleeding time at day 28. However, unlike ticlopidine, the inhibitory effects of clopidogrel were not significant at day 9, especially with 75 mg/od, a dose which was found to significantly protect patients in a chronic situation. Hence, although the clinical outcome for patients included in this limited study was the same in the four groups, these results suggest that the dose regime of clopidogrel should be more extensively investigated during the early period following
coronary artery bypass graft, facing an overproduction of young and hyperreactive platelets. By analogy, the dose regime should be also investigated in other situations with an acute risk of arterial thrombotic occlusion.

3. Clopidogrel in Peripheral Arterial Disease

(1) Violi F, Loffredo L, Annessi M

[THE FUTURE PROSPECTS OF ANTITHROMBOTIC THERAPY IN PERIPHERAL VASCULOPATHY]. [ARTICLE IN ITALIAN]

Ann Ital Med Int 1999 Jul-Sep;14(3):185-91

Istituto di Clinica Medica I, Universita degli Studi La Sapienza di Roma.

Peripheral vascular disease is characterized by progressive atherosclerotic deterioration of peripheral arteries and coronary and cerebral vascular complications. Antiplatelet treatment retards the progression of peripheral atherosclerosis but it is still unclear if this is associated with a reduced risk of amputation. Vasodilator prostaglandins have been administered in critical ischemia but the results have been disappointing. An alternative approach to enhance peripheral vasodilation is to increase nitric oxide production, which is reduced in peripheral vascular disease, particularly in the case of severe ischemia. Critical ischemia secondary to thromboembolism has been treated with thrombolysis within 7 days of the acute episode, but this approach is no more effective than vascular surgery in reducing amputation; earlier treatment should be planned to further investigate its clinical efficacy. The effect of antiplatelet treatment in preventing cardiovascular events was investigated in three randomized trials with negative results. A post-hoc analysis of the CAPRIE study demonstrated that clopidogrel is superior to aspirin in preventing cardiovascular disease. This suggests that antiplatelet treatment may be efficacious in this setting; future study should assess if its combination with other drugs, such as statins, that retard coronary atherosclerotic progression, could further reduce cardiovascular complications in peripheral vascular disease.

(2) Hilleman DE

MANAGEMENT OF PERIPHERAL ARTERIAL DISEASE.


Department of Pharmacy Practice, School of Pharmacy, Creighton University, Omaha, NE 68178, USA.

The risk factors, epidemiology, diagnosis, and treatment of peripheral arterial disease are reviewed. Peripheral arterial disease is characterized by a gradual reduction in blood flow to one or more limbs secondary to atherosclerosis. Risk factors include smoking, diabetes mellitus, hyperlipidemia, and hypertension. The most common clinical manifestation is intermittent claudication. The prevalence of intermittent claudication in people over the age of 50 is 2-7% for men and 1-2% for women. The ankle:brachial pressure index (ABPI) is a useful measure of disease severity; an ABPI of 0.5-0.9 is common in intermittent claudication. The goals of therapy are to relieve or reduce ischemic symptoms, alleviate disability, improve in functional capacity, prevent progression that may result in gangrene and limb loss, and prevent cardiovascular and cerebrovascular events. Treatment includes risk-factor modification, drug therapy (primarily with antiplatelet agents), and revascularization procedures. Aspirin has been shown to be effective in reducing the associated risk of myocardial infarction and stroke. Ticlopidine appears to be a reasonable alternative for patients who are hypersensitive to aspirin. Clopidogrel has been shown to be more effective than aspirin in patients with recent myocardial infarction, recent stroke, or established peripheral arterial disease. There is controversy over the appropriate treatment for acute arterial occlusions. Risk-factor modification and antiplatelet drugs are the mainstays of therapy for patients with intermittent claudication, the most common manifestation of peripheral arterial disease.

4. Clopidogrel in Stroke Prevention

Clopidogrel more effectiv than Aspirin but as safe as it!
(3) Alvarez-Sabin J, Montaner-Villalonga J
[ANTIPLATELET THERAPY OF SECONDARY STROKE PREVENTION AFTER
ESPS-2 AND CAPRIE]. [ARTICLE IN SPANISH]
Rev Neurol 1999 Oct 16-31;29(8):780-4

Unidad Cerebrovascular, Hospital General Universitario de la Vall d'Hebron, Barcelona, Espana.
INTRODUCTION: Antiplatelet therapy is effective for secondary prevention of atherothrombotic stroke. Aspirin, the more frequently used antiplatelet drug, prevents 13 to 17% of ischemic events after stroke. New and more effective antiplatelet therapies are needed. DEVELOPMENT: Two large secondary stroke prevention trials have been recently published (CAPRIE and ESPS-2), including more than 25,000 patients. As well TACIP trial designed to assess the efficacy of triflusal, is close to end. The combination of ticlopidine and Aspirin has shown synergistic effect. CONCLUSIONS: Clopidogrel, like ticlopidine, increase 9% the relative risk reduction of stroke over Aspirin. Clopidogrel has a better safety profile than ticlopidine. Dipyridamole is an effective antiplatelet drug, but in combination with low doses of Aspirin is more effective. The possible efficacy of clopidogrel-Aspirin combination should be evaluated.

(4) Hankey GJ, Warlow CP
TREATMENT AND SECONDARY PREVENTION OF STROKE: EVIDENCE, COSTS,
AND EFFECTS ON INDIVIDUALS AND POPULATIONS.

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This review of the effectiveness of treatment for acute stroke and methods of secondary prevention shows that the highest priority for providers of a stroke service must be to establish a stroke unit and multidisciplinary team that delivers organised stroke care. Acute ischaemic stroke patients should be immediately started on aspirin 300 mg daily, and, if possible, many of them should be entered into further trials of thrombolysis and other promising treatments. After the acute phase, aspirin should be continued in a lower dose, 75 mg daily; smoking should be discouraged; high blood pressure treated initially with a diuretic; and fibrillating ischaemic stroke/transient ischaemic attack survivors anticoagulated long-term with warfarin or given aspirin if anticoagulation is not sensible. Statins are probably indicated in patients who already have symptomatic coronary heart disease. Adding dipyridamole to aspirin, substituting clopidogrel for aspirin, and carotid endarterectomy are all expensive interventions to prevent stroke, but if ways could be found to focus them on those patients at especially high risk, they would become more affordable.

(5) Paciaroni M, Bogousslavsky J
CLOPIDOGREL FOR CEREBROVASCULAR PREVENTION.
Cerebrovasc Dis 1999 Sep-Oct;9(5):253-60

Service de Neurologie, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.
Ischemic stroke, myocardial infarction and peripheral arterial disease are different clinical manifestations commonly due to the same underlying disease, i.e. atherosclerosis with subsequent thrombosis/embolism (atherothrombosis). Many clinical trials of secondary prevention after stroke or TIA have evaluated the benefit of long-term use of antiplatelet drugs in reducing the risk of subsequent vascular events. Aspirin and ticlopidine have been shown to be effective in placebo-controlled studies for the composite outcome of stroke, myocardial infarction, or vascular death. Contrasting with these benefits, there were potentially serious, though rare, adverse effects. These considerations certainly justify the development of new antiplatelet agents. Clopidogrel is a new ADP-receptor antagonist, with a greater activity in animal models of thrombosis. CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) was a randomized, blinded, international trial designed to assess the relative efficacy of clopidogrel and aspirin in reducing the risk of the outcome cluster of ischemic stroke, myocardial infarction, or vascular death, as well as to assess their relative safety. 19,185 patients were recruited. The intention-to-treat analysis showed that the relative risk reduction was 8.7% (95% CI 0.3-16.5, p = 0.043) in favor of clopidogrel from an overall annual event rate of ischemic stroke, myocardial infarction, or vascular death, ranging from
5.83% in the aspirin group to 5.33% in the clopidogrel group. The percentage of adverse events reported was higher in the aspirin group for all categories except rash, diarrhea, and abnormal liver function. It seems likely that clopidogrel will replace ticlopidine for stroke prevention, because of its better safety profile, and comparable efficacy. Clopidogrel probably will not replace aspirin as the first line therapy for many clinicians because of its higher cost and lack of widespread experience. However, other clinicians have already decided that they will use clopidogrel as first choice, because of the significant advantage over aspirin demonstrated in the CAPRIE study.

(6) Boysen G

BLEEDING COMPLICATIONS IN SECONDARY STROKE PREVENTION BY ANTIPLATELET THERAPY: A BENEFIT-RISK ANALYSIS.

*J Intern Med* 1999 Sep;246(3):239-45

Department of Neurology, Bispebjerg Hospital, University of Copenhagen, Denmark.

This review analyses the benefit-risk ratio of antiplatelet drugs in secondary stroke prevention and is based on the published data from eight large stroke prevention trials. In patients with prior transient ischaemic attack (TIA) or stroke, aspirin prevented one to two vascular events (stroke, AMI, or vascular death) per 100 treatment-years with an excess risk of fatal and severe bleeds of 0.4-0.6 per 100 treatment-years. The gastrointestinal bleeding risk was significantly lower with ticlopidine and clopidogrel, which were both somewhat more effective than aspirin in the prevention of vascular events. The combination of dipyridamole and aspirin prevented 2.82 strokes at the expense of an excess risk of 0.61 (95% CI = 0.27-0.95) fatal or severe bleeds per 100 treatment-years. In the acute phase of stroke, the aspirin-associated risk of haemorrhagic complications was much increased compared with that in the stable phase after stroke, with 0.48 (95% CI = 0.13-0.83) fatal or severe bleeds per 100 treated patients for the first 4 weeks after stroke in the Chinese Acute Stroke Trial and 0.41 (95% CI = 0.05-0.77) in the International Stroke Trial. Still, there was a net benefit with the prevention of about one death or non-fatal ischaemic stroke per 100 treated patients.

(7) Gent M, Kusmierek J

CLOPIDOGREL, ASPIRIN, AND FIRST LINE THERAPY.

*Cerebrovasc Dis* 1998 Sep-Oct;8(5):303; discussion 303-4

(8) Easton JD

WHAT HAVE WE LEARNED FROM RECENT ANTIPLATELET TRIALS?

*Neurology* 1998 Sep;51(3 Suppl 3):S36-8

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Aspirin's benefit in preventing vascular outcomes is well established. It reduces the relative risk for stroke, myocardial infarction, and vascular death by about 25% compared with placebo. Almost 10 years ago we learned that ticlopidine is more effective than aspirin (about 12% relative risk reduction for stroke or death). However, ticlopidine has important adverse effects. In 1996, the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial showed that clopidogrel, a new thienopyridine similar to ticlopidine, is also more effective than aspirin (by a similar amount) and is as safe as aspirin. Also in 1996, the European Stroke Prevention Study 2 (ESPS-2) showed that dipyridamole alone prevents stroke and that when combined with aspirin it is more effective, probably comparable to ticlopidine and clopidogrel. Dipyridamole combined with aspirin reduced the relative risk for stroke or death by about 13% compared with aspirin alone. Both clopidogrel and dipyridamole are safe but will cost more than aspirin. Aspirin also appears beneficial for acute stroke treatment. The Chinese Acute Stroke Trial (CAST) and the International Stroke Trial (IST) demonstrated that aspirin given at the time of an acute ischemic stroke reduces the risk for early death (about 5 less/1,000 treated), recurrence or death (about 10 less/1,000 treated), and dependence (about 5 less/1,000 treated). Overall, the benefits of aspirin in acute stroke treatment and stroke prevention are definite but modest. Combination therapy with antiplatelet agents that act through different mechanisms is a promising way to maximize the benefits of antiplatelet treatment.
Aspirin is an established therapy for the management of acute myocardial infarction (AMI) and unstable angina. Secondary prevention with chronic aspirin therapy is also indicated for patients with stable angina. Aspirin inhibits cyclo-oxygenase-I, a key enzyme in the biosynthetic pathway leading to the production of thromboxane A2. It therefore inhibits only one of the many activation pathways leading to platelet aggregation. Other antiplatelet agents that have also been evaluated in clinical trials include ticlopidine and clopidogrel, which inhibit adenosine diphosphate-mediated platelet aggregation, but these agents are known to be effective against only one of the 90 known agonists that stimulate platelet aggregation. The final common pathway for platelet aggregation involves the glycoprotein IIb/IIIa receptor combining with fibrinogen. Several inhibitors of the glycoprotein IIb/IIIa receptor have been developed and have an important role as adjunctive therapy in angioplasty. Recent trials have been performed in patients with unstable angina, and trials of adjunctive therapy are currently underway in patients receiving thrombolyis for AMI, and for secondary prevention. These drugs have various different features, including specificity for blockade of the glycoprotein IIb/IIIa receptor, half life, duration of the haemostatic effect and potential for antigenicity. Recently concluded and ongoing trials of both intravenous and oral agents are expected to provide further support for the introduction of these agents into clinical management of patients with acute coronary syndromes.

Several new drugs for the management of thromboembolic disorders have recently become available. Low-molecular-weight heparins are being evaluated for the prophylaxis of medical and surgical deep venous thrombosis and pulmonary embolism; for the treatment of pre-existing thrombosis; and for cases of coronary syndrome (unstable angina, myocardial infarction), thrombotic and ischemic stroke, interventional cardiology, pregnancy, cancer, and transplantation-associated thrombosis. A chemically synthesized heparin pentasaccharide, which has purely anti-factor Xa activity and does not induce thrombocytopenia, is also in clinical trial. Thrombin inhibitors, such as hirudin and argatroban, are a practical anticoagulant substitute where heparin cannot be used. They are also useful for the management of coronary syndrome and as adjunct therapy. The antiplatelet agent ticlopidine and its analogue, clopidogrel, which does not produce blood dyscrasias, are effective for the secondary prevention of thrombotic stroke and the management of combined arterial thrombotic syndromes. Glycoprotein-targeting antibodies, synthetic derivatives, and peptides (some of which are orally bioavailable) have added a new dimension to the management of arterial thrombosis and high-risk patients having angioplasty. Plasma-derived agents, such as antithrombin III, are available for the management of thrombophilia and disseminated intravascular coagulation. Compression devices and the foot pump, alone and in combination with pharmacologic agents, have been used successfully. Combination therapy using various agents in different proportions have also been found useful. Although there is much enthusiasm in this quickly developing area and clinical trials are demonstrating the antithrombotic efficacy of the new drugs, safety considerations require additional clinical validation. Long-term outcomes and costs also need to be addressed objectively.

(12) Boneu B, Destelle G

**PLATELET ANTI-AGGREGATING ACTIVITY AND TOLERANCE OF CLOPIDOGREL IN ATHEROSCLEROTIC PATIENTS.**


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The anti-aggregating activity of five rising doses of clopidogrel has been compared to that of ticlopidine in atherosclerotic patients. The aim of this study was to determine the dose of clopidogrel which should be tested in a large scale clinical trial of secondary prevention of ischemic events in patients suffering from vascular manifestations of atherosclerosis [CAPRIE (Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events) trial]. A multicenter study involving 9 haematological laboratories and 29 clinical centers was set up. One hundred and fifty ambulatory patients were randomized into one of the seven following groups: clopidogrel at doses of 10, 25, 50, 75 or 100 mg OD, ticlopidine 250 mg BID or placebo. ADP and collagen-induced platelet aggregation tests were performed before starting treatment and after 7 and 28 days. Bleeding time was performed on days 0 and 28. Patients were seen on days 0, 7 and 28 to check the clinical and biological tolerability of the treatment. Clopidogrel exerted a dose-related inhibition of ADP-induced platelet aggregation and bleeding time prolongation. In the presence of ADP (5 microM) this inhibition ranged between 29% and 44% in comparison to pretreatment values. The bleeding times were prolonged by 1.5 to 1.7 times. These effects were non significantly different from those produced by ticlopidine. The clinical tolerability was good or fair in 97.5% of the patients. No haematological adverse events were recorded. These results allowed the selection of 75 mg once a day to evaluate and compare the antithrombotic activity of clopidogrel to that of aspirin in the CAPRIE trial.

(13) Verstraete M

**NEW DEVELOPMENTS IN ANTIPLATELET AND ANTITHROMBOTIC THERAPY.**

*Eur Heart J* 1995 Nov;16 Suppl L:16-23

Center for Molecular and Vascular Research, University of Leuven, Belgium.

Several agents which inhibit platelet aggregation (aspirin, ticlopidine, dipyridamole), and anticoagulants (vitamin K antagonists, unfractionated heparin, low molecular weight heparins and heparinoids) are in clinical use. The search for more effective antiaggregating agents has resulted in the development of clopidogrel, a chemical analogue of ticlopidine with minimal bone-marrow suppressing effects, thromboxane synthase inhibitors and receptor blockers, and antagonists of platelet receptor glycoproteins Ib and IIb/IIIa. In addition there is increasing therapeutic experience with chimeric monoclonal antibodies against the platelet receptors, glycoprotein Ib/IIa, and, to a minor extent, with synthetic peptides or non-peptide inhibitors against the same receptors. Although new anticoagulants have become available, their efficacy has only been tested in animal models of thrombosis: tissue factor pathway inhibitor, factor Xa inhibitors (recombinant tick anticoagulant peptide, antistasin, natural pentasaccharide and DX-9065), recombinant thrombomodulin and recombinant protein C have been tested in this manner. Considerable clinical progress has been made with direct thrombin inhibitors, such as recombinant hirudin and hirulog which appear to be effective antithrombotic agents in patients. There is also clinical experience with argatroban, an arginine derivative which is a competitive antagonist to thrombin. However, PPACK, a tripeptide synthetic compound which irreversibly blocks the active catalytic site of thrombin, has not been investigated in the clinical setting.

5. Clopidogrel in Stent Thrombosis Prevention

(1) Brookes CI, Sigwart U

**TAMING PLATELETS IN CORONARY STENTING: TICLOPIDINE OUT, CLOPIDOGREL IN?**

*Heart* 1999 Dec;82(6):651-2

(2) Schalcher C, Sutsch G, Amann FW

**TO STENT OR NOT TO STENT.**

*Schweiz Med Wochenschr* 1999 Nov 13;129(45):1679-96
Department of Internal Medicine, University Hospital, Zurich.

**Coronary artery stenting** has definitely been proven to improve results of percutaneous revascularisation in a large number of patients. Stenting reduces restenosis in large vessels above 3 mm diameter. Stenting has not solved the problem of restenosis but in spite of the inevitable in-stent restenosis due to neointimal proliferation seems to yield better long-term results than conventional PTCA. Adjunctive pharmacological treatment with aspirin and clopidogrel in combination with improved stent deployment techniques has reduced the incidence of subacute stent thrombosis. GP IIb/IIIa inhibition is a promising mean for the reduction of procedure related ischaemic events and complications not only with stent implantation but also with conventional PTCA. Other new devices may further influence the treatment choices of stenting versus conventional PTCA in the future. Novel approaches such as brachytherapy and molecular genetic approaches to reduce in-stent restenosis are currently being investigated but to date no conclusions can be drawn as to their future place in clinical practice. From a mechanistic standpoint it seems obvious to give all our efforts to protect patients with coronary atherosclerosis from loss of myocardium either with coronary artery bypass grafting or percutaneous revascularisation. As both approaches are palliative in nature, it may be useful to attempt percutaneous revascularisation in patients amenable to this therapy and thus obviate or delay the need for definitive revascularisation by coronary artery bypass grafting. At the end of this discussion we would like to remind that medical therapy for coronary artery disease is of utmost importance as all revascularisation procedures do not influence the underlying disease. Besides symptomatic relief of angina, treatment of heart failure, and other beneficial strategies to improve endothelial function, medical therapy with lipid lowering compounds together with risk factor control offers the possibility to delay progression of coronary artery disease.

(3) Gurbel PA, O'Connor CM, Cummings CC, Serebruany VL

**CLOPIDOGREL: THE FUTURE CHOICE FOR PREVENTING PLATELET ACTIVATION DURING CORONARY STENTING?**


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Ticlopidine has become an established therapy in patients with stroke, and during stenting in patients with coronary artery disease. Clopidogrel, another thienopyridine, is a safe and promising alternative, that irreversibly inhibits ADP-induced platelet aggregation, and reduces formation of both arterial and venous thrombi. In a recent, large, well-controlled trial (CAPRIE), clopidogrel has been shown to be superior to aspirin in terms of prevention of ischaemic stroke, myocardial infarction and death in patients with atherosclerotic vascular disease. Clopidogrel provides a safe opportunity to enhance reperfusion when administered during stent placement, by protecting platelets from excessive activation. However, the ability of clopidogrel to be superior to ticlopidine in terms of its antiplatelet properties in the clinical setting of coronary stenting, is unknown. The effects of clopidogrel versus ticlopidine on platelet and endothelial function are yet to be determined and may strongly affect the outcome, benefits, and complications following coronary stent placement. Further clinical trials, well-designed, and carefully conducted, should elucidate possible benefits of clopidogrel during coronary interventions, especially in conjunction with new and aggressive reperfusion techniques. The benefits of clopidogrel in an expanding array of clinical conditions, including myocardial infarction, may be directly related to platelet inhibition. Moreover, marginal clinical benefits, and recently reported severe bleeding events in some patients after oral platelet glycoprotein IIb/IIIa therapy, may advance clopidogrel as a safe, and efficient alternative during coronary interventions. This review summarises the latest, and often confusing data on the effects of thienopyridines on certain haemostatic characteristics in interventional cardiology. 1999 Academic Press. Copyright 1999 Academic Press.


**EFFECTS OF CLOPIDOGREL, ASPIRIN AND COMBINED THERAPY IN A PORCINE EX VIVO MODEL OF HIGH-SHEAR INDUCED STENT THROMBOSIS.**

AIMS: Use of ticlopidine in coronary stenting is limited by delayed onset of action. We studied the effects of clopidogrel, a rapidly acting analog of ticlopidine alone, and in combination with aspirin, in inhibiting stent thrombosis.

METHODS: Unpolished nitinol stents were deployed in a porcine ex vivo arteriovenous shunt and exposed to flowing arterial blood at a shear rate of approximately 1500 s⁻¹. Stent thrombus, platelet aggregation and bleeding times were measured at baseline and after treatment.

RESULTS: Intravenous clopidogrel produced a rapid (within 30 min) and dose-dependent inhibition of stent thrombosis, with 87% reduction at a dose of 10 mg.kg⁻¹ (P < 0.001). Aspirin alone (10 mg.kg⁻¹) was minimally effective (20% inhibition P > 0.05) in inhibiting stent thrombosis. Combined treatment with clopidogrel and aspirin produced 95-98% inhibition of stent thrombosis, even at low doses of clopidogrel (2.5-5.0 mg.kg⁻¹) (P < 0.0001). At effective doses both clopidogrel and combined therapy produced significant prolongation of bleeding time (P < 0.05) and inhibition of platelet aggregation (P < 0.05).

CONCLUSION: Clopidogrel, either alone or combined with aspirin, may have a potential role in preventing stent thrombosis in high-risk clinical situations.

6. Clopidogrel for Ischaemic Events

(1) Caro JJ, Migliaccio-Walle K

GENERALIZING THE RESULTS OF CLINICAL TRIALS TO ACTUAL PRACTICE: THE EXAMPLE OF CLOPIDOGREL THERAPY FOR THE PREVENTION OF VASCULAR EVENTS. CAPRA (CAPRIE ACTUAL PRACTICE RATES ANALYSIS) STUDY GROUP. CLOPIDOGREL VERSUS ASPIRIN IN PATIENTS AT RISK OF ISCHAEMIC EVENTS.


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PURPOSE: An important element in translating the results obtained in clinical trials of a new treatment to clinical practice is the estimated event rate in patients who would be eligible to receive that treatment. We estimated the effect of clopidogrel, compared with aspirin, in actual practice using the relative risk reduction observed in the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial. SUBJECTS AND METHODS: Ischemic event rates were estimated for 12,931 aspirin users drawn from the Saskatchewan Health population between 1990 and 1995 who had an index diagnosis of myocardial infarction, ischemic stroke, or peripheral arterial disease. To estimate the absolute risk reduction, the 8.7% relative risk reduction from clopidogrel compared with aspirin that was observed in CAPRIE was applied to these rates. RESULTS: The
rates of ischemic events were greater in actual practice than among the control patients in the CAPRIE trial. In the Saskatchewan population, patients experienced an outcome event (myocardial infarction, stroke including intracranial hemorrhage, or death) at a rate of 15.9 per 100 patient-years, compared with only 6.9 per 100 patient-years in CAPRIE. If the same 8.7% relative risk reduction seen in the CAPRIE trial is also true for patients seen in routine clinical practice, the greater absolute risk in actual practice would reduce the number needed to treat to prevent one event from 200 patients to 70 patients. CONCLUSION: Absolute risk rates may be substantially greater in clinical practice than in the selected patients enrolled in randomized trials. As a result, similar reductions in relative risk, if true for clinical practice, may yield substantially more benefit in clinical practice than in randomized trials.

7. Clopidogrel antagonism by Aprotinin

(1) Herbert JM, Bernat A, Maffrand JP

APROTININ REDUCES CLOPIDOGREL-INDUCED PROLONGATION OF THE BLEEDING TIME IN THE RAT.


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High doses of aprotinin have been shown to reduce blood loss and blood transfusion requirements in patients undergoing open heart surgery and recent studies in animals have shown that aprotinin was able to reduce bleeding associated with rt-PA administration. Our study was designed to demonstrate an effect of aprotinin (Iniprol) on the prolongation of the bleeding time associated with the treatment with a potent analogue of ticlopidine: clopidogrel. Bleeding time was determined in rats by transection of the tip of the tail. 2 hours after a single oral administration, clopidogrel (5 mg/kg, p.o.), induced a 4-fold increase in the bleeding time. Aprotinin administered as a bolus iv injection followed by continuous infusion strongly reduced bleeding time prolongation associated with clopidogrel treatment. This effect was dose-related and reached a maximum (congruent to 50% inhibition--P < 0.001) at and above the total dose of 40 U Ph Eur/kg (80,000 KIU/kg). After administration of a total dose of 60 U Ph Eur/kg (120,000 KIU/kg), aprotinin modified neither the antiaggregating effect of clopidogrel nor its antithrombotic activity, as determined in various experimental models. For this reason, aprotinin might constitute a useful antagonist of the haemorrhagic risk associated with interventional therapy under treatment with ticlopidine or clopidogrel.

1. Clopidogrel induced Complications

Complications with Clopidogrel are rare as little as with ASA

B. Clopidogrel induced Complications

1. Clopidogrel induced Nephropathy

(1) Tholl U, Anlauf M, Helmchen U

CLOPIDOGREL AND MEMBRANOUS NEPHROPATHY.

Lancet 1999 Oct 23;354(9188):1443-4

Membranous nephropathy with nephrotic syndrome occurred in a patient with anterior myocardial infarction 2 months after the start of clopidogrel treatment. Sensitisation by prior treatment with ticlopidine is discussed.

2. Clopidogrel effect on Naproxen induced GI bleeding


EFFECT OF CLOPIDOGREL ON NAPROXEN-INDUCED GASTROINTESTINAL BLOOD LOSS IN HEALTHY VOLUNTEERS.


Centre for Clinical Pharmacology, UZ Gasthuisberg, K.U.Leuven, Belgium.

The effect of clopidogrel, a potent inhibitor of platelet aggregation, on naproxen-induced faecal blood loss was investigated in 30 healthy volunteers in a randomized, double-blind, placebo-controlled, two parallel treatment groups study. All subjects first received naproxen 250 mg b.i.d. during 7 days, after which they were randomly allocated to additionally receive either clopidogrel 75 mg once daily (n = 15) or matching placebo (n = 15) for 11 days. Faecal blood loss was measured by the 51Cr-labelled erythrocyte method during the last four days of each of the four study periods, i.e. baseline, treatment with naproxen alone, combined treatment and wash-out. Mean daily faecal blood loss was below 0.5 ml/day during the baseline period in both treatment groups and increased during treatment with naproxen alone to (mean +/- SD) 1.14 +/- 0.58 ml/day in the naproxen + placebo group and to 1.93 +/- 1.51 ml/day in the naproxen + clopidogrel group. Addition of clopidogrel to naproxen treatment was associated with an increase of the mean daily blood loss to 6.83 +/- 9.32 ml/day, which was statistically significantly higher than 1.75 +/- 1.40 ml/day observed during treatment with naproxen + placebo. During the wash-out period, mean daily blood loss decreased to 0.98 +/- 0.51 ml/day in the naproxen + placebo group and to 1.07 +/- 0.46 ml/day in the naproxen + clopidogrel group. Based on these results, it can be concluded that clopidogrel increases naproxen-induced gastrointestinal blood loss in healthy volunteers. Caution should therefore be called for when these drugs are coadministered.

3. Clopidogrel Interactions

(1) Easton JD

**CLINICAL ASPECTS OF THE USE OF CLOPIDOGREL, A NEW ANTIPLATELET AGENT.**

*Semin Thromb Hemost* 1999;25 Suppl 2:77-82

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Clopidogrel, a new platelet ADP receptor antagonist, is more effective than aspirin in reducing the risk of subsequent vascular ischemic events in patients with a broad spectrum of symptomatic atherosclerosis (recent ischemic stroke, recent myocardial infarction, or symptomatic peripheral arterial disease). In CAPRIE (clopidogrel versus aspirin in patients at risk of ischemic events), a randomized, blinded, active control trial in 19,185 high-risk patients, clopidogrel reduced the combined risk of ischemic stroke, myocardial infarction or vascular death by 8.7% compared with aspirin (p = 0.043). The CAPRIE cohort had a mean age of 62.5 years, which was reflected in the high proportion of patients who had medical conditions other than symptomatic atherosclerosis, and in the extensive use of concurrent therapies, including commonly used cardiovascular drugs. For all concomitant medications analysed, there was no evidence of statistically or clinically significant interactions with clopidogrel. The CAPRIE data confirm the findings of earlier clinical studies, which suggested that clinically significant drug interactions with clopidogrel are rare, that it can safely be prescribed with a range of other drugs (including phenobarbital, cimetidine, estrogen, digoxin, theophylline, atenolol, nifedipine, or nifedipine-atenolol in combination), and that the clinically proven dose of 75 mg once daily is suitable for all age groups studied. Moreover, CAPRIE demonstrated that there is no need for an adjustment of clopidogrel dose on the basis of gender, weight or race, and that there is no need for routine hematological monitoring. Additional clinical pharmacology studies have shown that the absorption of clopidogrel is unaffected by food or antacids, and that no dose adjustment is necessary in patients with renal impairment or with mild-to-moderate hepatic impairment. Due to pharmacologic considerations and limited clinical data, clopidogrel should be used cautiously with heparin, warfarin or non-steroidal anti-inflammatory drugs. With a simple regimen of 75 mg once daily indicated for all patients, clopidogrel combines a favorable risk/benefit ratio with ease of use in clinical practice.

**D. Platelet Glycoprotein IIb/IIIa Receptor Inhibitor**

A. Function and Fields of Use

1. GPIIb/IIIa Inhibitor General Aspects
For the long-term prevention of thromboembolic events in patients with atherosclerotic vascular disease, aspirin is the preferred antiplatelet drug. Only clopidogrel was shown to be more effective and at least as safe as medium-dose aspirin in direct comparative large-scale trials. Aspirin inhibits the cyclooxygenase dependent pathway of platelet aggregation while ticlopidine and clopidogrel selectively bind to adenosine diphosphate (ADP) receptors on the platelet surface. Compounds which inhibit the synthesis of thromboxane synthase, block the thromboxane receptor or have the dual activity were effective in experimental thrombosis models in animals but not predictive of results in humans. Activation of the platelet glycoprotein (GPIIb/IIIa) receptor on the platelet surface is the final pathway of platelet aggregation, regardless of the initiating stimulus. Inhibitors of GPIIb/IIa receptors include monoclonal antibodies (abciximab) against this receptor and peptidic as well as non-peptidic synthetic specific receptor blockers. Abciximab exchanges between and binds to platelets for as long as two weeks whereas synthetic GPIIb/IIa inhibitors inhibit ex vivo platelet aggregation for only a few hours after the end of infusion but have the advantage of being also orally active. In the secondary prevention of atherothrombosis, large scale trials were successfully conducted with aspirin, dipyridamole and clopidogrel. In the first large-scale trials with GPIIb/IIa inhibitors with abciximab was investigated. In aggregate, this class of platelet inhibitors, combined with aspirin and heparin, was shown to reduce ischaemic events in patients with high- and low-risk coronary intervention, stents, unstable angina and non-Q-wave infarction with long-term preservation of the initial benefit. With synthetic GPIIb/IIa inhibitors there is no suppression of clinical evident restenosis 6 months after the end of treatment. With the doses presently used, bleeding occurs more often with the synthetic GPIIb/IIa inhibitors (used for 3 days) than with abciximab (used for 12 hours) but there are no direct comparisons between these drugs.

Aggregation of platelets leading to thrombosis is one of the hallmarks of unstable angina, acute myocardial infarction, and ischaemic complications following coronary angioplasty. Activated platelets bind to fibrinogen through the glycoprotein IIb/IIIa integrin receptor. New agents have been developed to bind this receptor and thus prevent aggregation of platelets. One such compound (integrelin) is a cyclical peptide that has been shown to be a potent inhibitor of the glycoprotein IIb/IIa receptor in man. A number of phase I and phase II clinical trials have been completed to evaluate this agent for the indications of unstable angina, acute myocardial infarction, as well as an adjunct to coronary angioplasty. This article will focus on the clinical investigation of integrelin with particular emphasis on its use during angioplasty. It has been consistently shown across different trials that integrelin can inhibit between 70% and 95% of platelet aggregation responses to 20 mumols of ADP at a variety of dosages used in the phase II trials. Preliminary data also suggest that a more clinically unstable patient may require a higher dose of integrelin to cause a near complete inhibition of the platelet aggregation response to ADP. Future studies will need to explore more definitively the relationship between dose of glycoprotein IIb/IIa receptor blockers and clinical instability.

2. GPIIB/IIIA Inhibitor in Myocardial Ischemia
(1) Holper EM, Giugliano RP, Antman EM

GLYCOPROTEIN IIB/IIIA INHIBITORS IN ACUTE ST SEGMENT ELEVATION MYOCARDIAL INFARCTION.

Coron Artery Dis 1999 Dec;10(8):567-73

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Limitations in the standard treatment of acute myocardial infarction have focused attention on inhibition of platelet activity by its final common pathway of activation, the glycoprotein IIb/IIa receptor. Animal studies have suggested that a glycoprotein IIb/IIa inhibitor could accelerate thrombolysis and prevent reocclusion after successful thrombolysis. Studies evaluating the use of a glycoprotein IIb/IIa inhibitor alone without thrombolysis or percutaneous transluminal coronary revascularization do not suggest that isolated use of glycoprotein IIb/IIa inhibitors restores TIMI 3 flow in a sufficient proportion of patients. Clinical studies evaluating the combination of thrombolytic therapy and glycoprotein IIb/IIa inhibitors appear most promising, with evidence of improved angiographic outcomes. Reducing the dose of thrombolytic agents may result in reduction in bleeding risk. Current and future trials will investigate reduced-dose reteplase with abciximab and eptifibatide with reduced-dose alteplase. Available evidence suggests that glycoprotein IIb/IIa inhibition may facilitate thrombolysis, thus adding a new element to future reperfusion regimens.

(2) Silveira C, Ferreira RC, Quininha J, Ferreira M de L, Goncalves JM, Ramos JS, Figueiredo L, Antunes AM

THE USE OF ABCIXIMAB IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION UNDERGOING DIRECT PERCUTANEOUS CORONARY REVASCULARIZATION.

Rev Port Cardiol 1999 Sep;18(9):815-9

Servico de Cardiologia do Hospital de Santa Marta, Lisboa.

OBJECTIVE: To evaluate the initial experience, in our Centre, with Abciximab in patients with acute myocardial infarction undergoing direct percutaneous transluminal coronary angioplasty (PTCA). METHODS: Between October 1996 and May 1998, 65 patients (51 males, mean age 56.9 +/- 11 years) underwent direct PTCA for acute myocardial infarction. In thirty-seven patients the myocardial infarction was anterior and 40 had multivessels disease. Mainly to compare the incidence of bleeding complications we considered 2 groups: Group A--17 patients submitted to PTCA without the use of Abciximab, and Group B--48 patients submitted to PTCA and to a bolus followed by a 12 hour infusion of Abciximab. All the patients were treated with aspirin and heparin (5,000 to 15,000 U according to ACT) and ticlopidine in case of stent implantation. RESULTS: Percutaneous coronary revascularization was successfully achieved in 92.3% of the patients. The total number of bleeding complications was ten cases (20.8%) in Group B and 1 case (5.8%) in Group A. Most of the bleeding complications in the Abciximab Group were minor and related to the femoral vascular access site (9 cases--18.7%) and were easily resolved with local measures (8 cases). There were also 3 cases of hematemesis and one of oral bleeding, all well tolerated. Major bleeding complications were identified in only one patient of the Abciximab Group related to the vascular access site, however there was an absolutely similar case in Group A (2% versus 5.8%). CONCLUSIONS: Although bleeding complications were more frequent in patients receiving Abciximab, mostly related to the vascular access site, they were transient and well tolerated.

(3) Montalescot G

IIB/IIIA INHIBITORS IN ACUTE MYOCARDIAL INFARCTION.

Blood Coagul Fibrinolysis 1999 Feb;10 Suppl 1:S71-5

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Platelets play a key role both in ischemic complications after percutaneous transluminal coronary angioplasty (PTCA) and in the pathogenesis of acute myocardial infarction (AMI). Until recently, there was no treatment to dissolve the platelet clot. Indeed, the plasminogen activators achieve fibrin lysis but their platelet activating side-effects and their prothrombotic effects led to failure in PTCA trials and to a significant rate of reocclusions in thrombolysis trials. A new class of platelet...
antagonists directed against the platelet membrane glycoprotein IIb/IIIa receptor has undergone extensive evaluation in the prevention of ischemic complications of PTCA. In contrast, its development in the treatment of AMI is just starting. This class of medications has the potential to improve clinical outcome of AMI treated either with primary angioplasty or with thrombolysis.

(4) Foster RH, Wiseman LR
**ABCIXIMAB. AN UPDATED REVIEW OF ITS USE IN ISCHAEMIC HEART DISEASE.**
*Drugs* 1998 Oct;56(4):629-65

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Abciximab is a glycoprotein IIb/IIIa receptor antagonist that has proven to be of significant clinical value in improving patient outcome after percutaneous coronary revascularisation. Primarily, the drug (a) inhibits platelet aggregation, but it may also have (b) anticoagulant activity and other beneficial effects, such as (c) inhibiting migration and (d) promoting apoptosis of smooth muscle cells. Large well designed studies have found administration of abciximab (as an adjunct to heparin and aspirin) during percutaneous coronary revascularisation to significantly reduce the incidence of ischaemic complications occurring in the 30 days after the procedure. Significant benefit, particularly on the incidence of myocardial infarction, was still evident after 6 months in 2 of 4 major trials. Abciximab provides particular benefit in patients with unstable angina or myocardial infarction who are undergoing percutaneous coronary revascularisation. The benefits of the drug are additive to those achieved with coronary stenting. Very preliminary data suggest that abciximab may improve coronary blood flow after myocardial infarction and allow reperfusion to be achieved with reduced thrombolytic doses. Caution is required to minimise the risk of bleeding complications with the use of abciximab in combination with heparin and aspirin. Careful patient selection, use of an appropriate heparin regimen, early vascular sheath removal and meticulous femoral artery access site care are recommended. Thrombocytopenia can occur with abciximab treatment, but severe cases are uncommon (<2% of patients) and can be treated with platelet transfusions. The high acquisition cost of abciximab may be partly or fully offset by the costs averted by the reduced incidence of ischaemic complications and need for urgent and/or repeat revascularisation in high risk patients who receive the drug. However, if bleeding complications occur, this adds to treatment costs. Cost effectiveness analyses generally support the use of abciximab in high risk patients. CONCLUSIONS: Abciximab can be recommended for the prevention of acute ischaemic events in most patients undergoing percutaneous coronary revascularisation, but careful patient selection and strict adherence to the recommended treatment protocol are required to reduce the risk of bleeding complications and thrombocytopenia. Its use in high risk patients is largely supported by pharmacoeconomic data. Further pharmacoeconomic information is needed to establish the drug as a standard of care for all patient groups. The indications for abciximab are likely to expand as more data on its use in acute coronary syndromes become available.

**COMBINED ACCELERATED TISSUE-PLASMINOGEN ACTIVATOR AND PLATELET GLYCOPEPTRIN IIb/IIIa INTEGRIN RECEPTOR BLOCKADE WITH INTEGRILIN IN ACUTE MYOCARDIAL INFARCTION. RESULTS OF A RANDOMIZED, PLACEBO-CONTROLLED, DOSE-RANGING TRIAL. IMPACT-AMI INVESTIGATORS.**
*Circulation* 1997 Feb 18;95(4):846-54

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BACKGROUND: Platelet activation and aggregation may be key components of thrombolytic failure to restore and maintain perfusion in acute myocardial infarction. We performed a placebo-controlled, dose-ranging trial of Integrlin, a potent inhibitor of platelet aggregation, with heparin, aspirin, and accelerated alteplase. METHODS AND RESULTS: We assigned 132 patients in a 2:1 ratio to receive a bolus and continuous infusion of one of six Integratin doses or placebo. Another 48 patients were randomized in a 3:1, double-blind fashion to receive the highest Integratin dose from the first phase or placebo. All patients received accelerated alteplase, aspirin, and intravenous heparin infusion; all but two groups also received an intravenous heparin bolus. The highest Integratin dose group from the nonrandomized phase and the randomized patients were pooled for analysis and compared with placebo-
treated patients. The primary end point was Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow at 90-minute angiography. Secondary end points were time to ST-segment recovery, an in-hospital composite (death, reinfarction, stroke, revascularization procedures, new heart failure, or pulmonary edema), and bleeding variables. The highest Integrilin dose groups had more complete reperfusion (TIMI grade 3 flow, 66% versus 39% for placebo-treated patients; \( P = .006 \)) and a shorter median time to ST-segment recovery (65 versus 116 minutes for placebo; \( P = .05 \)). The groups had similar rates of the composite end point (43% versus 42% for placebo-treated patients) and severe bleeding (4% versus 5%, respectively). CONCLUSIONS: The incidence and speed of reperfusion can be enhanced when a potent inhibitor of the glycoprotein IIb/IIIa integrin receptor, such as Integrilin, is combined with accelerated alteplase, aspirin, and intravenous heparin.

Comment in: Circulation 1997 Feb 18;95(4):793-5

(6) Bates ER

PLATELET GLYCOPROTEIN IIB/IIIA INHIBITOR THERAPY IN ACUTE MYOCARDIAL INFARCTION.


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There are many limitations to reperfusion therapy for acute myocardial infarction. Preliminary studies have explored the potential of using more potent antiplatelet therapy. Abciximab, eptifibatide, and lamifiban are new agents that inhibit platelet glycoprotein IIb/IIa, which serves as the final common pathway for platelet aggregation. Infarct artery patency occurs more rapidly, normal coronary blood flow is more often restored, and reperfusion is more stable when these agents are used with standard- or reduced-dose fibrinolytic therapy. Moreover, abciximab monotherapy has thrombolytic activity and facilitates primary angioplasty or stenting. Further studies are needed to define safety, efficacy, and cost effectiveness.

3. GPIIB/IIIA Inhibitor in Coronary Interventions

(1) Popma JJ

USE OF GLYCOPROTEIN IIB/IIIA INHIBITORS IN PATIENTS WITH ACUTE CORONARY SYNDROMES UNDERGOING CORONARY REVASCULARIZATION.

Haemostasis 1999 Dec;29 Suppl S1:69-71

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This paper briefly reviews the results from three recent large-scale clinical trials evaluating the benefit of glycoprotein IIb/IIa inhibitors in patients with acute coronary syndromes (ACS). The available data suggest that these are promising agents for the management of ACS, particularly in improving the immediate outcome in the acute setting. Copyright 1999 S. Karger AG, Basel

(2) Bell DM

ANALYSIS OF NUMBER NEEDED TO TREAT AND COST OF PLATELET GLYCOPROTEIN IIB/IIIA INHIBITORS IN PERCUTANEOUS CORONARY INTERVENTIONS AND ACUTE CORONARY SYNDROMES.

Pharmacotherapy 1999 Sep;19(9):1086-93

School of Pharmacy, West Virginia University, Morgantown, USA.

This retrospective review and analysis of pivotal clinical trials compared acquisition costs and outcomes of platelet glycoprotein IIb/IIa inhibitors. Absolute reduction in the number of deaths and nonfatal myocardial infarctions at 30 days, number of patients that need to be treated to prevent one event, and drug costs expended to prevent one event were assessed. In patients undergoing percutaneous coronary intervention (PCI), abciximab is the better value, especially in high-risk patients. In those with unstable angina and non-Q wave myocardial infarction, costs of eptifibatide and tirofiban were not significantly different, but the cost of tirofiban was more variable. These agents have the potential to be cost-effective if administered to populations at high risk for adverse
outcomes of acute coronary syndromes or PCI. Prospective methods to identify these high-risk patients are being developed.

(3) Matos V, Marques AM, Oliveira H, Ramos D, Lopes P, Camacho M, Gonsalves A
[ADJUVANT THERAPY WITH A GLYCOPROTEIN IIb-IIa INHIBITOR (ABCIXIMAB) IN CORONARY ANGIOPLASTIES WITH A HIGH THROMBOTIC RISK] [ARTICLE IN PORTUGESE].
Rev Port Cardiol 1998 Dec;17(12):1001-5

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INTRODUCTION: We retrospectively studied our experience with adjunctive therapy with glycoprotein IIb-IIIa inhibitor (abciximab) on patients with a high risk of thrombotic complications during coronary angioplasty (PTCA). PATIENTS AND METHODS: From September 1996 to November 1997, we performed PTCA in 210 patients, and abciximab was given to 38 (18%) of them. The interventions were urgent (primary PTCA in acute myocardial infarction) in 55% of the cases. The mean age of patients was 68.6 +/- 12 years and 71% were male. The reasons for coronary intervention were: acute myocardial infarction in 21 patients (55.3%), unstable angina in 9 (23.7%) and stable angina in 8 (21%). Coronary stents were implanted in 13 patients (34%) and an intra aortic balloon pump was used in 4 (11%). The reasons for using abciximab were: thrombus containing lesion: 22 (57.9%); other type B2/C lesion characteristics: 6 (15.9%); acute closure post balloon PTCA: 9 (23.7%), sub-acute stent thrombosis: 1 (2.6%). Oral acetilsalicilic acid and intravenous heparin were given to all patients at the beginning of the intervention. The mean APTT was 124 +/- 32 seconds at the end of the procedure. RESULTS: The arterial sheaths (8 French) were removed six hours after procedure, according to the normalisation of APTT values. Angiographic success in this group of patients was 100%. One patient died during hospitalisation due to left ventricular failure. There was no need for repeated angioplasty or coronary bypass grafting during hospital stay. The main complications related to the use of abciximab were: bleeding (requiring transfusion) in four patients (10.5%); severe thrombocytopenia (< 50,000 platelets/mm3): 1 (2.6%): cardiac tamponade (requiring pericardiocentesis): 1 (2.6%) and pseudo-aneurysm of femoral artery (requiring vascular surgery): 1 (2.6%). CONCLUSIONS: The use of abciximab as adjunctive therapy in this small group of patients undergoing coronary interventions with high risk of thrombotic complications is associated with high procedural success, but at the expense of high rates of bleeding complications. Therefore, special care must be applied during and after the procedure to enhance the safety of the patients treated with this drug.

(4) Lincoff AM
TRIALS OF PLATELET GLYCOPROTEIN IIb/IIIa RECEPTOR ANTAGONISTS DURING PERCUTANEOUS CORONARY REVASCULARIZATION.
Am J Cardiol 1998 Oct 22;82(8B):36P-42P

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Selective inhibition of the platelet glycoprotein (GP) IIb/ IIIa surface receptor is a potent mechanism to inhibit platelet aggregation and thrombus formation. Over 15,000 patients have been enrolled in pivotal trials of GP IIb/IIIa receptor blockade with the parenteral inhibitors abciximab, epifibatide, and tirofiban during coronary intervention, unequivocally establishing the clinical efficacy of this class of therapy in this setting. Reductions of up to 50-60% in the risk of important clinical endpoints have been achieved with these agents, a treatment effect that extends to all components of the composite clinical endpoints (death, myocardial infarction, and emergency revascularization). Inhibition of ischemic events by GP IIb/IIIa blockade is achieved early and almost invariably maintained without attenuation over long-term follow-up, although an influence of these agents on the risk of restenosis has not been consistently observed. All patients undergoing intervention appear to benefit from this class of therapy, irrespective of their risk profile or indication for revascularization, and clinical benefit is independent of the device or modality (stent, balloon, atherectomy) used. Patients undergoing coronary revascularization for acute ischemic syndromes such as unstable angina may derive exceptional treatment effect. Excessive bleeding risk associated with these agents may be markedly diminished without loss of efficacy by reduction in conjunctive heparin dosing.
(5) Topol EJ

EVOlution of improved antithrombotic and antiplatelet agents: Genesis of the comparison of Abciximab complications with Hirulog [and back-up Abciximab] events trial.

*Cardiol* 1998 Oct 22;82(8B):63P-68P

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Enhanced adjunctive pharmacotherapy for percutaneous coronary revascularization is evolving. New modifications to the original antithrombotic, antiplatelet combination of heparin and aspirin have become part of standard practice. Platelet glycoprotein (GP) IIb/IIIa receptor inhibitors have been shown to decrease the incidence of death or nonfatal myocardial infarction at 30 days by approximately 50%. However, there are continuing concerns with this class of agents, including bleeding complications, cost, and the inability to identify which patients are most likely to benefit from their use. Bivalirudin, a direct thrombin inhibitor capable of inactivating clot-bound thrombin, has demonstrated enhanced short-term efficacy with a significantly decreased incidence of bleeding compared with heparin in patients with acute coronary syndromes. These findings provided a basis for a new, large-scale trial—Comparison of Abciximab Complications with Hirulog [and Back-Up Abciximab] Events Trial (CACHET)—which compares primary abciximab plus aspirin and heparin with aspirin plus intraprocedural bivalirudin and ad hoc abciximab. All patients who are candidates for stenting will receive clopidogrel before coronary intervention, and if stenting is performed, maintenance clopidogrel for 30 days. The trial aims to evaluate improved anticoagulation with bivalirudin and preprocedural oral antiplatelet protection and the use of ad hoc abciximab as a basis for a practical, acceptable antithrombotic, antiplatelet strategy to improve outcomes in percutaneous coronary revascularization.

(6) Cannon CP

Advances in the medical management of acute coronary syndromes.

*Curr Opin Cardiol* 1998 Sep;13(5):327-47

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Many advances in the treatment of acute coronary syndromes have been realized over recent years. In ST elevation myocardial infarction, new aggressive thrombolytic regimens improve early reperfusion and improve survival. The current focus is on bolus thrombolysis, glycoprotein IIb/IIIa inhibition, and low-molecular-weight heparin as adjuncts. In unstable angina and non-ST elevation myocardial infarction, two major advances are IIb/IIIa inhibition and low-molecular-weight heparin, each of which significantly improves the outcome of patients and which have just been approved for use by the Food and Drug Administration. Following acute coronary syndromes, cholesterol lowering with statin drugs has a major effect, even in the large group of patients with average cholesterol levels. Use of clopidogrel, a more potent antiplatelet agent than aspirin, appears to decrease recurrent ischemic events, which has highlighted the potential benefits of oral IIb/IIIa inhibitors, which are much more potent antiplatelet agents. An additional focus has been on ensuring that patients actually receive the currently available medications. With a great number of new medical treatments, the outcome of patients with acute coronary syndromes has improved and will continue to improve as we enter the next millennium.


Administration of abciximab during percutaneous coronary intervention reduces both ex vivo platelet thrombus formation and fibrin deposition: Implications for a potential anticoagulant effect of abciximab.


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Abciximab (c7E3 Fab, ReoPro), a platelet glycoprotein (GP) IIb/IIIa inhibitor, decreases acute ischemic complications after percutaneous coronary interventions. Recently, abciximab was shown to
decrease thrombin generation in vitro in a static system. To assess whether abciximab can decrease fibrin formation in blood from patients, we quantified both platelet thrombi and fibrin deposition by using an ex vivo flow chamber model. We prospectively studied 18 consecutive patients who underwent percutaneous interventions for unstable coronary syndromes. Blood was perfused directly from the patient through an ex vivo perfusion chamber at a high shear rate, thus mimicking mildly stenosed coronary arteries. Perfusion chamber studies were performed when patients were being treated with heparin plus aspirin before the procedure (baseline) and then repeated after the procedure, when patients were on either aspirin plus heparin alone (group 1, no abciximab, control) or aspirin plus heparin plus abciximab (group 2, abciximab treated). Group 1 demonstrated no significant change in thrombus area before versus after the procedure; in contrast, treatment with abciximab reduced total thrombus area by 48% in group 2 (after the procedure versus baseline, \( P=0.01 \)). This decline was due to significant reductions in both platelet aggregates (55%, \( P=0.005 \)) and fibrin layers (45%, \( P=0.03 \)). The addition of abciximab to heparin and aspirin in patients undergoing coronary interventions significantly decreases ex vivo thrombus formation on an injured vascular surface. Treatment with abciximab appears to reduce both the platelet and the fibrin thrombus components. This finding supports a potential role for GP IIb/IIIa receptor blockade in decreasing fibrin formation in addition to inhibition of platelet aggregation. Thus, potent inhibitors of GP IIb/IIIa may also act as anticoagulants.

(8) No Authors Listed

INHIBITION OF PLATELET GLYCOPROTEIN IIB/IIIa WITH EPTIFIBATIDE IN PATIENTS WITH ACUTE CORONARY SYNDROMES. THE PURSUIT TRIAL INVESTIGATORS. PLATELET GLYCOPROTEIN IIB/IIIa IN UNSTABLE ANGINA: RECEPTOR SUPPRESSION USING INTEGRILIN THERAPY.


BACKGROUND: Aggregation of platelets is the pathophysiologic basis of the acute coronary syndromes. Eptifibatide, a synthetic cyclic heptapeptide, is a selective high-affinity inhibitor of the platelet glycoprotein Iib/IIIa receptor, which is involved in platelet aggregation. We tested the hypothesis that inhibition of platelet aggregation with eptifibatide would have an incremental benefit beyond that of heparin and aspirin in reducing the frequency of adverse outcomes in patients with acute coronary syndromes who did not have persistent ST-segment elevation. METHODS: Patients who had presented with ischemic chest pain within the previous 24 hours and who had either electrocardiographic changes indicative of ischemia (but not persistent ST-segment elevation) or high serum concentrations of creatine kinase MB isoenzymes were enrolled in the study. They were randomly assigned, in a double-blind manner, to receive a bolus and infusion of either eptifibatide or placebo, in addition to standard therapy, for up to 72 hours (or up to 96 hours, if coronary intervention was performed near the end of the 72-hour period). The primary end point was a composite of death and nonfatal myocardial infarction occurring up to 30 days after the index event. RESULTS: A total of 10,948 patients were enrolled between November 1995 and January 1997. As compared with the placebo group, the eptifibatide group had a 1.5 percent absolute reduction in the incidence of the primary end point (14.2 percent, vs. 15.7 percent in the placebo group; \( P=0.04 \)). The benefit was apparent by 96 hours and persisted through 30 days. The effect was consistent in most major subgroups except for women (odds ratios for death or nonfatal myocardial infarction, 0.8 [95 percent confidence interval, 0.7 to 0.9] in men, and 1.1 [0.9 to 1.3] in women). Bleeding was more common in the eptifibatide group, although there was no increase in the incidence of hemorrhagic stroke. CONCLUSIONS: Inhibition of platelet aggregation with eptifibatide reduced the incidence of the composite end point of death or nonfatal myocardial infarction in patients with acute coronary syndromes who did not have persistent ST-segment elevation.

4. GPIIB/IIIa Inhibitor in Unstable Angina /Non Q Wave Myocardial Infarction

(1) Ambrose JA, Dangas G

UNSTABLE ANGINA: CURRENT CONCEPTS OF PATHOGENESIS AND TREATMENT.


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During the past 15 years, we have learned an enormous amount about the pathogenesis and treatment of unstable angina. In most cases of unstable rest angina, the pathogenesis is a mural thrombus formation on a ruptured or eroded atherosclerotic plaque. However, any process that acutely changes the supply-demand ratio (decreased supply or increased demand in the presence of a decrease in supply) can precipitate the clinical presentation of unstable angina. Standard acute antithrombotic drug therapy is effective in decreasing progression to infarction. Newer agents (low-molecular-weight heparin and platelet glycoprotein IIb/IIIa inhibitors) are more effective, and their use is evolving. Percutaneous intervention and bypass surgery can reduce symptoms and multiple hospitalizations, in most cases without a decrease in the long-term mortality rate. Because the cost of hospitalization is extremely high and the clinical presentation and outcome are heterogeneous, better triage methods are required.

(2) No Authors Listened

INHIBITION OF THE PLATELET GLYCOPROTEIN IIB/IIIA RECEPTOR WITH TIROFIBAN IN UNSTABLE ANGINA AND NON-Q-WAVE MYOCARDIAL INFARCTION. PLATELET RECEPTOR INHIBITION IN ISCHEMIC SYNDROME MANAGEMENT IN PATIENTS LIMITED BY UNSTABLE SIGNS AND SYMPTOMS (PRISM-PLUS) STUDY INVESTIGATORS.


BACKGROUND: Antithrombotic therapy improves the prognosis of patients with acute coronary syndromes, yet the syndromes remain a therapeutic challenge. We evaluated tirofiban, a specific inhibitor of the platelet glycoprotein IIb/IIIa receptor, in the treatment of unstable angina and non-Q-wave myocardial infarction. METHODS: A total of 1915 patients were randomly assigned in a double-blind manner to receive tirofiban, heparin, or tirofiban plus heparin. Patients received aspirin if its use was not contraindicated. The study drugs were infused for a mean (+/-SD) of 71.3 +/- 20 hours, during which time coronary angiography and angioplasty were performed when indicated after 48 hours. The composite primary end point consisted of death, myocardial infarction, or refractory ischemia within seven days after randomization. RESULTS: The study was stopped prematurely for the group receiving tirofiban alone because of excess mortality at seven days (4.6 percent, as compared with 1.1 percent for the patients treated with heparin alone). The frequency of the composite primary end point at seven days was lower among the patients who received tirofiban plus heparin than among those who received heparin alone (12.9 percent vs. 17.9 percent; P=0.004). The rates of the composite end point in the tirofiban-plus-heparin group were also lower than those in the heparin-only group at 30 days (18.5 percent vs. 22.3 percent, P=0.03) and at 6 months (27.7 percent vs. 32.1 percent, P=0.02). At seven days, the frequency of death or myocardial infarction was 4.9 percent in the tirofiban-plus-heparin group, as compared with 8.3 percent in the heparin-only group (P=0.006). The comparable figures at 30 days were 8.7 percent and 11.9 percent (P=0.03), respectively, and those at 6 months were 12.3 percent and 15.3 percent (P=0.06). The benefit was consistent in the various subgroups of patients and in those treated medically as well as those treated with angioplasty. Major bleeding occurred in 3.0 percent of the patients receiving heparin alone and 4.0 percent of the patients receiving combination therapy (P=0.34). CONCLUSIONS: When administered with heparin and aspirin, the platelet glycoprotein IIb/IIIa receptor inhibitor tirofiban was associated with a lower incidence of ischemic events in patients with acute coronary syndromes than in patients who received only heparin and aspirin.


(3) No Authors Listened

EFFECTS OF PLATELET GLYCOPROTEIN IIB/IIIA BLOCKADE WITH TIROFIBAN ON ADVERSE CARDIAC EVENTS IN PATIENTS WITH UNSTABLE ANGINA OR ACUTE MYOCARDIAL INFARCTION UNDERGOING CORONARY ANGIOPLASTY. THE RESTORE INVESTIGATORS. RANDOMIZED EFFICACY STUDY OF TIROFIBAN FOR OUTCOMES AND RESTENOSIS.

Circulation 1997 Sep 2;96(5):1445-53

BACKGROUND: Adverse cardiovascular events associated with thrombotic occlusion occur in 4% to 12.8% of patients after coronary angioplasty. Recently, potent antiplatelet agents have been used to reduce those thrombotic complications. Tirofiban is a highly selective, short-acting inhibitor of fibrinogen binding to platelet glycoprotein (GP) IIb/IIIa that inhibits ex vivo platelet aggregation in response to a variety of agonists. METHODS AND RESULTS: The RESTORE trial (Randomized
Efficacy Study of Tirofiban for Outcomes and REStenosis) was a randomized, double-blind, placebo-controlled trial of tirofiban in patients undergoing coronary interventions (balloon angioplasty or directional atherectomy) within 72 hours of presentation with an acute coronary syndrome (unstable angina pectoris or acute myocardial infarction). The end points of the study were death from any cause, myocardial infarction, coronary bypass surgery due to angioplasty failure or recurrent ischemia, repeat target-vessel angioplasty for recurrent ischemia, and insertion of a stent due to actual or threatened abrupt closure of the dilated artery, and the primary end point was a composite representing the occurrence of any of these events. The prespecified primary hypothesis of the study was that tirofiban, administered as a bolus of 10 microg/kg over a 3-minute period and followed by a 36-hour infusion of 0.15 microg x kg(-1) x min(-1), would result in a reduction in the 30-day composite end point compared with placebo. Patients (n=2139) who were already receiving treatment with aspirin and heparin were randomized to receive tirofiban or placebo. The primary composite end point at 30 days was reduced from 12.2% in the placebo group to 10.3% in the tirofiban group, a 16% relative reduction (P=.160). However, 2 days after angioplasty, the tirofiban group had a 38% relative reduction in the composite end point (P< or =.005), and at 7 days there was a 27% relative reduction (P=.022), largely because of a reduction in nonfatal myocardial infarction and the need for repeat angioplasty. When repeat angioplasty or coronary artery bypass surgery procedures were included in the composite only if performed on an urgent or emergency basis, the composite 30-day event rates were 10.5% for the placebo group and 8.0% for the tirofiban group, a relative reduction of 24% (P=.052). Major bleeding, including transfusion, was not significantly different between the two groups (3.7% in the placebo group and 5.3% in the tirofiban group; P=.096). When the Thrombolysis In Myocardial Infarction (TIMI) criteria for major bleeding were used, the incidence was 2.1% in the placebo group compared with 2.4% in the tirofiban group (P=.662). Thrombocytopenia was similar in the placebo and tirofiban groups (0.9% for the placebo group versus 1.1% for the tirofiban group; P=.709). CONCLUSIONS: In patients undergoing coronary angioplasty for acute coronary syndromes, tirofiban protects against early adverse cardiac events related to thrombotic closure. At 30 days, however, the reduction in adverse cardiac events was no longer statistically significant. The bleeding observed with tirofiban was not statistically different from that observed with placebo.

FIRST CHRONIC PLATELET GLYCOPROTEIN IIb/IIIa INTEGRIN BLOCKADE. A RANDOMIZED, PLACEBO-CONTROLLED PILOT STUDY OF XEMILOFIBAN IN UNSTABLE ANGINA WITH PERCUTANEOUS CORONARY INTERVENTIONS.
Circulation 1997 Jul 1;96(1):76-81

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BACKGROUND: Clinical studies have demonstrated the efficacy of intravenous administration of agents that block platelet glycoprotein IIb/IIIa receptors in the setting of percutaneous coronary revascularization. Although the optimal duration of treatment has not been determined, more prolonged receptor blockade has been associated with increased efficacy. Orally active glycoprotein IIb/IIIa receptor antagonists may be advantageous and required for chronic therapy. METHODS AND RESULTS: Thirty patients with unstable angina who were undergoing percutaneous coronary interventions were randomized to placebo or Xemilofiban 35 mg orally before and 20 to 25 mg TID for 30 days after angioplasty. Bleeding events, platelet aggregation, and pharmacokinetic and hematologic parameters were assessed during hospitalization and at 2 and 4 weeks after drug initiation. Xemilofiban produced a rapid, sustained, marked inhibition of platelet aggregation. ADP-induced platelet aggregation at 2 hours after the initial dose at 2 and 4 weeks was 15%, 8%, and 11% in the Xemilofiban group compared with 80%, 68%, and 69% in the placebo group. Among 20 patients randomized to Xemilofiban there was 1 death after emergency coronary bypass surgery complicated by severe bleeding diathesis, and 3 patients had major bleeding events. Patients on Xemilofiban for 30 days reported episodes of mild mucocutaneous bleeding. CONCLUSIONS: Xemilofiban, an orally active glycoprotein IIb/IIIa receptor inhibitor, produced rapid, sustained, extensive inhibition of platelet aggregation for a period of up to 30 days. At the dose initially tested, however, acute major bleeding and mucocutaneous bleeding during chronic administration were encountered.

(5) Schulman SP, Goldschmidt-Clermont PJ, Topol EJ, Califf RM, Navetta FI, Willerson JT, Chandra NC, Guerci AD, Ferguson JJ, Harrington RA, Lincoff AM, Yakubov SJ, Bray PF,

EFFECTS OF INTEGRIN, A PLATELET GLYCOPROTEIN IIb/IIIa RECEPTOR ANTAGONIST, IN UNSTABLE ANGINA. A RANDOMIZED MULTICENTER TRIAL.

Circulation 1996 Nov 1;94(9):2083-9

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BACKGROUND: Although aspirin is beneficial in patients with unstable angina, it is a relatively weak inhibitor of platelet aggregation. The effect of Integrin, which inhibits the platelet fibrinogen receptor glycoprotein (GP) IIb/IIIa, on the frequency and duration of Holter ischemia was evaluated in 227 patients with unstable angina. METHODS AND RESULTS: Patients received intravenous heparin and standard ischemic therapy and were randomized to receive oral aspirin and placebo Integrin; placebo aspirin and low-dose Integrin. 45 micrograms/kg bolus followed by a 0.5 microgram.kg-1.min-1 continuous infusion; or placebo aspirin and high-dose Integrin, 90 micrograms/kg bolus followed by a 1.0-microgram.kg-1.min-1 constant infusion. Study drug was continued for 24 to 72 hours, and Holter monitoring was performed. Patients randomized to high-dose Integrin experienced 0.24 +/- 0.11 ischemic episodes (mean +/- SEM) on Holter lasting 8.41 +/- 5.29 minutes over 24 hours of study drug infusion. Patients randomized to aspirin experienced a greater number (1.0 +/- 0.33, P < .05) and longer duration (26.2 +/- 9.8 minutes, P = .01) of ischemic episodes than the high-dose Integrin group. There was no evidence of rebound ischemia after withdrawal of study drug. In 46 patients, platelet aggregation was rapidly inhibited by Integrin in a dose-dependent fashion. The number of clinical events was small, and there were no bleeding differences in the three treatment arms. CONCLUSIONS: Intravenous Integrin is well tolerated, is a potent reversible inhibitor of platelet aggregation, and added to full-dose heparin reduces the number and duration of Holter ischemic events in patients with unstable angina compared with aspirin.


INCREASED RISK OF NON-Q WAVE MYOCARDIAL INFARCTION AFTER DIRECTIONAL ATERECTOMY IS PLATELET DEPENDENT: EVIDENCE FROM THE EPIC TRIAL. EVALUATION OF C7E3 FOR THE PREVENTION OF ISCHEMIC COMPLICATIONS.


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OBJECTIVES: We sought to determine the effects of platelet glycoprotein IIb/IIIa receptor blockade on adverse outcomes, especially non-Q wave myocardial infarction, in patients undergoing directional atherectomy in the Evaluation of c7E3 for the Prevention of Ischemic Complications (EPIC) trial. BACKGROUND: Randomized trials comparing directional atherectomy with percutaneous transluminal coronary angioplasty (PTCA) have demonstrated modest benefits favoring atherectomy but at a cost of increased acute ischemic complications, notably non-Q wave myocardial infarction. The mechanism for this excess risk is unknown. METHODS: Of 2,038 high risk patients undergoing coronary intervention in the EPIC trial, directional atherectomy was performed in 197 (10%). Patients randomly received the chimeric glycoprotein IIb/IIIa antibody 7E3 (c7E3), as a bolus or a bolus and 12-h infusion or placebo. Study end points included death, myocardial infarction, repeat intervention or bypass surgery. RESULTS: Patients undergoing directional atherectomy had a lower baseline risk for acute complications but had a higher incidence of any myocardial infarction (10.7% vs. 6.3%, p = 0.021) and non-Q wave myocardial infarction (9.6% vs. 4.9%, p = 0.006). Bolus and infusion of c7E3 reduced non-Q wave myocardial infarctions by 71% after atherectomy (15.4% for placebo vs. 4.5% for bolus and infusion, p = 0.046). Non-Q wave myocardial infarction rates after PTCA were not affected by c7E3, although Q wave myocardial infarctions were reduced from 2.6% to 0.8% (p = 0.017). CONCLUSIONS: The EPIC trial confirmed the increased risk of non-Q wave myocardial infarction with directional atherectomy use compared with PTCA. A bolus and 12-h infusion of the glycoprotein IIb/IIIa receptor inhibitor c7E3 abolished this excess risk. Directional atherectomy-related non-Q wave myocardial infarction appears to be platelet aggregation dependent.

5. GPIIB/IIIA Inhibitor in Arterial thromboses
(1) Wallace RC, Furlan AJ, Moliterno DJ, Stevens GH, Masaryk TJ, Perl J 2nd

**BASILAR ARTERY RETROMBOSIS: SUCCESSFUL TREATMENT WITH PLATELET GLYCOPROTEIN IIb/IIa RECEPTOR INHIBITOR.**


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We describe the use of abciximab to prevent rethrombosis of the basilar artery after transluminal angioplasty. A 60-year-old patient with vertebral basilar insufficiency and acute occlusion of the basilar artery underwent revascularization with urokinase and angioplasty. Despite the repeated use of urokinase and angioplasty under anticoagulation with heparin, the basilar artery immediately rethrombosed. In a final attempt to prevent rethrombosis, abciximab was administered before the final angioplasty, resulting in a widely patent basilar artery and no rethrombosis.

6. GPIIb/IIa Inhibitor in STENT Thrombosis


**OUTCOMES AT 1 YEAR AND ECONOMIC IMPLICATIONS OF PLATELET GLYCOPROTEIN IIb/IIa BLOCKADE IN PATIENTS UNDERGOING CORONARY STENTING: RESULTS FROM A MULTICENTRE RANDOMISED TRIAL. EPISTENT INVESTIGATORS. EVALUATION OF PLATELET IIb/IIa INHIBITOR FOR STENTING.**


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BACKGROUND: We assessed in a randomised trial the long-term outcomes for potent adjunctive antplatelet therapy given at the time of coronary stenting. METHODS: In 63 hospitals in the USA and Canada, 2399 patients were randomly assigned stenting with abciximab, stenting with placebo, or balloon angioplasty with abciximab. Standard adjunctive therapy with aspirin, ticlopidine, and heparin was used. The major outcomes of death and myocardial infarction were assessed at 1-year follow-up by intention to treat. We also investigated the 1-year cost-effectiveness of combined stenting and abciximab therapy. FINDINGS: At 1-year follow-up, eight (1.0%) of 794 patients in the stent plus abciximab group had died, compared with 19 (2.4%) of 809 in the stent plus placebo group (hazard ratio 0.43 [95% CI 0.19-0.97], p=0.037). The combined endpoint of death or large myocardial infarction occurred in 42 (5.3%) and 89 (11.0%), respectively (0.46 [0.32-0.67], p<0.001). By multivariate modelling, the factors independently associated with improved survival were assignment to stenting with abciximab (p=0.027) and greater preprocedural stenosis (p=0.002); those associated with worse survival were age greater than 70 years (p<0.001), previous heart failure (p=0.001), diabetes treated with insulin (p=0.02), and postprocedural occlusion (p<0.001). Relative to stenting plus placebo and balloon angioplasty plus abciximab, the incremental 1-year costs of stenting plus abciximab were US$581 and S$932. The corresponding cost-effectiveness ratios were US$5291 and S$6213 per added life-year. INTERPRETATION: Coronary stenting with abciximab, compared with stenting alone or balloon angioplasty with abciximab, is associated with improved survival and is an economically attractive therapy by conventional standards.

(2) Robbins MA, Marso SP, Wolski K, Peterson J, Lincoff AM, Brener S

**CHEST PAIN--A STRONG PREDICTOR OF ADVERSE CARDIAC EVENTS FOLLOWING PRECUTANEOUS INTERVENTION (FROM THE EVALUATION OF PLATELET IIb/IIa INHIBITOR FOR STENTING TRIAL [EPISENT]).**

*Am J Cardiol* 1999 Dec 1;84(11):1350-3, A8

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Postprocedural chest pain remains a common problem, and irrespective of electrocardiographic changes, is associated with a higher incidence of early cardiac events. A return to the catheterization laboratory is unlikely to benefit patients with postprocedural chest pain without electrocardiographic changes with documented irreversible intraprocedural complications, or those with late postprocedural pain.
(3) Steinhubl SR, Tan WA, Foody JM, Topol EJ

INCIDENCE AND CLINICAL COURSE OF THROMBOTIC THROMBOCYTOPENIC PURPURA DUE TO TICLOPIDINE FOLLOWING CORONARY STENTING. EPISTENT INVESTIGATORS. EVALUATION OF PLATELET IIb/IIIa INHIBITOR FOR STENTING.

JAMA 1999 Mar 3;281(9):806-10

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CONTEXT: Thrombotic thrombocytopenic purpura (TTP) is a rare and often fatal disorder characterized by thrombocytopenia, microangiopathic hemolytic anemia, mental status changes, and renal dysfunction. Ticlopidine hydrochloride is 1 of several drugs that have been associated with this disorder and is currently used routinely in the approximately 500000 patients per year in the United States who undergo a percutaneous coronary intervention involving a stent. OBJECTIVES: To determine the incidence and describe the clinical course of TTP due to ticlopidine therapy following stenting. DESIGN: Retrospective analysis of cohort of all patients undergoing coronary stenting at the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) study sites. SETTING: Sixty-three centers throughout the United States and Canada. PATIENTS: A total of 43322 patients who underwent a percutaneous coronary intervention and received a coronary stent during a 1-year period from 1996 to 1997. MAIN OUTCOME MEASURES: Cases of TTP following stenting during the 1-year period to determine the incidence of TTP due to ticlopidine therapy following coronary stenting. Additional cases were collected from these and other centers across North America to further describe the clinical presentation and course of TTP due to ticlopidine therapy following stenting. RESULTS: Nine cases of TTP following stenting were recognized at the 63 centers during the specified period, giving an incidence of 1 case per 4814 patients treated (0.02%; 95% confidence interval, 1 case per 2533 to 1 case per 10 541 patients treated). Ten additional cases of TTP related to ticlopidine therapy following stenting were identified from other centers, were identified from the primary centers outside the pre-defined period, or involved a noncoronary stent. Four patients (21%) received ticlopidine for 2 weeks or fewer, 14 patients (74%) for 2 to 4 weeks, and 1 patient (5%) for 8 weeks. The mean time of ticlopidine treatment prior to TTP diagnosis was 22 days (range, 5-60 days). The overall mortality rate was 21% (4/19), with all 4 deaths occurring in patients not treated with plasmapheresis, whereas there were no deaths among the 13 patients who received plasmapheresis. CONCLUSION: The findings of a TTP incidence of 0.02% in our cohort of ticlopidine-treated patients following coronary stenting suggests that TTP occurs much more commonly in this population than the estimated incidence of 0.0004% in the general population. The mortality rate for this rare complication exceeds 20%. Limiting ticlopidine therapy to 2 weeks after stenting does not prevent the development of TTP. Rapid diagnosis and treatment that includes plasmapheresis are critical for improved survival.

(4) Berkompas DC

ABCIXIMAB COMBINED WITH ANGIOPLASTY IN A PATIENT WITH RENAL ARTERY STENT SUBACUTE THROMBOSIS.

Cathet Cardiovasc Diagn 1998 Nov;45(3):272-4

Thoracic and Cardiovascular Institute, Lansing, Michigan 48910, USA. II

Following renal artery angioplasty and stenting, a female hypertensive patient suffered left renal artery stent subacute thrombosis. A second successful angioplasty was performed using 5000 U heparin i.v. and 0.25-mg/kg bolus followed by a 12-hr 10-microg/min infusion of abciximab. Normal renal flow was re-established and remained normal at 1-year follow-up.

7. GPIIB/IIIa Inhibitor in Kawasaki Disease

(1) Etheridge SP, Tani LY, Minich LL, Revenaugh JR

PLATELET GLYCOPROTEIN IIb/IIIa RECEPTOR BLOCKADE THERAPY FOR LARGE CORONARY ANEURYSMS AND THROMBI IN KAWASAKI DISEASE.

Cathet Cardiovasc Diagn 1998 Nov;45(3):264-8

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A 4-month-old girl with Kawasaki disease, large coronary artery aneurysms, and coronary thrombi was treated with standard therapy followed by abciximab, a platelet glycoprotein IIb/IIIa antagonist, in addition to standard heparin and warfarin sodium anticoagulation and low-dose aspirin. She did not develop evidence of ischemia, had no complications from the therapy, and showed resolution of the aneurysms and thrombi after 6 wk of therapy.

8. GPIIB/IIIa Inhibitor in Angioplasty

(1) Marso SP, Lincoff AM, Ellis SG, Bhatt DL, Tanguay JF, Kleiman NS, Hammoud T, Booth JE, Sapp SK, Topol EJ

OPTIMIZING THE PERCUTANEOUS INTERVENTIONAL OUTCOMES FOR PATIENTS WITH DIABETES MELLITUS: RESULTS OF THE EPISTENT (EVALUATION OF PLATELET IIb/IIIa INHIBITOR FOR STENTING TRIAL) DIABETIC SUBSTUDY.

Circulation 1999 Dec 21-28;100(25):2477-84

Department of Cardiology, Cleveland Clinic Foundation, Cleveland, Ohio 44195, USA.

BACKGROUND: Stenting likely decreases the need for target-vessel revascularization procedures in diabetic patients compared with balloon angioplasty. However, the efficacy of stenting with platelet glycoprotein IIb/IIia blockade has not yet been assessed in diabetics. METHODS AND RESULTS: We analyzed the outcomes of 491 diabetic patients within the multicenter Evaluation of Platelet IIb/IIia Inhibitor for Stenting Trial (EPISTENT). Diabetic patients were a prospectively defined subset: 173 were randomized to stent-placebo, 162 to stent-abciximab, and 156 to balloon angioplasty-abciximab. The main end point for this analysis was combined 6-month death, myocardial infarction (MI), or target-vessel revascularization (TVR). The composite end point occurred in 25.2% of stent-placebo, 23.4% of balloon-abciximab, and 13.0% of stent-abciximab patients (P=0.005). Abciximab therapy, irrespective of revascularization strategy (stent or balloon angioplasty), resulted in a significant reduction in the 6-month death or MI rate: 12.7% for stent-placebo, 7.8% for balloon angioplasty-abciximab, and 6.2% for the stent-abciximab group (P=0.029). The 6-month TVR rate was 16.6% for stent-placebo, 18.4% for balloon-abciximab, and 8.1% for stent-abciximab (P=0.021). Compared with stent-placebo, stent-abciximab therapy was associated with a significant increase in angiographic net gain (0.88 versus 0.55 mm; P=0.011) and a decrease in the late loss index (0.40 versus 0.60 mm; P=0.061). The 1-year mortality rate for diabetics was 4.1% for stent-placebo and 1.2% for stent-abciximab patients (P=0.11). CONCLUSIONS: The combination of stenting and abciximab therapy among diabetics resulted in a significant reduction in 6-month rates of death, MI, and TVR compared with stent-placebo or balloon-abciximab therapy.

(2) Gibson CM, Goel M, Cohen DJ, Piana RN, Deckelbaum LI, Harris KE, King SB 3rd

SIX-MONTH ANGIOGRAPHIC AND CLINICAL FOLLOW-UP OF PATIENTS PROSPECTIVELY RANDOMIZED TO RECEIVE EITHER TIROFIBAN OR PLACEBO DURING ANGIOPLASTY IN THE RESTORE TRIAL. RANDOMIZED EFFICACY STUDY OF TIROFIBAN FOR OUTCOMES AND RESTENOSIS.


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OBJECTIVES: This study sought to investigate the effects of tirofiban versus placebo on the incidence of adverse cardiac outcomes and coronary artery restenosis at 6 months. BACKGROUND: Tirofiban is a highly selective, short-acting inhibitor of fibrinogen binding to platelet glycoprotein IIb/IIia. In a recent clinical study, tirofiban reduced the incidence of adverse cardiovascular events at both 2 and 7 days after coronary angioplasty or directional coronary atherectomy. This reduction persisted but was no longer statistically significant at 30 days. METHODS: The Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE) trial was a randomized, double-blind, placebo-controlled trial of tirofiban in patients undergoing balloon angioplasty or directional atherectomy within 72 h of presentation with either unstable angina pectoris or acute myocardial infarction. All patients received an initial bolus (10 microg/kg body weight over 3 min), followed by a 36-h infusion (0.15 microg/kg per min) of either tirofiban or placebo. RESULTS: At 6 months the composite end point (either death from any cause, new myocardial infarction, bypass surgery for angioplasty failure or recurrent ischemia, repeat target vessel angioplasty or stent insertion for actual or threatened abrupt closure) occurred in 1,070
placebo group patients (27.1%) and 1,071 tirofiban group patients (24.1%, p = 0.11). Analysis of 6-month coronary arteriograms by means of quantitative coronary arteriography showed no significant difference between placebo- and tirofiban-treated patients in either the incidence of a > or =50% diameter stenosis (57% vs. 51%, p = NS), a loss of > or =50% of lumen diameter gained (50% vs. 50%, p = NS) or a loss of > or =0.72 mm of lumen diameter (44% vs. 42%, p = NS). CONCLUSIONS: The 3% absolute reduction in the incidence of the composite end point at 6 months (27.1% placebo vs. 24.1% tirofiban) was similar to that previously reported at 2 days (8.7% vs. 5.4%, p < 0.005), and there does not appear to be any late effect of tirofiban on clinical end points between day 2 and 6 months. Tirofiban did not reduce the incidence of restenosis at 6 months when defined in a number of ways.

B. GPIIB/IIIa induced Complications

1. GPIIb/IIIa Inhibitors and Bleeding Complications

a) GPIIb/IIIa Inhibitors and Bleedings General Aspects

(1) Blankenship JC
BLEEDING COMPLICATIONS OF GLYCOPROTEIN IIB-IIIa RECEPTOR INHIBITORS.

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Large clinical studies have demonstrated an unequivocal clinical benefit of antithrombotic therapy with inhibitors of the platelet surface-membrane glycoprotein (GP) IIb-IIIa receptor in a broad range of patients with ischemic heart disease. Potent antiplatelet effects of these agents, however, may increase the risk of bleeding complications, as occurred in the first large evaluation of this therapy, the Evaluation of c7E3 for Prevention of Ischemic Complications (EPIC) trial with abciximab (c7E3 Fab; ReoPro(TM); Centocor, Malvern, Pa). Although the incidence of bleeding events in subsequent studies has been reduced through the use of a low-dose, weight-adjusted heparin regimen and early removal of vascular sheaths in patients who have undergone percutaneous coronary interventions, hemorrhage continues to be the most common complication of GP IIb-IIIa inhibitor therapy. This review summarizes current experience related to bleeding complications with various GP IIb-IIIa inhibitors and suggests strategies for improved management of bleeding in patients receiving these agents.

(2) Aylward P
GLYCOPROTEIN IIB/IIIA INHIBITORS, SURGERY AND BLEEDING.

(3) Adgey AA
BLEEDING COMPLICATIONS WITH NEW ANTITHROMBOTICS USED IN ISCHAEMIC HEART DISEASE.

Royal Victoria Hospital, Belfast, UK.

Despite adjunctive therapy with heparin and aspirin, patients undergoing percutaneous transluminal coronary angioplasty (PTCA) continue to be at risk of abrupt vessel closure and acute ischaemic events. In an attempt to overcome the limitations of traditional antithrombotics, more potent agents have been developed, including direct thrombin inhibitors (e.g., hirudin and hirulog) and new antiplatelet agents [e.g., the glycoprotein IIb/IIIa receptor inhibitor c7E3 Fab (ReoPro(TM))]. Initial phase-III trials of hirudin in patients with acute coronary syndromes identified an excess incidence of major bleeding complications. Some of these trials have been recommenced using lower doses. Reports on phase-III trials of hirulog should be forthcoming soon. Of the new agents, the chimeric monoclonal antibody fragment c7E3 Fab has the most extensive available data. In the phase-III evaluation of 7E3 for the Prevention of Ischemic Complications trial, the administration of a c7E3
Fab bolus plus c7E3 Fab infusion reduced the rate of major ischaemic events by 35% at 30 days (p = 0.008) in patients undergoing high-risk PTCA. Major bleeding episodes occurred more frequently with this regimen than with placebo, although rates of intracranial haemorrhage or surgery for bleeding did not differ between groups. The findings suggest that the risk of bleeding complications might be reduced, without compromising efficacy, by administering heparin on a weight-adjusted basis in patients treated with c7E3 Fab.

(4) Armstrong PW, Mant MJ

BLEEDING RISKS, RISK FACTORS AND MANAGEMENT OF BLEEDING COMPlications AFTER TREATMENT WITH ANTICOAGulants, SPECIFIC ANTIvTHROMBINS, THROMBolytics IIb-IIIa RECEPTor BLOCKERS.

Eur Heart J 1995 Nov;16 Suppl L:75-80

Department of Medicine, University of Alberta, Edmonton, Canada.

Assessment of the risks of new antithrombotic therapies is best undertaken by evaluating risk factors for bleeding in individual patients, and risks associated with specific antithrombotic agents. This forms the basis for the development of a management strategy for major bleeding complications. Patient-related risk factors for bleeding with oral anticoagulants include: trauma, invasive procedures, history of bleeding disorder, high anticoagulant intensity, concomitant use of antiplatelet drugs, presence of underlying severe disease, advanced age, and prior history of cerebrovascular accident, or gastrointestinal bleeding. Weight-adjusted and other nomograms are more successful in achieving a balance between therapeutic effect and safety with intravenous heparin. The most important complication of thrombolytic therapy is intracranial haemorrhage, and the risks increase with age > 65 years, weight under 70 k, hypertension on admission and the use of tissue plasminogen activator: this profile is helpful in assessing risk-benefit ratio amongst individual patients. Recent experience with the experimental use of antithrombin agents such as hirudin, indicates a delicate dose-response relationship as it relates to the risk of cerebral haemorrhage, when used in conjunction with thrombolytic agents. A definitive answer regarding the role of hirudin and the balance of safety and efficacy awaits completion of ongoing trials. Novel IIb/IIIa platelet inhibitors appear to offer a significant therapeutic advance: major bleeding is variable and depends in part on the use of concomitant procedures, and heparin therapy. It is important to identify the source and severity of bleeding with the use of antithrombotic therapy and its haemodynamic consequences in constructing a management plan. Well developed treatment algorithms for patients with severe bleeding exist, and although laboratory testing may be helpful, it is on balance of marginal benefit since patients usually require urgent therapy. Future investigation promises more readily available, rapid and specific laboratory testing, and newer antithrombotic agents that are easier to administer and monitor. Molecular targeting with fusion proteins that attract to a specific antigen, thereby delivering more effective and safe therapy, offer new promise.

b) GPIIb/IIIa Inhibitors and Massive Pulmonary Hemorrhage

(1) Sitges M, Villa FP

MASSIVE PULMONARY HEMORRHAGE IN A PATIENT TREATED WITH A PLATELET GLYCOPROTEIN IIb/IIIa INHIBITOR.

Int J Cardiol 1997 Dec 19;62(3):269-271

Institut Clinic de Malalties Cardiovasculars, Barcelona, Spain.

Novel platelet glycoprotein IIb/IIIa receptor inhibitors have appeared as promising antithrombotic agents. However, their increased risk of bleeding complications, although known, is not well established. We report the case of a serious bleeding complication, a massive pulmonary hemorrhage, in a patient who was treated with one of these agents. Further studies defining guidelines and indications of treatment with platelet glycoprotein IIb/IIIa inhibitors are needed before their routine application to daily practice.

(2) Coller BS, Anderson K, Weisman HF

NEW ANTIPLATELET AGENTS: PLATELET GPIIB/IIIa ANTAGONISTS.

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The GPIIb/IIa (alpha IIb beta 3) receptor plays a crucial role in platelet aggregation and platelet thrombus formation. Inhibition of GPIIb/IIa with the Fab fragment of the mouse/human chimeric monoclonal antibody 7E3, snake venom peptides containing the arginine-glycine-aspartic acid (RGD) sequence, or peptides or peptidomimetics based on the RGD sequence results in abolition of platelet aggregation and platelet thrombus formation. The Phase III EPIC study demonstrated that c7E3 Fab, given as bolus followed by a 12 h infusion, reduced the risk of acute ischemic complications after coronary angioplasty by approximately 35% in patients at high risk of suffering such complications. Treated patients had an approximately 2-fold increased risk of major bleeding, but no increase in cerebral hemorrhage or lethal bleeding. Treatment with c7E3 Fab may have had a beneficial effect on clinical restenosis at 6 months, but this needs to be confirmed. A possible anticoagulant effect of c7E3 Fab was also identified in EPIC, and in vitro studies support this possibility. With the approval of c7E3 Fab (abciximab; ReoPro) for patients undergoing high-risk angioplasty in the US and several European and Scandinavian countries, GPIIb/IIa inhibition joins the armamentarium of antithrombotic agents.

c) GPIIb/IIa inhibitor induced Cardiac Bleeding and Tamponade

(1) Gammie JS, Zenati M, Kormos RL, Hattler BG, Wei LM, Pellegrini RV, Griffith BP, Dyke CM

ABCIXIMAB AND EXCESSIVE BLEEDING IN PATIENTS UNDERGOING EMERGENCY CARDIAC OPERATIONS.


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BACKGROUND: Abciximab (ReoPro; Eli Lilly and Co, Indianapolis, IN) is a monoclonal antibody that binds to the platelet glycoprotein IIb/IIa receptor and produces powerful inhibition of platelet function. Clinical trials of abciximab in patients undergoing coronary angioplasty have demonstrated a reduction in thrombotic complications and have encouraged the widespread use of this agent. We have observed a substantial incidence of excessive bleeding among patients who receive abciximab and subsequently require emergency cardiac operations. METHODS: The records of 11 consecutive patients who required emergency cardiac operations after administration of abciximab and failed angioplasty or stent placement were reviewed. RESULTS: The interval from the cessation of abciximab administration to operation was critical in determining the degree of coagulopathy after cardiopulmonary bypass. The median values for postoperative chest drainage (1,300 versus 400 mL; p = 0.01), packed red blood cells transfused (6 versus 0 U; p = 0.02), platelets transfused (20 versus 0 packs; p = 0.02), and maximum activated clotting time (800 versus 528 seconds; p = 0.01) all were significantly greater in the early group (cardiac operation < 12 hours after abciximab administration; n = 6) compared with the late (cardiac operation >12 hours after abciximab administration; n = 5) group. CONCLUSIONS: This report suggests that the antiplatelet agent abciximab is associated with substantial bleeding when it is administered within 12 hours of operation.

(2) Bottner RK, Hardigan KR

CARDIAC TAMPONADE FOLLOWING STENT IMPLANTATION WITH ADJUVANT PLATELET IIb/IIIa RECEPTOR INHIBITOR ADMINISTRATION.


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This case report describes a previously unreported complication of stent implantation in association with the use of adjuvant platelet IIb/IIIa receptor inhibitor administration. Following stent implantation, the patient developed cardiac tamponade, treated successfully with percutaneous pericardiocentesis and autologous platelet administration.
d) GPIIIa Inhibitor associated Bleedings of Femoral Puncture site

(1) Madan M, Blankenship JC, Berkowitz SD

BLEEDING COMPLICATIONS WITH PLATELET GLYCOPROTEIN IIb/IIIa RECEPTOR ANTAGONISTS.

_Curr Opin Hematol_ 1999 Sep;6(5):334-41

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Platelet glycoprotein (GP) IIb/IIIa receptor antagonists are being used with increasing frequency in the settings of percutaneous coronary interventions and acute ischemic syndromes. The development of bleeding complications following GPIIb/IIIa blockade represents a significant limitation to its effectiveness. Baseline characteristics predictive of future bleeding events in patients receiving platelet GPIIb/IIIa receptor antagonist include older age, low body weight, evolving myocardial infarction, and female sex. In patients undergoing percutaneous coronary interventions with adjunctive GPIIb/IIIa inhibition, the risk of bleeding, particularly from the femoral vascular access site, may be reduced through the use of low-dose, weight-adjusted heparin (70 U/kg), avoidance of postprocedural heparin, and early vascular sheath removal. Strategies to reduce the incidence of bleeding complications in patients receiving GPIIb/IIIa inhibitors are proposed in this article.

2. GPIIIa Inhibitor induced Thrombopenia

(1) Llevadot J, Coulter SA, Giugliano RP

A PRACTICAL APPROACH TO THE DIAGNOSIS AND MANAGEMENT OF THROMBOCYTOPENIA ASSOCIATED WITH GLYCOPROTEIN IIb/IIIa RECEPTOR INHIBITORS.

_J Thromb Thrombolysis_ 2000 Feb;9(2):175-180

Cardiovascular Division, Brigham & Women's Hospital, and Harvard Medical School, Boston, Massachusetts, USA.

The introduction of drugs that inhibit the GP IIb/IIIa receptor represents one of the most important new developments in the field of cardiovascular pharmacotherapeutics of the past decade. Thrombocytopenia associated with a GP IIb/IIIa inhibitor can occur in up to 5% of patients and is associated with poor clinical outcomes. Monitoring of the platelet count early after administration of these drugs is recommended and further assessment of the platelet count should be performed with long-term oral administration. Confirmation of true thrombocytopenia and an investigation of other potential etiologies are crucial initial diagnostic steps that should be taken when a platelet count of <100,000/cm(3) is encountered. In patients receiving concomitant heparin, identification of heparin-induced thrombocytopenia using an enzyme-linked immunosorbent assay to detect anti-heparin-PF4 antibodies is preferred. Treatment recommendations depend upon the severity of thrombocytopenia and presence of bleeding. In general, GP IIb/IIIa inhibitor therapy should be stopped; conventional critical care instituted; and platelet transfusions considered if the platelet count is <10,000/cm(3), if there is severe bleeding, or if an emergency invasive procedure is required. Readministration of GP IIb/IIIa inhibitors may be associated with an increased risk of thrombocytopenia in selected circumstances, and caution is advised if the patient had previously experienced a significant decline in the platelet count or developed drug-induced antibodies following prior use. Future areas of research should target the mechanism(s) of thrombocytopenia, more accurate diagnostic methods, and the risk of thrombocytopenia when these drugs are combined with other antiplatelet and anticoagulant agents.

(2) Madan M, Berkowitz SD

UNDERSTANDING THROMBOCYTOPENIA AND ANTIGENICITY WITH GLYCOPROTEIN IIb-IIIa INHIBITORS.

_Am Heart J_ 1999 Oct;138(4 Pt 2):317-26

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Platelet glycoprotein (GP) IIb-IIIa receptor antagonists are being used with increasing frequency in the settings of percutaneous coronary interventions and acute ischemic syndromes. The development
of thrombocytopenia after GP IIb-IIIa blockade has been observed to some extent with all parenteral GP IIb-IIIa inhibitors studied to date and could potentially limit their effectiveness. The incidence and severity of thrombocytopenia has varied in large clinical trials with GP IIb-IIIa inhibitors, presumably as a consequence of the different structural and pharmacokinetic characteristics of the agents, the dose administered and duration of use, repetition of exposure, and the various drugs coadministered with these agents. Certain baseline characteristics may be predictive. In most cases, severe thrombocytopenia associated with the use of GP IIb-IIIa receptor antagonists was readily reversible with platelet transfusion and was not usually associated with major clinical sequelae. Although the exact mechanisms responsible for thrombocytopenia after GP IIb-IIIa blockade are poorly understood, an immune mechanism is suggested in which the binding of the antagonist to GP IIb-IIIa receptors leads to the exposure of ligand-induced binding sites recognized by preexisting or induced antibodies. Alternatively, the receptor-drug metabolite complex itself may induce an immune response. All patients receiving parenteral GP IIb-IIIa inhibitors should be monitored within 24 hours of initiation of therapy for the development of thrombocytopenia. An algorithm for the detection and management of thrombocytopenia after GP IIb-IIIa inhibitor therapy is proposed.

(3) Peter K, Straub A, Kohler B, Volkmann M, Schwarz M, Kuhler W, Bode C

**PLATELET ACTIVATION AS A POTENTIAL MECHANISM OF GP IIB/IIIA INHIBITOR-INDUCED THROMBOCYTOPENIA.**

*Am J Cardiol* 1999 Sep 1;84(5):519-24

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The blockade of the platelet integrin glycoprotein (GP) IIb/IIIa has proved to be an effective antiplatelet therapy. Profound thrombocytopenia has repeatedly been described as an adverse effect in patients treated with GP IIb/IIIa inhibitors, but its mechanism has not been elucidated yet. With use of flow cytometry, the activation status of platelets was monitored in 26 patients presenting with acute myocardial infarction who were treated with the GP IIb/IIIa inhibitor abciximab alone or in combination with the fibrinolytic agent reteplase. Fibrinogen and PAC-1 (a GP IIb/IIIa activation-specific monoclonal antibody) binding, as well as P-selectin expression on unstimulated platelets were constant in 25 patients throughout a follow-up of 7 days. In 1 patient (D.F.), the percentage of platelet-binding fibrinogen increased from 2.2% to 17.8%, for PAC-1 from 2.8% to 13.2%, and for P-selectin expression from 10.2% to 58.3% 10 minutes after the start of treatment. Furthermore, D.F. had a decrease in single platelet count in ethylenediaminetetraacetic acid-, citrate-, and heparin-anticoagulated and native blood. Blood films revealed platelet aggregates. In vitro testing of D.F.’s blood 2 and 4 weeks after initial admission demonstrated a reinduction of fibrinogen and PAC-1 binding to platelets, an increase of P-selectin expression, and the formation of platelet aggregates following exposition of platelets to abciximab in vitro. In summary, this report describes the induction of platelet activation by a GP IIb/IIIa inhibitor in vivo and reinduction in vitro in direct association with thrombocytopenia. Platelet activation by GP IIb/IIIa inhibitors may be one potential mechanism for GP IIb/IIIa inhibitor-induced thrombocytopenia.

(4) Pinton P

**[ABCIXIMAB-INDUCED THROMBOPENIA DURING TREATMENT OF ACUTE CORONARY SYNDROMES BY ANGIOPLASTY]. [ARTICLE IN FRENCH]**

*Ann Cardiol Angeiol (Paris)* 1998 May;47(5):351-8

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ReoPro (abciximab) is the Fab fragment of a chimeric monoclonal antibody directed against platelet glycoprotein IIb-IIIa. Its efficacy to prevent ischaemic complications after PTCA has been demonstrated in 3 studies: EPIC, EPILOG, UPTAKE. One hundred and sixty five cases of thrombocytopenia (< 100,000/microliter) were reported in a series of 5461 patients randomized in these 3 studies (i.e. 3.0%), including 46 (2.03%) with placebo and 119 (3.73%) with abciximab. Among the 2270 patients randomized to receive placebo, 11 (0.48%) cases of severe thrombocytopenia (< 50,000/microliter) were observed versus 34 (1.07%) with abciximab. Major acute thrombocytopenia (< 20,000/microliter and < 24 hours) occurred in 0.60% (20 patients) of cases with abciximab. Their mechanism remains unknown. A therapeutic challenge did not modify either their incidence, or their severity. The development of thrombocytopenia did not worsen the patient’s prognosis and course was always favourable. Twenty five cases of thrombocytopenia (0.60%), including 3 cases of acute major thrombocytopenia (0.08%) were spontaneously reported in France among the first 4000 patients treated.
with abciximab post-marketing. All patients treated with abciximab must be monitored by platelet count, 2 to 4 hours after the bolus administration, then 12 and 24 hours later. These platelet counts should be performed on 3 tubes (EDTA, citrate, heparin) in order to eliminate pseudothrombocytopenia and a differential diagnosis. In the case of true thrombocytopenia (< 10,000/l), treatment should be suspended and the platelet count should be repeated daily until return to normal. In the case of thrombocytopenia less than 60,000/microliter, heparin and aspirin should also be systematically discontinued and, below 50,000/microliter, platelet transfusion is justified.

(5) Cines DB

GLYCOPROTEIN IIB/IIIA ANTAGONISTS: POTENTIAL INDUCTION AND DETECTION OF DRUG-DEPENDENT ANTIPLATELET ANTIBODIES.

*Am Heart J* 1998 May;135(5 Pt 2 Su):S152-9

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Development of acute, severe thrombocytopenia has been reported in several patients treated with a chimeric monoclonal antibody fragment to the platelet glycoprotein IIb/IIia (GPIIb/IIia) complex. However, the propensity of oral GPIIb/IIa antagonists to induce antibody-mediated thrombocytopenia or platelet dysfunction with chronic exposure is unknown. There is evidence to suggest that a small percentage of otherwise healthy individuals have preexisting serum antibodies to conformation-dependent epitopes in the GPIIb/IIa complex that are induced by certain members of this class of compounds that function as mixed agonists/antagonists. Additional studies are needed to identify the epitopes recognized by these antibodies and the requirement for the drug or a drug-metabolite to be present for antibody binding and detection. Detailed immunologic studies of antibodies from patients in whom immune thrombocytopenia develops after receiving oral GPIIb/IIa antagonists may also provide insight into the mechanism by which activated platelets are normally cleared from the circulation.

E. Dipyridamole

A. Dipyridamole Function and Fields of Use

1. Dipyridamole General Aspects

(1) Hankey GJ.

CURRENT ORAL ANTIPLATELET AGENTS TO PREVENT ATHEROTHROMBOSIS.

*Cerebrovasc Dis* 2001 Apr;11 Suppl 2:11-17.

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Aspirin inhibits platelet activation by irreversibly inhibiting platelet cyclooxygenase and thromboxane production, and reduces the odds of serious vascular events (stroke, myocardial infarction or vascular death) by about one quarter in a range of patients with symptomatic atherosclerosis at high risk of a subsequent event. The adenosine diphosphate (ADP) receptor antagonists clopidogrel and ticlopidine are significantly more effective than aspirin in high-risk vascular patients, further reducing the odds of serious vascular events by about 10% (95% CI 2-19%) over the benefit provided by aspirin. The ADP receptor antagonists are also associated with a significant 30% reduction in the odds of gastrointestinal haemorrhage (odds ratio 0.71, 95% CI 0.59-0.86). Ticlopidine increases the odds of skin rash and of diarrhoea by more than twofold compared with aspirin, whereas clopidogrel is associated with a one-third increase in the odds of rash and of diarrhoea. Only ticlopidine increases the odds of neutropenia compared with aspirin. There is no clear evidence as yet for the benefit of dipyridamole or an oral GP IIb/IIia receptor antagonist as single antiplatelet agents in atherothrombotic patients. Amongst high vascular risk patients, the combination of low-dose aspirin and high-dose dipyridamole is associated with about a 10% (95% CI 0-20%) reduction in the odds of a serious vascular event. Most of this reduction is due to a 23% reduction in non-fatal stroke. The size of this estimate continues to be investigated in an ongoing study of patients with transient ischaemic attack and stroke. The combined use of aspirin and ticlopidine is markedly superior to heparin, warfarin and aspirin for reducing thrombotic complications after coronary artery stenting. Clopidogrel plus aspirin has been shown to be safer
than aspirin and ticlopidine in coronary stenting, and is now under long-term evaluation in unstable angina, and other conditions in which patients are at high risk of atherothrombotic events. Copyright 2001 S. Karger AG, Basel

(2) Raitakari OT, Toikka J, Laine H, Viikari J, Knuuti J, Hartiala J
REDUCED MYOCARDIAL FLOW RESERVE DOES NOT IMPAIR EXERCISE CAPACITY IN ASYMPTOMATIC MEN.
Am J Cardiol 1999 Nov 15;84(10):1253-5, A8

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We examined whether impaired coronary flow reserve in healthy men is associated with changes in cardiac performance and exercise-induced ischemia. A comparison between 7 asymptomatic men with low flow reserve (<3.5) and 8 men with normal flow reserve (>3.5) showed no differences in these parameters, suggesting that the mechanisms that control myocardial blood flow during exercise remain normal despite the alterations in the mechanisms that control the vasodilatory reaction to dipyridamole.

(3) Travain MI, Wexler JP
PHARMACOLOGICAL STRESS TESTING.

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Pharmacological stress in conjunction with radionuclide myocardial perfusion imaging has become a widely used noninvasive method of assessing patients with known or suspected coronary artery disease. In the United States, over one third of perfusion imaging studies are performed with pharmacological stress. Pharmacological stress agents fall into two categories: coronary vasodilating agents such as dipyridamole and adenosine, and cardiac positive inotropic agents such as dobutamine and arbutamine. For both, in the presence of coronary artery disease (CAD), perfusion image abnormalities result from heterogeneity of coronary blood flow reserve. Vasodilating agents work directly on the coronary vessels to increase blood flow, whereas inotropic agents work indirectly by increasing myocardial work load, which then leads to an increase in coronary blood flow. Both classes of agents have high accuracies for diagnosing coronary artery disease, and they have excellent safety records with acceptably low occurrences of side effects. For dipyridamole-planar thallium imaging, pooled analysis yields a sensitivity of 85% and a specificity of 87% for diagnosis of coronary disease, but there is a large variation in reported values depending on various factors, such as the extent of postcatheterization referral bias, the type of imaging (planar versus single photon emission computed tomography [SPECT]), the types of patients being studied (single versus multivessel disease, men versus women), and the imaging agent used (thallium versus one of the technetium-based agents). Diagnostic accuracies for adenosine are similar to those of dipyridamole, with reported overall sensitivities ranging from 83% to 97%, and specificities ranging from 38% to 94%. For dobutamine, pooled analyses yield a sensitivity of 82% and a specificity of 75%. There is some concern that dobutamine may interfere with uptake of technetium-99m sestamibi, lowering the sensitivity for detection of disease, and thus the vasodilating agents are generally preferred. Pharmacological stress testing has high clinical use for risk stratifying patients with known or suspected CAD, in patients after myocardial infarction, and in patients needing noncardiac surgery. Vasodilating agents are particularly advantageous in assessing post-myocardial infarction patients, allowing testing as soon as 2 days after the event. Like patients undergoing exercise stress testing, patients with normal perfusion images by pharmacological stress have a <1% annual incidence of cardiac events. The likelihood of an event increases with the extent and severity of perfusion abnormalities. However, it is important to consider clinical variables when using perfusion imaging for risk stratification, particularly in the presurgery patients. As with exercise testing, adjunct markers such as ST segment depression during testing, lung uptake of radiotracer (if thallium is used), and ventricular cavity dilatation add additional prognostic information to that available from the perfusion images alone. The aim of current research is to find better agents that are easier to use and that have fewer side effects. MRE-0470 is an experimental vasodilating agent that is more receptor selective than adenosine and promises a lower incidence of hypotension. Arbutamine more closely simulates exercise than dobutamine, and it can be administered by a
closed-loop computerized delivery device. Work is also underway to look at novel uses of pharmacological stress agents, such as acquiring gated SPECT images during dobutamine infusion to enhance detection of myocardial viability. With increasing use of noninvasive testing in elderly patients and in patients with comorbidities that preclude adequate exercise, pharmacological stress testing has become an indispensable tool for radionuclide myocardial perfusion imaging studies. A good understanding of pharmacological stress testing is essential for performing high-quality nuclear cardiology.

(4) Hezard N, Metz D, Simon G, Droulle C, Daliphard S, Potron G
[NO TITLE AVAILABLE]. [ARTICLE IN FRENCH]
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Platelet activation and/or platelet reactivity have been reported to be associated with coronary heart disease. Whole blood flow cytometry allows to analyze platelets in their physiological environment, while other assays need platelet separation, susceptible to induce platelet modifications. But flow cytometric assay also have limitations. We studied preanalytical conditions in healthy volunteers, using two monoclonal antibodies directed against CD62 and CD63 (two specific markers of platelet degranulation), and two markers which recognize GPIIb/IIIa activation (PAC1 and bound fibrinogen). Preanalytical requirements were as follow: 1) whole blood samples need antagonists of platelet activation i.e., a mixture of theophylline, adenosine and dipyridamole, since artefactual platelet activation rapidly occurred in citrated whole blood, 2) whole blood should be immediately immunolabeled when samples arrived to laboratory, because fixation did not prevent artefactual time dependent activation, 3) the stability of immunolabeling was determinated for each monoclonal antibody: paraformaldehyde as fixative solution was mandatory for both CD62 and CD63, whereas it enhanced bound fibrinogen and PAC1 expression, 4) platelets can be easily identified and gating on a dual scatter (forward scatter x side scatter) dot plot with no specified labeling. The whole blood flow cytometric assay must be standardized in future clinical studies, especially regarding to preanalytical requirements.

(5) Castaigne A, Benacerraf S, Le Roux A
[NO TITLE AVAILABLE]. [ARTICLE IN FRENCH]
Rev Prat 1999 Oct 1;49(15):1635-9
Federation des services de medecine cardiologique, Hopital Henri-Mondor, Creteil.
Platelet active drugs are part of the antithrombotics. Their biological effect is not assessed in current practice. Their clinical efficacy has been firmly established in randomised controlled trials. Aspirin has been the most widely tested drug and is effective in various forms of coronary artery disease and in the secondary prevention after a first ischaemic stroke; in these settings, aspirin reduces the incidence of myocardial infarction, stroke and cardiac death; aspirin has been tested in various daily doses from 30 to 1300 mg: best evidence has been gathered for dosages between 75 and 300 mg; good clinical practice is to use the lowest effective dose. Ticlopidine and clopidogrel have been shown to be superior to aspirin in 2 trials where the incidence of myocardial infarction has been lowered by the new drugs; nevertheless the superiority is apparent only in patients with lower limb atherosclerosis and after stroke. The combination of dipyridamole and aspirin has been proven to be superior to aspirin in the secondary prevention of stroke in one trial contrasting with the other trials performed with other combinations of those two drugs. Glycoprotein GP IIb/IIIa antagonists have been tested in coronary angioplasty and in acute coronary syndromes and only in short intravenous administration; these drugs reduce the incidence of myocardial infarction without any effect on 6-month mortality.

(6) Lecompte T
[NO TITLE AVAILABLE]. [ARTICLE IN FRENCH]
Rev Prat 1999 Oct 1;49(15):1627-33
CHU de Nancy.
Antiplatelet agents have a well established effect against thrombosis complicating atherosclerosis. Drugs currently in use in France are: aspirin and flurbiprofen, inhibiting thromboxane synthesis;
ticlopidine and clopidogrel, inhibiting platelet activation by adenosine diphosphate; dipyridamole, inhibiting platelet activation through adenosine; abciximab, acting on the mechanism of aggregation. Their molecular and cellular pharmacology is in agreement with the clinical effects and the guidelines for practical use. These drugs have in common that they carry a risk of hemorrhage, albeit low but difficult to cope with in case of invasive procedures. There is no antidote. They also have specific contraindications. No laboratory tests aimed at assessing their effect on primary haemostasis are proved of any clinical value.

(7) Alvarez-Sabin J, Montaner-Villalonga J
[NO TITLE AVAILABLE]. [ARTICLE IN SPANISH]
Rev Neurol 1999 Oct 16-31;29(8):780-4

Unidad Cerebrovascular, Hospital General Universitario de la Vall d'Hebron, Barcelona, Espana.

INTRODUCTION: Antiplatelet therapy is effective for secondary prevention of atherothrombotic stroke. Aspirin, the more frequently used antiplatelet drug, prevents 13 to 17% of ischemic events after stroke. New and more effective antiplatelet therapies are needed. DEVELOPMENT: Two large secondary stroke prevention trials have been recently published (CAPRIE and ESPS-2), including more than 25,000 patients. As well TACIP trial designed to assess the efficacy of triflusal, is close to end. The combination of ticlopidine and Aspirin has shown synergistic effect. CONCLUSIONS: Clopidogrel, like ticlopidine, increase 9% the relative risk reduction of stroke over Aspirin. Clopidogrel has a better safety profile than ticlopidine. Dipyridamole is an effective antiplatelet drug, but in combination with low doses of Aspirin is more effective. The possible efficacy of clopidogrel-Aspirin combination should be evaluated.

2. Dipyridamole for Stroke Prevention

(1) Pettigrew LC.
ANTITHROMBOTIC DRUGS FOR SECONDARY STROKE PROPHYLAXIS.

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Stroke is the third most common cause of adult mortality in the United States. Antithrombotic agents form the mainstay of stroke prevention. Aspirin produces a modest reduction in the risk of second stroke and is widely recommended for initial therapy. The thienopyridines ticlopidine and clopidogrel are alternatives for secondary prevention in patients who do not respond to or cannot take aspirin. They are no more effective than aspirin and have been associated with thrombotic thrombocytopenic purpura. The combination of aspirin and extended-release dipyridamole has several mechanisms of action and an additive effect on reducing stroke risk compared with either agent alone. A 2-fold increase in risk reduction and favorable safety profile suggest that the combination can serve as first-line prophylaxis against a second stroke.

(2) Hankey GJ, Warlow CP
TREATMENT AND SECONDARY PREVENTION OF STROKE: EVIDENCE, COSTS, AND EFFECTS ON INDIVIDUALS AND POPULATIONS.

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This review of the effectiveness of treatment for acute stroke and methods of secondary prevention shows that the highest priority for providers of a stroke service must be to establish a stroke unit and multidisciplinary team that delivers organised stroke care. Acute ischaemic stroke patients should be immediately started on aspirin 300 mg daily, and, if possible, many of them should be entered into further trials of thrombolysis and other promising treatments. After the acute phase, aspirin should be continued in a lower dose, 75 mg daily; smoking should be discouraged; high blood pressure treated initially with a diuretic; and fibrillating ischaemic stroke/transient ischaemic attack survivors
anticoagulated long-term with warfarin or given aspirin if anticoagulation is not sensible. Statins are probably indicated in patients who already have symptomatic coronary heart disease. Adding dipyridamole to aspirin, substituting clopidogrel for aspirin, and carotid endarterectomy are all expensive interventions to prevent stroke, but if ways could be found to focus them on those patients at especially high risk, they would become more affordable.

(3) Hervey PS, Goa KL
EXTENDED-RELEASE DIPYRIDAMOLE/ASPIRIN.
Drugs 1999 Sep;58(3):469-75; discussion 476-7
Adis International Limited, Mairangi Bay, Auckland, New Zealand.
The fixed-dose combination of extended-release dipyridamole/aspirin (Aggrenox/Asasantin Retard) combines 2 antiplatelet agents with different mechanisms of action. The combination reduced thrombus formation in human and animal models. Coadministration of extended-release dipyridamole and aspirin in healthy volunteers had no significant effects on the plasma concentrations of either agent. Twice-daily oral extended-release dipyridamole/aspirin (400/50 mg/day) was twice as effective as either agent alone in the secondary prevention of stroke in a large clinical trial involving patients with prior stroke or transient ischaemic attack. The rate of the combined end-point of stroke and death tended to be lower with the combination than with other treatments. The incidence of death was not significantly reduced by any treatment. Most adverse events with extended-release dipyridamole/aspirin were mild and similar to those with either agent alone. Bleeding was more common with the combination than with extended-release dipyridamole alone, as was headache when compared with aspirin alone. Limited pharmacoeconomic analyses suggest that treatment with extended-release dipyridamole/aspirin was cost saving and was cost effective compared with aspirin monotherapy for the secondary prevention of stroke.

ANTIPLATELET TREATMENT DOES NOT REDUCE THE SEVERITY OF SUBSEQUENT STROKE. EUROPEAN STROKE PREVENTION STUDY 2 WORKING GROUP.
Neurology 1999 Sep 11;53(4):825-9
Department of Neurology, University of Kuopio, Finland. juhani.sivenius@finnet.fi
OBJECTIVE: To assess the effect of antiplatelet therapy on the severity of subsequent stroke in patients with stroke and TIA. BACKGROUND: The Second European Stroke Prevention Study (ESPS2) recruited 6,602 patients in four treatment groups: placebo, 2 x 25 mg acetylsalicylic acid (ASA), 2 x 200 mg dipyridamole (DP), and the combination of 50 mg ASA and 400 mg DP per day. Seventy-six percent of the patients had had a stroke as the qualifying event, whereas 24% had a TIA. All patients were followed at 3-month intervals for 2 years. ESPS2 showed a benefit from antiplatelet treatment compared with placebo and an additional benefit using ASA and DP together compared with either of these antiplatelet agents alone. METHODS: In the ESPS2, the study protocol included assessment of severity of end point stroke with the modified Rankin scale once the stroke had clinically stabilized, and no further impairment was observed. There were 824 new stroke events during follow-up. In 701 of them, the initial Rankin scale was known, and this was also evaluated after each nonfatal recurrent stroke. The difference in Rankin scale between treatment groups was analyzed after recurrent stroke, and the progress in Rankin scale between entry and recurrent stroke was quantified by calculating the number of patients with a change of one or more degrees in the scale. RESULTS: There were no significant differences in these changes in Rankin scale between the treatment groups. The mean time to reach an end point of stroke was longest in patients who used ASA + DP (p = 0.057). However, there was no difference among the treatment groups in the time to death during follow-up. CONCLUSION: This study suggests that antiplatelet therapy does not influence the severity of recurrent stroke as evaluated with the Rankin scale. However, antiplatelet therapy seems to lengthen the time the patient remains free from a recurrent stroke.

(5) Wilterdink JL, Easton JD
DIPYRIDAMOLE PLUS ASPIRIN IN CEREBROVASCULAR DISEASE.
Arch Neurol 1999 Sep;56(9):1087-92
Department of Neurology, Rhode Island Hospital, Providence 02903, USA.

BACKGROUND: The second European Stroke Prevention Study (ESPS-2) recently reported a substantial benefit of dipyridamole combined with aspirin over aspirin alone in the prevention of stroke. This appears to be at odds with previous studies suggesting that dipyridamole adds nothing to aspirin alone. OBJECTIVES: To review and compare the results of ESPS-2 and previous studies of dipyridamole plus aspirin and aggregate them in a meta-analysis. METHODS: We combined the detailed data provided by the Antiplatelet Trialists’ Collaboration on the previous studies of dipyridamole plus aspirin with the results from ESPS-2. The data on the previous trials were listed in the appendix of the 1994 publication of the Antiplatelet Trialists’ Collaboration. RESULTS: The results of our meta-analysis demonstrate that for the outcome of nonfatal stroke, ESPS-2 overpowers previous data, which, even in the aggregate, did not include enough patients or outcome events to exclude efficacy for the combination of dipyridamole and aspirin. Differences between ESPS-2 and previous studies, which may have contributed to different results, include the doses and preparations of aspirin and dipyridamole. CONCLUSIONS: The ESPS-2 showed that dipyridamole alone prevents stroke. More importantly, it showed a substantial benefit for dipyridamole combined with aspirin over aspirin alone. When the ESPS-2 data are aggregated with the 14 previous trials of dipyridamole combined with aspirin over aspirin alone, the combination reduces the risk of stroke by 23% over aspirin alone. Nevertheless, important questions remain unanswered. We conclude that another randomized clinical trial showing a significant benefit of the combination of dipyridamole plus aspirin over aspirin alone may be needed before the addition of dipyridamole to aspirin is widely accepted for prevention of stroke.

(6) Crassard I, Bousser MG
[ANTIPLATELET DRUGS FOR PREVENTION OF CEREBRAL ISCHEMIC ACCIDENTS]. [ARTICLE IN FRENCH]
Rev Neurol (Paris) 1999 Sep;155(8):531-41

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Antiplatelet (AP) drugs play a major role in stroke prevention. Aspirin (50-1300 mg), ticlopidine (500 mg), clopidogrel (75 mg) and dipyridamole (400 mg) are effective in secondary prevention of atherothrombotic brain infarcts. Aspirin has been the most extensively studied drug and remains the most cost-effective one. The optimal dose is still debated; doses between 100 and 300 mg are the most widely used. The preventive efficacy of aspirin is already present at the acute phase of cerebral infarct. In primary prevention, aspirin nearly halves the risk of myocardial infarction but does not reduce that of stroke. Cardiac diseases with a high embolic risk require the use of oral anticoagulation. In non valvular atrial fibrillation, the choice of antithrombotic drugs depends on risk stratification: oral anticoagulants are indicated in high risk subjects whereas aspirin is recommended in low risk subjects and when oral anticoagulants are contraindicated. Studies with new associations of AP and with new drugs are required to increase the yield of the antiplatelet approach in high risk subjects; this should be done in parallel with efforts to detect and to treat the vascular risk factors associated with the development of a mass approach for stroke primary prevention.

(7) Boysen G
BLEEDING COMPLICATIONS IN SECONDARY STROKE PREVENTION BY ANTIPLATELET THERAPY: A BENEFIT-RISK ANALYSIS.
J Intern Med 1999 Sep;246(3):239-45

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This review analyses the benefit-risk ratio of antiplatelet drugs in secondary stroke prevention and is based on the published data from eight large stroke prevention trials. In patients with prior transient ischaemic attack (TIA) or stroke, aspirin prevented one to two vascular events (stroke, AMI, or vascular death) per 100 treatment-years with an excess risk of fatal and severe bleeds of 0.4-0.6 per 100 treatment-years. The gastrointestinal bleeding risk was significantly lower with ticlopidine and clopidogrel, which were both somewhat more effective than aspirin in the prevention of vascular events. The combination of dipyridamole and aspirin prevented 2.82 strokes at the expense of an excess risk of 0.61 (95% CI = 0.27-0.95) fatal or severe bleeds per 100 treatment-years. In the acute phase of stroke, the aspirin-associated risk of haemorrhagic complications was much increased.
compared with that in the stable phase after stroke, with 0.48 (95% CI = 0.13-0.83) fatal or severe bleeds per 100 treated patients for the first 4 weeks after stroke in the Chinese Acute Stroke Trial and 0.41 (95% CI = 0.05-0.77) in the International Stroke Trial. Still, there was a net benefit with the prevention of about one death or non-fatal ischaemic stroke per 100 treated patients.

(8) Almdal TP, Eldrup E, Godtfredsen J, Kofoed-Enevoldsen A
[DIPYRIDAMOLE PLUS ACETYLSALICYLIC ACID--WHO IS TO BE TRUSTED]?
[ARTICLE IN DANISH]

(9) Aronow WS
ANTIPLATELET AGENTS IN THE PREVENTION OF CARDIOVASCULAR MORBIDITY AND MORTALITY IN OLDER PATIENTS WITH VASCULAR DISEASE.
Drugs Aging 1999 Aug;15(2):91-101

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Antiplatelet drugs have been demonstrated to reduce the incidence of myocardial infarction (MI), stroke or vascular death in patients with vascular disease. There are no data suggesting that antiplatelet therapy acts differently in older people than in younger people and recommendations based on randomised clinical trials are probably generalisable to older people. Aspirin (acetylsalicylic acid) has been shown to reduce the incidence of non-fatal MI, nonfatal stroke and vascular death in patients with acute MI, a previous MI, angina pectoris or peripheral occlusive arterial disease (POAD), and to reduce cardiovascular morbidity and mortality in patients with a prior ischaemic stroke or transient ischaemic attack (TIA). It has also been shown to reduce the incidence of thrombus formation after coronary artery bypass graft surgery and percutaneous transluminal angioplasty, and in patients with atrial fibrillation and heart valve replacements. Deep vein thrombosis and pulmonary embolism after surgery are also prevented by aspirin. The available data allows the following recommendations to be made. Aspirin 160 to 325 mg daily should be administered to older men and women without contraindications to aspirin who have acute MI, prior MI, unstable or stable angina pectoris, ischaemic stroke, TIA or POAD, and continued indefinitely to reduce the risk of MI, stroke or vascular death. Aspirin should be started in patients before or immediately after revascularisation, and after heart valve replacement. Older men and women with nonvalvular atrial fibrillation who have contraindications to oral anticoagulant therapy but no contraindications to aspirin should be treated with aspirin 325 mg daily. It is reasonable to treat older men and women with nonvalvular atrial fibrillation who have contraindications to aspirin and dipyridamole to oral anticoagulant therapy but no contraindications to aspirin should be treated with aspirin 325 mg daily. It is reasonable to treat older men and women without contraindications to aspirin with aspirin 160 to 325 mg daily if they are at high risk for developing new coronary events. The incidence of stroke, MI or vascular death in patients after a stroke or TIA is reduced by ticlopidine. Therefore, ticlopidine 250 mg twice daily may be used in older men and women with a history of stroke or TIA who do not respond to or who cannot tolerate aspirin. Patients at high risk for coronary artery stent thrombosis benefit from combined therapy with aspirin plus ticlopidine. The annual incidence of ischaemic stroke, MI or vascular death was significantly reduced by clopidogrel in the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial. Therefore, clopidogrel 75 mg daily may be used in older men and women with symptomatic atherosclerosis who do not respond to or who cannot tolerate aspirin to reduce the incidence of ischaemic stroke, MI or vascular death. It should be noted that the acquisition cost for either ticlopidine or clopidogrel is considerably greater than that for aspirin. Most data indicate that the combination of aspirin and dipyridamole is not more effective than aspirin alone in preventing vascular events, and available data do not support the use of sulfinpyrazone in patients with vascular disease.

(10) Millan-Guerrero R, Isais-Cardenas M
[INTRAVENOUS DIPYRIDAMOLE IN ACUTE CEREBRAL INFARCT. IS IT EFFICACIOUS]? [ARTICLE IN SPANISH]

Unidad de Investigacion Epidemiologia Clinica, HGZ MF 1, Colima, Col.

OBJECTIVE: To evaluate the efficiency of intravenous dipyridamole in the evolution of patients with acute ischemic stroke. METHODS: A double-blind clinical trial was conducted with 60 patients having a 24-h evolution of acute vascular stroke at the Hospital General No. 1 IMSS in the city of
Colima, Mexico. After diagnosis, the patients were randomly assigned to two study groups. 10 mg of dipyridamole were administered intravenously every 8 h to the patients in one group, and 300 mg of aspirin were administered orally every 24 h to patients in the other. The patients in both groups received 25 to 50 ml/kg of saline solution over a 24-h period. Basal conditions were registered using five parameters (food intake, walking, eye opening, motor activity and verbal responsiveness) during the first 5 days of evolution. RESULTS: Six patients died, four from the group treated with dipyridamole and two treated with aspirin. There was no significant difference between the groups in reference to age (66 +/- 11 years) or sex, nor was there a difference in the severity of stroke between the groups. When the values of the parameters recorded for both groups were compared before and after treatment, the group receiving dipyridamole showed no significant change (p < 2), while the group receiving aspirin showed an improvement in three of the parameters (food intake, walking and motor activity (p < 0.003). CONCLUSION: Our results indicate that dipyridamole does not modify basal conditions in patients suffering from acute ischemic stroke, while aspirin mildly favors improvement in these patients. We conclude that appropriate medical care, in the absence of complications, is the underlying condition permitting a satisfactory evolution in patients afflicted with brain vascular disease.

(11) Diener HC, Kurth T, Leonhardt G
[SECONDARY PREVENTION OF ISCHEMIC INFARCT].
[ARTICLE IN GERMAN]
Z Arztl Fortbild Qualitatssich 1999 May;93(3):209-12
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Secondary prevention of transient or permanent cerebral ischemia is performed with antiplatelet drugs, e.g. aspirin, ticlopidine, clopidogrel or dipyridamole. The four substances have different indications and different side effect profiles. Patients with proven or suspected cardiac source of embolism are treated with anticoagulants. Patients with > 70% stenosis of the internal carotid artery and TIA or minor stroke receive carotid endarterectomy in combination with aspirin. Stroke risk is reduced between 20 and 65% by these measures.

(12) Kase CS
[NO TITLE AVAILABLE]. [ARTICLE IN SPANISH]
Rev Neurol 1999 May 16-31;28(10):1013-6
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OBJECTIVE: To present current information on the use of antiaggregant agents and the possibilities of their further development. DEVELOPMENT: Aspirin is an established treatment for the prevention of cerebrovascular accidents (CVA) in patients with transitory ischemic attacks (TIA) or minor CVA. This agent reduces the risk by 20%. Ticlopidine has a slightly greater antiaggregant effect than Aspirin, but has the disadvantage of being more expensive and having serious haematological effects such as thrombotic thrombocytopenic purpura. In combination with Aspirin, ticlopidine is valuable in maintaining coronary stents permeable. Dipyridamole, used in combination with Aspirin reduces the risk of CVA by 37% which is more than either drug used alone. Clopidogrel, chemically related to ticlopidine, has a slightly greater protective effect without the serious haematological side-effects of the latter. Use of Aspirin in CVA, alone or combined with subcutaneous heparin, is effective in the early secondary prevention of CVAs. Future development of antiaggregant treatment includes various aspects, such as the use of Aspirin in primary and secondary prevention of CVA, its value in combination with other antiaggregant, antithrombotic and neuroprotector agents. CONCLUSIONS: Antiaggregant agents have meant a great advance in the treatment of CVA. In view of the relatively modest degree of protection given by Aspirin, future strategies will probably include combining it with other antiaggregant agents, antithrombotic drugs and neuroprotectors.

(13) Albers GW, Tijssen JG
ANTIPLATELET THERAPY: NEW FOUNDATIONS FOR OPTIMAL TREATMENT DECISIONS.
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Individuals who experience a stroke or a transient ischemic attack require long-term treatment to prevent a subsequent stroke. According to the current guidelines, patients with a first cerebrovascular event due to cardioembolism should be treated with oral anticoagulants, barring any contraindications. Individuals with ischemic cerebral events due to atherothrombosis should typically receive antiplatelet agents. Aspirin is the best-studied antiplatelet agent and has been used in stroke prevention for many years. Trials evaluating aspirin have, over time, enrolled more patients and tested lower aspirin doses. No individual trial conducted in cerebrovascular patients has established the optimal aspirin dose for prevention of vascular events, but meta-analyses of trials at different dose ranges and the two single trials that directly compared different doses strongly suggest that the benefit of aspirin is independent of dose in this patient population. Lower doses (50–325 mg daily) are now recommended because of their more favorable side-effect profiles. Because its value is established, aspirin has been used as a control to evaluate other antiplatelet agents. On the basis of large clinical trials versus aspirin, three other antiplatelet agents (ticlopidine, clopidogrel, and the combination of aspirin plus extended-release dipyridamole) have all been shown to be effective for stroke prevention. Physician opinions regarding the efficacy of these agents in indirect comparisons and the differences in their safety profiles, availability, and cost will influence the choice of agent for the individual patient (14) Leys D

[PREVENTION OF CEREBRAL ISCHEMIA: ANTI-PLATELET AGENTS].
[ARTICLE IN FRENCH]
Rev Neurol (Paris) 1999;155(9):688-93

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Besides the optimal management of risk factors for stroke and carotid surgery, antiplatelet agents are the cornerstone for prevention of cerebral ischemia. The aim of this overview is to determine their role in the prevention of cerebral ischemia, from available literature. In primary prevention, the benefit of aspirin has been established only for patients with non-valvular atrial fibrillation and a low risk of cardioembolism, or as an alternative choice of warfarin, and in subjects at high risk of atherosclerosis. In secondary prevention, antiplatelet agents are effective to reduce the risk in patients with ischemic stroke due to atherosclerosis: aspirin (50 to 1300 mg), ticlopidine (500 mg), clopidogrel (75 mg) and dipyridamole (400 mg) are effective, but the higher levels of risk reduction are obtained with clopidogrel, ticlopidine and the association aspirin–dipyridamole. Aspirin is recommended in most other causes of cerebral ischemia, except in high risk cardiopathies when anticoagulation is possible. Other domains should still be explored: are antiplatelet agents also effective to reduce the risk of cerebral ischemia in patients with other causes, especially lipohyalinosis of the deep perforators leading to lacunar infarcts? In daily practice, does prescription follow recommendations? Will it be possible to reproduce the results of the European Stroke Prevention Study (ESPS)2? Are antiplatelet agents other than aspirin effective in non-valvular atrial fibrillation? Are other associations of antiplatelet agents more effective than these agents alone? Finally, what will be the role of new antiplatelet agents in the future?

3. Dipyridamole Stress Echocardiography

(1) Shivalkar B, Flameng W, Szilard M, Pislaru S, Borgers M, Vanhaecke J

REPEATED STUNNING PRECEDES MYOCARDIAL HIBERNATION IN PROGRESSIVE MULTIPLE CORONARY ARTERY OBSTRUCTION.
J Am Coll Cardiol 1999 Dec;34(7):2126-36

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OBJECTIVE: The aim of this study was to characterize a regional myocardial flow-function relationship in collateral dependent myocardium produced by multiple coronary artery obstruction. METHODS: Ameroid constrictors were placed around the proximal right (RC) and circumflex (CX)
coronary arteries and a silicon tubing cuff around the proximal LAD (left anterior descending artery) (luminal stenosis +/- 77%) in 18 dogs. Weekly two-dimensional echocardiography was performed for regional function (anterior [A], inferoposterior [IP], wall thickening [WT]), and fractional shortening (FS). Colored microspheres injected at baseline and before sacrifice, before and after dipyridamole (0.5 mg/kg) injection, determined resting flow (RF) and coronary reserve (CR), respectively. RESULTS: Coronary angiography performed at four weeks after surgery confirmed occlusion of RC and CX with collateralization and a tight stenosis of LAD. Initially, an episodic reduction in A and IP WT was observed which became persistent later (AWT: 16 +/- 3%; IPWT: 16 +/- 4%, FS: 20 +/- 4%, p < 0.005 vs. baseline [BS]). With dobutamine a biphasic response (improvement in A and IP WT between 5-15 and dysfunction between 20-30 microg/kg/min) was observed. Seven dogs were sacrificed at eight weeks and showed normal RF but reduced transmural CR (A: 75 +/- 18%; IP: 46 +/- 22% of control). Seven dogs underwent PTCA of the LAD at eight weeks and showed gradual improvement in AWT with normalization at 12 weeks (AWT: 30 +/- 5%, p < 0.001 vs. eight weeks). At sacrifice RF and CR in the A wall were normal but there was reduced subendocardial RF in the IP region (64% of BS). Further, biopsy samples showed normal histological findings and high energy phosphate content in all dogs. Radioligand binding assays using 125I-iodocyanopindolol showed downregulation of beta-adrenergic receptor density in the dysfunctional regions compared with control. CONCLUSIONS: In this canine model of viable, collateral dependent and reversibly dysfunctional myocardium, there was early episodic dysfunction followed by persistent dysfunction which was initially associated with normal RF and later with subendocardial hypoperfusion.

(2) Picano E, Trivieri MG
PHARMACOLOGIC STRESS ECHOCARDIOGRAPHY IN THE ASSESSMENT OF CORONARY ARTERY DISEASE.

Curr Opin Cardiol 1999 Nov;14(6):464-70
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Pharmacologic stress echocardiography has gained widespread popularity in recent years because it is more feasible for the patient and less technically demanding for the echocardiographer than exercise stress testing. The two most popular pharmacologic stresses are dobutamine and dipyridamole. These agents provide similar prognostic value and diagnostic accuracy for angiographically assessed coronary artery disease; dobutamine has marginally higher sensitivity in single-vessel disease, and dipyridamole has marginally higher specificity in patients with normal coronary arteries. Both stresses are safe, but a physician should always be in attendance when they are administered: Life-threatening reactions can occur in one of 300 to 500 cases with dobutamine and in one of 700 to 1500 cases with dipyridamole. For dipyridamole and dobutamine echocardiography, outcome data are available from multicenter, international, observational, prospective studies, such as the EPIC (Echo Persantine International Cooperative) and EDIC (Echo Dobutamine International Cooperative).

PROGNOSTIC VALUE OF PHARMACOLOGICAL STRESS ECHOCARDIOGRAPHY IN PATIENTS WITH KNOWN OR SUSPECTED CORONARY ARTERY DISEASE: A PROSPECTIVE, LARGE-SCALE, MULTICENTER, HEAD-TO-HEAD COMPARISON BETWEEN DIPYRIDAMOLE AND DOBUTAMINE TEST. ECHO-PERSANTINE INTERNATIONAL COOPERATIVE (EPIC) AND ECHO-DOBUTAMINE INTERNATIONAL COOPERATIVE (EDIC) STUDY GROUPS.

J Am Coll Cardiol 1999 Nov 15;34(6):1769-77
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OBJECTIVES: The study compared the prognostic value of dipyridamole and dobutamine stress echocardiography in patients with known or suspected coronary artery disease. BACKGROUND: Extensive information is available on the relative diagnostic accuracy of the two tests assessed in a head-to-head fashion, whereas comparative data on their prognostic yield are largely preliminary to date. METHODS: Dipyridamole (up to 0.84 mg/kg over 10 min) atropine (up to 1 mg over 4 min) (DIP) and dobutamine (up to 40 microg/kg/min)-atropine (1 mg over 4 min) (DOB) stress tests were
performed in 460 patients with known or suspected coronary artery disease. Patients were followed up for 38+/-21 months. RESULTS: The DIP was negative in 253 and positive in 207 patients. The DOB was negative in 242 and positive in 218 patients. During the follow-up, there were 80 cardiac events. For all cardiac events, the negative and positive predictive value were 83% and 17% for DOB, 84% and 19% for DIP, respectively (p = NS). Considering only cardiac death, by univariate analysis Wall-Motion Score Index (WMSI) at DIP peak dose (chi-square 13.80, p<0.0002) was the strongest predictor, followed by WMSI DOB (chi2 = 8.02, p<0.004) and WMSI at rest (chi2 = 6.85, p<0.008). By stepwise analysis, WMSI at DIP peak dose was the most important predictor (RR [relative risk] 7.4, p<0.0001). CONCLUSIONS: In patients at low-to-moderate risk of cardiac events, pharmacological stress echocardiography with either dobutamine or dipyridamole allows effective and grossly comparable, risk stratification on the basis of the presence, severity and extension of the induced ischemia.

PERIOPERATIVE PROGNOSTIC VALUE OF DIPYRIDAMOLE ECHOCARDIOGRAPHY IN VASCULAR SURGERY : A LARGE-SCALE MULTICENTER STUDY IN 509 PATIENTS.
_Circulation_ 1999 Nov 9;100(19 Suppl):II269-74
CNR Institute of Clinical Physiology, Pisa, Italy.
Background-Patients undergoing major vascular surgery are at a relatively high risk of cardiac events, and pharmacological stress echocardiography is increasingly used for perioperative risk stratification. The aim of the current study was to evaluate the value of dipyridamole echocardiography test (up to 0.84 mg/kg over 10 minutes) in predicting cardiac events in a large-scale, multicenter, prospective, observational study design. Methods and Results-Five hundred nine patients (mean age 66+/-10 years) were studied before vascular surgery by dipyridamole stress echocardiography in 11 different centers. All patients underwent preoperative clinical risk assessment according to the American Heart Association guidelines. No major complications occurred during dipyridamole stress echocardiography. Technically adequate images were obtained in all patients; however, in 4 patients only the low dipyridamole dose (0.56 mg/kg over 4 minutes) was given for limiting side effects. Eighty-eight (17.3%) had a positive test. Perioperative events occurred in 31 (6.1%) patients: 6 deaths, 11 myocardial infarctions, and 14 episodes of unstable angina. Sensitivity and specificity of dipyridamole stress echocardiography for predicting spontaneous cardiac events were 81% and 87%, respectively, with a positive predictive value of 28% and negative predictive value of 99%. By multivariate analysis, the difference between wall motion score index at rest and peak stress (DeltaWMSI), test positivity, and ST-segment depression during dipyridamole infusion were independent predictors of any perioperative cardiac event. Conclusions-Dipyridamole stress echocardiography is safe and well tolerated in patients undergoing major vascular surgery and provides an effective preoperative screening test for the risk stratification of these patients, mainly because of the extremely high negative predictive value, which is a potent predictor of complication-free procedure.

(5) Landolfo CK, Landolfo KP, Hughes GC, Coleman ER, Coleman RB, Lowe JE
INTERMEDIATE-TERM CLINICAL OUTCOME FOLLOWING TRANSMYOCARDIAL LASER REvascularization IN PATIENTS WITH REFRACTORY ANGINA PECTORIS.
_Circulation_ 1999 Nov 9;100(19 Suppl):II128-33
Duke University Medical Center, Departments of Internal Medicine, Surgery, and Radiology, Divisions of Cardiology (C.K.L.), Cardiothoracic Surgery (K.P.L., G.C.H., R.B.C., J.E.L.), and Nuclear Medicine (E.R.C.), Durham, NC.
Background-This study was conducted to examine the intermediate-term clinical outcomes in patients with refractory angina pectoris treated with transmyocardial laser revascularization (TMR) at our institution. TMR is an alternative surgical technique for the treatment of myocardial ischemia and angina pectoris not amenable to conventional percutaneous or surgical revascularization. Limited data exist evaluating the natural history and duration of clinical improvement in angina
pectoris following TMR. Methods and Results—Thirty-four patients with severe coronary artery disease unsuitable for treatment with standard revascularization techniques underwent TMR in myocardial regions determined to be ischemic by preoperative SPECT (201)Tl perfusion imaging following dipyridamole stress. Patients were assessed postoperatively at 3, 6, and 12 months for clinical outcomes including death, myocardial infarction, functional class of angina pectoris, and hospitalizations for unstable angina. Myocardial perfusion imaging by (201)Tl scintigraphy was also assessed at these temporal end points. Overall mortality at 1 year was 14.7% (n=5). Nonfatal myocardial infarction occurred in 3 patients (8.8%). Among the patients with complete 12-month follow-up (n =27), mean anginal class improved from 3.5+/−0.5 pre-TMR to 2.8+/−0.7 and 2.5+/−0.7 at 3 and 6 months, respectively, and 2.8+/−0.9 at 12 months. Overall improvement in angina pectoris was sustained at 1 year by at least one functional class in 50% of patients. Mean hospitalizations per year for unstable angina declined from 2.4+/−1.6 pre-TMR to 1.7+/−2.0 post-TMR (P=0.01). There was no significant improvement in perfusion by SPECT (201)Tl imaging at any temporal end point post-TMR. Conclusions—Despite the lack of demonstrable improvement in perfusion by SPECT (201)Tl imaging, TMR improved the functional class of angina pectoris in patients with end stage coronary artery disease to a modest degree. Although the maximal benefit in symptoms occurred at 6 months post-TMR, mild sustained clinical improvement above baseline was evident in 50% of patients at 1 year.

(6) Parthenakis FI, Skalidis EI, Kochiadakis GE, Zacharis EA, Karidis CS, Chlouverakis GI, Vardas PE

ASSESSMENT OF LEFT VENTRICULAR EJECTION DYNAMICS IN PATIENTS WITH CORONARY ARTERY DISEASE DURING DIPYRIDAMOLE-STRESS DOPPLER ECHOCARDIOGRAPHY.

Coron Artery Dis 1999 Oct;10(7):471-7

Cardiology Department, University Hospital of Heraklion, Crete, Greece.

OBJECTIVES: To investigate the contribution of Doppler-echocardiographically derived aortic indexes of left ventricular systolic function during dipyridamole-stress to the diagnosis of coronary artery disease (CAD). DESIGN: This was a clinical study. METHODS: Echocardiographic studies under baseline and peak dipyridamole stresses were performed on 15 normal subjects and 32 patients with angiographically confirmed CAD. Peak Doppler velocity, acceleration, and acceleration time of the ascending aorta, as well as segmental left ventricular wall motion, were analyzed. RESULTS: The sensitivity, specificity and overall accuracy of wall-motion abnormalities induced by dipyridamole for the detection of CAD were 62.5, 100, and 74.5%, respectively. When wall-motion abnormalities were combined with the percentage changes in peak aortic velocity and acceleration, the overall sensitivities were 84.38 and 78.15%, respectively, the specificities were 66.7 and 80.00%, respectively, and the accuracy was 78.72% for both models. When all three parameters were combined, the sensitivity, specificity and overall accuracy of the method were 87.5, 86.7, and 87.2%, respectively. CONCLUSIONS: Doppler-echocardiographically derived aortic indexes of left ventricular systolic function during dipyridamole stress could be a useful adjunct to two-dimensional echocardiography by improving its sensitivity in the diagnosis of CAD.

(7) Heiba SI, Jacobson AF, Shattuc S, Ferreira MJ, Sharma PN, Cerqueira MD

THE ADDITIVE VALUES OF LEFT VENTRICULAR FUNCTION AND EXTENT OF MYOCARDIUM AT RISK TO DIPYRIDAMOLE PERFUSION IMAGING FOR OPTIMAL RISK STRATIFICATION PRIOR TO VASCULAR SURGERY.


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Although the increased risk of cardiac complications in surgical patients with diminished left ventricular ejection fraction (LVEF) is well-established, this method has been supplanted in recent years by assessment of ischaemic burden using myocardial perfusion imaging (MPI). This study was conducted to determine if MPI and LVEF determination provide complementary or redundant information in preoperative evaluation of vascular surgery patients. A total of 101 patients were studied with dipyridamole MPI and radionuclide ventriculography before surgery. Single photon emission tomographic MPI images were scored for defect severity and categorized as either fixed or reflecting ischaemia. Resting left ventricular cavity was also categorized as normal or dilated. LVEF
was subdivided into normal (> or = 50%) and abnormal (< 50%). Seventeen patients had cardiac events. Events were more frequent in patients with ischaemia, in patients with a LVEF < 50% and in those with dilated left ventricular chambers. The mean number of ischaemic segments was also higher in the cardiac event group. Higher event rates were seen when a combination of these factors was present. A history of myocardial infarct, congestive heart failure or coronary artery disease was also a significant predictor of subsequent events. Thus, both abnormal left ventricular function and extent of ischaemic myocardium have independent and complementary predictive power for cardiac events in vascular surgery patients.

(8) Spac J, Nemcova H, Hlinomaz O, Blaha M, Dvorak I

[IMPORTANCE OF DIPYRIDAMOLE TRANSESOPHAGEAL ECHOCARDIOGRAPHY IN THE DIAGNOSIS OF ISCHEMIC HEART DISEASE]. [ARTICLE IN CZECH]

Vnitr Lek 1996 Aug;42(8):528-32

II. vnitri klinika LF MU Brno.
The importance of dipyridamol echocardiography in the diagnosis of ischaemic heart disease (IHD) was described repeatedly. Nevertheless in roughly 20% patients the transthoracic echocardiographic examination at rest is inaccurate or cannot be carried out because the ultrasonic visibility is poor. In these patients transoesophageal dipyridamol echocardiography (TEE Dip) can provide a suitable alternative. This is why the authors evaluated 36 patients examined on account of IHD before and after administration of 0.80 mg/kg dipyridamol. The left ventricle was visualized in the transgastric short axis and from the apical view. Angiography revealed significant stenosis of the coronary arteries in 23 patients. In 18 patients after administration of dipyridamol new motility disorders developed, in 5 patients with motility of the left ventricular wall, impaired at rest, no new disorder of kinetics developed, i.e. the test was falsely negative. Thirteen patients had no signs of stenosis of the coronary arteries and three developed disorders of the motility of the left ventricular wall. The sensitivity of TEE Dip for the diagnosis of left ventricular ischaemia was 78% and the specificity 79%. Dipyridamol load transoesophageal echocardiography is a method suitable for clinical application with a still satisfactory sensitivity and very good specificity and it can be implemented without involving the risk of serious side-effects.


[USEFULNESS OF THE MEASUREMENT OF THE LEFT-VENTRICULAR ISOMETRIC RELAXATION TIME BY ECHO-DOPPLER DURING THE ADMINISTRATION OF DIPYRIDAMOLE OR DOBUTAMINE AS A METHOD OF INDUCING MYOCARDIAL ISCHEMIA]. [ARTICLE IN SPANISH]


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Myocardial isquemia prolongs ventricular relaxation. The purpose of this study was to assess the isovolumetric relaxation time of the left ventricle (IVRT) as a parameter of global ventricular relaxation, during the administration of Dipyridamol or Dobutamine intravenously. We studied 58 patients with ischemic heart disease uncovered by the administration of pharmacological agents. They were divided in two groups: 22 patients in the group of Dipyridamole, which was administered intravenously at a dose of 0.84 mg/kg during 10 minutes and 36 patients in the group of Dobutamine administered at a dose of 5, 10, 20, 30 and 40 mcg/kg/min in stepping fashion every three minutes. Coronariography was performed in all patients. The measurements of the maximal velocities of the E and A waves, as well as the deceleration time of the E wave and the pressure half time of the mitral flow did not show significant changes in both groups. If the study was positive by criterion of alteration of the wall motion, the IVRT corrected from the heart rate (IVRT/C) had an increase in 54% (p < 0.01) with respect to baseline values in the same patient in the Dipyridamole group and in the Dobutamine group the increment of the IVRT/C was 26% (p < 0.20). The sensibility (Sen), specificity (Sp) and positive predictive value (PPV) of the IVRT/C increments in detecting proximal significant obstruction of the left anterior descending coronary artery of trivascular disease in the Dipyridamole group was of 50%, 100% and 100% respectively. In the Dobutamine group the Sen
was of 74%, the Sp of 60% and the PPV of 89%. Nor Dipyridamol neither Dobutamine produced a significant prolongation of IVRT/C when alterations of wall motion were absent or when the existing alterations were not exacerbated. On the basis of these results we concluded that the measurement of the IVRT/C in studies of myocardial ischemia with pharmacological provocative maneuvers is an additional useful parameter together with segmental alterations of wall motion to differentiate positive from negative studies.

(10) Spač J, Nemcova H, Blaha M, Hlinomaz O, Dvorak I
[THE EFFECT OF DIPYRIDAMOLE ON PULMONARY VENOUS FLOW IN PATIENTS WITH ISCHEMIC HEART DISEASE]. [ARTICLE IN CZECH]
Vnitr Lek 1995 May;41(5):298-301

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In 56 patients with ischaemic heart disease the authors evaluated the blood flow in the pulmonary veins, using transoesophageal echocardiography by the pulsed Doppler technique in the left upper pulmonary vein. They assessed the peak systolic velocity (pVS), the systolic integral time-velocity (S-VTI), the peak diastolic velocity (pVD) and the integral time velocity in the diastolic part of the flow (D-VTI). They found a statistically significant correlation between the ratio pVS/pVD and the LVEDP assessed by the invasive method (r = 0.812). In 36 patients the authors evaluated the flow rate and time-velocity integral at rest and after administration of 0.78 mg/kg dipyridamol by the i.v. route. In 17 patients with affections of 2 or 3 coronary arteries (group A) after the administration of dipyridamol an increase of the maximal flow rate occurred in the diastolic portion of the flow (at rest 54.7 +/- 12.5, after dipyridamol 64.9 +/- 14.8 cm/s). The systolic flow velocities did not change in this group of patients (at rest 52.2 +/- 3.0, after dipyridamol 54.3 +/- 14.0 cm/s). In 19 patients with a negative coronaryographic finding (group B) or with stenosis of one coronary artery after dipyridamol administration the systolic peak velocity increased (from 58.0 +/- 10 to 70.2 +/- 14.8 cm/s). The pVD values increased slightly after dipyridamol (at rest 42.5 +/- 14.3, after dipyridamol 52.1 +/- 15.6 cm/s).

(11) Erbel R, Ge J, Haude M, Gorge G
[ALTERNATIVE METHODS IN INTERVENTIONAL THERAPY OF CORONARY HEART DISEASE]. [ARTICLE IN GERMAN]
Z Kardiol 1995;84 Suppl 2:53-64

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Percutaneous high-frequency coronary rotablation using the rotablator is able to remove arteriosclerotic material from the vessel wall. A diamond-coated (30-80 microns) brass burr drill fastened to a flexible drive shaft rotating and tracking along a drill coaxial guide wire is used. The turbine rotates the drive shaft in excess of 150,000-190,000 rpm. High-frequency rotational angioplasty was successful in > 90% of patients, but in about 90% additional PTCA is necessary. No increase of bypass surgery compared to PTCA is observed. CK and CR-MB elevation is more often found than after PTCA. Vessel perforation is rarely observed. All vessels were open at 24-h control. The restenosis rate seems not to be increased. The main indications for high-frequency rotational angioplasty are rigid and calcified sclerotic lesions which cannot be passed by conventional balloon catheters. Whether the restenosis rate can be reduced by this method will be judged in part by the COBRA study. In order to avoid acute complications of PTCA and to reduce restenosis rate, coronary stents were developed. Self-expandable and balloon expandable stents are available. It could be demonstrated that these stents can be used as a bail-out system and can block elastic recoil of coronary arteries. The major remaining problem is subacute closure of coronary vessels. In order to prevent thrombosis treatment with coumarine, acetylsalicily acid, and dipyridamol is necessary. Coronary stents can be successfully delivered in more than 90% of the patients. In a highly selected patient group using single stents restenosis rate could be significantly reduced.

4. Dipyridamole after Bypass Graft Surgery
(1) Tan ES, van der Meer J, Jan de Kam P, Dunselman PH, Mulder BJ, Ascoop CA, Pfisterer M, Lie KI

**WORSE CLINICAL OUTCOME BUT SIMILAR GRAFT PATENCY IN WOMEN VERSUS MEN ONE YEAR AFTER CORONARY ARTERY BYPASS GRAFT SURGERY OWING TO AN EXCESS OF EXPOSED RISK FACTORS IN WOMEN.**

CABADAS. RESEARCH GROUP OF THE INTERUNIVERSITY CARDIOLOGY INSTITUTE OF THE NETHERLANDS. CORONARY ARTERY BYPASS GRAFT OCCLUSION BY ASPIRIN, DIPYRIDAMOLE AND ACENOCOUMAROL/PHENOPROCOUMON STUDY.

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OBJECTIVES: This retrospective study sought to assess differences in graft patency and clinical outcome between women and men after coronary artery bypass graft surgery (CABG).

BACKGROUND: A less favorable clinical outcome has been reported in women as compared with men. Its relation to graft patency has not been studied.

METHODS: We analyzed one-year follow-up data of 912 patients (120 women) who entered a randomized clinical drug trial. All patients received vein grafts; in 494 patients (56 women) internal mammary artery (IMA) grafts were also used. Graft patency was assessed by coronary angiography at one year. Primary clinical end points were myocardial infarction, revascularization procedures and death; secondary clinical end points included recurrent angina, heart failure and arrhythmias.

RESULTS: Occlusion rates of vein grafts were 16.7% in women and 12.4% in men (odds ratio [OR] 1.62, 95% confidence interval [CI] 0.88 to 3.00, p = 0.12); occlusion rates of IMA grafts were 3.4% and 5.7% in women and men, respectively (OR 0.56, 95% CI 0.08 to 3.96, p = 0.56). Primary clinical end points were observed in 16.7% of women and 9.2% of men (OR 1.97, 95% CI 1.10 to 3.34, p = 0.022), and any clinical end point in 41.7% of women and 25.8% of men (OR 2.06, 95% CI 1.39 to 3.04, p = 0.0004). Myocardial infarction (15% vs. 7.6%, OR 2.15, 95% CI 1.24 to 3.75, p = 0.013) and recurrent angina (26.7% vs. 15.4%, OR 2.00, 95% CI 1.28 to 3.11, p = 0.004) occurred most frequently. Multivariate regression analysis did not identify gender as an independent risk factor for graft occlusion or the clinical end points. Graft occlusion was an independent predictor of the composite primary clinical end point (OR 2.75, 95% CI 1.59 to 4.75, p = 0.0003) and each of the secondary clinical end points. The observed differences were due to an imbalance of risk factors at baseline and to surgical and graft characteristics.

CONCLUSIONS: One-year occlusion rates of vein and IMA grafts were comparable in women and men. Clinical outcome was related to graft patency and was less favorable in women owing to their uneven distribution of risk factors among both groups.

(2) Figueredo VM, Diamond I, Zhou HZ, Camacho SA

**CHRONIC DIPYRIDAMOLE THERAPY PRODUCES SUSTAINED PROTECTION RDIAIC ISCHEMIA-REPERFUSION INJURY.**


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Sustained protection against ischemia-reperfusion injury is not available for patients at risk for myocardial infarction who may require emergent reperfusion therapy. Whereas ischemic preconditioning and adenosinergic agents reduce myocardial injury, they are only effective when given immediately before ischemia or reperfusion. We recently found chronic ethanol exposure, an adenosine uptake inhibitor, produced sustained cardioprotection against ischemia-reperfusion injury. We now ask whether chronic dipyridamole therapy, a clinically usable nucleoside transport inhibitor, induces similar cardioprotection. Perfused hearts from guinea pigs, given dipyridamole (4 mg. kg(-1). day(-1)) in their water for 2-6 wk (n = 10 for each group), underwent ischemia-reperfusion. Injury was assessed by recovery of left ventricular developed (LVDP) and end-diastolic (LVEDP) pressures and creatine kinase release. During reperfusion, hearts from dipyridamole-treated animals (6 wk) had 74% higher LVDP, 28% lower LVEDP, and 61% lower creatine kinase release versus controls. Adenosine A(1)-receptor antagonism (8-cyclopentyl-1,3-dipropylxanthine; 200 nM) abolished the protection of dipyridamole but A(2) antagonism (3,7-dimethyl-1-
propargylxanthine; 10 mM) did not. Dipyridamole therapy produces sustained protection against ischemia-reperfusion injury in guinea pigs. This cardioprotection requires adenosine A(1) receptor signaling at the time of ischemia.


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Even in the era of coronary stenting, acute coronary artery occlusion continues to represent a significant limitation of percutaneous transluminal coronary angioplasty (PTCA). Despite application of heparin and aspirin, abrupt vessel closure still occurs in 2-8%, depending on the definition applied. Especially patients receiving PTCA for acute coronary syndromes are at high risk for abrupt vessel closure. The formation of an intracoronary thrombus plays a central role in the pathogenesis of abrupt vessel closure. Dipyridamole induces dilatation of coronary arteries and prevents platelet aggregation by a mechanism that differs from that of aspirin. The primary purpose of the study was to evaluate whether adjunctive local intracoronary therapy with dipyridamole could reduce the incidence of coronary artery occlusion following PTCA. Secondary endpoints were defined as myocardial infarction, necessity for bypass grafting, and death. In 939 PTCA procedures performed for stable angina and in 155 angioplasty procedures for acute coronary syndromes (unstable angina, acute myocardial infarction), patients were randomized to receive conventional pretreatment consisting of heparin 15,000 I.E. and aspirin 500 mg i.v. or additional intracoronary infusion of dipyridamole (0.5 mg/kg body weight). Dipyridamole was applied in 550 interventions (455 interventions in men, 95 interventions in women, age = 59.2 +/- 8.4; 74 emergency procedures); conventional pretreatment was performed in 544 interventions (444 interventions in men, 100 interventions in women, age 58.3 +/- 7.9; 81 emergency procedures). Intracoronary application of dipyridamole resulted in a significant reduction in the incidence of abrupt vessel closure following PTCA. This significant reduction was observed in patients presenting with stable ischemia as well as in patients receiving PTCA for acute coronary syndromes. Concerning secondary end points, intracoronary application of dipyridamole did not affect the need for bypass grafting or the incidence of death following PTCA. Intracoronary application of dipyridamole was associated with a reduction in the incidence of myocardial infarction following PTCA which, however, failed to reach significance.

5. Dipyridamole to prevent Stent Occlusion

(1) Sukavaneshvar S, Solen KA, Mohammad SF DEVICE INDUCED THROMBOEMBOLISM IN A BOVINE IN VITRO CORONARY STENT MODEL. ASAIO J 1998 Sep-Oct;44(5):M393-6

Chemical Engineering Department, Brigham Young University, Provo, Utah 84602, USA.

The potential of a new bovine in vitro model to evaluate various aspects of device induced thromboembolism was studied using two test modes. First, the effect of an antithrombotic drug on stent induced thromboembolism was assessed. The antithrombotic potential of an antiplatelet agent was compared with that of the other conventional antithrombotic agents (aspirin, dipyridamole) used in the past with this in vitro model. Stent associated thrombus was assessed gravimetrically at the end of the experiment. Emboli were assessed continuously using a light scattering microemboli detection system. Second, the sensitivity of the model to flow induced thromboembolism was studied using a combination of surface roughness and stenosis. Thrombus was assessed visually, and emboli were assessed as described earlier. The results show that 1) this in vitro model is sensitive to the action of antithrombotic drugs, and to the effect of hemodynamics on thromboembolism; 2) the antiplatelet drug used in this study was effective in attenuating thromboembolism; 3) a stenosis in
combination with roughness produced more emboli than roughness alone; and 4) the model was useful for the study of physical and biochemical aspects of thromboembolism.

(2) Zidar JP
LOW MOLECULAR WEIGHT HEPARIN IN CORONARY STENTING.

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A pilot clinical study called Enoxaparin and Ticlopidine after Elective Stenting (ENTICES) was designed to determine whether the combination of enoxaparin, ticlopidine and acetylsalicylic acid (ASA) is superior to the conventional five-drug regimen routinely used after elective stent placement (warfarin, unfractionated heparin, dextran, dipyridamole and ASA). Compared with patients on conventional therapy (44), those randomly assigned to enoxaparin and ticlopidine (79) had a lower composite rate of in-hospital bleeding and vascular complications (5% versus 16%; P = 0.005), a significantly lower composite end-point rate (death, nonfatal myocardial infarction, stent thrombosis of urgent revascularization) at 30 days (5% versus 20%; P = 0.001), a significantly lower incidence of stent thrombosis in the first 30 days (0% versus 7%; P = 0.04) and the same incidence of death or repeat angioplasty at six months. The Antiplatelet Therapy versus Lovenox plus Antiplatelet Therapy for Patients with an Increased Risk of Stent Thrombosis (ATLAST) trial was subsequently designed to compare the efficacy of the combination therapy enoxaparin, ASA and ticlopidine with that of antiplatelet therapy alone after coronary stent placement in patients at increased risk of stent thrombosis. Target enrolment of 2000 patients began in December 1996 and is expected to be complete by the end of 1998. In summary, the ENTICES pilot study demonstrated that the low molecular weight heparin enoxaparin is safe and effective for use with ASA and ticlopidine for elective stent patients. The ATLAST trial should provide results on whether enoxaparin is beneficial in patients at high risk for stent thrombosis.

REDUCTION OF THROMBOTIC AND HEMORRHAGIC COMPLICATIONS AFTER STENT IMPLANTATION.
*Am Heart J* 1996 Dec;132(6):1119-26

Department of Cardiology, Hospital Reina Sofia, Cordoba, Spain.

This study compared two consecutive antithrombotic strategies after Palmaz-Schatz stent implantation and involved 918 patients. Patients treated between May 1991 and May 1994 (group 1; n = 379) received aspirin, dipyridamole, and intravenous unfractionated heparin until oral anticoagulation was effective, between June 1994 and August 1995, 539 patients (group 2) were treated for 1 month with subcutaneous low-molecular-weight heparin (Fragmin), ticlopidine, and aspirin. There were no differences between the groups in terms of sex, clinical condition, vessel diameter, and severity and location of stenosis. Patients in group 1 were younger than those in group 2 (4% were > 70 years old compared with 12%, respectively; p < 0.01). Group 1 patients had more frequent unplanned stenting (48% vs 18%, respectively; p < 0.01) and fewer endoprostheses in the same artery than those in group 2 (1.1 +/- 0.5 vs 1.2 +/- 0.5, respectively; p < 0.01). Among group 2 patients, there was a significant reduction in thrombotic and hemorrhagic complications compared with group 1 patients. No subacute thrombosis occurred in patients in group 2 in contrast with a 5.8% incidence in patients in group 1 (p < 0.01). In addition, a lower incidence of groin and systemic bleeding was observed in patients in group 2 compared with patients in group 1 (2.6% vs 15%, respectively; p < 0.01). The association of low-molecular-weight heparin and antiplatelets provides a simpler antithrombotic strategy in patients treated with intracoronary stents and reduces the incidence of stent thrombosis and hemorrhagic complications. Our findings suggest that this antithrombotic regimen may prevent or completely avoid stent thrombosis.

(4) Erbel R, Ge J, Haude M, Gorge G
[ALTERNATIVE METHODS IN INTERVENTIONAL THERAPY OF CORONARY HEART DISEASE]. [ARTICLE IN GERMAN]
*Z Kardiol* 1995;84 Suppl 2:53-64
Abteilung Kardiologie, Universitat-Gesamthochschule, Essen.

Percutaneous high-frequency coronary rotablation using the rotablator is able to remove arteriosclerotic material from the vessel wall. A diamond-coated (30-80 microns) brass burr drill fastened to a flexible drive shaft rotating and tracking along a drill coaxial guide wire is used. The turbine rotates the drive shaft in excess of 150,000-190,000 rpm. High-frequency rotational angioplasty was successful in > 90% of patients, but in about 90% additional PTCA is necessary. No increase of bypass surgery compared to PTCA is observed. CK and CR-MB elevation is more often found than after PTCA. Vessel perforation is rarely observed. All vessels were open at 24-h control. The restenosis rate seems not to be increased. The main indications for high-frequency rotational angioplasty are rigid and calcified sclerotic lesions which cannot be passed by conventional balloon catheters. Whether the restenosis rate can be reduced by this method will be judged in part by the COBRA study. In order to avoid acute complications of PTCA and to reduce restenosis rate, coronary stents were developed. Self-expandable and balloon expandable stents are available. It could be demonstrated that these stents can be used as a bail-out system and can block elastic recoil of coronary arteries. The major remaining problem is subacute closure of coronary vessels. In order to prevent thrombosis treatment with coumarine, acetylsalicylic acid, and dipyridamol is necessary. Coronary stents can be successfully delivered in more than 90% of the patients. In a highly selected patient group using single stents restenosis rate could be significantly reduced.

6. Dipyridamole in Coronary Arterial Disease


**EFFECT OF DIPYRIDAMOLE ON QT DISPERSION IN VASOSPASTIC ANGINA PECTORIS.**

*Amer J Cardiol* 1999 Oct 1;84(7):807-10

Department of Cardiology, Yokohama Minami Kyosai Hospital, Yokohama-city, Japan.

Life-threatening ventricular arrhythmias have frequently been documented in patients with vasospastic angina. Moreover, the incidence of ventricular arrhythmias has been closely associated with increased QT dispersion. However, the underlying mechanism responsible for this arrhythmogenesis has not been clarified. The effects of dipyridamole and subsequent aminophylline administration on QT dispersion were examined in 35 patients with vasospastic angina and 30 patients with atypical chest pain. None of the patients enrolled in this study revealed any significant stenosis in coronary angiography. QT dispersion during dipyridamole followed by aminophylline administration was compared between the 2 groups. The baseline QT dispersion was similar in both groups (vasospastic angina: 27 +/- 8 ms; atypical chest pain: 28 +/- 7 ms). No significant changes in QT dispersion were observed in patients with atypical chest pain by dipyridamole (23 +/- 9 ms) and subsequent aminophylline administration (23 +/- 5 ms). However, the QT dispersion in patients with vasospastic angina increased significantly by dipyridamole administration (53 +/- 14 ms, p <0.0001) and returned to baseline by subsequent aminophylline administration (26 +/- 10 ms). Our data suggest that the disparity of ventricular repolarization in vasospastic angina may be mediated by increased endogenous adenosine.

(2) Anikin VV

**[DIPYRIDAMOLE (CURANTIL) TREATMENT OF ANGINAL PATIENTS: RESULTS OF TREATMENT FOR MANY YEARS]. [ARTICLE IN RUSSIAN]**

*Ter Arkh* 1999;71(8):34-7

AIM: To assess effect of curantil optimal doses on clinical condition, coronary reserves, systemic microcirculation and peripheral hemodynamics in patients with stable angina pectoris (AP) given a course or continuous treatment. MATERIALS AND METHODS: A 2-month treatment with curantil with a gradual increase of the daily dose to 0.45 g was given to 261 patients with AP. After that the treatment was continued to 3 years in 38 patients. The coronary reserves were examined with bicycle exercise tests, peripheral hemodynamics and microcirculation were investigated with tachooscillography and conjunctival biomicroscopy. RESULTS: The 2-month curantil treatment was effective in 81% of the patients with AP functional class II-III and 60% of those with AP class 4. Exercise tolerance increased in AP of functional class II-III and IV by 50 and 24%, respectively. Ischemic depression of ECG ST segment induced by the exercise shortened. Prolongation of the
treatment to 1 year resulted in further regression of AP and provided a 57% increase in muscular performance. The 3-year treatment maintained the 1-year effectiveness which was associated with lowering of postload and improvement of microcirculation, in particular, a 2-fold decrease in manifestations of sludge. CONCLUSION: The antianginal effect of optimal daily doses of curantil is more potent in angina of effort, grows step-by-step and reaches maximum if continued for a year. A hemodynamic effect of curantil manifests with lowering of postload and improvement of microcirculation. This allows to recommend curantil in combined treatment of chronic coronary heart disease.

7. Dipyridamole for Antiphospholipid Syndrome

(1) Sakaguchi S, Kitazawa K, Watanabe M, Mukai K, Totsuka D, Shibata T, Sugisaki T
A CASE OF PRIMARY ANTIPHOSPHOLIPID ANTIBODY SYNDROME WITH ACUTE RENAL FAILURE SHOWING THROMBOTIC MICROANGIOPATHY.

Department of Nephrology, Showa University School of Medicine, Tokyo, Japan.

An 18-year-old woman complained of fever and edema and was admitted to Showa University Hospital for treatment of thrombocytopenia and deteriorating renal function. Laboratory studies demonstrated the presence of lupus anticoagulant (LA), prolongation of prothrombin time, hemolytic anemia, a negative Coombs' test, the absence of antinuclear antibodies, and a normal fibrinogen level. Renal biopsy revealed mesangial hypercellularity, severe endocapillary cell damage, and double contour of the basement membrane walls. Immunofluorescence studies demonstrated focal, peripheral, and finely granular deposits for IgG, IgM, and IgA but were negative for fibrinogen. Electron microscopy showed glomerular capillary loops with subendothelial widening and subendothelial deposits, mesangiolysis, mesangial interposition, and marked luminal narrowing. Biopsy findings were consistent with thrombotic microangiopathy. The patient was treated with hemodialysis, methylprednisolone pulse therapy, and dipyridamole. After treatment, LA disappeared, the prothrombin time became normal, and renal function improved. The renal lesions in this patient were caused by primary antiphospholipid antibody syndrome. This case strongly suggests an important causal relationship between LA and renal lesions in thrombotic microangiopathy. We present this case to promote understanding of the pathogenesis of primary antiphospholipid antibody syndrome. Copyright Copyright 1999 S. Karger AG, Basel

(2) Ohtomo Y, Matsubara T, Nishizawa K, Unno A, Motohashi T, Yamashiro Y
NEPHROPATHY AND HYPERTENSION AS MANIFESTATIONS IN A 13-Y-OLD GIRL WITH PRIMARY ANTIPHOSPHOLIPID SYNDROME.

Department of Paediatrics, Juntendo University School of Medicine, Tokyo, Japan.

Severe renal hypertension due to both unilateral renal arterial occlusion and renal thrombotic microangiopathy developed in a 13-y-old girl as a manifestation of primary antiphospholipid antibody syndrome. The combination of the intravenous high-dose urokinase therapy and oral anticoagulation therapy, comprising aspirin, warfarin and dipyridamole, was significantly effective in improving her renal function and preventing thrombotic events during an 18-month follow-up period.

[A CASE OF GLOMERULONEPHRITIS WITH SINGULAR HIGH TITER OF ANTICARDIOLIPIN ANTIBODY]. [ARTICLE IN JAPANESE]
Nippon Jinzo Gakkai Shi 1998 Feb;40(2):54-9

Kidney Center, Tsukuba Gakuen Hospital.

We report here a case of severe membranoproliferative glomerulonephritis with a singular high titer of anticardiolipin antibody (aCL). A 19-year-old Japanese female was admitted to Tsukuba Gakuen Hospital after complaining of general edema for 5 months. She had no past history of thrombosis,
thrombocytopenia, or spontaneous abortion. Laboratory findings revealed that she had nephrotic syndrome and moderate renal dysfunction. Immunological test showed a high titer of aCL with a high-normal limit of antinuclear antibody, negativity for anti-beta(2) glycoprotein I antibody and negativity for anti-DNA antibody. In the renal biopsy tissue, most glomeruli showed global sclerosis and the remaining glomeruli revealed membranoproliferative change with crescent formation. Steroid therapy with warfarin and dipyridamole was effective and her renal function improved gradually. This case lacked the typical symptoms of primary antiphospholipid syndrome and did not satisfy the criteria of SLE. In spite of these findings, the singular high titer of aCL with membranoproliferative glomerulonephritis characterized this case.

(4) Vivaldi P, Andreotti C, Mazzon C, Pedrazzoli M
A "PRIMITIVE" CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME.

Second Medical Division, St. Chiara General Hospital, Trento, Italy.

A female patient affected by a thrombotic syndrome due to non SLE-related antiphospholipid antibodies (APA), developed a serious, non inflammatory, thrombotic macroangiopathy and uremic-hemolytic syndrome during oral anticoagulant therapy. She was treated with aspirin, dipyridamole i.v. and with a total of 14 fresh frozen plasma exchange (PEX), but the thrombotic syndrome only showed a partial response with the APA titre dropping considerably. Renal failure did not improve because of acute cortical necrosis. The patient died from infective complications.

(5) Menashe Y, Ben-Baruch G, Greenspoon JS, Carp HJ, Rosen DJ, Mashiach S, Many A
SUCCESSFUL PREGNANCY OUTCOME WITH COMBINATION THERAPY IN WOMEN WITH THE ANTIPHOSPHOLIPID ANTIBODY SYNDROME.

Department of Obstetrics and Gynecology, Chaim Sheba Medical Center, Tel Hashomer, Israel.

Four women with the antiphospholipid syndrome associated with lupus anticoagulant and a poor obstetric history were treated with a combination of glucocorticosteroids, anticoagulants and platelet inhibitor therapy. All patients had at least one previous miscarriage while receiving prednisone and low-dose aspirin. The treatment regimen included: aspirin, dipyridamole, prednisone, and warfarin or heparin. This treatment resulted in a successful pregnancy outcome in all cases, without preeclampsia or recurrence of thrombosis. One patient developed a vertebral compression fracture while receiving heparin and prednisone. Two pregnancies required cesarean delivery for fetal distress at 32 and 34 weeks. All four infant birth weights were appropriate for the gestational age. This regimen may be a therapeutic option for patients with the antiphospholipid antibody syndrome, especially if they have failed other commonly used treatments.

(6) Vrethem M, Ernerudh J, Lindstrom F, Olsson JE
CEREBRAL ISCHEMIA ASSOCIATED WITH ANTICARDIOLIPIN ANTIBODIES.

Department of Neurology, Linkoping University Hospital, Sweden.

Eight patients, 3 with systemic lupus erythematosus (SLE) or "SLE-like" disease, 1 with sarcoidosis, and 4 with no connective tissue disease had transient ischemic attacks (TIA) or cerebral infarctions associated with high levels of anticardiolipin antibodies (ACA). Cerebral ischemic events included amaurosis fugax, recurrent hemispheric TIA, cerebral infarction, and multi-infarction dementia. Treatment with acetylsalicylic acid was ineffective in 3 patients. Warfarin, alone or in combination with dipyridamole or steroids, may reduce the risk of further cerebrovascular events.

8. Dipyridamole in Cancer Therapy as a Chemosensitizer

a) Dipyridamole as Modulators of Cancertherapy Response General Aspects
(1) Boven E, Jansen WJ, Hulscher TM, Beijnen JH, van Tellingen O

THE INFLUENCE OF P170-GLYCOPROTEIN MODULATORS ON THE EFFICACY AND THE DISTRIBUTION OF VINCRISTINE AS WELL AS ON MDR1 EXPRESSION IN BRO/MDR1.1 HUMAN MELANOMA XENOGRAFTS.

*Eur J Cancer* 1999 May;35(5):840-9

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Multidrug resistance modulators may increase the antitumour efficacy of drugs affected by P170-glycoprotein (Pgp) in Pgp-positive tumours in vivo. Inhibition of Pgp function in normal tissues, however, may enhance side-effects. Dexniguldipine-HCl, its analogues B9203-009 and B9303-036, and the dipyridamole derivative BIBW22BS could reverse vincristine (VCR) resistance in BRO/mdr1.1 cells (transfected with full-length MDR1 cDNA) and 2780AD cells (selected for doxorubicin resistance) in vitro. VCR resistance in BRO/mdr1.1 xenografts grown subcutaneously (s.c.) in the nude mouse was not or only slightly affected by the Pgp modulators. VCR concentrations in normal mouse tissues increased with the dose of the Pgp modulator administered and this was most pronounced in liver, kidney, small gut and colon. Dexniguldipine 40 mg/kg intraperitoneally (i.p.) given once 4 h before VCR 1 mg/kg (i.v.) resulted in increased VCR concentrations in BRO/mdr1.1 xenograft tissue. Surprisingly, when dexniguldipine 40 mg/kg i.p. was administered daily x3 before VCR, tumour VCR concentrations were not affected. This phenomenon was not observed in normal mouse tissues. Upregulation of MDR1 mRNA to 2.7- to 3.8-fold higher levels than control mRNA in BRO/mdr1.1 xenograft tissue occurred after VCR or dexniguldipine at 4-8 h and up to 1.7-fold at 24-28 h after injection. The combination showed 3.6- to 3.7-fold increased levels at 4 h after VCR injection. The lower VCR concentrations measured in BRO/mdr1.1 xenograft tissue after pretreatment with dexniguldipine for 3 days relative to animals treated with dexniguldipine only once will likely be caused by a gradual increase of Pgp expression as a response to the upregulation of MDR1.

(2) Hejna M, Raderer M, Zielinski CC

INHIBITION OF METASTASES BY ANTICOAGULANTS.


Department of Medicine I, University Hospital, Vienna, Austria.

Metastasis involves several distinct steps, including one in which the tumor cell, after entry into the bloodstream, comes to rest in a capillary located at the distant site where a metastatic tumor will ultimately form. Components of the blood-clotting pathway may contribute to metastasis by trapping cells in capillaries or by facilitating adherence of cells to capillary walls. Conceivably, anticoagulants could interfere with this step in the metastatic process. In this review, we have summarized current knowledge on the interaction of malignant cells, clotting factors, and anticoagulants. We used computerized (MEDLINE) and manual searches to identify studies done in humans, in animals, and in vitro systems that were published in English between 1952 and 1998. We found many reports that the formation of metastatic tumors could be inhibited by heparin, a vitamin K antagonist (warfarin), and inhibitors of platelet aggregation (prostacyclin and dipyridamole). Despite these encouraging preliminary results and a compelling biochemical rationale, only limited information exists on the clinical use of anticoagulants for the prevention or treatment of metastatic cancer because there have been so few controlled and prospectively randomized studies on this topic. In view of the preliminary results, anticoagulants may hold promise for the prevention and treatment of metastases. We believe that larger controlled investigations are strongly warranted to evaluate the clinical potential of anticoagulants for the prevention and treatment of metastases in humans.

(3) Hosoi E, Hirose M, Hamano S, Morimoto M, Kuroda Y

EFFECT OF MDR ANTAGONISTS ON THE CIDAL ACTIVITY OF VINCRISTINE FOR CELLS EXPRESSING MDR-1 IS SUPERIOR TO THOSE EXPRESSING MRP.


School of Medical Science, The University of Tokushima, Tokushima City, Tokushima 770, Japan.
In an attempt to identify the target protein, P-GP or mrp, of each MDR antagonist, verapamil (Ver), dipyridamole (Dip), or cyclosporin A (Cy-A), this study was designed to compare the activity of the three afore-mentioned drugs and to test their combined effect on the cidal activity of vincristine (VCR) in five types of wild and the corresponding VCR-resistant cultured cell lines from human leukemia and lymphoma. Three of the VCR-resistant cell lines are characterized by the overexpression of mdr-1, while two cell lines overexpress mrp. We found that all three antagonists additively to synergistically enhanced the cidal activity of VCR for the five wild-type and VCR-resistant cell lines in a dose dependent manner when used singly. Combinations consisting of a 20% inhibitory concentration (IC20) of VCR plus two antagonists also showed additive to synergistic effects on both wild and VCR-resistant cell lines. It is of interest that the combined effect of IC20 VCR plus MDR antagonists on the three VCR-resistant cell lines expressing mdr-1 was significantly superior to those of the two cell lines expressing the mrp gene. These results suggest that the combined effect of MDR antagonists work better than their single use and that the MDR antagonists work more efficiently in cells showing drug resistance through mdr-1 than in those utilizing mrp.

(4) Chen WH, Yin HL, Chang YY, Lan MY, Hsu HY, Liu JS
ANTIPLATELET DRUGS INDUCE APOPTOSIS IN CULTURED CANCER CELLS.
Kao Hsiung I Hsueh Ko Hsueh Tsai Chih 1997 Oct;13(10):589-97
Department of Neurology, Kaohsiung Medical College Hospital, Taiwan, Republic of China.
In order to understand if antiplatelet drugs possess direct antineoplastic property, we tested the apoptotic effect of 5 popularly marketed antiplatelet drugs in Taiwan in 6 cultured cancer cell lines (Hep 3B hepatocarcinoma, U87-MG malignant glioma, PC-3 prostate adenocarcinoma, HeLa cervical adenocarcinoma, HL-60 preleukemia and K-562 chronic myelogenous leukemia). While acetylsalicylate and flunarizine exerted no effect on these cancer cells, pentoxifyline (PTX), dipyridamole (DYA) and ticlopidine hydrochloride (T. HCl) displayed a time and dose-dependent apoptotic effect on them except for HL-60 and K-562 cells. PTX induced apoptosis in U87-MG, Hep 3B and HeLa cells, DYA in HeLa cells, while T. HCl in U87-MG, Hep 3B, PC-3 and HeLa cells. Adriamycin also provoked apoptotic effect in all 6 cell lines but neither PTX, DYA nor T. HCl acted synergy with adriamycin to HeLa cells, implicating that they may share a similar pathway for inducing apoptosis. Therefore, our results show that the antiplatelet drugs do possess antineoplastic property in vitro. A co-administration of antiplatelet drugs is noteworthy for an alternative adjunctive therapy in cancer patients.

(5) Desai PB, Duan J, Sridhar R, Damle BD
REVERSAL OF DOXORUBICIN RESISTANCE IN MULTIDRUG RESISTANT MELANOMA CELLS IN VITRO AND IN VIVO BY DIPYRIDAMOLE.
Department of Medicinal Chemistry and Pharmaceutics, Northeast Louisiana University, Monroe, USA.
The occurrence of multidrug resistance (MDR) decreases the clinical utility of several anticancer agents, including doxorubicin (DOX). A transmembrane efflux pump, P-glycoprotein (P-gp), is frequently implicated in the development of MDR in tumor cells. Dipyridamole (DP), a clinically used antiplatelet drug, enhances the cytotoxicity of the anticancer drugs affected by MDR. Although this aspect has been studied extensively in cell culture models, the effectiveness of DP to overcome multidrug resistance has not been investigated using in vivo models of multidrug-resistant solid tumors. Therefore, the objective of this study was to evaluate the role of DP in the reversal of resistance to DOX in tumor-bearing mice in the context of its anti-MDR activity in vitro. For this purpose, drug-sensitive murine melanoma cells (B16V) and their DOX-selected MDR variant, B16VDR cells, were used. In vitro, the reversal of DOX resistance of B16VDR cells by DP was determined using clonogenic assays, and the influence of DP on the transport of DOX was evaluated by measurement of steady-state accumulation as well as efflux of DOX in B16VDR cells. Antitumor activity of different treatments was assessed by monitoring tumor growth. Pharmacokinetics of DOX, with or without DP, were evaluated in C57BL/6 mice bearing B16V or B16VDR tumors. DP produced a 6.4-fold reversal of resistance to DOX in vitro; this was accompanied by an increase (3.6-fold) in the steady-state intracellular accumulation of DOX and a marked reduction in the efflux of DOX from B16VDR cells. Furthermore, a linear correlation was observed between the EC50 values and the steady-state intracellular levels of DOX in the multidrug-resistant cells. In the in vivo
experiments, similar growth patterns were seen for the DOX alone and the DOX+DP groups for B16V tumors. The results with B16VDXR tumors were in sharp contrast. The DOX+DP treatment caused a significant delay in the growth of B16VDXR tumors compared to treatment with DOX alone or controls. DP did not alter the plasma pharmacokinetics of DOX in C57BL/6 mice but resulted in a significant increase in the intratumoral accumulation of DOX.

(6) Stewart DJ, Dahrouge S, Agboola O, Girard A
CRANIAL RADIATION AND CONCOMITANT CISPLATIN AND MITOMYCIN-C PLUS RESISTANCE MODULATORS FOR MALIGNANT GLIOMAS.
J Neurooncol 1997 Apr;32(2):161-8

Ontario Cancer Treatment and Research Foundation, Ottawa Regional Cancer Centre, Canada.

We studied the toxicity and efficacy of adding in sequence 4 resistance modulators to combination chemotherapy and radiotherapy in the treatment of glioblastoma multiforme and poor prognosis anaplastic astrocytomas. Patients received cisplatin plus mitomycin-C concurrently with and following 60 Gy of radiotherapy administered over 6 weeks. Resistance modulators were added in sequence to chemotherapy in each cohort of 6 patients as follows: metronidazole + pentoxifylline (cohort 1); + dipyridamole (cohort 2), + beta carotene (cohort 3). Central nervous system toxicity (which ranged from drowsiness to seizures and loss of consciousness) was frequent. The incidence of gastrointestinal symptoms was substantial, but was usually mild to moderate in severity. Three of 11 patients evaluable for response achieved a partial remission with treatment. The median survival duration for all patients was 26 weeks from initial diagnosis. The study was terminated prematurely because of significant toxicity (in this study as well as in parallel concurrent studies of similar design in other tumor types) and apparent lack of benefit.

(7) Stewart DJ, Goel R, Cripps MC, Huan S, Yau J, Verma S
MULTIPLE RESISTANCE MODULATORS COMBINED WITH CARBOPLATIN FOR RESISTANT MALIGNANCIES: A PILOT STUDY.
Invest New Drugs 1997;15(4):267-77

Ontario Cancer Treatment and Research Foundation, University of Ottawa, Faculty of Medicine, Canada.

BACKGROUND: Chemotherapy resistance is probably multifactorial; hence, we assessed the feasibility of adding to carboplatin 6 concurrent resistance modulators in 53 patients with resistant cancers. METHODS: Pentoxifylline and dipyridamole were added to carboplatin 400 mg/m2 in cohort 1, and metronidazole was also given in cohort 2. Mannitol and saline were administered in each cohort with the theoretical objective of improving carboplatin delivery to tumors by reducing blood viscosity. Because of excessive toxicity in cohort 2, cohort 3 received the same modulators as in cohort 2 but with a reduced dose of carboplatin (200 mg/m2). Subsequent patients had the following drugs added to those in the previous cohort: novobiocin (cohort 4), tamoxifen (cohort 5), ketoconazole (cohort 6). Cohort 7 patients received the 6 cohort 6 modulators along with carboplatin 300 mg/m2. RESULTS: Thrombocytopenia was excessive in early cohorts with a carboplatin dose of 400 mg/m2, but was minimal at lower doses. Other toxicity was generally tolerable and reversible, particularly at carboplatin doses < or = 300 mg/m2, although gastrointestinal and neurological toxicity tended to worsen as additional modulators were added. No major responses (but 4 minor responses) were seen in this patient population with heavily pretreated or primarily resistant cancers. CONCLUSIONS: Acceptable doses for phase II studies are carboplatin 300 mg/m2, 20% mannitol 250 ml plus normal saline 500 ml over 1 hr prior to carboplatin, pentoxifylline 700 mg/m2/day p.o. from 3 days before carboplatin to cessation of therapy, dipyridamole 100 mg/m2 p.o. q6h x 6 days starting 24 hr before carboplatin, metronidazole (750 mg/m2 p.o. 12 hr and immediately before, and 24 hr after carboplatin; 250 mg/m2 suppository p.r. 12 hr and immediately before, and 6 and 24 hr after carboplatin; and 500 mg/m2 i.v. right after carboplatin), novobiocin 600 mg/m2 p.o. q12h x 6 days starting 24 hr before carboplatin, and tamoxifen 100 mg/m2/day plus ketoconazole 700 mg/m2/day x 3 days starting the day before carboplatin, with oral dexamethasone and ondansetron as antimetics.
(8) Stewart DJ, Cripps MC, Goel R, Dahrouge S, Yau J, Tomiak E, Huan S, Soltys K, Prosser A, Davies RA

PILOT STUDY OF MULTIPLE CHEMOTHERAPY RESISTANCE MODULATORS PLUS EPIRUBICIN IN THE TREATMENT OF RESISTANT MALIGNANCIES.

*Cancer Chemother Pharmacol* 1997;41(1):1-8

The Ontario Cancer Treatment and Research Foundation, Ottawa Regional Cancer Centre, Canada.

We studied the toxicity and efficacy of adding to epirubicin five resistance modulators in the treatment of resistant solid tumors. Additional drugs were added in successive cohorts of patients, such that cohort 1 patients received two drugs along with their epirubicin, while cohort 4 patients received five modulators along with their epirubicin. Metronidazole, tamoxifen (cohort 1), dipyridamole (cohort 2), ketoconazole (cohort 3) and cyclosporin (cohort 4) were administered with epirubicin. A total of 22 patients were treated. Nausea and vomiting was usually mild to moderate. There was an unexpectedly high incidence of possible cardiac toxicity associated with treatment, although in some patients it was uncertain whether or not observed cardiac events were related to treatment. Granulocytopenia was significant in all four cohorts, but it was unclear whether it was increased by the modulators. There were two febrile neutropenic events in cohorts 1 and 2 successfully treated with antibiotics, and three septic deaths (one in each of cohorts 1, 2 and 4). It was elected to discontinue enrollment on the study prematurely in light of cardiac and other toxicity seen in the first two patients accrued in cohort 4. A single response was observed. While this approach is feasible, the observed toxicity and the difficulty patients experienced in ingesting the large number of prescribed pills will make further exploration of this approach difficult.


PHASE I STUDY OF N-(PHOSPHONACETYL)-L-ASPARTATE WITH FLUOROURACIL AND WITH OR WITHOUT DIPYRIDAMOLE IN PATIENTS WITH ADVANCED CANCER.

*Clin Cancer Res* 1996 Jul;2(7):1107-14

Comprehensive Cancer Center of Wake Forest University, Winston-Salem, North Carolina 27157, USA.

We conducted a combined biochemical modulation trial of N-(phosphonacetyl)-L-aspartate (PALA), dipyridamole (DP), and fluorouracil (5-FU) in patients with cancer. Eighty-eight patients with advanced cancer were entered into this Phase I trial. During the first part of the study, four doses of PALA (125, 250, 500, and 1000 mg/m2, administered on day 1) were evaluated to determine the PALA dose with maximal suppression of aspartate transcarbamylase (ATCase) activity that was clinically tolerable. Patients were randomized to receive DP (or no DP), 50 mg/m2, p.o. every 6 h on days 1-6, and all patients received 5-FU, 400 mg/m2, by bolus administration on days 2-5. Prior to and during therapy, WBCs were collected and assayed for ATCase activity. After the maximally tolerated PALA dose with 400 mg/m2 5-FU +/- 50 mg/m2 DP was defined, the 5-FU dose was escalated using the same administration schedule of 5-FU, PALA, and DP. The dose of 5-FU was escalated by 25% in each of the DP cohorts until dose-limiting toxicity was reached. ATCase activity was inhibited in a dose-dependent manner with PALA doses of 125, 250, 500, and 1000 mg/m2, resulting in 0, 13, 17, and 49% inhibition of ATCase activity. Only at the higher PALA doses (i.e., 500 and 1000 mg/m2) was ATCase activity suppressed during days 2-5, but the activity returned to pretreatment levels by day 15. Based on the clinical tolerance and significant suppression of ATCase activity, a PALA dose of 500 mg/m2 was selected for the 5-FU dose escalation phase. At a 5-FU dose of 625 mg/m2, dose-limiting toxicity (leukopenia, stomatitis, and diarrhea) occurred in both DP cohorts. We recommend that for this monthly treatment schedule, 500 mg/m2 PALA and 500 mg/m2 5-FU, with or without 50 mg/m2 DP, be used in subsequent Phase II trials.

(10) Ford JM

MODULATORS OF MULTIDRUG RESISTANCE. PRECLINICAL STUDIES.

The study of the cellular, biochemical, and molecular biology and pharmacology of MDR has provided one of the most active and exciting areas within cancer research for translation into potential clinical benefit. Although convincing evidence for the functional role of P-gp in mediating clinical drug resistance in humans remains scant, studies of the clinical expression of P-gp and trials of chemosensitizers with cancer chemotherapy suggest “resistance modification” strategies may be effective in some tumors with intrinsic or acquired drug resistance. However, even if P-gp-associated MDR proves to be a relevant and reversible cause of clinical drug resistance, numerous problems remain to be solved before effective clinical chemosensitization may be achieved. Such factors as absorption, distribution, and metabolism, the effect of chemosensitizers on chemotherapeutic drug clearance, toxicity to normal tissues expressing P-gp, and the most efficacious modulator regimens all remain to be defined in vivo. Clearly, the identification of more specific, more potent, and less clinically toxic chemosensitizers for clinical use remains critical to the possible success of this approach. However, the finding that a number of pharmacologic agents can antagonize a well-characterized form of experimental drug resistance provides promise for potential clinical applications. Further study of chemosensitizers in humans and the rational design of novel chemosensitizers with improved activity should define the importance of MDR to clinically resistant cancer.

(11) Sotomatsu M, Yugami S, Shitara T, Kuroume T

**DIPYRIDAMOLE ENHANCEMENT OF DRUG SENSITIVITY IN ACUTE LYMPHOBLASTIC LEUKEMIA CELLS.**


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The effect of dipyridamole (DPM) on cell sensitivity to anticancer drugs was examined in acute lymphoblastic leukemia (ALL) cell lines. We established two ALL cell lines (KMO-90 and KMO-R) from bone marrow samples of a 12-year-old girl with ALL. The drug concentrations needed to reduce optical density to 50% of that of control cells (IC50) showed that KMO-R was about twofold more resistant to doxorubicin (DOX), mitoxantrone (MIT), vincristine (VCR), and etoposide (VP-16) than was KMO-90. Considering that both KMO-90 and KMO-R were established from a patient with ALL at the time of presentation and relapse, respectively, these two cell lines might be novel and useful models for research into the acquisition of drug resistance in ALL cells. Although cytotoxicity of DPM in KMO-90 was about 6% at 1 microgram/ml, DPM enhanced cell sensitivity to DOX, MIT, VCR, and VP-16 at this concentration. In KMO-R, DPM enhanced cell sensitivity to these four drugs in a dose-dependent manner. The plasma concentrations achieved by oral administration of DPM is about 1 microgram/ml. At clinically achievable concentrations, DPM enhanced cell sensitivity to DOX, MIT, VCR, and VP-16 in both KMO-90 and KMO-R, thus showing DPM to be a useful agent for potentiating anticancer chemotherapy of hematopoietic malignancy.

(12) Hirose M, Takeda E, Kuroda Y

**OVERCOMING OF VINCRISTINE RESISTANCE IN HL-60 HUMAN PROMYELOCYTIC LEUKEMIA CELL LINE BY DIPYRIDAMOLE.**


Division of Blood Transfusion, School of Medicine, University of Tokushima, Japan.

Dipyridamole enhanced the anti-cancer activity of VCR toward both wild type HL-60 and VCR-resistant subline, HL-60/R, which had a 15 fold greater resistance to VCR as compared with the wild type cell line. The resistance to VCR of HL-60/R cells was associated with a marked decrease in the intracellular VCR accumulation. After incubation with VCR for 24 hrs, 0.61 and 0.24 pmol VCR per one million cells were accumulated in the wild and the resistant cells, respectively. Dipyridamole dose-dependently increased the intracellular VCR accumulation in the wild type cells and also it restored the intracellular VCR accumulation in the VCR-resistant cells. Addition of 10 microM dipyridamole to the culture medium enhanced the intracellular accumulation of VCR during 24 hr incubation by 2.6 fold and 6.0 fold in HL-60 and HL-60/R cells, respectively. The VCR-resistance in HL-60/R cells was able to be overcome by the addition of 2.5 microM dipyridamole to the culture medium. This concentration of dipyridamole could be obtained by the intravenous administration.
b) Dipyridamole in Lung Cancer therapy

(1) Curtin NJ, Turner DP
DIPYRIDAMOLE-MEDIATED REVERSAL OF MULTIDRUG RESISTANCE IN MRP
OVER-EXPRESSING HUMAN LUNG CARCINOMA CELLS IN VITRO.


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Expression of the multidrug resistance-associated protein (MRP) is widespread in human
malignancies, high levels are associated with poor prognosis and may be responsible for intrinsic and
radiotherapy-induced chemoresistance. In this study, the nucleoside transport inhibitor,
dipyridamole (DP), was investigated as a chemosensitiser of MRP. In growth inhibition assays MRP-
over-expressing COR L23/R cells were 20 times more resistant to VP16 and doxorubicin compared
with the parental COR L23/R human lung carcinoma cells, DP caused an approximately 8-fold
sensitisation of the resistant cells and a 2-fold sensitisation of the parental cells. DP enhanced the
accumulation of VP16 1.5 to 2-fold in the parental cells, but had only a modest effect on VP16
accumulation in the resistant cells. VP16 efflux was rapid in both cell lines. DP caused a modest and
transient inhibition of the initial efflux in the resistant cells but not the parental cells. Incubation with
DP caused a progressive decrease in GSH levels which was more rapid and profound in COR L23/R
cells than in COR L23/P cells. Thus, chemosensitisation to VP16 by DP in MRP-overexpressing COR
L23/R cells appears to be caused by depletion of cellular GSH rather than a direct effect of DP on
MRP-mediated drug accumulation and efflux.

(2) Vallejo CT, Rabinovich MG, Perez JE, Rodriguez R, Machiavelli MR, Leone BA, Romero
HIGH-DOSE CISPLATIN WITH DIPYRIDAMOLE IN ADVANCED NON-SMALL CELL
LUNG CANCER. A GRUPO ONCOLOGICO COOPERATIVO DEL SUR STUDY.

Grupo Oncologico Cooperativo del Sur (GOCS), Neuqeen, Argentina.

From March 1991 to October 1992, 41 patients with advanced non-small cell lung cancer (NSCLC)
(20 stage IIIB and 21 stage IV) received a regimen consisting of cisplatin (CP) 100 mg/m2 i.v. days 1
and 8, and dipyridamole (DPD) 100 mg p.o. 75 minutes before CP, and then at hours 6, 12, and 18 as
first-line chemotherapy. Cycles were repeated every 28 days for a total of 3. Median age was 56 years
(range: 40-70). All patients had a performance status 0 to 1 and a weight loss < or = 10%. Squamous-
cell carcinoma was diagnosed in 19 patients; adenocarcinoma in 16, and large-cell carcinoma in 6. A
total of 37 patients were fully evaluable for response, whereas 39 were assessable for toxicity. No
complete responses were observed: 5 patients (14%) achieved partial response; 23 patients (62%)
showed no change, and progressive disease was observed in 9 (24%). The median time to treatment
failure was 4 months, whereas median survival was 8 months. The average dose intensity received at
the end of the third course of therapy was 46 mg/m2/week. There were no drug-related deaths.
Toxicity was mild to moderate, with a high incidence of ototoxicity (54%) and emesis (67%). In
conclusion, these results failed to demonstrate any significant advantage from a high-dose CP
regimen modulated by DPD in patients with advanced NSCLC.

[5-FLUOROURACIL + LOW-DOSE LEUCOVORIN AND CISPLATIN SEQUENTIAL
CHEMOTHERAPY WITH DIPYRIDAMOLE FOR ADVANCED NONRESECTABLE
SQUAMOUS CELL CARCINOIMA OF THE LUNG: A CASE REPORT]. [ARTICLE IN
JAPANESE]
Gan To Kagaku Ryoho 1993 Feb;20(2):287-90
A 62-year-old man diagnosed as **Stage IIIB advanced non-resectable squamous cell carcinoma** of the lung was treated with a sequential combination of 5-fluorouracil (5-FU) and cisplatin (CDDP), with concurrent administration of leucovorin and dipyridamole as a biochemical modulator for 5-FU. After 3 cycles, the mass reduced in size more than 70% in CT scan and the patient underwent a thoracotomy. Histologically, the primary lesion was completely necrotized and of the 10 metastatic regional lymph nodes, only one lymph node contained a small amount of viable cells and 3 additional cycles were conducted. The patient is still alive 30 months after initial chemotherapy. This regimen appears to be potentially useful for **non-small-cell lung cancer** and warrants further clinical study.

c) Dipyridamole in Gastric cancer Treatment

(1) Kohnoe S, Maehara Y, Takahashi I, Emi Y, Baba H, Sugimachi K

TREATMENT OF ADVANCED GASTRIC CANCER WITH 5-FLUOROURACIL AND CISPLATIN IN COMBINATION WITH DIPYRIDAMOLE.


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We investigated the efficacy of combination chemo-therapy using 5-fluorouracil (5-FU), cisplatin (CDDP), and dipyridamole (DP), which is based on the concept of double biochemical modulation. Twenty-eight patients with **advanced gastric cancer** were treated with the simultaneous continuous intravenous (i.v.) infusion of 5-FU (800 mg/m2/day) and DP (4 mg/kg/day), and i.v. infusion of CDDP (20 mg/m2/day) for 5 days. The cycles were repeated every 4 weeks. Twelve patients (43%) had a partial response (PR), while stable disease (NC) occurred in 13 patients (46%), and progression (PD) in 3 patients (11%). An improved performance status was observed in 20 patients (71%). The carcinoembryonic antigen (CEA) level was markedly decreased in 75% of the CEA-positive patients. Toxicity was acceptable. The mean steady state plasma concentration of total DP was 6.40.5 microM, which thus seemed adequate to potentiate the cytotoxicity of 5-FU. The treatment regimen described herein thus appears to be effective, safe and well tolerated by patients with **advanced gastric cancer**.

d) Dipyridamole in Pancreatic Cancer Treatment

(1) Todd KE, Gloor B, Lane JS, Isacoff WH, Reber HA

RESECTION OF LOCALLY ADVANCED PANCREATIC CANCER AFTER DOWNSTAGING WITH CONTINUOUS-INFUSION 5-FLUOROURACIL, MITOMYCIN-C, LEUCOVORIN, AND DIPYRIDAMOLE.

*J Gastrointest Surg* 1998 Mar-Apr;2(2):159-66

Department of Surgery, UCLA School of Medicine, Los Angeles, CA, USA.

Patients with **locally advanced pancreatic adenocarcinoma** who receive conventional therapy with radiation of 5-fluorouracil (5-FU) have median survivals ranging from 8 to 12 months. Here we report our experience with a four-drug chemotherapeutic regimen that resulted in sufficient downstaging of tumor in some patients to justify surgical reexploration and resection. From April 1991 through April 1994, 38 patients received 5-FU as a continuous infusion (200 mg/m2/day), calcium leucovorin weekly by intravenous bolus injection (30 mg/m2), mitomycin-C every 6 weeks (10 mg/m2 intravenously), and dipyridamole daily orally (75 mg) for locally advanced unresected pancreatic cancer. All of these patients were evaluable for response, toxicity, and survival. There were 14 partial responses and one complete response—a 39% response rate. The median survival for **all patients** was 15.5 months; the 1-year survival rate from time of initial diagnosis was 70%. Six of 15 responding patients had sufficient **tumor regression** to meet clinical criteria for resectability and reexploration, four of whom underwent a curative resection. The median survival of these six patients was 28 months from the time of original diagnosis. The **1-year survival** was 83%, **with one patient still alive** and **free of disease** at 53 months. We believe this unique experience from a single institution justifies a prospective multi-institutional trial to evaluate the efficacy of this approach in a larger number of patients.
e) Dipyridamole in Colorectal Cancer Treatment

(1) Berti E, Carrara M, Ragazzi E, D'Ancona S, Berti T


Department of Pharmacology Egidio Meneghetti, University of Padova, 35131 Padova, Italy.

This study was designed to compare the activity of two MDR modulators, verapamil and dipyridamole, on the in vitro growth of a human colon carcinoma cell line. The aims were: a) to investigate the different sensitivity of the parental cell line (LoVo S) and the doxorubicin-resistant one (LoVo R) towards the treatment with several antiblastics and their associations with verapamil or dipyridamole; b) to evaluate if the combined use of these drugs with verapamil or dipyridamole increases their cytotoxicity; c) to understand whether the mechanism of action of each modulator is the same. Idarubicin and vinblastine were the most active drugs on both cell lines. LoVo R cells showed cross-resistance to vinblastine, teniposide and mitoxantrone, while chemosensitivity towards cisplatin and cyclophosphamide was almost the same in both cell lines. The inhibitory effect on cell growth was enhanced when the drugs were associated with verapamil, but no difference was detected with cisplatin and cyclophosphamide. Verapamil is thus an effective MDR modulator when used with drugs actively pumped out of tumour cells by P-glycoprotein, while it is ineffective with drugs that induce resistance by different mechanisms. When combined with dipyridamole, a significant result was observed in the case of cisplatin, where a marked increase of cytotoxicity was detected.


[COMPARATIVE STUDY OF THE COMBINED EFFECT OF HCFU AND DIPYRIDAMOLE (DP) IN COLORECTAL CARCINOMA--TS INHIBITION RATE. KINKI COOPERATIVE STUDY GROUP OF CHEMOTHERAPY FOR COLORECTAL CARCINOMA]. [ARTICLE IN JAPANESE] *Gan To Kagaku Ryoho* 1996 May;23(6):715-20

Dept. of Surgery, Takarazuka City Hospital, Japan.

In the forty-seven medical centers in the Kinki district, a comparative trial was conducted to investigate the enhancement of the efficacy of HCEU due to dipyridamol (DP), which is a biochemical modulator in patients with colorectal cancer who have had a curative resection. The trial consisted of two comparative groups: one group (Group A) received HCFU only for five days before operation and for two years from the second week, and the other group (Group B) was given HCFU + DP for the same trial period as Group A. The total number of patients collected was 653 (Group A: 327 patients; Group B: 326 patients) during the two-year trial period from October, 1991. Thymidylate Synthetase (TS) activity in the primary lesions, which is an index of proximity effect, was measured, and the TS inhibition rate (TSIR) was calculated from the activities. The results showed that the TSIR in the primary lesions for the HCFU + DP group (Group B: 0.33) was significantly higher than that of the HCFU group (Group A: 0.27) (p = 0.0006). There was no increase in the side effects of HCFU due to combined administration with DP. From the above results, the therapy with HCFU + DP is expected to be useful for patients with colorectal cancer who have undergone curative resection.

(3) Kohne CH


Abteilung Hamatologie/Onkologie, Medizinische Hochschule Hannover.

BACKGROUND: Despite its low antineoplastic activity 5-fluorouracil remains the most active compound for the treatment of patient with metastatic colorectal cancer. PATIENTS AND METHODS: Within 5 consecutive trials (2 were randomized) 174 patients have been treated with...
bolus 5-FU 600 mg/m² plus folinic acid 300 mg/m² day 2 to 4 with or without dipryridamole 3 x 75 mg p.o. day 1 to 5; 74 patients with bolus 5-FU 300 to 350 mg/m², folinic acid 200 mg/m² and interferon 5 x 10⁹ U/m² s.c. day 1 to 5; 18 patients with PALA 250 mg/m², MTX 250 mg/m² day 1 and bolus FU 600 mg/m² day 2 q day 14 and 86 patients with FU 2.6 g/m² given as 24-h infusion plus interferon 3 x 10⁹ (9) IU s.c. and 133 patients with FU 2.6 g/m² given as 24-h infusion, folinic acid 500 mg/m² as 2-h infusion with or without interferon 3 x 10⁹ (9) IU s.c. RESULTS: The response rate was 11 to 14% for the i.v. push schedules and 21 to 36% for the 24-h continuous infusion regimens. The responses lasted for a median of 4.5 months and 12 months, respectively, if bolus or infusion schedules were applied. Median time to tumor progression was 4.5 months and 7 months for continuous infusion. The median patient survival was 10 to 12.7 months (bolus regimens) and 13 to 15 months for infusional 5-FU schedules. CONCLUSION: By weekly high dose infusional 5-FU the response rate, response duration, time to tumor progression and patient survival may be prolonged especially when modulated by folinic acid compared to modulated bolus regimens. This retrospective comparison however needs to be confirmed by the intergroup trial of AIO (#1/95) and EORTC (#40952).

(4) Labianca R, Pessi A, Facendola G, Pirovano M, Luporini G

MODULATED 5-FLUOROURACIL (5-FU) REGIMENS IN ADVANCED COLORECTAL CANCER: A CRITICAL REVIEW OF COMPARATIVE STUDIES.

Eur J Cancer 1996;32A Suppl 5:S7-12

Division of Medical Oncology, San Carlo Borromeo Hospital, Milano, Italy.

Several modifications to the administration schedule of 5-fluorouracil (5-FU) alone or in combination with other agents have been investigated in advanced colorectal cancer. Biochemical modulation of 5-FU with leucovorin (LV) increases response rate compared with 5-FU alone, but without improvement of overall survival. The best treatment schedule and optimal dose of LV remain unclear, although low doses seem equally as effective as high doses, with the advantage of reduced cost. Methotrexate can increase the activity of 5-FU to a similar degree as LV and a recent meta-analysis showed a slight improvement in survival. The combination of 5-FU + interferon has been disappointing, with phase III trials showing similar activity to 5-FU + LV, but with high toxicity. Other modulators (e.g. hydroxyurea, N-phosphonacetyl-L-aspartate, dipryridamole) show promising but sometimes conflicting results. Standardisation of assessment criteria should be considered when comparing these data to the activity of new drugs such as 'Tomudex' (ralitrexed, previously known as ZD1694), CPT-11 and oxaliplatin.


FAILURE OF ORALLY ADMINISTERED DIPYRIDAMOLE TO ENHANCE THE ANTINEOPLASTIC ACTIVITY OF FLUOROURACIL IN COMBINATION WITH LEUCOVORIN IN PATIENTS WITH ADVANCED COLORECTAL CANCER: A PROSPECTIVE RANDOMIZED TRIAL.

J Clin Oncol 1995 May;13(5):1201-8

Department of Hematology/Oncology, Hannover Medical School, Germany.

PURPOSE: A randomized trial was performed to investigate the ability of the nucleoside transport inhibitor dipryridamole (DP) to enhance the antitumor activity of fluorouracil (5-FU)/leucovorin (folinic acid [FA]). PATIENTS AND METHODS: One hundred eighty-one untreated patients with advanced colorectal cancer were randomized to receive 5-FU 600 mg/m² plus FA 300 mg/m² on days 2 to 4 with or without DP 75 mg orally three times daily on days 1 to 5. Cycles were repeated every 3 weeks. Only patients with documented tumor progression before therapy were eligible. 5-FU pharmacokinetics using high-performance liquid chromatography (HPLC) were assessed in 11 nonrandomized patients receiving paired cycles with or without DP. RESULTS: One hundred seventy-four patients were assessable for toxicity and response. There was no significant difference in toxicity, except DP-related headache in 24% of patients. An objective response rate of 15% (one complete response [CR] and 13 partial responses [PRs]) for 5-FU/FA and 13% (two CRs and nine PRs) for 5-FU/FA/DP was observed. The dose-intensity of 5-FU delivered was significantly higher (1.09- to 1.16-fold) for the DP-containing arm. Pharmacokinetic parameters of 5-FU did not differ significantly, except for a prolonged half-life (t1/2) induced by DP. The median time to progression (P = .8) and the median survival time (11.6 months for 5-FU/FA v 9.3 months for 5-FU/FA/DP; P = .14,
log-rank test) were not different between treatment arms. CONCLUSION: Orally administered DP did not improve the antineoplastic activity of 5-FU/FA in patients with advanced colorectal cancer when used at this dose and schedule. The observed increase in 5-FU dose-intensity for FU/FA/DP was not clinically relevant.

f) Dipyridamole and Melanoma

(1) Damle BD, Sridhar R, Desai PB

DIPYRIDAMOLE MODULATES MULTIDRUG RESISTANCE AND INTRACELLULAR AS WELL AS NUCLEAR LEVELS OF DOXORUBICIN IN B16 MELANOMA CELLS. 

*Int J Cancer* 1994 Jan 2;56(1):113-8

Division of Medicinal Chemistry and Pharmaceutics, School of Pharmacy, Northeast Louisiana University, Monroe 71209.

Simultaneous occurrence of resistance to many chemotherapeutic agents, termed multidrug resistance (MDR), is a complex phenotype. MDR occurs due to several reasons, including over-expression of a 170-kDa membrane-bound protein, called P-glycoprotein (P-gp), which apparently participates in active drug efflux. Multidrug-resistant cells also frequently exhibit an altered pattern of intracellular drug distribution, resulting in a reduction in the nuclear level of drugs such as doxorubicin (DOX). In this study, the effect of dipyridamole (DP) on drug resistance and on intracellular as well as nuclear levels of DOX in multidrug-resistant melanoma cells has been examined. For this purpose, drug-sensitive murine melanoma cells (B16V) and their multidrug-resistant variant cells, (B16VDXR; selected for resistance to DOX) which over-produce P-gp, were employed. B16VDXR cells were cross-resistant to several anti-cancer agents including etoposide (VP-16) and mitoxantrone (Mitox). DP (10 microM) significantly potentiated the cytotoxicity of DOX, VP-16 and Mitox towards multidrug-resistant B16VDXR cells but not in parental drug-sensitive B16V cells. The presence of DP resulted in a 3.7-fold increase in the total cellular level and a 4.2-fold increase in the nuclear content of DOX in the resistant cells. Isobologram analysis indicates that DP at several pharmacologically relevant concentrations synergistically potentiates the activity of DOX in B16VDXR cells.

(2) Damle B, Desai P

DIPYRIDAMOLE REVERSES THE RESISTANCE TO TOPOISOMERASE II INHIBITORS BUT NOT TO ANTIMICROTUBULE AGENTS IN MULTIDRUG-RESISTANT MELANOMA CELLS.

*Oncol Res* 1994;6(2):49-57

Division of Medicinal Chemistry and Pharmaceutics, School of Pharmacy, Northeast Louisiana University, Monroe 71209.

The influence of dipyridamole (DP) on the cytotoxicity and cellular disposition of several DNA topoisomerase II (topo II) inhibitors and antimitotic agents in multidrug-resistant B16VDXR cells was examined. B16VDXR cells, derived from parental B16V cells by step-wise treatment with doxorubicin (DOX), overexpress a 170 kDa P-glycoprotein (P-gp). Additionally, the resistance to DOX in B16VDXR cells is associated with decreased frequency of DNA strand breaks compared to that in the drug-sensitive B16V cells. DP (10 microM) significantly (P < 0.01) potentiated the cytotoxicity of DOX (6.4-fold), mitoxantrone (2.3-fold), and etoposide (14-fold) in the drug-resistant B16VDXR cells. This was accompanied by a 3.7-fold and 4.2-fold increase in the total intracellular and nuclear levels of DOX, respectively. Surprisingly, no significant change in the intracellular and nuclear levels or the efflux of etoposide was observed in B16VDXR cells. Combination index (CI) analysis, however, indicated that DP interacted synergistically with DOX as well as etoposide. Further, it was intriguing to observe that DP (10 microM) failed to modulate the resistance to vincristine, vinblastine, and taxol. This was despite a significant increase in the accumulation of vinblastine (3.3-fold) and taxol (3.9-fold) in B16VDXR cells in the presence of DP (10 microM). The observed pattern of chemosensitization suggests that in addition to interaction with P-gp, the multidrug-resistance modulating activity of DP may involve P-gp independent mechanism(s). The possibilities include that (i) DP interacts with topo II or (ii) DP promotes the formation and/or obstructs the repair of DNA strand breaks caused by topo II inhibitors.
g) Dipyridamole and Breast Cancer

(1) Budd GT, Herzog P, Bukowski RM

PHASE I/II TRIAL OF DIPYRIDAMOLE, 5-FLUOROURACIL, LEUKOVORIN, AND MITOXANTRONE IN METASTATIC BREAST CANCER.


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Based upon the hypothesis that dipyridamole would potentiate the cytotoxicity of mitoxantrone and the combination of 5-fluorouracil (5-FU) and leukovorin, we performed a phase I/II trial of the combination of dipyridamole, 5-FU, leukovorin, and mitoxantrone in patients with metastatic breast cancer. The dose of dipyridamole was fixed at 175 mg/m² by mouth every 6 h (700 mg/m²/day), based upon a previous phase I trial of oral dipyridamole with 5-FU and leukovorin. Dipyridamole therapy began 24 h prior to the first dose of chemotherapy and continued until 24 h after the last dose of chemotherapy for each course of treatment. At the initial dose level, leukovorin 200 mg/m² was given intravenously immediately prior to 5-FU 375 mg/m² intravenously on days 1-5. Mitoxantrone 6 mg/m² was given as a single dose on day 3. Unacceptable toxicity was observed at this dose level, leading to successive dose decrements rather than dose increments. The maximum tolerated dose was leukovorin 200 mg/m² days 1-2, 5-FU 375 mg/m² days 1-2, mitoxantrone 6 mg/m² on day 2, and dipyridamole 175 mg/m² every 6 h on days 0-3. Two responses were produced in 15 patients. This regimen is not recommended for further investigation in the treatment of breast cancer.

9. Dipyridamole and SPECT

(1) Haluska B, Case C, Short L, Anderson J, Marwick TH.

EFFECT OF POWER DOPPLER AND DIGITAL SUBTRACTION TECHNIQUES ON THE COMPARISON OF MYOCARDIAL CONTRAST ECHOCARDIOGRAPHY WITH SPECT.

Heart 2001 May;85(5):549-555.

University of Queensland, Department of Medicine, Princess Alexandra Hospital, Ipswich Road, Brisbane, Qld 4102, Brisbane, Australia.

OBJECTIVE: To compare the accuracy and feasibility of harmonic power Doppler and digitally subtracted colour coded grey scale imaging for the assessment of perfusion defect severity by single photon emission computed tomography (SPECT) in an unselected group of patients. DESIGN: Cohort study. SETTING: Regional cardiothoracic unit. PATIENTS: 49 patients (mean (SD) age 61 (11) years; 27 women, 22 men) with known or suspected coronary artery disease were studied with simultaneous myocardial contrast echo (MCE) and SPECT after standard dipyridamole stress. MAIN OUTCOME MEASURES: Regional myocardial perfusion by SPECT, performed with (99m)Tc tetrafosmin, scored qualitatively and also quantitated as per cent maximum activity. RESULTS: Normal perfusion was identified by SPECT in 225 of 270 segments (83%). Contrast echo images were interpretable in 92% of patients. The proportion of normal MCE by grey scale, subtracted, and power Doppler techniques were respectively 76%, 74%, and 88% (p < 0.05) at > 80% of maximum counts, compared with 65%, 69%, and 61% at < 60% of maximum counts. For each technique, specificity was lowest in the lateral wall, although power Doppler was the least affected. Grey scale and subtraction techniques were least accurate in the septal wall, but power Doppler showed particular problems in the apex. On a per patient analysis, the sensitivity was 67%, 75%, and 83% for detection of coronary artery disease using grey scale, colour coded, and power Doppler, respectively, with a significant difference between power Doppler and grey scale only (p < 0.05). Specificity was also the highest for power Doppler, at 55%, but not significantly different from subtracted colour coded images. CONCLUSIONS: Myocardial contrast echo using harmonic power Doppler has greater accuracy than with grey scale imaging and digital subtraction. However, power Doppler appears to be less sensitive for mild perfusion defects.
OBJECTIVES: We sought to perform a direct comparison between perfusion scintigraphic results and intracoronary-derived hemodynamic variables (fractional flow reserve [FFR]; absolute and relative coronary flow velocity reserve [CFVR and rCFVR, respectively]) in patients with two-vessel disease. BACKGROUND: There is limited information on the diagnostic accuracy of intracoronary-derived variables (CFVR, FFR and rCFVR) in patients with multivessel disease. METHODS: Dipyridamole technetium-99m sestamibi (MIBI) single-photon emission computed tomography (SPECT) was performed in 127 patients. The presence of reversible perfusion defects in the region of interest was determined. Within one week, angiography was performed; CFVR, rCFVR and FFR were determined in 161 coronary lesions after intracoronary administration of adenosine. The predictive value for the presence of reversible perfusion defects on MIBI SPECT of CFVR, rCFVR and FFR was evaluated by the area under the curve (AUC) of the receiver operating characteristics curves. RESULTS: The mean percentage diameter stenosis was 57% (range 35% to 85%), as measured by quantitative coronary angiography. Using per-patient analysis, the AUCs for CFVR (0.70 +/- 0.052), rCFVR (0.72 +/- 0.051) and FFR (0.76 +/- 0.050) were not significantly different (p = NS). The percentages of agreement with the results of MIBI SPECT were 76%, 78% and 77% for CFVR, rCFVR and FFR, respectively. Per-lesion analysis, using all 161 measured lesions, yielded similar results. CONCLUSIONS: The diagnostic accuracy of three intracoronary-derived hemodynamic variables, as compared with the results of perfusion scintigraphy, is similar in patients with two-vessel coronary artery disease. Cut-off values of 2.0 for CFVR, 0.65 for rCFVR and 0.75 for FFR can be used for clinical decision-making in this patient cohort. Discordant results were obtained in 23% of the cases that require prospective evaluation for appropriate patient management.

Chiamvimonvat V, Goodman SG, Langer A, Barr A, Freeman MR.

PROGNOSTIC VALUE OF DIPYRIDAMOLE SPECT IMAGING IN LOW-RISK PATIENTS AFTER MYOCARDIAL INFARCTION.


Background. The prognostic value of perfusion imaging was assessed in low-risk patients after myocardial infarction (MI) and compared with clinical and angiographic variables. Methods and Results. Rest thallium and dipyridamole technetium 99m sestamibi single photon emission computed tomography imaging was performed in 203 (91%) low-risk patients 3 to 21 days after MI who were enrolled in a trial of low-dose warfarin sodium and aspirin. Patients were considered low risk with planned nonintervention, on the basis of an uncomplicated course after MI, negative submaximal stress electrocardiography, and the absence of significant angiographic disease requiring revascularization. During a minimum follow-up of 12 months, 69 patients (34%) had clinical events: 1 cardiac death, 7 MI, 26 admissions for unstable angina, 18 coronary bypass grafting, and 17 angioplasty. Univariate analysis identified the extent of significant angiographic stenoses (> = 70%) and the extent of scintigraphic defect as predictive of future events. On multivariate analysis, the presence of any scintigraphic reversibility had the strongest correlation with clinical events, with better predictive value than angiographic multivessel stenoses (P =.0006 vs P =.003). Conclusions. In the low-risk population after MI, scintigraphic reversibility remains a strong predictor of cardiac events, with greater prognostic value than angiographic data. The extent of scintigraphic reversibility was directly correlated with clinical events. Therefore scintigraphic imaging remains clinically relevant for risk stratification in the current low-risk population after MI.

Departments of Nuclear Medicine and Internal Medicine and the Cardiovascular Institute, Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, Korea.

Background. Because dipyridamole is used to assess heart rate (HR) variability, we investigated whether a low HR response during dipyridamole single photon emission computed tomography (SPECT) in patients with diabetes indicates the presence of cardiac autonomic neuropathy (CAN).

Methods and Results. Subjects were 61 non-insulin-dependent diabetes patients without perfusion defects, myocardial infarction, or arrhythmia who underwent thallium 201 SPECT imaging. The control group comprised 28 subjects without diabetes. HR was measured during infusion of dipyridamole at a rate of 0.14 mg/kg/min, and peak-baseline ratios of 1.20 or less were defined as low. CAN severity was classified by standard autonomic function tests as severe (n = 22), mild (n = 19), or none (n = 20). HR ratios were significantly attenuated in patients with diabetes compared with those in control subjects (1.22 +/- 0.12 vs 1.32 +/- 0.12, P <.001). Among the patients with diabetes, HR ratios decreased as CAN severity increased from none (1.32 +/- 0.10) to mild (1.23 +/- 0.12, P <.05) to severe (1.13 +/- 0.08, P <.005). There was good correlation between HR ratio and R-R interval ratio to deep breathing and to Valsalva, and patients with low HR ratios showed an attenuated response to both tests (all P <.001). The sensitivity and specificity of HR ratios in the detection of CAN were 77% and 74% for severe CAN and 63% and 90% for mild-to-severe CAN, respectively. Conclusions. In patients with diabetes who have normal dipyridamole SPECT results, an attenuated HR response observed during stress indicates a high likelihood of CAN. Further work that assesses these results in diabetes patients with coronary artery disease is warranted.

B. Dipyridamole Complications

1. Dipyridamole induced Gallstones

(1) No Authors listed GALLSTONES CONTAINING DIPYRIDAMOLE. Prescrire Int 1999 Feb;8(39):20

(1) During lengthy treatment, dipyridamole can be blended into gallstones. (2) Gallstones containing dipyridamole carry the same risk of acute complications as other gallstones.

2. Dipyridamole associated Headaches


Departments of Clinical Research.

AIMS: In the Second European Stroke Prevention Study headaches associated with dipyridamole frequently (8% of patients taking dipyridamole or dipyridamole plus acetylsalicylic acid (ASA) vs 2% of patients taking ASA or placebo) led to discontinuation of therapy. We have now used data from a recent trial comparing the bioequivalence of two formulations of the fixed combination of 200 mg dipyridamole in an extended release formulation and 25 mg ASA to explore predicting factors for headaches associated with this drug combination. METHODS: The bioequivalence trial employed a two-way crossover, randomised, open design. Trial medication was given for two periods of five days separated by a 72 h washout period. Statistical methods were employed to explore the prevalence, the time course, and the relation to individual pharmacokinetic parameters of treatment associated headaches. RESULTS: Headache episodes, being mostly mild and transient, rapidly declined from 67% of the volunteers on the first day of treatment to 3% on the final days of treatment (days 4-5 of the second period). During the first days the prevalence of the headaches peaked 2-3 h after the
morning administration, which coincided with the peak of the plasma concentrations of dipyridamole. The occurrence of headaches was not related to interindividual differences of the pharmacokinetic parameters. CONCLUSIONS: The rapid decrease in the incidence of headaches over time implies that most patients quickly develop tolerance to dipyridamole-associated headaches. Appropriate information given to the patient when prescribing and dispensing dipyridamole/ASA may reduce early withdrawals from treatment and increase compliance.

3. Dipyridamole Fatal Toxicity

(1) Zimnukhov VV, Bakhareva NA, Travenko EN, Udalov AV

[FATAL DIPYRIDAMOLE POISONINGS]. [ARTICLE IN RUSSIAN]
Sud Med Ekspert 1999 May-Jun;42(3):34

II. ANTICOAGULANTS

A. Warfarin (WAR) (Vitamin K Inhibitor)

A. Function and Fields Of Use

1. WAR in Periphervascular disease

(1) Sarac TP, Huber TS, Back MR, Ozaki CK, Carlton LM, Flynn TC, Seeger JM

WARFARIN IMPROVES THE OUTCOME OF INFRAINGUINAL VEIN BYPASS GRAFTING AT HIGH RISK FOR FAILURE.
Vasc Surg 1998 Sep;28(3):446-57

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OBJECTIVE: Patients with marginal venous conduit, poor arterial runoff, and prior failed bypass grafts are at high risk for infrainguinal graft occlusion and limb loss. We sought to evaluate the effects of anticoagulation therapy after autogenous vein infrainguinal revascularization on duration of patency, limb salvage rates, and complication rates in this subset of patients. RESULTS: Sixty-one of the 64 bypass grafts were performed for rest pain or tissue loss, and 3 were performed for short-distance claudication. There were no differences between the groups in ages, indications, bypass graft types, risk classifications (ie, conduit, runoff, or graft failure), or comorbid conditions (except diabetes mellitus). The cumulative 5-year survival rate was similar between the groups. The incidence rate of postoperative hematoma (32% vs 3.7%; P = .004) was greater in the WAR group, but no differences were seen between the WAR group and the aspirin group in the number of packed red blood cells transfused, in the incidence rate of overall nonhemorrhagic wound complications, or in the overall complication rate (62% vs 52%). The immediate postoperative primary graft patency rates (97.3% vs 85.2%) and limb salvage rates (100% vs 88.9%) were higher in the WAR group as compared with the aspirin group. Furthermore, the cumulative 3-year primary, primary assisted, and secondary patency rates were significantly greater in the WAR group versus the aspirin group (74% vs 51%, P = .04; 77% vs 56%, P = .02) and cumulative limb salvage rates were higher in the WAR group (81% vs 31%, P = .01). CONCLUSIONS: Perioperative anticoagulation therapy with heparin increases the incidence rate of wound hematomas, but long-term anticoagulation therapy with warfarin improves the patency rate of autogenous vein infrainguinal bypass grafts and the limb salvage rate for patients at high risk for graft failure.

2. WAR in Atrial Fibrillation
Segal JB, McNamara RL, Miller MR, Kim N, Goodman SN, Powe NR, Robinson KA, Bass EB

PREVENTION OF THROMBOEMBOLISM IN ATRIAL FIBRILLATION: A META-ANALYSIS OF TRIALS OF ANTICOAGULANTS AND ANTIPLATELET DRUGS.


OBJECTIVE: Appropriate use of drugs to prevent thromboembolism in patients with atrial fibrillation (AF) involves comparing the patient's risk of stroke and risk of hemorrhage. This review summarizes the evidence regarding the efficacy of these medications. METHODS: We conducted a meta-analysis of randomized controlled trials of drugs used to prevent thromboembolism in adults with nonpostoperative AF. Articles were identified through the Cochrane Collaboration's CENTRAL database and MEDLINE until May 1998. MAIN RESULTS: Eleven articles met criteria for inclusion in this review. Warfarin was more efficacious than placebo for primary stroke prevention (aggregate odds ratio [OR] of stroke = 0.30, 95% confidence interval [CI] 0.19, 0.48), with moderate evidence of more major bleeding (OR 1.90; 95% CI 0.89, 4.04). Aspirin was inconclusively more efficacious than placebo for stroke prevention (OR 0.56, 95% CI 0.19, 1.65), with inconclusive evidence regarding more major bleeds (OR 0.81, 95% CI 0.37, 1.77). For primary prevention, assuming a baseline risk of 15 strokes per 1,000 patient-years, warfarin could prevent 30 strokes at the expense of only 6 additional major bleeds. Aspirin could prevent 17 strokes, without increasing major hemorrhage. In direct comparison, there was evidence suggesting fewer strokes among patients on warfarin than among patients on aspirin (aggregate OR 0.64, 95% CI 0.43, 0.96), with only suggestive evidence for more major hemorrhage (OR 1.60, 95% CI 0.77, 3.35). However, in younger patients, with a mean age of 65 years, the absolute reduction in stroke rate with warfarin compared with aspirin was low (5.5 per 1,000 person-years) compared with an older group (15 per 1,000 person-years). CONCLUSION: In general, the evidence strongly supports warfarin for patients with AF at average or greater risk of stroke. Aspirin may prove to be useful in subgroups with a low risk of stroke, although this is not definitively supported by the evidence.

Your patient is a 60-year-old hypertensive, alcoholic woman whose symptomless atrial fibrillation was first documented 3 months ago. An echocardiogram shows an enlarged left atrium, rendering successful cardioversion unlikely. She tells you that both of her parents had severe strokes that made the last years of their lives horrible, and she is terrified of having a stroke. You know that a meta-analysis of 5 randomized trials of warfarin in nonvalvular atrial fibrillation demonstrated a 68% relative risk reduction (RRR) in stroke (1). You consider prescribing warfarin for this patient but know that she would not have qualified for the study because alcoholism increases her risk for major hemorrhage.

Comment in: ACP J Club 1998 Nov-Dec;129(3):A17

Nademane K, Kosar EM

LONG-TERM ANTITHROMBOTIC TREATMENT FOR ATRIAL FIBRILLATION.

Am J Cardiol 1998 Oct 16;82(8A):37N-42N

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Nonvalvular atrial fibrillation (AF) is the most common cardiac disorder causing stroke and systemic emboli. Recent clinical trials have clearly demonstrated the effects of antithrombotic treatment in preventing these devastating complications of AF. This review summarizes the salient findings of the first 5 published studies the Atrial Fibrillation, 1) Aspirin, Anticoagulation Study (AFASAK) from Copenhagen, Denmark; 2) the Boston Area Anticoagulation Trial for Atrial Fibrillation (BATAFF); 3) the Canadian Atrial Fibrillation Anticoagulation study (CAFA);4) the Stroke Prevention in Non-rheumatic Atrial Fibrillation (SPINAF) study; and 5) the Stroke Prevention in Atrial Fibrillation study (SPAF I) from the United States. These trials emphasize the unequivocal benefits of warfarin therapy compared with no treatment. SPAF II showed that aspirin is quite effective in younger patients (<75 years) who have no risk factors. The European Atrial Fibrillation Trial (EAFT) and SPAF
ILL demonstrated that in older patients (>75 years) who had associated risk factors, warfarin therapy at the target international normalized ratio (INR) of 2-3, is the best treatment; however, a combination of low intensity fixed-dose warfarin and aspirin is ineffective. Thus, the guidelines recommended by the American College of Chest Physicians should be followed in treating patients with AF.

(4) Ang SY, Peterson GM, Friesen WT, Vial JH
REVIEW OF ANTITHROMBOTIC DRUG USAGE IN ATRIAL FIBRILLATION.
J Clin Pharm Ther 1998 Apr;23(2):97-106

Tasmanian School of Pharmacy, Faculty of Health Science, University of Tasmania, Hobart Tas, Australia.

BACKGROUND: The important prophylactic role of antithrombotic therapy against stroke in nonrheumatic atrial fibrillation (AF) has been clearly established in recent clinical trials.

RESULTS: The 228 patients included in the study had a mean (+/-SD) age of 75.3 +/- 10.9 years. Sixty-eight per cent had chronic AF and 32% had paroxysmal AF. According to two risk stratification criteria, 91% and 86% of the patients with previously diagnosed chronic or paroxysmal nonrheumatic AF (n=186) had a high risk of developing stroke at the time of admission to hospital care. However, less than one-third of these patients were receiving warfarin (or warfarin plus aspirin), with almost another one-third receiving no antithrombotic agent. Of those who were not taking warfarin, about 60% had no apparent contraindication to warfarin. For those high risk patients who had a possible contraindication to warfarin, only approximately one-third had been prescribed aspirin. Only a slight increase in the use of antithrombotic agents had occurred by the time of discharge from hospital care. The majority of international normalized ratio (INR) values on admission for patients who had been taking warfarin were subtherapeutic.

CONCLUSIONS: While a number of published trials have demonstrated that antithrombotic agents confer substantial protection against stroke in patients with nonrheumatic AF, the drugs were underused in our setting. There is a need to improve antithrombotic use and to develop a better monitoring system for the provision of safer and more effective antithrombotic therapy.

3. WAR in Stroke Prevention

(1) Mendelson G, Aronow WS
UNDERUTILIZATION OF WARFARIN IN OLDER PERSONS WITH CHRONIC NONVALVULAR ATRIAL FIBRILLATION AT HIGH RISK FOR DEVELOPING STROKE.

Department of Geriatrics and Adult Development, Mount Sinai School of Medicine, New York, New York, USA.

OBJECTIVE: To investigate the prevalence of the use of warfarin to maintain an international normalized ratio (INR) between 2.0 and 3.0 in older persons with chronic nonvalvular atrial fibrillation (AF), and without contraindications to warfarin, who are at high risk for developing new thromboembolic (TE) stroke. DESIGN: A retrospective analysis of charts from all older persons seen during 1997 at an academic hospital-based geriatrics practice. PATIENTS: Three hundred eighty men and 1183 women, mean age 80 +/- 8 years (range 59 to 103 years), were included in the study. MEASUREMENTS AND MAIN RESULTS: Of 1563 persons studied, 141 (9%) had chronic nonvalvular AF. Of 141 persons with AF, 127 (90%) were at high risk for developing TE stroke because they had either a previous thromboembolism, congestive heart failure, or echocardiographic evidence of abnormal left ventricular systolic function; a systolic blood pressure >160 mm Hg; or they were women older than 75 years of age. Of the 127 persons with AF at high risk for developing TE stroke, three (2%) had contraindications to warfarin. Of the 124 persons with AF at high risk for developing TE stroke and no contraindications to warfarin, 61 (49%) were treated with warfarin to maintain an INR between 2.0 and 3.0, and 45 (36%) were treated with 325 mg aspirin daily. Of 14 persons with AF at low risk for developing TE stroke, one (7%) was treated with warfarin to maintain an INR between 2.0 and 3.0, and six (43%) were treated with 325 mg aspirin daily. CONCLUSIONS: Warfarin is
underutilized as a treatment to maintain an INR between 2.0 and 3.0 in older persons with chronic nonvalvular AF at high risk for developing TE stroke.

(2) Brass LM, Krumholz HM, Scinto JD, Mathur D, Radford M
WARFARIN USE FOLLOWING ISCHEMIC STROKE AMONG MEDICARE PATIENTS WITH ATRIAL FIBRILLATION.

Center for Outcomes Research and Evaluation, Yale-New Haven Hospital, Yale University School of Medicine, Conn 06520-8018, USA. lawrence.brass@yale.edu

BACKGROUND: Elderly patients with ischemic stroke and atrial fibrillation are at especially increased risk for recurrent stroke. Warfarin sodium is highly effective in reducing this risk.

RESULTS: Among 635 patients (402 women; 585 white; 218 \( \geq \)85 years old; 147 with a new diagnosis of atrial fibrillation), 334 had stroke as a principal diagnosis. Among those discharged alive after a stroke, only 147 (53%) of 278 were prescribed warfarin at discharge. Furthermore, among 130 (47%) of 278 patients not prescribed warfarin at discharge, 81 (62%) of 130 were also not prescribed aspirin. Increased potential benefit (additional vascular risk factors) was not associated with a higher rate of warfarin use. Low risk for anticoagulation (lack of risk factors for bleeding) was associated with a slightly higher rate of warfarin use. Among those with an increased risk of stroke and a low risk for bleeding (ideal candidates), 124 (62%) of 278 were discharged on a regimen of warfarin.

CONCLUSION: Anticoagulation of elderly stroke patients with atrial fibrillation, even among ideal candidates, is underused. The increased use of warfarin among these patients represents an excellent opportunity for reducing the risk of recurrent stroke in this high-risk population.

(3) Venketasubramanian N, Chua HC
SUBCUTANEOUS LOW MOLECULAR WEIGHT HEPARIN IN PLACE OF HEPARIN INFUSION DURING WARFARIN DOSE OPTIMISATION IN CEREBRAL ISCHAEMIA.
Clin Neurol Neurosurg 1998 Sep;100(3):193-5

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We explored the feasibility of using subcutaneous low-molecular-weight-heparin (LMWH) injections in place of unfractionated heparin (UFH) while anticoagulating patients with cerebral ischemia. In this open-labeled, prospective study, patients admitted to our hospital with transient ischemic attacks or stroke requiring anticoagulation who were otherwise medically fit for discharge home were enrolled. The LMWH nadroparin (Fraxiparine) 4100 antiXa BID was administered. In those on UFH, this was stopped after the first dose of LMWH. Patients were sent home and LMWH was administered on an outpatient basis with simultaneous oral warfarin titration till INR reached 2.0. Fifteen patients (13 inpatients, two outpatients) were enrolled; 12 had stroke, one each had crescendo transient ischemia attacks (TIAs) while on aspirin, TIAs and intracranial arterial stenosis, TIA and atrial fibrillation. Inpatients were discharged home within a median of 1 day (range 1-3 days). Median duration of LMWH therapy was 9 days (range 4-47 days); nine required LMWH for 10 days or less. Two patients reported bruising at the injection site. There was no death, cerebral ischaemia recurrence or major hemorrhage. Using LMWH in place of UFH in patients with cerebral ischaemia is a feasible and safe way of achieving optimal oral anticoagulation and can be done on an outpatient basis.

(4) Gullov AL, Koefoed BG, Petersen P, Pedersen TS, Andersen ED, Godtfredsen J, Boysen G
FIXED MINIDOSE WARFARIN AND ASPIRIN ALONE AND IN COMBINATION VS ADJUSTED-DOSE WARFARIN FOR STROKE PREVENTION IN ATRIAL FIBRILLATION: SECOND COPENHAGEN ATRIAL FIBRILLATION, ASPIRIN, AND ANTICOAGULATION STUDY.
Arch Intern Med 1998 Jul 27;158(14):1513-21

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BACKGROUND: Despite the efficacy of warfarin sodium therapy for stroke prevention in atrial fibrillation, many physicians hesitate to prescribe it to elderly patients because of the risk for bleeding complications and because of inconvenience for the patients. METHODS: The Second
Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation Study was a randomized, controlled trial examining the following therapies: warfarin sodium, 1.25 mg/d; warfarin sodium, 1.25 mg/d, plus aspirin, 300 mg/d; and aspirin, 300 mg/d. These were compared with adjusted-dose warfarin therapy (international normalized ratio of prothrombin time [INR], 2.0-3.0). Stroke or a systemic thromboembolic event was the primary outcome event. Transient ischemic attack, acute myocardial infarction, and death were secondary events. Data were handled as survival data, and risk factors were identified using the Cox proportional hazards model. The trial was scheduled for 6 years from May 1, 1993, but due to scientific evidence of inefficiency of low-intensity warfarin plus aspirin therapy from another study, our trial was prematurely terminated on October 2, 1996. RESULTS: We included 677 patients (median age, 74 years). The cumulative primary event rate after 1 year was 5.8% in patients receiving minidose warfarin; 7.2%, warfarin plus aspirin; 3.6%, aspirin; and 2.8%, adjusted-dose warfarin (P = .67). After 3 years, no difference among the groups was seen. Major bleeding events were rare. CONCLUSIONS: Although the difference was insignificant, adjusted-dose warfarin seemed superior to minidose warfarin and to warfarin plus aspirin after 1 year of treatment. The results do not justify a change in the current recommendation of adjusted-dose warfarin (INR, 2.0-3.0) for stroke prevention in atrial fibrillation.


4. WAR in Orthopedic Surgery

(1) Motykie GD, Mokhtee D, Zebala LP, Caprini JA, Kudrna JC, Mungall DR

THE USE OF A BAYESIAN FORECASTING MODEL IN THE MANAGEMENT OF WARFARIN THERAPY AFTER TOTAL HIP ARTHROPLASTY.

J Arthroplasty 1999 Dec;14(8):988-93

Department of Surgery, Evanston Northwestern Healthcare, Illinois 60201, USA.

This study was performed to compare the computer-based and physician-based management of warfarin therapy after total hip arthroplasty (THA). The computer-assisted and control groups of patients were placed on warfarin postoperatively and followed for a 1-month period. A significant difference (P<.05) was found between the mean number of days needed to reach therapeutic anticoagulation in the control group (4.7+/-3.0 days) and the experimental group (2.8+/-1.4 days) and the proportion of patients in each group who were discharged with a subtherapeutic international normalized ratio (INR) (INR <1.5). The computer-based management of warfarin therapy was more efficient than unaided physician-based management and therefore may lead to improved, cost-effective patient care by reducing length of hospital stay and complications attributable to nontherapeutic anticoagulation in THA patients.

(2) Dearborn JT, Harris WH

POSTOPERATIVE MORTALITY AFTER TOTAL HIP ARTHROPLASTY. AN ANALYSIS OF DEATHS AFTER TWO THOUSAND SEVEN HUNDRED AND THIRTY-SIX PROCEDURES.

J Bone Joint Surg Am 1998 Sep;80(9):1291-4

Department of Orthopaedic Surgery, Massachusetts General Hospital, Boston 02114, USA.

We retrospectively determined the prevalence and nature of mortality as many as ninety days after 2736 primary and revision total hip arthroplasties performed in 2002 patients by one surgeon at a teaching hospital between January 1969 and December 1996. All but seventy-one of the patients had received prophylaxis against venous thromboembolic disease. There were no intraoperative deaths, and no events during the operation could be linked directly to postoperative mortality. Eight deaths (mortality rate, 0.3 per cent) occurred within ninety days after the 2736 procedures. Four deaths (mortality rate, 0.15 per cent) occurred during the initial hospitalization. The cause of seven of the deaths was determined. Three patients died as a result of preexisting disease (severe hepatorenal disease, metastatic esophageal cancer, or severe cardiac disease), and one patient died from sepsis with a gram-negative organism during a thoracotomy eight days postoperatively. A bleeding complication that occurred while the patient was receiving warfarin therapy led to the death of two other patients; one of these deaths occurred in 1974 and the other, in 1982. At the time that these patients were managed, the desired prothrombin time was considered to be twice the control value. The remaining patient, who had had a clip placed on the inferior vena cava after a pulmonary embolus occurred in 1970, died secondary to
acute, severe thrombosis of this vessel after a total hip arthroplasty in 1971. The patient for whom the cause of death was not determined had had an artificial aortic valve and had been receiving chronic warfarin therapy. She died suddenly eighty-nine days postoperatively; no autopsy was performed. No patient died as the direct result of a known pulmonary embolus. No deaths related to venous thromboembolic disease or its prophylaxis or treatment occurred after 1982 (1458 operations). We attribute this, in part, to reduced levels of warfarin prophylaxis and improved management with warfarin. The ninety-day postoperative mortality rate after 2736 procedures performed over nearly three decades was low (0.3 per cent). This span of time included the period before the introduction of many current improvements in perioperative care, such as routine intubation of patients under general anesthesia, continuous monitoring of the electrocardiogram intraoperatively, and blood-gas determinations. When the patients who died as a result of known, severe preexisting disease were excluded, the mortality rate was 0.18 per cent (five of 2733).

5. WAR Thromboprophylaxis in Cancer Patients

(1) Kakkar AK, Williamson RC
THROMBOPROPHYLAXIS IN THE CANCER PATIENT.
Haemostasis 1998 Nov;28 Suppl S3:61-65

Department of Surgery, Imperial College School of Medicine, Hammersmith Hospital, London, UK.

Thrombosis is a common complication in patients with malignant disease resulting from tumour elaboration of procoagulants and subsequent activation of intravascular coagulation. Cancer therapies (operation, chemotherapy and the use of central venous lines) further heighten the risk of thrombosis. The risk of thrombosis in cancer operations is of sufficient magnitude to necessitate routine thromboprophylaxis, for which low-dose unfractionated heparin or the low-molecular-weight heparins (LMWHs) have been proven effective and safe. Thrombotic complications with chemotherapy have been extensively described in women receiving either adjuvant or palliative cytotoxic or hormonal therapy for breast carcinoma. The problems are common, but of all the suitable prophylactic modalities available, only oral anticoagulants have been evaluated for this indication. Thrombosis complicates the use of central venous catheters in the cancer patient and both low-dose warfarin and LMWHs are effective in protecting against line-associated thrombi. Recent evidence from the retrospective analyses of randomized studies comparing unfractionated heparin and LMWH in the treatment of deep vein thrombosis have shown a striking mortality reduction among cancer patients who received LMWH. The use of LMWHs to prolong survival in patients with advanced malignant disease is currently the subject of a prospective, randomized, placebo-controlled study.

6. WAR Deep Vein Thromboses

(1) Schulman S
LONG-TERM PROPHYLAXIS IN VENOUS THROMBOEMBOLISM: LMWH OR ORAL ANTICOAGULATION?
Haemostasis 1998 Nov;28 Suppl S3:17-21

Coagulation Unit, Department of Haematology and Infectious Disease, Karolinska Hospital, Stockholm, Sweden.

Warfarin remains the standard drug for secondary prophylaxis following venous thromboembolism, however this treatment is not ideal. In patients for whom monitoring is problematic or who have a high risk of bleeding complications, other possible solutions have been explored. Unfractionated heparin has been used to a limited extent in these situations and requires dose adjustment in order to achieve an acceptable efficacy. Low-molecular-weight heparin (LMWH) is a valuable alternative to warfarin for these patients and for thromboprophylaxis during pregnancy. In several subgroups of patients with venous thromboembolism the use of a LMWH instead of warfarin could offer specific advantages. The combination of warfarin and LMWH is warranted in patients for whom it is predicted that warfarin treatment alone may fail. The optimal dose of LMWH in long-term prophylaxis has not been evaluated in a properly designed study and the optimal duration of prophylaxis with LMWH is thought to be similar to that for warfarin.
(2) AbuRahma AF, Stickler DL, Robinson PA

A PROSPECTIVE CONTROLLED STUDY OF THE EFFICACY OF SHORT-TERM ANTICOAGULATION THERAPY IN PATIENTS WITH DEEP VEIN THROMBOSIS OF THE LOWER EXTREMITY.


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PURPOSE: The long-term risk for recurrent deep venous thrombosis (DVT) and the incidence of post-thrombotic syndrome (PTS) after long-term anticoagulation (LTA) therapy have been widely debated. In this study, we compare the results of short-term anticoagulation therapy versus conventional LTA therapy in patients with DVT of the lower extremity. METHODS: Baseline assessments of DVT symptoms and risk factors were recorded in 105 patients. Diagnosis was made using duplex ultrasound/venography. Patients were sequentially assigned to 1 of the following treatment protocols: (A) conventional LTA therapy, which included initial intravenous standard heparin followed by warfarin on days 3 to 5 and was continued for 3 months for patients without pulmonary embolism (PE); or (B) short-term therapy, which included the same heparin therapy followed by warfarin on days 2 to 3 and was continued for 6 weeks only. Clinical and duplex ultrasound follow-up was done at 6 weeks, 3 and 6 months, and every 6 months thereafter. RESULTS: Risk factors, location of DVT, and mean age of the 2 groups were comparable. Mean follow-up was 59 months. There were 4 immediate major complications in patients of group A (4 of 54 [7%]; 2 PEs and 2 significant bleeds) and 3 in patients of group B (3 of 51 [6%]; 1 PE and 2 bleeds). On long-term follow-up, 18 of 43 (42%) patients in group A and 20 of 44 (46%) patients in group B had PTS. Similarly, 10 of 43 (23%) patients in group A and 9 of 44 (20%) patients in group B had 1 or more recurrent thromboembolic events (not statistically significant). A significant difference was demonstrated only in patients with cancer; LTA was favored in reducing recurrent DVT and PTS. Two other patients in group A had late significant complications secondary to warfarin (hemorrhage in 1 and coumadin necrosis in the other), with no complications in group B. The mean number of days of hospitalization were fewer for patients in group B (5 versus 8 days), which is mainly due to earlier initiation of warfarin therapy for group B.

CONCLUSION: In this study of our local population, we observed that short-term anticoagulation therapy was as effective as LTA therapy and less costly for use in most patients. It may also carry less risk of long-term warfarin complications, such as bleeding or skin necrosis.

7. WAR Thromboprophylaxis in Pregnancy

(1) Ginsberg JS, Hirsh J

USE OF ANTITHROMBOTIC AGENTS DURING PREGNANCY.

*Chest* 1998 Nov;114(5 Suppl):524S-530S

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Anticoagulant therapy is indicated during pregnancy for the prevention and treatment of VTE, for the prevention and treatment of systemic embolism in patients with mechanical heart valves, and, in combination with aspirin, for the prevention of pregnancy loss in women with APLA and previous pregnancy losses. Several questions concerning anticoagulant therapy remain unanswered. Oral anticoagulants are fetopathic, but the true risks of the warfarin embryopathy and CNS abnormalities are unknown. There is some evidence that warfarin embryopathy occurs only when oral anticoagulants are administered between the 6th and the 12th weeks of gestation and that oral anticoagulants may not be fetopathic when administered in the first 6 weeks of gestation. Oral anticoagulant therapy should be avoided in the weeks before delivery because of the risk of serious perinatal bleeding caused by the trauma of delivery to the anticoagulated fetus. The safety of aspirin during the first trimester of pregnancy is still a subject of debate. There is a concern about the efficacy of unfractionated heparin in the prevention of arterial embolism in pregnant women with mechanical heart valves. Finally, the role of LMWH and heparinoids and appropriate dosing have still to be determined. Because it is safe for the fetus, heparin is the anticoagulant of choice during pregnancy for situations in which its efficacy is established. The evidence for the efficacy of heparin for the prevention and treatment of VTE disorders during pregnancy is based on level IV studies. There is some doubt that heparin is effective for the prevention of systemic embolism in patients with mechanical heart valves.
Low doses of heparin or poorly controlled heparin therapy are not effective in preventing systemic embolism in patients with mechanical heart valves.

8. WAR in Pediatric Therapy

Less intense Warfarin treatment in Children may be required!


ENHANCED THROMBIN REGULATION DURING WARFARIN THERAPY IN CHILDREN COMPARED TO ADULTS.


Department of Pediatrics, McMaster University, Hamilton, Ontario, Canada.

The intensity of warfarin therapy for prevention of primary and secondary thromboembolic complications in paediatric patients, is extrapolated from guidelines for adults, which may not be optimal. Therefore, we assessed thrombin regulation ex vivo and in vitro in plasmas from 40 children (1 to 18 years old with a median age of 13 years) and 27 adults receiving warfarin with an international normalized ratio of 2 to 3 (child: 2.5 +/- 0.15; adult: 2.4 +/- 0.14). Ex vivo concentrations of prothrombin fragment 1.2 were significantly lower in children (0.30 +/- 0.03 nM) compared to adults (0.45 +/- 0.04 nM; p < 0.01). Thrombin generation in defibrinated plasmas (Arvin) was decreased and delayed for children compared to adults when activated by either activated partial thromboplastin time (child = 32 +/- 1.7, adult = 45 +/- 1.9 microM x s) or prothrombin time (child = 35 +/- 0.7, adult = 46 +/- 1.0 microM x s) reagents (p < 0.01 for both). Although plasma concentrations of factors (F) II, FVII, FIX, FX, protein C and protein S were similar, more of the thrombin generated was complexed to alpha2 macroglobulin (alpha2M) at times close to peak thrombin activity (60 s) in plasma from children (general linear analysis of variance; p < 0.03). Thus, increased alpha2M levels may enhance thrombin regulation in paediatric compared to adult patients receiving warfarin, suggesting that clinical trials in children, using less intense warfarin treatment, may be required to determine optimum therapy.

9. WAR Antiphospholipid Syndrome

a) Antiphospholipidsyndrome Management

(1) Bick RL, Arun B, Frenkel EP

ANTIPHOSPHOLIPID-THROMBOSIS SYNDROMES.

Haemostasis 1999 Dec;29(2-3):100-110

Division of Hematology Oncology, Department of Medicine, University of Texas Southwestern Medical Center, Dallas, Tex., USA.

Antiphospholipid antibodies are strongly associated with thrombosis and appear to be the most common of the acquired blood protein defects causing thrombosis. Based upon our experience, approximately 25% of patients with unexplained venous thrombosis, approximately 60% of patients with cerebrovascular thrombosis, approximately 37% of patients with transient ischemic attacks, approximately 18% with premature coronary artery thrombosis and approximately 60% of patients with recurrent fetal loss (recurrent miscarriage syndrome) harbor antiphospholipid antibodies. Although the precise mechanism(s) whereby antiphospholipid antibodies alter hemostasis to induce a hypercoagulable state remain unclear, several theories have been advanced. Since the aPTT is unreliable in patients with lupus anticoagulant and is not usually prolonged in patients with anticardiolipin antibodies, definitive tests, ELISA for IgG, IgA and IgM anticardiolipin antibodies and the dilute Russel's viper venom time (followed by cephalin correction for confirmation) for lupus anticoagulant should be immediately ordered when suspecting the antiphospholipid syndrome in individuals with otherwise unexplained thrombotic or thromboembolic events or recurrent fetal loss. However, if one strongly suspects antiphospholipid thrombosis syndrome clinically and assays for lupus anticoagulants and anticardiolipin antibodies are negative, specific assays for all three idiotypes of phosphatidyserine, phosphatidylethanolamine, phosphatidylcholine, phosphatidylglycerol and phosphatidylglycerol are available and should be considered. These may clearly be indicated for difficult diagnostic cases of fetal wastage syndrome, and cerebrovascular
events, but their significance in other types of thrombosis, particularly venous, remains unclear at present. Since about 65% of patients with antiphospholipid antibodies will fail warfarin therapy (rethrombose), it is important to define this common defect and institute appropriate antithrombotic therapy for appropriate time periods. Copyright 1999 S Karger AG, Basel

(2) Kobayashi N, Agematsu K, Urasawa R, Kitahara M, Ichikawa M, Mori T, Komiyama A
[A CASE OF SLE WITH POSITIVE ANTIPHOSPHOLIPID ANTIBODY AND VARIOUS COAGULOPATHY]. [ARTICLE IN JAPANESE]

Department of Pediatrics, Shinshu University School of Medicine.

We described an 11 year-old boy with systemic lupus erythematosus (SLE) and various coagulopathy. He had purpura on the legs, pancytopenia, positive anti-DNA antibodies and hypocomplementemia. Hematological examination also showed that platelet counts were 80 x 10(3)/microliter, lupus anticoagulant and anticardiolipin antibodies were positive. The aPTT was remarkably prolonged. Those laboratory findings fulfilled the criteria of antiphospholipid syndrome. Following treatment with predonisolone and heparin, thrombocytopenia improved. When heparin discontinued and renal biopsy was performed, severe thrombocytopenia recurred. FDP and FDP-DD became high, but the aPTT was not prolonged. Thrombocytopenia didn't improved by the therapy with heparin, high dose of methylpredonisolone, FOY and gamma-globulin. However by the therapy with both warfarin and cyclophosphamide, remarkable improvement of coagulopathy was absorbed. Probably anticardiolipin antibodies and disseminated intravascular coagulation (DIC) participate in the various coagulopathy in this case.

(3) Ihara M, Tanaka H, Nishimura Y
PRIMARY ANTIPHOSPHOLIPID SYNDROME WITH RECURRENT TRANSIENT ISCHEMIC ATTACKS: REPORT OF A CASE AND ITS SUCCESSFUL TREATMENT.

Department of Neurology, Nishi-Kobe Medical Center, Kobe, Hyogo.

A 35-year-old woman was admitted to our hospital with complaints of a two-year history of recurrent, daily episodes of transient ischemic attacks; the symptoms consisted of scotoma of her left eye, vertical diplopia, and paresthesia of her right arm. The presence of lupus anticoagulants and anticardiolipin antibodies led to the diagnosis of antiphospholipid syndrome (APS). After thrombotest values had decreased to 30% (international normalized ratio: 1.5) with warfarin, her symptoms did not recur. This suggests that anticoagulant therapy is effective for the prevention of recurrence of ischemic events complicated by primary APS, even when they occur repeatedly.

(4) Ohtomo Y, Matsubara T, Nishizawa K, Unno A, Motohashi T, Yamashiro Y
NEPHROPATHY AND HYPERTENSION AS MANIFESTATIONS IN A 13-Y-OLD GIRL WITH PRIMARY ANTIPHOSPHOLIPID SYNDROME.

Department of Paediatrics, Juntendo University School of Medicine, Tokyo, Japan.

Severe renal hypertension due to both unilateral renal arterial occlusion and renal thrombotic microangiopathy developed in a 13-y-old girl as a manifestation of primary antiphospholipid antibody syndrome. The combination of the intravenous high-dose urokinase therapy and oral anticoagulation therapy, comprising aspirin, warfarin and dipyridamole, was significantly effective in improving her renal function and preventing thrombotic events during an 18-month follow-up period.

(5) Khamashta MA
MANAGEMENT OF THROMBOSIS AND PREGNANCY LOSS IN THE ANTIPHOSPHOLIPID SYNDROME.
Lupus 1998;7 Suppl 2:S162-5
Lupus Research Unit, The Rayne Institute, St Thomas' Hospital, London, UK.
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More than a decade has gone by since the detailed clinical description of the Antiphospholipid (Hughes) Syndrome. Because of the wide spectrum of manifestations, virtually any physician may encounter patients with this potentially treatable condition. Because of limited controlled, prospective data, current therapy remains empirical and directed at coagulation mechanisms, immune mechanisms, or both. There is now good evidence that patients with antiphospholipid-associated thrombosis will be subject to recurrences and require prophylactic therapy. Although most authorities agree about the efficacy of warfarin alone or warfarin plus low-dose aspirin in preventing recurrences of venous and arterial thrombosis, there is still doubt regarding the intensity and duration of warfarin therapy. Steroids and immunosuppressive drugs have not provided long-term benefit. Controlled clinical trials of the treatment of pregnant women with antiphospholipid antibody demonstrated that prednisolone is ineffective, and possibly detrimental, in treatment of recurrent pregnancy loss and that heparin plus low-dose aspirin is beneficial.

(6) Asherson RA
Lupus 1998;7 Suppl 2:S55-62

Department of Medicine, University of Cape Town School of Medicine and The Groote Schuur Hospital, South Africa.

A review of 50 patients who manifest features of the catastrophic antiphospholipid syndrome (CAPS) is presented. The clinical features comprise mainly organ involvement as opposed to large-vessel venous or arterial occlusions as is seen in patients with 'simple' antiphospholipid syndrome (APS), which makes the pathogenesis of this unusually rare complication perhaps somewhat different from that of patients with the APS. The mortality of the condition is 50%, most patients dying as a result of a combination of cardiac and respiratory failure. Fifteen patients (28%) suffered from disseminated intravascular coagulation (DIC) as well, which may have contributed to the multiorgan thrombotic microangiopathy characteristic of the CAPS. Although most patients were treated with high-dose i.v. steroids, heparin, cyclophosphamide and other modalities of therapy (such as i.v. globulin), plasmapheresis (advocated for TTP, a similar microangiopathic condition) seemed to offer some benefit (68% recovery). The systemic inflammatory response syndrome (SIRS) was responsible for some of the clinical manifestations such as adult respiratory distress syndrome (ARDS) seen in 15 patients. Pathogenesis of the CAPS seems dependent on a 'two-hit' or even 'three-hit' hypothesis in patients already suffering from a hypercoagulable state. Precipitating factors include infections, trauma (surgical), drug administration and warfarin withdrawal. A recent view that the multiple thrombotic lesions themselves may contribute to further thrombosis ('thrombotic storm') is also discussed.

(7) Greco TP, Conti-Kelly AM, Ijdo J
IMPACT OF THE ANTIPHOSPHOLIPID SYNDROME: A CRITICAL COAGULATION DISORDER IN WOMEN.
Medscape Womens Health 1997 Jan;2(1):7

Department of Internal Medicine, Yale University School of Medicine, New Haven, Conn.
Antiphospholipid (aPL) syndrome, or APS,—a cluster of conditions that includes arterial or venous thromboses and thrombocytopenia, as well as recurrent fetal loss associated with elevation of aPL antibody—has been reported to occur 2-5 times more frequently in women than men. Strong familial associations lead to the suspicion that aPL positivity, estimated to be present in 2% of the population, is a heritable trait in some cases. Currently, 2 major categories of the illness are recognized—primary and secondary. Secondary APS may be associated with autoimmune disease, malignancy, infectious disease, or drug-induced states. Two assays, one for lupus anticoagulant antibodies and the other for anticardiolipin (aCL) antibodies, are recognized to be the gold standards for serologic diagnosis of the disease. Despite extensive attempts at international standardization of aCL test results, no consensus exists for a value beyond which the test is considered positive. Interestingly, a "dose-effect" relationship for aCL antibody titers has been noted—higher titers of the antibody correlate with increased numbers of thrombotic events. An experimental assay for antibody against beta 2-glycoprotein 1 (beta-2-GP1), a phospholipid-binding protein, may become the most important assay for aPL. Skin findings in APS include
livedo reticularis, ulceration, gangrene, or purpura, and, when present, may be the key to diagnosis of this sometimes insidious syndrome. Anticoagulation, usually with warfarin, is the mainstay of therapy, although steroids, immunosuppressive agents, hydroxychloroquine sulfate, and plasmapheresis may all be beneficial adjunctive therapy.

b) Antiphospholipid Syndrome Anticoagulation Monitoring


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The recommended therapeutic range of International Normalized Ratio (INR) for oral anticoagulant treatment in patients with the antiphospholipid syndrome remains controversial. As a part of this controversy, it has been suggested that lupus anticoagulants (LA) could interfere with the determination of prothrombin time, thus questioning the validity of monitoring the treatment of these patients using INR. To clarify this point, we compared the values of INR obtained in the plasmas of two groups of patients, one without LA (n = 47), and the other with LA (n = 43). INR were determined using 8 different thromboplastin reagents on the same automated coagulation instrument. Chromogenic factor X, which is supposed to be insensitive to the presence of LA, was also measured. The results are the following: provided INR was calculated using calibrated reference plasmas, there was no significant difference between INR values obtained with the 8 reagents, both in the non-LA and in the LA groups (CV: 5.9 and 6.7%, respectively). Closer examination revealed that INR results obtained with one reagent (the recombinant thromboplastin Innovin) diverged from those of the 7 others, leading to an overestimation of INR, to a very large extent in some instances. However this effect was restricted to a subset of the patient population with LA (6 out of 43). Finally, the relationship between INR (average value obtained using the 8 reagents) and factor X was identical in non-LA and in LA patient groups. We conclude that, provided the reagents which display the LA interference are identified and excluded for this purpose, the INR system is valid for monitoring oral anticoagulant treatment in patients with LA.

10. WAR Drug Interactions

Warfarin interacts with many Drugs. We have taken only a few of them

a) WAR Interaction with Acetaminophen

(1) Shek KL, Chan LN, Nutescu E

WARFARIN-ACETAMINOPHEN DRUG INTERACTION REVISITED. Pharmacotherapy 1999 Oct;19(10):1153-8

Department of Pharmacy Practice, University of Illinois at Chicago, College of Pharmacy, 60612, USA.

Physicians and pharmacists routinely advise patients receiving warfarin to take acetaminophen for pain or fever because of its relative safety; however, a recent study questioned the safety of such practice. A comprehensive search of MEDLINE and IPA for human studies and case reports from 1966-1999 revealed evidence that acetaminophen may potentiate the effect of warfarin by a mechanism that has yet to be elucidated. Due to lack of a safer alternative, acetaminophen still should be the analgesic and antipyretic of choice in patients taking warfarin, as long as excessive amounts and prolonged administration (> 1.3 g acetaminophen/day for > 2 wks) are avoided. With the high degree of interpatient variability and the unpredictability of various drug-drug interactions with warfarin, close and frequent monitoring of international normalized ratios is the key for safe oral anticoagulation therapy.
THE EFFECTS OF ACETAMINOPHEN ON PHARMACOKINETICS AND PHARMACODYNAMICS OF WARFARIN.


Department of Pharmacy, Sunnybrook Health Science Centre, North York, Ontario, Canada.

The oral anticoagulant warfarin is clinically administered as a racemic mixture of two enantiomers, (R) and (S). Many relevant drug interactions with warfarin have been attributed to the specific metabolic inhibition of the elimination of the more pharmacologically active (S)-enantiomer. To investigate reports that acetaminophen can potentiate the anticoagulant effect of warfarin, 20 healthy male volunteers were each given single oral 20 mg doses of racemic warfarin on three separate occasions:

1. alone,
2. after 1 day of acetaminophen (4 g/d), and
3. after 2 weeks of acetaminophen (4 g/d).

The urinary excretion pattern of acetaminophen and its metabolites was not significantly altered over its course of administration. The (R)- and (S)-enantiomers of warfarin exhibited significantly different pharmacokinetic properties. However, acetaminophen did not alter the disposition of either (R)- or (S)-warfarin. All subjects exhibited a pharmacodynamic response to racemic warfarin. The response was not significantly altered in the presence of acute or chronic acetaminophen dosing, as assessed by prothrombin time and factor VII concentrations.

ACETAMINOPHEN AND OTHER RISK FACTORS FOR EXCESSIVE WARFARIN ANTICOAGULATION.

*JAMA* 1998 Mar 4;279(9):657-62

Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston 02114, USA.

Warfarin is highly effective in preventing thromboembolism, but increases the risk of hemorrhage, particularly at an international normalized ratio (INR) greater than 4.0. Identifying causes of excessive anticoagulation in clinical practice could help target patients at risk for elevated INRs.

**OBJECTIVE:** To determine causes of INRs greater than 6.0 in a clinical practice setting.

**PATIENTS:** Outpatients followed up prospectively from April 1995 to March 1996 who had been taking warfarin for more than 1 month, had a target INR of 2.0 to 3.0, and were able to be interviewed within 24 hours of their reported INR. Case patients had INRs greater than 6.0; controls were randomly selected from patients having INRs between 1.7 and 3.3.

**MAIN OUTCOME MEASURES:** Factors associated with INRs greater than 6.0, including medication use, recent diet, illness, alcohol consumption, and actual warfarin use.

**RESULTS:** A total of 93 cases and 196 controls were interviewed; they did not differ in age, indication for warfarin, length of therapy, warfarin dose, number of prescription medications, or previous INR or long-term INR variability. Acetaminophen ingestion was independently associated in a dose-dependent manner with having an INR greater than 6.0 (P for trend <.001). For the highest-dose category of acetaminophen intake, 9100 mg/wk or more, the odds of having an INR greater than 6.0 were increased 10-fold (95% confidence interval [CI], 2.6-37.9). Other factors independently associated with an INR greater than 6.0 were new medication known to potentiate warfarin (odds ratio [OR], 8.5; 95% CI, 2.9-24.7), advanced malignancy (OR, 16.4; 95% CI, 2.4-111.0), recent diarrheal illness (OR, 3.5; 95% CI, 1.4-8.6), decreased oral intake (OR, 3.6; 95% CI, 1.3-9.7), and taking more warfarin than prescribed (OR, 8.1; 95% CI, 2.2-30.0). Higher vitamin K intake (OR, 0.7; 95% CI, 0.5-0.9) and habitual alcohol consumption of from 1 drink every other day to 2 drinks a day (OR, 0.2; 95% CI, 0.1-0.7) were associated with decreased risk.

**CONCLUSIONS:** These data suggest that acetaminophen is an underrecognized cause of overanticoagulation in the outpatient setting. Several other clinically important risk factors were identified. Increased monitoring of INR values when such risk factors are present or modification of the risk factors themselves should reduce the frequency of dangerously high levels of anticoagulation.
(4) Estrada C  
**ACETAMINOPHEN AND RISK FACTORS FOR EXCESS ANTICOAGULATION WITH WARFARIN.**  
*JAMA* 1998 Aug 26;280(8):695; discussion 697  
Comment on: JAMA 1998 Mar 4;279(9):657-62

(5) Gray CD  
**ACETAMINOPHEN AND RISK FACTORS FOR EXCESS ANTICOAGULATION WITH WARFARIN.**  
*JAMA* 1998 Aug 26;280(8):695; discussion 697  
Comment on: JAMA 1998 Mar 4;279(9):657-62

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**ACETAMINOPHEN AND RISK FACTORS FOR EXCESS ANTICOAGULATION WITH WARFARIN.**  
*JAMA* 1998 Aug 26;280(8):695-6; discussion 697  
Comment on: JAMA 1998 Mar 4;279(9):657-62

(7) Pedell L  
**ACETAMINOPHEN AND RISK FACTORS FOR EXCESS ANTICOAGULATION WITH WARFARIN.**  
*JAMA* 1998 Aug 26;280(8):696; discussion 697  
Comment on: JAMA 1998 Mar 4;279(9):657-62  
Comment on: JAMA 1998 Mar 4;279(9):702-3

(8) Riser J, Gilroy C, Hudson P, McCay L, Willis TA  
**ACETAMINOPHEN AND RISK FACTORS FOR EXCESS ANTICOAGULATION WITH WARFARIN.**  
*JAMA* 1998 Aug 26;280(8):696; discussion 697  
Comment on: JAMA 1998 Mar 4;279(9):657-62  
Comment on: JAMA 1998 Mar 4;279(9):702-3

(9) Eliason BC, Larson W  
**ACETAMINOPHEN AND RISK FACTORS FOR EXCESS ANTICOAGULATION WITH WARFARIN.**  
*JAMA* 1998 Aug 26;280(8):696-7  
Comment on: JAMA 1998 Mar 4;279(9):657-62

(10) Brown D  
**POTENTIATION OF WARFARIN BY ACETAMINOPHEN.**  
*J Fam Pract* 1998 Jun;46(6):456-7  
Physician Center at Mililani, Hawaii, USA. brownd@jabsom.biomed.hawaii.edu

b) WAR interaction with Macrolides

(1) Rodvold KA  
**CLINICAL PHARMACOKINETICS OF CLARITHROMYCIN.**  
College of Pharmacy, University of Illinois at Chicago, USA. kar@uic.edu
Clarithromycin is a macrolide antibacterial that differs in chemical structure from erythromycin by the methylation of the hydroxyl group at position 6 on the lactone ring. The pharmacokinetic advantages that clarithromycin has over erythromycin include increased oral bioavailability (52 to 55%), increased plasma concentrations (mean maximum concentrations ranged from 1.01 to 1.52 mg/L and 2.41 to 2.85 mg/L after multiple 250 and 500 mg doses, respectively), and a longer elimination half-life (3.3 to 4.9 hours) to allow twice daily administration. In addition, clarithromycin has extensive diffusion into saliva, sputum, lung tissue, epithelial lining fluid, alveolar macrophages, neutrophils, tonsils, nasal mucosa and middle ear fluid. Clarithromycin is primarily metabolised by cytochrome P450 (CYP) 3A isozymes and has an active metabolite, 14-hydroxyclarithromycin. The reported mean values of total body clearance and renal clearance in adults have ranged from 29.2 to 58.1 L/h and 6.7 to 12.8 L/h, respectively. In patients with severe renal impairment, increased plasma concentrations and a prolonged elimination half-life for clarithromycin and its metabolite have been reported. A dosage adjustment for clarithromycin should be considered in patients with a creatinine clearance < 1.8 L/h. The recommended goal for dosage regimens of clarithromycin is to ensure that the time that unbound drug concentrations in the blood remains above the minimum inhibitory concentration is at least 40 to 60% of the dosage interval. However, the concentrations and in vitro activity of 14-hydroxyclarithromycin must be considered for pathogens such as Haemophilus influenzae. In addition, clarithromycin achieves significantly higher drug concentrations in the epithelial lining fluid and alveolar macrophages, the potential sites of extracellular and intracellular respiratory tract pathogens, respectively. Further studies are needed to determine the importance of these concentrations of clarithromycin at the site of infection. Clarithromycin can increase the steady-state concentrations of drugs that are primarily depend upon CYP3A metabolism (e.g., astemizole, cisapride, pimozide, midazolam and triazolam). This can be clinically important for drugs that have a narrow therapeutic index, such as carbamazepine, cyclosporin, digoxin, theophylline and warfarin. Potent inhibitors of CYP3A (e.g., omeprazole and ritonavir) may also alter the metabolism of clarithromycin and its metabolites. Rifampin (rifampin) and rifabutin are potent enzyme inducers and several small studies have suggested that these agents may significantly decrease serum clarithromycin concentrations. Overall, the pharmacokinetic and pharmacodynamic studies suggest that fewer serious drug interactions occur with clarithromycin compared with older macrolides such as erythromycin and troleandomycin.

(2) Gooderham MJ, Bolli P, Fernandez PG

CONCOMITANT DIGOXIN TOXICITY AND WARFARIN INTERACTION IN A PATIENT RECEIVING CLARITHROMYCIN.


University of Western Ontario, London, Canada.

OBJECTIVE: To report a case of a clarithromycin-associated warfarin interaction and digoxin toxicity in a patient. CASE SUMMARY: A 72-year-old white woman with chronic atrial fibrillation receiving long-standing therapy with digoxin 0.25 mg/d and warfarin 22.5 mg/wk was prescribed clarithromycin 500 mg three times daily for eradication of Helicobacter pylori. The patient presented to the emergency department with gastrointestinal symptoms, weakness, dizziness, and visual changes 12 days after initiation of clarithromycin. Laboratory results revealed a serum digoxin concentration of 4.6 ng/mL (normal 1.0-2.6) and an international normalized ratio of 7.3 (2.0-3.0). Digoxin, warfarin, and clarithromycin were discontinued and the patient was admitted to the hospital for treatment to resolve the symptoms and to return laboratory values to a safe range. Reduced dosages of digoxin (0.125 mg/d) and warfarin (17.5 mg/wk) were restarted on day 7 of hospitalization. The patient was discharged on day 11 in good condition. DISCUSSION: Several reports of clarithromycin-induced drug interactions with digoxin and with warfarin have been published. Previously, case reports of macrolide-associated interactions mainly involved erythromycin, but more recently have implicated clarithromycin. The interaction between clarithromycin and warfarin is thought to occur from an inhibition of the cytochrome P450 drug metabolizing system. Clarithromycin is thought to cause digoxin toxicity by an alteration of the digoxin-metabolizing gut flora, thereby causing an increase in the digoxin concentration in susceptible individuals. Drug interactions can occur by different mechanisms in the same patient. CONCLUSIONS: Potential drug interactions can occur between commonly prescribed medications. It is important to monitor patients for symptoms and alterations in laboratory values to prevent not only serious complications, but also unnecessary hospitalizations.
Azithromycin is considered unlikely to interact with warfarin. Unlike other macrolide antibiotics, it is not hepatically metabolized and did not produce an interaction with warfarin in a single-dose study. A 71-year-old woman with a prosthetic heart valve, stabilized with warfarin, had international normalized ratios (INRs) maintained between 2.5 and 3.5. Six days after she received a prescription for a 5-day course of azithromycin, her INR was 15.16. Phytonadione 10 mg was administered subcutaneously, and warfarin was held for 3 days until her INR fell to 2.10. She then was restabilized with warfarin. Until more information is known about the safety of warfarin and azithromycin, caution is advised when the agents are given together. Close monitoring of INR is recommended, and warfarin dosage adjustment may be necessary.

Zaremba CD
COMMENT: COULD ACETAMINOPHEN HAVE PLAYED A ROLE IN A POSSIBLE AZITHROMYCIN-WARFARIN INTERACTION?

Woldtvedt BR, Cahoon CL, Bradley LA, Miller SJ
POSSIBLE INCREASED ANTICOAGULATION EFFECT OF WARFARIN INDUCED BY AZITHROMYCIN.
Ann Pharmacother 1998 Feb;32(2):269-70

c) WAR Interaction with Intra Venous Lipids “Resistance” High Dose Propofol

McKillop D, Wild MJ, Butters CJ, Simcock C
EFFECTS OF PROPOFOL ON HUMAN HEPATIC MICROSONMAL CYTOCHROME P450 ACTIVITIES.
Xenobiotica 1998 Sep;28(9):845-53

The potential of propofol to inhibit the activity of major human cytochrome P450 enzymes has been examined in vitro using human liver microsomes. Propofol produced inhibition of CYP1A2 (phenacetin O-deethylation), CYP2C9 (tolbutamide 4'-hydroxylation), CYP2D6 (dextromethorphan O-demethylation) and CYP3A4 (testosterone 6beta-hydroxylation) activities with IC50 = 40, 49, 213 and 32 microM respectively. Ki for propofol against all of these enzymes with the exception of CYP2D6, where propofol showed little inhibitory activity, was 30, 30 and 19 microM respectively for CYPs 1A2, 2C9 and 3A4. (2) Furafylline, sulphaphenazole, quinidine and ketoconazole, known selective inhibitors of CYPs 1A2, 2C9, 2D6 and 3A4 respectively, were much more potent than propofol having IC50 = 0.8, 0.5, 0.2 and 0.1 microM; furafylline and sulphaphenazole yielded Ki = 0.6 and 0.7 microM respectively. (3) The therapeutic blood concentration of propofol (20 microM; 3-4 microg/ml) together with the in vitro Ki estimates for each of the major human P450 enzymes have been used to estimate the extent of cytochrome P450 inhibition, which may be produced in vivo by propofol. This in vitro-in vivo extrapolation indicates that the degree of inhibition of CYP1A2, 2C9 and 3A4 activity which could theoretically be produced in vivo by propofol is relatively low (40-51%); this is considered unlikely to have any pronounced clinical significance. (4) Although propofol has now been used in > 190 million people since its launch in 1986, there are only single reports of possible drug interactions between propofol and either alfentanil or warfarin. Consequently, it is difficult to conclude from either the published literature or the ZENECA safety database whether there is any evidence to indicate that propofol produces clinically significant drug interactions through inhibition of cytochrome P450-related drug metabolism.
MacLaren R, Wachsman BA, et al. (2) 
WARFARIN RESISTANCE ASSOCIATED WITH INTRAVENOUS LIPID ADMINISTRATION: DISCUSSION OF PROPOFOL AND REVIEW OF THE LITERATURE. 
Pharmacotherapy 1997 Nov;17(6):1331-1337

Department of Clinical Pharmacy, University of Tennessee, Baptist Memorial Hospital, Memphis 38163, USA.

Intravenous lipids are often required for parenteral nutritional (PN) support in critically ill patients and are administered with continuous sedation if patients are receiving propofol, which contains soybean oil 10% as an emulsified preparation. High-dose propofol infusion was associated with reversal of enteral and intravenous warfarin anticoagulation in a 39-year-old woman with severe Crohn's disease. Despite increasing the daily dose of warfarin to 30 mg, anticoagulation was not achieved until propofol was discontinued. Reversal of anticoagulation recurred when PN support was supplemented with Liposyn II 20%. Lipid emulsions may interfere pharmacodynamically with warfarin activity by enhancing the production of clotting factors, facilitating platelet aggregation, or supplying vitamin K. They also may facilitate warfarin binding to albumin. Until further information regarding the mechanism of interference is elucidated, heparin therapy should be considered for initial anticoagulation in patients with intestinal absorptive deficiencies who receive high-dose lipid emulsions and require reliable anticoagulation. If warfarin is given, the international normalized ratio should be monitored daily to ensure adequate anticoagulation.

d) WAR Interaction with Coenzyme Q10 and Herbal products

(1) Smolinske SC
DIETARY SUPPLEMENT-DRUG INTERACTIONS. 
J Am Med Womens Assoc 1999 Fall;54(4):191-2,195

Children's Hospital of Michigan Regional Poison Control Center, USA.

Recent surveys show that 18% of adults in the United States use prescription drugs concurrently with herbal or vitamin products, placing an estimated 15 million patients at risk of potential drug-supplement interactions. Despite this widespread concurrent use of conventional and alternative medicines, documented drug-herb interactions are sparse. This review focuses on possible interactions between drugs and herbal medicines used for phytoestrogen-hormone and antiplatelet-oral anticoagulant therapy. Interactions with phytoestrogens are purely speculative, based on competitive estrogen-receptor binding or antiestrogenic effects. In contrast, several case reports document bleeding complications with Ginkgo biloba, with or without concomitant drug therapy. Case reports are also suggestive of interaction between warfarin and dong quai or Panax ginseng. Recommendations for counseling patients at highest risk of adverse interactions are given.

(2) Cupp MJ 
HERBAL REMEDIES: ADVERSE EFFECTS AND DRUG INTERACTIONS. 
Am Fam Physician 1999 Mar 1;59(5):1239-45

Drug Information Center, West Virginia University School of Pharmacy, Morgantown 26506-9550, USA.

A growing number of Americans are using herbal products for preventive and therapeutic purposes. The manufacturers of these products are not required to submit proof of safety and efficacy to the U.S. Food and Drug Administration before marketing. For this reason, the adverse effects and drug interactions associated with herbal remedies are largely unknown. Ginkgo biloba extract, advertised as improving cognitive functioning, has been reported to cause spontaneous bleeding, and it may interact with anticoagulants and antiplatelet agents. St. John's wort, promoted as a treatment for depression, may have monoamine oxidase-inhibiting effects or may cause increased levels of serotonin, dopamine and norepinephrine. Although St. John's wort probably does not interact with foods that contain tyramine, it should not be used with prescription antidepressants. Ephedrine-containing herbal products have been associated with adverse cardiovascular events, seizures and
even death. Ginseng, widely used for its purported physical and mental effects, is generally well tolerated, but it has been implicated as a cause of decreased response to warfarin. Physicians must be alert for adverse effects and drug interactions associated with herbal remedies, and they should ask all patients about the use of these products.

(3) Landbo C, Almdal TP

[INTERACTION BETWEEN WARFARIN AND COENZYME Q10].
[ARTICLE IN DANISH]

Ugeskr Laeger 1998 May 25;160(22):3226-7

H:S Hvidovre Hospital, medicinsk endokrinologisk afdeling.

Coenzyme Q10 (Ubidecarenone) is marketed as a dietary supplement. Drug interaction between coenzyme Q10 and warfarin has previously been reported. In the present case, a 72-year-old female treated with warfarin showed less responsiveness to warfarin than previously. It appeared she had taken coenzyme Q10, and when this was stopped, her responsiveness to warfarin was the same as before. Coenzyme Q10 is chemically similar to K-vitamins, which may explain the interaction with warfarin. Patients in treatment with warfarin should be aware of the possible risk of treatment failure when taking coenzyme Q10. The need for questioning patients concerning not only medications but also use of dietary supplements and alternative medications is emphasised.

Comment in: Ugeskr Laeger 1998 Aug 17;160(34):4916

e) WAR with Common Cold Drugs and Piroxicam, Diclofenac Gel Analgesic Balms

(1) Chan TY

DRUG INTERACTIONS AS A CAUSE OF OVERANTICOAGULATION AND BLEEDINGS IN CHINESE PATIENTS RECEIVING WARFARIN.


Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories.

Little is known about the incidence and consequences of drug interactions in patients receiving warfarin. Hence, drug interactions as a cause of overanticoagulation and bleedings were determined in Chinese patients admitted to our medical unit during a 9-month period in 1994/95. Only patients with an admission international normalized ratio (INR) of > 3.0 (target range 2.0-2.5) were included since the drug interactions, if present, were more likely to be of clinical significance. Of 35 patients reviewed, 7 had a predisposing condition such as peptic ulcer and 19 received drugs or folk medicines that can interact with warfarin. Based on the temporal relationship between the initiation of the interacting agent(s) and the rise in INR/onset of bleedings, drug-warfarin interactions were definitely (n = 6) or possibly (n = 1) responsible in 7 patients (drugs for common cold 2, piroxicam plus piroxicam gel 2, medicated oil (15% methyl salicylate) plus Salvia miltiorrhiza Bge 1, "analgesic balm" (50% methyl salicylate) 1, diclofenac gel 1). These agents were prescribed by their physicians (n = 1), family doctors (n = 1) and other specialists (n = 1) or bought over-the-counter (n = 2). One other patient used the drugs from previous consultations. Five of the 7 patients developed bleedings. Drug interactions accounted for 20% of all patients with an INR of > 3.0 and 5 (36%) of 14 patients with bleedings. Patients receiving warfarin should be warned about the danger of self-medication. When prescribing warfarin, physicians should be aware of other medications that their patients are taking.

f) WAR with Tramadol

(1) Sabbe JR, Sims PJ, Sims MH

TRAMADOL-WARFARIN INTERACTION.


Samford University McWhorter School of Pharmacy, Department of Pharmacy Practice, Birmingham, Alabama, USA.
A 61-year-old women receiving warfarin after mitral valve replacement experienced extensive ecchymoses after starting tramadol therapy. Laboratory values revealed critical elevations of prothrombin time and international normalized ratio. The patient's coagulation values returned to acceptable levels after discontinuing tramadol and temporarily stopping warfarin. The mechanism for this interaction is unknown. Practitioners should be aware of the possibility of such a interaction and exercise caution when tramadol is prescribed for a patient receiving warfarin.

g) WAR with Antihyperlipidemic Therapy

(1) Lin JC, Ito MK, Stolley SN, Morreale AP, Marcus DB
THE EFFECT OF CONVERTING FROM PRAVASTATIN TO SIMVASTATIN ON THE PHARMACODYNAMICS OF WARFARIN.
Cardiovascular Pharmacodynamics Laboratory, Veterans Administration Healthcare System, San Diego, California, USA.
Forty-six adult patients maintained on warfarin therapy were converted from pravastatin to simvastatin. Mean international normalized ratio (INR) significantly increased from 2.42 to 2.74, p = 0.002. Although warfarin doses were reduced in 7 patients and increased in 4 patients following the post-conversion INR measurements, the pre- and postconversion median weekly warfarin dose of all 46 patients did not differ significantly. The number of patients with an INR > 3.0 increased significantly from 6 to 16 following the conversion. There was no report of unusual episodes of bleeding. The results indicate that antihyperlipidemic therapy can be changed safely from pravastatin to simvastatin in patients who are taking warfarin concomitantly. Additional anticoagulation monitoring is not necessary in institutions where patients are followed in formal anticoagulation clinics.

(2) Bays HE, Dujovne CA
DRUG INTERACTIONS OF LIPID-ALTERING DRUGS.
Louisville Metabolic and Atherosclerosis Research Center, Audubon Regional Medical Center, Kentucky, USA.
The use of lipid-altering drugs has been shown to reduce the progression of atherosclerotic lesions and reduce the risk of atherosclerotic events (such as myocardial infarction and stroke). In general, these lipid-altering drugs are well tolerated but there is the potential for drug interactions. For example, HMG-CoA reductase inhibitors may interact with macrolides, azalides,azole antifungals and cyclosporin. Resins (such as cholestyramine and colestipol) may impair the absorption of many concurrent medications. Fibrates have potential drug interactions with warfarin, furosemide (frusemide), oral hypoglycaemics and probenecid. Nicotinic acid (niacin) may have potential drug interactions with high dose aspirin (acetylsalicylic acid), uricosuric agents (such as sulfapyrazone) and alcohol (ethanol). Finally, probucol may have potential drug interactions with antidysrhythmics, tricyclic antidepressants and phenothiazines. In addition, lipid-altering drugs, used in combination, may have the potential for drug interactions, enhancing some of the risks of adverse effects, such as myositis and hepatotoxicity. Therefore, in order to use lipid-altering drugs in the most effective, and safest manner, it is important for the clinician to have an understanding of the mechanisms of potential drug interactions, which drug interactions may theoretically occur, and specifically, which specific drug interactions have already been described.

(3) Rindone JP, Keng HC
GEMFIBROZIL-WARFARIN DRUG INTERACTION RESULTING IN PROFOUND HYPOPROTHROMBINEMIA.
Veterans Affairs Medical Center, Prescott, Ariz 86313, USA.
The following describes a patient on a stable regimen of warfarin who developed severe hypoprothrombinemia and bleeding 4 weeks after starting gemfibrozil. Despite a warning by the
manufacturer, only one report of this interaction has been published in the literature. This interaction may be overlooked by clinicians, which may result in a serious bleeding risk for patients on warfarin.

(4) Beringer TR  
**WARFARIN POTENTIATION WITH BEZAFIBRATE.**  

Department of Health Care for the Elderly, Royal Group of Hospitals, Belfast, Northern Ireland.

h) WAR with Antacids and Ulcus Drugs

(1) Saltiel E, Fask A  
**PREVALENCE OF POTENTIAL PROTON-PUMP INHIBITOR DRUG INTERACTIONS: A RETROSPECTIVE REVIEW OF PRESCRIPTIONS IN COMMUNITY PHARMACIES.**  
*Clin Ther* 1999 Oct;21(10):1812-9

Cedars-Sinai Medical Center, Los Angeles, California 90035, USA.

Drug interactions are a major cause of drug-related problems. This study assessed the comparative frequency of potential drug-drug interactions in patients receiving either omeprazole or lansoprazole. We reviewed prescription data from 144 community pharmacies in 25 states for the period of October 12, 1996, through October 20, 1997, from which the rates at which patients received either proton-pump inhibitor concurrently with > or =1 potentially interacting drugs were determined. A total of 7306 patients received only omeprazole, and 2486 received only lansoprazole. In this sample, 722 patients (9.9%) who received omeprazole also received a potentially interacting medication at the same time, compared with 8 patients (0.3%) who received lansoprazole (P<0.001). These data suggest that clinicians should be conscientious when selecting or dispensing drugs for patients taking omeprazole, given the relatively high prevalence of potential drug interactions in clinical practice.

(2) Humphries TJ, Merritt GJ  
**REVIEW ARTICLE: DRUG INTERACTIONS WITH AGENTS USED TO TREAT ACID-RELATED DISEASES.**  
*Aliment Pharmacol Ther* 1999 Aug;13 Suppl 3:18-26

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Patients with acid-related diseases often need to take multiple medications. Treatment of Helicobacter pylori infection often includes either a histamine type 2 (H2)-receptor antagonist or a proton pump (H+,K(+)−ATPase) inhibitor (proton pump inhibitor), administered in conjunction with one or more antimicrobials. Also, treatment for acid-related diseases often requires extended therapy during which many concomitant medications may be administered for concurrent disease states. Polypharmacy may be the result, particularly in elderly patients, who are at increased risk for both acid-related and many other diseases. Thus, it is important to understand the potential for clinically significant drug-drug interactions in this setting. H2-receptor antagonists and proton pump inhibitors can influence the pharmacokinetic profiles of other commonly administered medications by elevating intragastric pH, which can alter drug absorption, and by interacting with the cytochrome P (CYP) 450 enzyme system, which can affect drug metabolism and clearance. Such interactions are particularly important when they affect the pharmacokinetics of drugs with narrow therapeutic ranges (e.g. warfarin, digoxin). In these cases, drug-drug interactions can result in significant toxicity and even death. There are marked differences among H2-receptor antagonists and proton pump inhibitors in their potential for such interactions. The oldest drugs in each class, cimetidine and omeprazole, respectively, have the greatest potential to alter CYP activity and change the pharmacokinetics of other drugs. The most recently developed H2-receptor antagonist, famotidine, and the newer proton pump inhibitors, rabeprazole and pantoprazole, are much less likely to induce or inhibit CYP and thereby change the metabolism of other medications. These differences are important when choosing medications for the safe treatment of patients with acid-related diseases.
Niopas I, Toon S, Aarons L, Rowland M

THE EFFECT OF CIMETIDINE ON THE STEADY-STATE PHARMACOKINETICS AND PHARMACODYNAMICS OF WARFARIN IN HUMANS.


Department of Pharmacy, Aristotle University of Thessaloniki, Greece.

OBJECTIVE: The interaction of multiple oral doses of cimetidine on the steady-state pharmacokinetics and pharmacodynamics of warfarin was investigated in six healthy male volunteers. METHODS: The subjects were given individually adjusted doses of warfarin to achieve therapeutic levels of prothrombin activity. The established daily maintenance oral dose of warfarin was kept stable throughout the trial and, on study days 8-14, each volunteer received a 800-mg daily dose of cimetidine. The degree of anticoagulant response produced by warfarin was quantified by the determination of both the prothrombin time and factor-VII clotting activity. RESULTS: Cimetidine co-administration had no significant effect on the pharmacokinetics of the more potent S-warfarin but significantly increased by 28% (P < 0.05) mean R-warfarin trough plasma concentrations and decreased by 23% (P < 0.05) mean R-warfarin apparent clearance. Both prothrombin time and factor-VII clotting activity displayed considerable inter-subject variability and were not significantly affected by concurrent cimetidine treatment. The reduction of apparent clearance of R-warfarin by cimetidine was found to be the effect of inhibition of the formation of warfarin metabolites as determined by apparent formation clearance values (+/-SD) of R-6-hydroxywarfarin (31.1+/-.4.5 ml/h at end of cimetidine treatment; P < 0.01), and R-7-hydroxywarfarin (6.9+/-.1.3 ml/h baseline; 4.3+/-.1.1 ml/h at end of cimetidine treatment; P < 0.01). CONCLUSION: Cimetidine stereoselectively affects the steady-state pharmacokinetics of warfarin by inhibiting the disposition of the less potent R-warfarin in humans. However, this interaction is likely to be of minimal clinical significance in most patients.

Bernareggi A

CLINICAL PHARMACOKINETICS OF NIMESULIDE.


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Nimesulide is a selective COX-2 inhibitor used in a variety of inflammatory, pain and fever states. After healthy volunteers received oral nimesulide 100 mg in tablet, granule or suspension form the drug was rapidly and extensively absorbed. Mean peak concentrations (Cmax) of 2.86 to 6.50 mg/L were achieved within 1.22 to 2.75 hours of administration. The presence of food did not reduce either the rate or extent of nimesulide absorption. When nimesulide was administered in the suppository form, the Cmax was lower and occurred later than after oral administration; the bioavailability of nimesulide via suppository ranged from 54 to 64%, relative to that of orally administered formulations. Nimesulide is rapidly distributed and has an apparent volume of distribution ranging between 0.18 and 0.39 L/kg. It is extensively bound to albumin; the unbound fraction in plasma was 1%. The unbound fraction increased to 2 and 4% in patients with renal or hepatic insufficiency. The estimated mean terminal elimination half-life varied from 1.80 to 4.73 hours. Excretion of the unchanged drug in urine and faeces is negligible. Nimesulide is largely eliminated via metabolic transformation and the principal metabolite is the 4'-hydroxy derivative (M1). Minor metabolites have been detected in urine and faeces, mainly in a conjugated form. The pharmacokinetic profiles of nimesulide and M1 in children and the elderly did not differ from that of healthy young individuals. Hepatic insufficiency affected the pharmacokinetics of nimesulide and M1 to a significant extent: the rate of elimination of nimesulide and M1 was remarkably reduced in comparison to the rate of elimination in healthy individuals. Therefore, a dose reduction (4 to 5 times) is required in patients with hepatic impairment. The pharmacokinetic profile of nimesulide and M1 was not altered in patients with moderate renal failure and no dose adjustment in patients with creatinine clearances higher than 1.8 L/h is envisaged. Pharmacokinetic interactions between nimesulide and other drugs given in combination [i.e. glibenclamide, cimetidine, antacids, furosemide (frusemide), theophylline, warfarin and digoxin] were absent, or of no apparent clinical relevance.
(5) Sauvet P, Schouler L  
**[OMEPRAZOLE AND LIVER FUNCTIONS]. [ARTICLE IN FRENCH]**  

Departement d'Hepato-gastro-enterologie, Hopital du Haut-Leveque, Bordeaux-Pessac.

Omeprazole is the first of a new class of drugs (proton pump blockers) approved in the United States and in Europe for its high efficiency as an inhibitor of gastric acid secretion. Omeprazole is a drug for short term use in patients with acid-peptic disease. A limited prevalence of hepatotoxic effects is reported by some authors (transitory rise in serum aminotransferase level) and it may be prescribed in patients with chronic liver disease although slower metabolism and greater bioavailability are observed. Omeprazole interacts with the cytochrome P-450 system in the liver: inhibition of several liver monoxygenases activities (inhibitory effect on diazepam, phenytoin and R-warfarin metabolism with prolonged elimination); induction of P-450 (IA1 and IA2) enzymes that may potentiate the hepatotoxic effect of phenacetin and acetaminophen or increase the tumorigenic effect of chemical carcinogens (polycyclic aromatic hydrocarbons, arylamines, aflatoxin). This latter concern is unfounded as based on a false extrapolation from the results of in vitro studies to those of in vivo situations. However, although omeprazole has proved to be remarkably free of side effects, postmarketing surveillance is recommended for potential interaction with other drugs that are known to be metabolized by the same liver enzymes.

(6) Greene W  
**DRUG INTERACTIONS INVOLVING CIMETIDINE--MECHANISMS, DOCUMENTATION, IMPLICATIONS.**  

In summary, cimetidine is a potent inhibitor of liver microsomal activity, which may also decrease hepatic blood flow. Other effects of the drug include inhibition of gastric secretion and intrinsic toxic properties. These effects, combined with the common use of cimetidine in clinical practice, make the risk of adverse drug interactions a relatively frequent risk in the clinical setting. Although a multitude of interactions with cimetidine has been evaluated, many of these are incompletely described or understood. At the present time, a potentially significant alteration of absorption appears to exist with only ketoconazole, elemental iron, vitamin B12 (long-term therapy), and pancreatic enzyme supplements (increased activity). Significant metabolic inhibition or decreased excretion appears to exist with warfarin, propranolol, theophylline, phenytoin, quinidine, possibly lidocaine and procainamide, and certain benzodiazepines. Other potential, but less well ascertained interactions may involve the narcotic analgesics, caffeine, ethanол, pentobarbital, imipramine, chloromethiazole, and metronidazole. In these settings, the clinician must be aware of interaction potential, and astutely monitor the patient during combination therapy. Other data indicate that concomitant administration of antacids may reduce the absorption of cimetidine, that the drug may protect against the toxic effects of acetaminophen overdose, and that combination with certain other myelosuppressants may carry a significant risk. Thus, in regard to these reports, cimetidine is a drug with complex effects on the absorption, elimination, and toxicity of other drugs. When used in the setting of multiple drug therapy, the clinician must be alert to potentially increased or decreased effects of the drugs mentioned in this review. In addition, one must be aware that other hepatically metabolised agents not mentioned here may be affected by the addition of cimetidine therapy. Because of the therapeutic successes demonstrated in the treatment of various disorders with cimetidine, one cannot disregard this agent. Thus, the responsibility for understanding and monitoring for the complex effects of this drug falls with the practicing physician.

i) WAR with Distalgesic

(1) Orme M, Breckenridge A, Cook P  
**WARFARIN AND DISTALGESIC INTERACTION.**  

(2) Jones RV  
**LETTER: WARFARIN AND DISTALGESIC INTERACTION.**  
j) WAR with Anti Cancer Drugs 5 FU = NO!

(1) Kolesar JM, Johnson CL, Freeberg BL, Berlin JD, Schiller JH

**WARFARIN-5-FU INTERACTION—A CONSECUTIVE CASE SERIES.**  
*Pharmacotherapy* 1999 Dec;19(12):1445-9

School of Pharmacy, University of Wisconsin-Madison, 53706-1515, USA.

Five patients from a single institution received concomitant warfarin and 5-fluorouracil (5-FU) during a 3-year period. The mean weekly warfarin dose before starting chemotherapy was 40.66 mg and during chemotherapy it was 24 mg (p=0.0026). All patients required a warfarin dosage reduction (range 18-74%, mean 44%). Two patients were hospitalized, one with a major retroperitoneal bleed, the other for fresh-frozen plasma administration and observation. Maximum international normalized ratios (INRs) ranged from 3.66-23.7. This series confirms a common, clinically significant interaction between warfarin and 5-FU. An interaction between capecitabine, the orally available prodrug of 5-FU, and warfarin also has been reported. We recommend weekly monitoring of prothrombin time and INR for all patients receiving concomitant warfarin and 5-FU or capecitabine.

(2) Brown MC

**AN ADVERSE INTERACTION BETWEEN WARFARIN AND 5-FLUOROURACIL: A CASE REPORT AND REVIEW OF THE LITERATURE.**  
*Chemotherapy* 1999 Sep-Oct;45(5):392-5

Division of Gastroenterology, Department of Medicine, University of Washington, Seattle, Wash., USA. mcbrown@u.washington.edu

Adverse interactions between warfarin and 5-fluorouracil (5-FU) have been reported. Such an interaction occurred in a patient with lung cancer receiving vinblastine and 5-FU. This case is the first involving a patient taking minidose warfarin for prophylaxis of catheter-associated thrombosis. Although the mechanism of the interaction is unclear, it has been postulated that 5-FU interferes with the synthesis of hepatic cytochrome P-450 2C9. Because warfarin and 5-FU are regularly coadministered, this adverse interaction might be occurring more frequently than is realized. Clinicians should be aware of this interaction and should regularly monitor the prothrombin time of patients receiving warfarin and 5-FU.

(3) Brown MC

**INTERACTION BETWEEN WARFARIN AND 5-FLUOROURACIL, NOT BETWEEN WARFARIN AND LEVAMISOLE.**  
*Clin Pharmacol Ther* 1998 Aug;64(2):233

k) WAR with Anti Fungeal Agents

1) Miconazole Oral Gel

(4) Pemberton MN, Sloan P, Ariyaratnam S, Thakker NS, Thornhill MH

**DERANGEMENT OF WARFARIN ANTICOAGULATION BY MICONAZOLE ORAL GEL.**  

Clinical Academic Group of Oral Medicine and Dental Diagnostic Science, University Dental Hospital of Manchester.

The potentiation of the anticoagulant effects of warfarin by miconazole, when used in oral gel form, is described in three patients. The associated morbidity is examined, emphasising the importance of considering this potentially serious interaction when prescribing antifungal agents to patients on oral anticoagulants.

2) Terbinafine
(5) Gupta AK, Ross GS

**INTERACTION BETWEEN TERBINAFINE AND WARFARIN.**

*Dermatology* 1998;196(2):266-7

Department of Medicine, Sunnybrook Health Science Center, Ont., Canada.

A 71-year-old woman presented with gastrointestinal bleeding. She had been stabilized on warfarin for the previous few months. Terbinafine had been started 32 days prior to this episode for the treatment of onychomycosis. The patient had been on cimetidine for the previous 2 years and on other medications for the last 10 years. At the time of admission for the gastrointestinal bleeding, the coagulation indices were all above the therapeutic range. Endoscopy of the gastrointestinal tract exhibited diffuse intestinal 'oozing' consistent with coagulopathy as the cause of bleeding. Terbinafine may have had an effect on the metabolism of warfarin since both are metabolized through the liver and cimetidine can reduce terbinafine clearance by 33% resulting in higher concentrations of the antifungal agent. Our experience suggests that caution should be exercised when prescribing terbinafine to a patient receiving warfarin.

I) WAR with Paracetamol

(1) Boeijinga JJ, Boerstra EE, Ris P, Breimer DD, Jeletich-Bastiaanse A

**INTERACTION BETWEEN PARACETAMOL AND COUMARIN ANTICOAGULANTS.**

*Lancet* 1982 Feb 27;1(8270):506

m) WAR with Propoxyphene

(2) Smith R, Prudden D, Hawkes C

**PROPOXYPHENE AND WARFARIN INTERACTION.**


n) WAR with Fluoroquinolones

(1) Byrd DC, Gaskins SE, Parrish AM, Freeman LB

**WARFARIN AND CIPROFLOXACIN INTERACTION: CASE REPORT AND CONTROVERSY.**

*J Am Board Fam Pract* 1999 Nov-Dec;12(6):486-8

Department of Pharmacy Practice, Auburn University School of Pharmacy, Auburn University, AL, USA.

(3) Colucci VJ, Rivey MP

**TOLTERODINE-WARFARIN DRUG INTERACTION.**


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colucci@selway.umt.edu

**OBJECTIVE:** To report two cases of warfarin therapy in which the addition of tolterodine resulted in prolonged international normalized ratios (INRs). **CASE SUMMARY:** Two patients, each receiving warfarin for stroke prophylaxis in association with chronic atrial fibrillation, developed adverse effects after the initiation of tolterodine for urinary disorders. Other medications for concurrent medical diagnoses had remained unchanged. One patient had an episode of prostatitis, which was treated with levofloxacin immediately prior to tolterodine initiation. The warfarin dosage had remained constant for many weeks in both patients prior to and during the tolterodine trials. In each patient, the initiation of tolterodine was associated with a significant increase in the patient’s INR measured 10-14 days later. Thus, tolterodine was ineffective in both patients and was discontinued one to two days before the elevated INRs were determined during routine clinic visits. INRs determined approximately two weeks after tolterodine was discontinued were similar to those.
obtained during the period before the use of the drug; the warfarin dosage remained unchanged. Rechallenge with tolterodine was not attempted in either patient. DISCUSSION: Several aspects of the reported cases support the validity of a proposed drug interaction when tolterodine is initiated in a patient stabilized on warfarin therapy. The temporal association of the course of tolterodine with an elevated INR, the return to the previous warfarin dose-INR response relationship after tolterodine discontinuation, and the absence of other causes for the elevated INR were factors found in both patients. Possible mechanisms to explain the suggested drug interaction are explored. CONCLUSIONS: Until further data are available, clinicians should be vigilant for a possible drug interaction when tolterodine therapy is initiated in a patient maintained on warfarin therapy.

(4) Balfour JA, Wiseman LR
Moxifloxacin.
Drugs 1999 Mar;57(3):363-73; discussion 374
Adis International Limited, Mairangi Bay, Auckland, New Zealand. demail@adis.co.nz
Moxifloxacin is a new fluoroquinolone antibacterial agent with a broad spectrum of activity, encompassing gram-negative and gram-positive bacteria. It has improved activity against gram-positive species (including staphylococci, streptococci, enterococci) and anaerobes compared with ciprofloxacin. This is offset by slightly lower activity against pseudomonal species and Enterobacteriaceae. In common with other fluoroquinolones, moxifloxacin attains good penetration into respiratory tissues and fluids and its bioavailability is substantially reduced by coadministration with an antacid or iron preparation. However, moxifloxacin does not interact with theophylline or warfarin. In clinical trials in patients with community-acquired pneumococcal pneumonia (CAP), acute exacerbations of chronic bronchitis (AECB) or acute sinusitis, moxifloxacin 400 mg once daily achieved bacteriological and/or clinical success rates of approximately 90% or higher. Moxifloxacin was as effective as amoxicillin 1 g 3 times daily and clarithromycin 500 mg twice daily in CAP and as effective as clarithromycin in AECB. In patients with sinusitis, a 7-day course of moxifloxacin 400 mg once daily was as effective as a 10-day course of cefuroxime axetil 250 mg twice daily. In contrast to some other fluoroquinolones, moxifloxacin appears to have a low propensity for causing phototoxic and CNS excitatory effects. The most common adverse events are gastrointestinal disturbances.

o) WAR interactions with Antidiabetics
(1) Loi CM, Young M, Randinitis E, Vassos A, Koup JR
Clinical Pharmacokinetics of Troglitazone.
Department of Pharmacokinetics, Dynamics and Metabolism, Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company, Ann Arbor, Michigan 48105, USA. CHOMING.LOI@WL.COM
Troglitazone is a new thiazolidinedione oral antidiabetic agent approved for use to improve glycaemic control in patients with type 2 diabetes. It is rapidly absorbed with an absolute bioavailability of between 40 and 50%. Food increases the absorption by 30 to 80%. The pharmacokinetics of troglitazone are linear over the clinical dosage range of 200 to 600 mg once daily. The mean elimination half-life ranges from 7.6 to 24 hours, which facilitates a once daily administration regimen. The pharmacokinetics of troglitazone are similar between patients with type 2 diabetes and healthy individuals. In humans, troglitazone undergoes metabolism by sulfation, glucuronidation and oxidation to form a sulfate conjugate (M1), glucuronide conjugate (M2) and quinone metabolite (M3), respectively. M1 and M3 are the major metabolites in plasma, and M2 is a minor metabolite. Age, gender, type 2 diabetes, renal impairment, smoking and race do not appear to influence the pharmacokinetics of troglitazone and its 2 major metabolites. In patients with hepatic impairment the plasma concentrations of troglitazone, M1 and M3 increase by 30%, 4-fold, and 2-fold, respectively. Cholestyramine decreases the absorption of troglitazone by 70%. Troglitazone may enhance the activities of cytochrome P450 (CYP) 3A and/or transporter(s) thereby reducing the plasma concentrations of terfenadine, cyclosporin, atorvastatin and fexofenadine. It also reduces the plasma concentrations of the oral contraceptive hormones ethinylestradiol, norethindrone and levonorgestrel. Troglitazone does not alter the pharmacokinetics of digoxin, glibenclamide (glyburide) or paracetamol (acetaminophen). There is no pharmacodynamic interaction between troglitazone and warfarin or alcohol (ethanol). Pharmacodynamic modelling showed that
improvement in fasting glucose and triglyceride levels increased with dose from 200 to 600 mg. Knowledge of systemic troglitazone exposure within a dose group does not improve the prediction of glucose lowering response or adverse effects beyond those based on the administered dose.

11. WAR Monitoring

(1) Carroll WE, Jackson RD, Carroll TA

WARFARIN MONITORING BY AN ANTICOAGULANT THERAPY FACTOR.

Res Commun Mol Pathol Pharmacol 1998 Aug;101(2):159-70

Department of Pathology, Santa Barbara Cottage Hospital, CA 93105, USA.

In a pilot study (1997) using POTENS+, our coagulation instrument, we determined that: (a) an Anticoagulant Therapy Factor (ATF) was comparable to the International Normalized Ratio (INR) for monitoring warfarin anticoagulant therapy, (b) one could use any of the four thromboplastins with which the ATF was derived with comparable results, and (c) the ATF could be proposed to monitor warfarin therapy. The ATF-INR comparisons correlated well statistically; but when individual ATF-INR comparisons were later studied, there were frequent discrepancies. The pilot study (1997) was based on hospitalized patients, so almost all patients were undergoing induction of warfarin anticoagulation. Since none of them had taken warfarin for at least six weeks, none of them could be considered "stable" on warfarin. In the present study, all patients were on warfarin therapy for at least six weeks, and the ATF equation was modified by multiplying it by the prothrombin ratio (PR) to give a corrected ATF (CATF). This CATF was then further modified to achieve agreement with the INR by adjusting the linear regression line by means of analytic geometry, so that the CATF-INR regression line now had a slope of one and passed through the origin. With these changes, the modified ATFs (MATF) and INRs correlated well and were nearly equal numerically when using two of the four thromboplastins. Reason for the discrepancies with the other two thromboplastins will be discussed.

(2) Triplett DA

CURRENT RECOMMENDATIONS FOR WARFARIN THERAPY. USE AND MONITORING.


Department of Pathology, Indiana University School of Medicine, USA.

With the aging population, the use of warfarin will continue to increase. The introduction of new thromboplastins with International Sensitivity Indices (ISI) of 1.0 to 1.5 has improved the efficacy of monitoring warfarin therapy with the prothrombin time (PT). Increasingly, outpatient oral anticoagulant clinics and home testing are the sites for PT monitoring.

12. WAR Low Dosage Effect on Factor VII and Protein S

(1) Coccheri S, Palareti G, Cosmi B

ORAL ANTICOAGULANT THERAPY: EFFICACY, SAFETY AND THE LOW-DOSE CONTROVERSY.

Haemostasis 1999 Dec;29(2-3):150-165

Chair and Department of Angiology and Blood Coagulation, University Hospital S. Orsola, Bologna, Italy.

The issue of optimal duration of oral anticoagulant therapy after a first episode of venous thromboembolism is still unresolved. However, recent data suggest that short (6 weeks to 3 months), intermediate (3–6 months) or indefinite-term anticoagulant therapy should be adopted on the basis of the classification of patients into low-, intermediate- and high-recurrence-risk groups, respectively. Oral anticoagulants have been shown to effectively prevent cardioembolic stroke in nonvalvular atrial fibrillation. Recent data seem to suggest that their safety can be ameliorated with adequate risk stratification on the basis of clinical and echocardiographic features. After unstable angina and non-Q-wave myocardial infarction, oral anticoagulant therapy (INR range 2-3) combined with aspirin
has been shown to be advantageous over aspirin alone, although at the cost of a slight increase in bleeding. Bleeding complications are major drawbacks of oral anticoagulant therapy thus limiting their generalized adoption in recognized indications. To sharply reduce the bleeding risk and need of laboratory control, the low- or fixed-dose oral anticoagulant approach has been evaluated. In primary prevention and in low or low-to-moderate thrombotic risk, minidose warfarin treatment has been shown to be advantageous. In secondary prevention, and in patients at high risk for recurrent venous or arterial thrombotic events, standard range (INR 2-3) or higher level of anticoagulation is needed. Copyright 1999 S. Karger AG, Basel

(2) Yamak B, Iscan Z, Mavitas B, Ulus AT, Katircioglu SF, Tasdemir O, Bayazit K

LOW-DOSE ORAL ANTICOAGULATION AND ANTIPLATELET THERAPY WITH ST. JUDE MEDICAL HEART VALVE PROSTHESIS.

J Heart Valve Dis 1999 Nov;8(6):665-73

Department of Cardiovascular Surgery, Turkiye Yuksek Ihtisas Hospital, Ankara, Turkey.

BACKGROUND AND AIM OF THE STUDY: Since 1986, the St. Jude Medical (SJM) mechanical heart valve prosthesis has been implanted in patients at the authors' institution. We present our experience of low-dose oral anticoagulation and antiplatelet therapy following SJM valve implantation. METHODS: Among 2,585 patients (mean age 40.3 +/- 13.5 years) living in a rural environment, 865 underwent aortic valve replacement (AVR), 1,231 mitral valve replacement (MVR) and 489 double valve replacement (DVR). All patients received 2.5 mg/day warfarin and a combination of antiaggregation therapy (dipyridamole 3 x 75 mg/day plus aspirin 100 mg/day), irrespective of their prothrombin time and cardiac rhythm. RESULTS: Postoperatively, 139 adverse events occurred (51 in AVR patients, 58 in MVR, 30 in DVR). Operative mortality rate was 5.9%, 4.7% and 6.1%, respectively, in the three groups (overall mortality rate 5.4%). The most frequent cause of operative mortality was low cardiac output. During follow up, there were 88 anticoagulant hemorrhages (1.2%/patient-year (pt-yr)), 11 paravalvular leaks (0.2%/pt-yr), 52 thromboembolisms (0.7%/pt-yr), 60 mechanical valve thromboses (0.8%/pt-yr) and 78 reoperations (1.1%/pt-yr). These complications occurred in 101 patients after AVR, in 125 after MVR, and in 63 after DVR (4.2%, 3.7% and 4.6% per pt-yr, respectively). Patient age (p = 0.0004), concomitant surgery (p = 0.0017) and late valve-related complications (p = 0.0159) were statistically significant mortality factors after AVR. Previous surgery was a significant risk factor for operative mortality after MVR (p <0.05). Female gender (p = 0.0059) and age (p = 0.017) were significant risk factors for operative mortality after DVR (p <0.01). CONCLUSIONS: Following implantation of the St. Jude Medical mechanical heart valve prosthesis, a fixed dose of 2.5 mg/day warfarin and combined dipyridamole/aspirin provided satisfactory results in terms of thrombosis, embolism and bleeding.

(3) Holm J, Hillarp A, Erhardt L, Berntorp E

CHANGES IN LEVELS OF FACTOR VII AND PROTEIN S AFTER ACUTE MYOCARDIAL INFARCTION: EFFECTS OF LOW-DOSE WARFARIN.

Thromb Res 1999 Nov 1;96(3):205-12

Department of Cardiology, Malmo University Hospital, Sweden.

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Persistent coagulation activity after an acute myocardial infarction may increase the risk of reinfarction. We prospectively investigated the effects on plasma coagulation of a low, fixed dose of warfarin in combination with aspirin after myocardial infarction. We also evaluated the influence of coagulation activity on clinical outcome. Plasma samples from 97 patients, randomised to 1.25 mg of warfarin daily in combination with 75 mg of aspirin or aspirin alone were drawn 4 days, 1 month, and 6 months after myocardial infarction. Patients receiving warfarin had a greater reduction in factor VII coagulation activity (FVII:C) after 6 months: 0.18 vs. 0.06 U/mL (95% CI, 0.02-0.22), whereas no differences were seen in levels of protein C, protein S, or prothrombin fragment 1+2. In the acute phase, the level of free protein S was lower than after 6 months in both groups: 25.6 vs. 28.8% (95% CI, 4.19-2.35). Cardiovascular mortality, reinfarction, and stroke were evaluated after 4 years (median). In a survival analysis, every 0.1 U/mL increase in the level of FVII:C1 month after myocardial infarction was associated with an 15% increase in risk of cardiovascular events (95% CI, 1.01-1.30). Warfarin at 1.25 mg daily reduces FVII:C but not systemic thrombin generation measured as prothrombin fragment 1 +2. Low levels of the anticoagulant protein S may contribute to a procoagulant state.
'B. Warfarin Complications

1. WAR induced Bowel Complications, Infarctions and Haematomas

(1) Muralikrishnan VP, Thomas DH, Haray PN

**WARFARIN-INDUCED HAEMORRHAGIC INFARCTION OF THE SMALL BOWEL.**

Department of Surgery, Prince Charles Hospital, Merthyr Tydfil, UK.

Haemorrhagic infarction of the small bowel is a rare complication of warfarin therapy. We take this opportunity to report a case that needed a resection of the small bowel.

(2) Norton SA, Armstrong CP

**LOWER GASTROINTESTINAL BLEEDING DURING ANTICOAGULANT THERAPY: A LIFE-SAVING COMPLICATION?**

Department of Surgery, Frenchay Hospital, Bristol.

Warfarin is commonly used in the prophylaxis or treatment of thromboembolic disease. Haemorrhage is a recognised complication which may be life-threatening. This paper describes eight cases in which lower gastrointestinal bleeding while on warfarin therapy resulted in the discovery of previously unrecognised large bowel malignancy. Diagnosis of an otherwise asymptomatic carcinoma in this way enabled surgery to be carried out at an earlier stage and so may have resulted in a better prognosis for these patients. Bleeding while on anticoagulant therapy is caused by a specific organic lesion in 30% to 50% of cases. This may be the case even when the prothrombin time is very prolonged. It is important, therefore, that such cases are fully investigated, especially in the elderly.

(3) Shah P, Kraklow W, Lamb G

**UNUSUAL COMPLICATION OF COUMADIN TOXICITY.**
*Wis Med J* 1994 May;93(5):212-4

Department of Medicine, Medical College of Wisconsin, Milwaukee.

Coumadin is a coumarin anticoagulant that induces a state similar to vitamin K deficiency and is routinely used for chronic oral anticoagulation. Intramural hematoma of the bowel is a rare complication of anticoagulant therapy. In this paper, we describe such a case of an anticoagulated patient who had complaints of abdominal pain and who had inadvertently been taking higher dose of coumadin. Although the diagnosis can usually be made by history and plain abdominal x-ray, we report here some radiographic signs that can be seen on a CT-scan of the abdomen and are relatively specific for this diagnosis. We stress the importance of recognizing the disorder because the management is conservative and surgery is reserved for cases in which no improvement is seen.

(4) Sinert R, Scalea T

**RETROPHARYNGEAL AND BOWEL HEMATOMAS IN AN ANTICOAGULATED PATIENT.**
*Acad Emerg Med* 1994 Jan-Feb;1(1):67-72

SUNY Health Science Center at Brooklyn Department of Emergency Medicine 11203, USA.

As the indications for oral anticoagulation therapy increase, the number of patients being treated with anticoagulants and at risk for complications also will rise. Major bleeding episodes have been reported to occur in approximately 2-4% of patients being treated with oral anticoagulants. The case report of a patient with concurrent spontaneous retropharyngeal and small-bowel hematomas from overanticoagulation with warfarin is presented. The authors review the subtle presentation of retropharyngeal hematomas, common medications that may enhance warfarin anticoagulation, and therapy of potentially life-threatening hematomas. Airway management and possible surgical therapies to treat the complications of hematomas are discussed. Depending upon the indication for the initial anticoagulation, interim anticoagulation with heparin may be indicated.
2. WAR may be responsible for **Calcifications in Arteries and Heart Valves**

(1) **Price PA, Faus SA, Williamson MK**

**WARFARIN CAUSES RAPID CALCIFICATION OF THE ELASTIC LAMELLAE IN RAT ARTERIES AND HEART VALVES.**

*Arterioscler Thromb Vasc Biol* 1998 Sep;18(9):1400-7

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High doses of warfarin cause focal calcification of the elastic lamellae in the media of major arteries and in aortic heart valves in the rat. Aortic calcification was first seen after 2 weeks of warfarin treatment and progressively increased in density at 3, 4, and 5 weeks of treatment. By 5 weeks, the highly focal calcification of major arteries could be seen on radiographs and by visual inspection of the artery. The calcification of arteries induced by warfarin is similar to that seen in the matrix Gla protein (MGP)-deficient mouse, which suggests that warfarin induces artery calcification by inhibiting gamma-carboxylation of MGP and thereby inactivating the putative calcification-inhibitory activity of the protein. Warfarin treatment markedly increased the levels of MGP mRNA and protein in calcifying arteries and decreased the level of MGP in serum. Warfarin treatment did not affect bone growth, overall weight gain, or serum calcium and phosphorus levels, and, because of the concurrent administration of vitamin K, prothrombin times and hematocrits were normal. The results indicate that the improved warfarin plus vitamin K treatment protocol developed in this study should provide a useful model to investigate the role of MGP in preventing calcification of arteries and heart valves.

3. **WAR induced Skin Necrosis**

(1) **Gelwix TJ, Beeson MS**

**WARFARIN-INDUCED SKIN NECROSIS.**


Department of Emergency Medicine, Summa Health System, Akron, OH 44304, USA.

Skin necrosis is an uncommon complication of warfarin (Coumadin; Dupont Pharma, Wilmington, DE) therapy. The presentation may mimic other disorders. This article reports a case of a 72-year-old woman who presented to the emergency department complaining of swelling and ecchymosis to her left breast and right foot. The patient had been hospitalized for coronary artery bypass grafting, and had been discharged from the hospital earlier that day. This article reviews the pathophysiology and clinical features of warfarin-induced skin necrosis.

(2) **Sallah S, Abdallah JM, Gagnon GA**

**RECURRENT WARFARIN-INDUCED SKIN NECROSIS IN KINDREDS WITH PROTEIN S DEFICIENCY.**

*Haemostasis* 1998 Jan-Feb;28(1):25-30

Division of Hematology/Oncology, Department of Medicine, East Carolina University, School of Medicine, Greenville, NC 27858-4354, USA.

Warfarin-induced skin necrosis is a rare complication of anticoagulant treatment. The incidence of this complication is undetermined, but it has been estimated to occur between 1:100 and 1:10,000 of patients treated with anticoagulants. Coumarin skin necrosis occurs almost exclusively in patients with venous thrombosis between the 3rd and 10th day after beginning anticoagulation. Although protein C deficiency is the most common underlying hypercoagulable state reportedly associated with warfarin skin necrosis, very few cases have been linked to congenital protein S deficiency. This article addresses the association of hereditary protein S deficiency and warfarin skin necrosis, and provides suggestions for management.

4. **WAR Spontaneous Retromammary Haemorrhage**
5. WAR induced Rhabdomyolysis interaction with Simvastatin

(1) Mogyorosi A, Bradley B, Showalter A, Schubert ML

**RHABDOMYOLYSIS AND ACUTE RENAL FAILURE DUE TO COMBINATION THERAPY WITH SIMVASTATIN AND WARFARIN.**


Simvastatin, an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, is widely used to treat hyperlipidaemia. Although myalgias are recognized adverse effects, clinically significant elevations in serum creatine phosphokinase (CPK) levels are uncommon. We describe a case of rhabdomyolysis and acute renal failure associated with concomitant use of simvastatin and warfarin. Rhabdomyolysis and renal failure occurred 7 days after warfarin (5 mg day⁻¹) was added to a chronic stable dose of simvastatin (20 mg day⁻¹) and resolved abruptly after discontinuation of simvastatin. We recommend careful monitoring when warfarin is given to patients receiving simvastatin.

**B. Heparin (HEP)**

A. Function and Fields of Use

1. HEP Dosing

a) HEP Weight Based Dosing

(1) Lackie CL, Luzier AB, Donovan JA, Feras HI, Forrest A

**WEIGHT-BASED HEPARIN DOSING: CLINICAL RESPONSE AND RESOURCE UTILIZATION.**


Department of Pharmacy Practice, State University of New York at Buffalo School of Pharmacy, USA.

The objective of this study was to assess a *weight-based heparin* (WBH) nomogram (80-U/kg bolus, 18-U/kg-per-hour initial infusion) and determine its clinical performance and impact on resource utilization. All patients treated with *heparin* for venous thromboembolism or unstable angina during a 15-week study period were included in this retrospective, chart-review study. Three groups were identified: patients treated with WBH, patients whose regimen deviated from the *weight-based nomogram* (DEV), and matched *historical controls* (HCs). In patients receiving heparin for more than 24 hours, those treated with WBH achieved threshold *activated partial thromboplastin time* (aPTT) levels significantly faster than did HC or DEV patients. However, 42% of WBH-treated patients were found to have initial supratherapeutic responses. Logistic regression analysis identified: a) age > or =67 years, b) prior warfarin therapy within 7 days of heparin, and c) high initial infusion rate as predictive of a *supratherapeutic aPTT response*; d) smoking was predictive of a *subtherapeutic response*. Bleeding events were not significantly different between groups. An infusion rate of 15 U/kg per hour was found to closely approximate our population’s *actual heparin infusion requirement*. Resource utilization was significantly different between the WBH and HC groups in terms of nursing interventions at 48 to 72 hours. We concluded that WBH rapidly drives patients’ aPTT response above the therapeutic threshold for heparin; however, prudent adjustment of the initial infusion rate is necessary to avoid a *supratherapeutic aPTT response*. Our data support a nomogram with an initial infusion rate of 15 U/kg per hour.
(2) Popma JJ, Prpic R, Lansky AJ, Piana R
HEPARIN DOSING IN PATIENTS UNDERGOING CORONARY INTERVENTION.
*Am J Cardiol* 1998 Oct 22;82(8B):19P-24P

Department of Internal Medicine, the Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115, USA.

Unfractionated heparin remains an essential component of the antithrombotic regimen in patients undergoing coronary intervention, although the timing, dosing, and duration of heparin therapy have evolved over the past several years. Complications associated with heparin use include bleeding events, which occur in 3.9-16.4% of patients receiving conventional heparin. Less commonly, clinically significant thrombocytopenia develops, related to the duration of heparin administration. In patients undergoing coronary intervention who do not receive platelet glycoprotein (GP) IIb/IIIa inhibitors, sufficient heparin should be given to achieve an activated clotting time (ACT) of 250-300 seconds with the HemoTec device and 300-350 seconds with the Hemochron device. There is a general trend to use lower, weight-adjusted heparin dosing (70-100 units/kg) to avoid excessive levels of anticoagulation, with additional heparin boluses to achieve a therapeutic ACT level. When GP IIb/IIIa inhibitors are used, weight-adjusted heparin dosing can be decreased to 70 units/kg to achieve a target ACT of 200 seconds with either the HemoTec or Hemochron device. After uncomplicated coronary intervention, there appears to be little value associated with continued heparin therapy, and the risk of bleeding complications clearly increases with longer durations and higher levels of anticoagulation after coronary intervention.

b) HEP High Dose

CONFIRMATION THAT HEPARIN IS AN ALTERNATIVE MEANS OF PROMOTING EARLY REPERFUSION.
*Coron Artery Dis* 1998;9(6):335-8

Coronary Care Unit, Hospital Portugues and Fundacao Bahiana de Cardiologia, Salvador, Brazil.

BACKGROUND: New strategies to increase coronary patency rate before primary angioplasty are under discussion. We tested the hypothesis that use of a high dose of a standard heparin bolus could achieve an acceptable rate of re-opening occluded infarct-related arteries thus providing an alternative to chemical thrombolysis before admission of the patient to hospital, and a pretreatment for primary angioplasty. METHODS: Forty-eight patients who presented within 12 h of acute myocardial infarction with ST segment elevation were assigned randomly to groups to receive aspirin (200 mg orally) and high-dose standard heparin 300 U/kg as an intravenous bolus (n = 25), or aspirin and placebo bolus (n = 23). Thereafter, all patients underwent coronary arteriography to assess their suitability for primary angioplasty. RESULTS: The high-dose heparin group had greater patency rate (Thrombolysis in Myocardial Infarction grade 2 or 3 flow in the infarct-related artery) than the placebo group (52% compared with 13%, P = 0.006). Hemorrhages related to the puncture site that required blood transfusion occurred in two of 25 and in one of 23 patients in the high-dose heparin and placebo groups, respectively. CONCLUSION: Our study suggests that high-dose standard heparin does have a thrombolytic action when administered as an intravenous bolus.

c) HEP Low Dose

(1) Gallus AS, Nurmohammed M, Kearon C, Prins M
THROMBOPROPHYLAXIS IN NON-SURGICAL PATIENTS: WHO, WHEN AND HOW?
*Haemostasis* 1998 Nov;28 Suppl S3:71-82

Flinders Medical Centre, Adelaide, Australia.

In these early studies, low-dose heparin and low-molecular-weight heparins prevented subclinical deep vein thrombosis in ischaemic stroke, myocardial infarction and among elderly medical inpatients. Although it is likely that these drugs also prevent subclinical deep vein thrombosis after spinal
cord injury or other major trauma, and when patients require intensive medical care, the supporting evidence in these circumstances comes mainly from cohort studies and poorly controlled comparisons. In contrast, the heparins have not reduced mortality or demonstrably prevented pulmonary embolism after ischaemic stroke or among elderly medical inpatients in large and well-conducted clinical endpoint trials, from which no clinically important benefit could be demonstrated. From analyses it is suggested that such benefit is probably more difficult to demonstrate for medical than for surgical patients. **In the absence of sufficient information that is specific to medical patients, various forms of prophylaxis known to be effective in surgery will continue to be applied in high-risk individuals.** After venous thromboembolism, it now appears that the best duration of oral anticoagulant therapy to prevent a recurrence is determined to a greater extent by whether the thrombotic episode was idiopathic or triggered by a clinically recognizable cause, whether it was transient or continuing, and whether the deep vein thrombosis was extensive, limited to the calf veins or was a first or recurrent event.

(2) Velmahos GC, Nigro J, Tatevosian R, Murray JA, Cornwell EE 3rd, Belzberg H, Asensio JA, Berne TV, Demetriades D

**INABILITY OF AN AGGRESSIVE POLICY OF THROMBOPROPHYLAXIS TO PREVENT DEEP VENOUS THROMBOSIS (DVT) IN CRITICALLY INJURED PATIENTS: ARE CURRENT METHODS OF DVT PROPHYLAXIS INSUFFICIENT?**


Department of Surgery, Los Angeles County + University of Southern California Medical Center, 90033-4525, USA.

**BACKGROUND:** Deep venous thrombosis (DVT) in severely injured patients is a life-threatening complication. Effective and safe thromboprophylaxis is highly desirable to prevent DVT. **Low-dose heparin (LDH)** and **sequential compression device (SCDs)** are the most frequently used methods. Inappropriate use of these methods because of the nature or site of critical injuries (eg, brain lesion, solid visceral or retroperitoneal hematoma, extremity fractures) may lead to failure of DVT prophylaxis. **STUDY DESIGN:** A prospective study was performed to evaluate the efficacy of a policy of aggressive use of LDH and SCDs in patients who are at very high risk for DVT. From January 1996 to August 1997, 200 critically injured patients were followed by weekly Doppler examinations to detect DVT at the proximal lower extremities. Only 3 patients did not receive any thromboprophylaxis. SCDs were applied in 97.5% and LDH was administered to 46% of the patients; 45% had both. **RESULTS:** DVT was found in 26 patients (13%). The majority (58%) developed DVT within the first 2 weeks, but new cases were found as late as 12 weeks after admission. The incidence of DVT was the same among patients who had SCDs only or a combination of LDH and SCDs. Mechanism of injury, type and number of operations, site of injury, Injury Severity Score, and the incidence of femoral lines were not different between patients with and without DVT. Differences were found in the severity of injury to the chest and the extremities and the need for high-level respiratory support. **Patients with DVT had prolonged ICU and hospital stays (on average, 34 and 49 days, respectively) and a high mortality rate (31%).** **CONCLUSIONS:** The incidence of DVT remains high among severely injured patients despite aggressive thromboprophylaxis. A combination of LDH and an SCD showed no advantage over SCD alone in decreasing DVT rates. Risk factors in this group of patients who are already at very high risk are hard to detect; Doppler examinations are justified for surveillance in all critically injured patients. Current methods of thromboprophylaxis seem to offer limited efficacy, and the search for more effective methods should continue.

(3) Gibbs NM, Bell R

**THE EFFECT OF LOW-DOSE HEPARIN ON HYPERCOAGULABILITY FOLLOWING ABDOMINAL AORTIC SURGERY.**


Department of Anaesthesia, Sir Charles Gairdner Hospital, Nedlands, Western Australia.

The effect of **low-dose heparin** on postoperative hypercoagulability was assessed using **thrombelastography (TEG)** in eighteen patients undergoing elective abdominal aortic surgery. Patients received **unfractionated heparin 5000IU** bd SC commencing on the first postoperative day. Native whole blood TEG was performed preoperatively and on day two postoperatively. A heparinase-modified TEG was performed at the same time as the native whole blood TEG on day two. There were no significant changes in the postoperative native whole **blood TEG variables** (r, K, alpha, MA) relative to
preoperative controls. In contrast, there were significant decreases in r and K, and increases in alpha in the heparinase-modified TEGs postoperatively (P < 0.01). There were significant differences between the postoperative native whole blood and heparinase-modified TEGs for all TEG variables (P < 0.01). The results indicate that low-dose heparin reduces postoperative hypercoagulability following abdominal aortic surgery as assessed by thrombelastography.

d) HEP Orally

(1) Baughman RA, Kapoor SC, Agarwal RK, Kisicki J, Catella-Lawson F, FitzGerald GA

ORAL DELIVERY OF ANTICOAGULANT DOSES OF HEPARIN: A RANDOMIZED, DOUBLE-BLIND, CONTROLLED STUDY IN HUMANS.


Background-Parenteral heparin is the anticoagulant of choice in hospitalized patients. Continued anticoagulation is achieved by subcutaneous administration of low-molecular-weight heparin or with an orally active anticoagulant such as warfarin. An oral heparin formulation would avoid the inconvenience of subcutaneous injection and the unfavorable drug interactions and adverse events associated with warfarin. A candidate delivery agent, sodium N-[8(-2-hydroxybenzoyl)amino]caprylate (SNAC), was evaluated with escalating oral heparin doses in a randomized, double-blind, controlled clinical study for safety, tolerability, and effects on indexes of anticoagulation. Methods and Results-Increases in activated partial thromboplastin time (aPTT), antifactors IIa and Xa, and tissue factor pathway inhibitor (TFPI) concentrations were detected when normal volunteers were dosed with 10.5 g SNAC/20 000 IU heparin by gavage in some subjects. For the entire group, 30 000 IU SNAC and heparin elevated TFPI from 74.9 +/- 7.6 to 254.2 +/- 12.3 mg/mL (P<0.001) 1 hour after dosing (P<0.001). Similar changes occurred in anti-factor IIa and anti-factor Xa. aPTT rose from 28 +/- 0.5 to 42.2 +/- 6.3 seconds 2 hours after dosing (P<0.01). No significant changes in vital signs, physical examination, ECGs, or clinical laboratory values were observed. Neither 30 000 IU heparin alone nor 10.5 g SNAC alone altered the hemostatic parameters. Emesis was associated with 10.5 g SNAC. A taste-masked preparation of SNAC 2.25 g was administered orally with heparin 30 000 to 150 000 IU. Both aPTT and anti-factor Xa increased with escalating doses of heparin. This preparation was well tolerated. Conclusions-Heparin, administered orally in combination with the delivery agent SNAC, produces significant elevations in 4 indexes of anticoagulant effect in healthy human volunteers. These results establish the feasibility of oral delivery of anticoagulant doses of heparin in humans and may have broader implications for the absorption of macromolecules.

e) HEP Nomograms for dosing

(1) de Groot MR, Buller HR, ten Cate JW, van Marwijk Kooy M

USE OF A HEPARIN NOMOGRAM FOR TREATMENT OF PATIENTS WITH VENOUS THROMBOEMBOLISM IN A COMMUNITY HOSPITAL.

Thromb Haemost 1998 Jul;80(1):70-3

Department of Internal Medicine, Sophia Hospital, Zwolle, The Netherlands.

BACKGROUND: The application of a heparin dosing nomogram in the treatment of patients with venous thromboembolism resulted in improvement of heparin therapy in clinical research settings. In 1992 a heparin nomogram was introduced in our hospital, which is a community hospital where anticoagulant therapy is supervised by the attending physicians. We studied whether comparable improvements were achieved in such a non-surveyed clinical setting. METHODS: Patients were identified from computerized discharge records, and classified into a pre-nomogram (discharged in 1990 or 1991) and a nomogram patient group (discharged in 1993 or 1994). The use of the nomogram was encouraged but the application remained on a voluntary basis. Since the definition of the target aPTT range was different in the pre-nomogram period as compared to the nomogram period, a formal analysis of pre- and post-nomogram results was not considered justified. RESULTS: The APTT ratio, six hours after the start of heparin treatment, was below the predefined lower limit in 72% of 127 patients in the pre-nomogram group and in 13% of 127 patients in the nomogram group. During 1043 days heparin
therapy in the nomogram group the morning APTT ratio was subtherapeutic in 8%. In 58% of all APTT results the physician responded according to the nomogram. The subsequent APTT was in the target range in 64% of the cases compared to 31% if the adjustment was not performed according to the nomogram (P<.0001). Major bleeding episodes occurred in 3.1% in the pre-nomogram period and in 0.7% in the nomogram period. CONCLUSION: The present study shows that the introduction of a heparin dosing nomogram in a non-research clinical setting results in more adequate heparin anticoagulation with low risks of bleeding.

2. HEP For Deep Vein Thrombosis

(1) Prandoni P

UNFRACTIONATED HEPARIN AND LOW-MOLECULAR-WEIGHT HEPARIN FOR THE INITIAL TREATMENT OF ACUTE VENOUS THROMBOEMBOLISM.

Haemostasis 1998 Nov;28 Suppl S3:85-90

Institute of Medical Semeiotics, University of Padua, Italy.

Anticoagulant drugs represent the therapy of choice for the initial treatment of venous thromboembolism. Unfractionated heparin (UFH) in adjusted doses and low-molecular-weight heparin (LMWH) in fixed doses are equally as effective and safe. Proper use of UFH requires considerable expertise, can cause inconvenience and has limitations. The use of LMWHs has multiple advantages over UFH including a more predictable dose-response and fixed administration dose. These properties make the treatment of suitable patients feasible in an outpatient setting. In two major clinical trials addressing the treatment of deep vein thrombosis, outpatient management with LMWH was associated with a substantial cost reduction compared with inpatient treatment using UFH. Recent studies have also shown that LMWHs are at least as effective and safe as UFH for the treatment of non-critical patients with pulmonary embolism. Whether or not home treatment of pulmonary embolism is feasible and safe remains to be demonstrated.

(2) Lensing AW

SURROGATE ENDPOINTS FOR THE ASSESSMENT OF EFFICACY IN VENOUS THROMBOEMBOLISM TREATMENT TRIALS.

Haemostasis 1998 Nov;28 Suppl S3:127-130

Centre for Haemostasis and Thrombosis, University of Amsterdam, The Netherlands.

For the assessment of the efficacy of anticoagulant therapy in patients with symptomatic venous thrombosis, the incidence of symptomatic venous thromboembolic complications is the outcome measure of choice. However, the low incidence of such complications necessitates the inclusion of a prohibitively large number of patients in randomized trials evaluating anticoagulant regimens. Therefore, alternative efficacy outcome measures are desirable. This paper discusses the validity of the following alternative tests: venography and compression ultrasound for deep vein thrombosis; and pulmonary angiography and perfusion lung scanning for pulmonary embolism. It is concluded that a combination of one of the deep vein thrombosis tests and perfusion lung scanning is the optimal approach. A thrombotic burden assessment, using repeat venography and perfusion lung scanning, has been performed at the end of treatment (day 10) with low-molecular-weight heparin and unfractionated heparin in 170 patients with symptomatic proximal deep vein thrombosis. An improved thrombotic burden was associated with a low number of subsequent symptomatic venous thromboembolic complications (4%), whereas this figure gradually increased for patients with an unchanged (10%) and deteriorated (29%) outcome (p < 0.005). It is concluded that the thrombotic burden assessment has potential to replace symptomatic outcomes, especially in dose-finding studies.

(3) Kirchmaier CM, Wolf H, Schafer H, Ehlers B, Breddin HK

EFFICACY OF A LOW MOLECULAR WEIGHT HEPARIN ADMINISTERED INTRAVENOUSLY OR SUBCUTANEOUSLY IN COMPARISON WITH INTRAVENOUS UNFRACTIONATED HEPARIN IN THE TREATMENT OF DEEP VENOUS THROMBOSIS. CERTOPARIN-STUDY GROUP.

Int Angiol 1998 Sep;17(3):135-45
BACKGROUND: The main objective of the study presented was to test if thrombus regression can be improved by treatment with an intravenously or subcutaneously administered low molecular weight heparin (LMWH). Patients with acute deep vein thrombosis were randomly assigned to receive either intravenous UFH (131 patients), intravenous (i.v.) LMWH (128 patients), or 8000 IU of the same LMWH bid subcutaneously (s.c.) (128 patients). All patients were treated with heparin for 14 to 16 days. Vitamin-K-antagonist prophylaxis was started between Day 12 and Day 14 after enrollment into the study. METHODS: Phlebographies and perfusion/ventilation lung scans were performed at baseline and on Days 12 to 16. Primary endpoint of the study was a reduction of the phlebographic Marder score. Secondary endpoints were recurrent thrombosis and pulmonary embolism (PE), major and minor bleedings and the rate of PE at inclusion and at the end of the study assessed by ventilation/perfusion scans. RESULTS: The Marder score improved by at least 30% in 32.4% (95% CI: 22.6 ... 42.2) of the patients receiving UFH, in 34.0% (95% CI: 24.9 ... 44.0) receiving LMWH i.v. and in 42.6% (95% CI: 32.8 ... 52.8) treated with the low molecular weight heparin s.c. The difference between LMWH s.c. and UFH was 10.2% (95% CI: -3.7% ... +24.5%) (p = 0.11). PE with clinical signs confirmed by objective methods occurred in three patients of the UFH group, one of whom died and was not observed in patients of the i.v. or s.c. LMWH-groups. During the first 15 days no patient receiving UFH or i.v. LMWH, and one patient on s.c. LMWH had a recurrent thrombosis. Major bleedings were observed in four patients receiving i.v. UFH compared to nine patients on i.v. LMWH (one of these patients died) and one patient on s.c. LMWH. Perfusion ventilation lung scans were obtained from 287 patients at baseline and from 246 patients on Days 12-16. PE, defined according to PIOPED-criteria as intermediate or high probability scans, was observed in 38.0% of the patients entering the study and in 18.3% on Days 12 to 16. New asymptomatic PE occurred less frequently in the groups on LMWH (7.1%, 7.5%, respectively) than in the UFH-group (12.6%) (not significant). CONCLUSIONS: S.c. treatment with a LMWH (certoparin) (b.i.d.) is at least as effective as UFH i.v. The hypothesis of increased efficacy of subcutaneous LMWH in resolving venous thrombi will have to be confirmed by an independent study comparing s.c. LMWH with UFH. The i.v. continuous infusion of the LMWH for 12 to 16 days does not result in a higher venous re-opening rate than intravenous standard heparin.

3. HEP for Acute Sinus Thrombosis

(1) Brucker AB, Vollert-Rogenhofer H, Wagner M, Stieglbauer K, Felber S, Trenkler J, Deisenhammer E, Aichner F

HEPARIN TREATMENT IN ACUTE CEREBRAL SINUS VENOUS THROMBOSIS: A RETROSPECTIVE CLINICAL AND MR ANALYSIS OF 42 CASES.

Cerebrovasc Dis 1998 Nov-Dec;8(6):331-337

Department of Neurology, Landesnervenklinik Wagner-Jauregg, Linz, Austria.

The only randomized data on heparin treatment in acute cerebral sinuses venous thrombosis (CSVT) are derived from a small number of patients. The rate of intracranial hemorrhages as a complication of high-dose heparin treatment is still unknown. This retrospective study evaluates the clinical features, neuroimaging monitoring and outcome of 42 patients with proven CSVT. Diagnosis was established by DSA, CT, MR tomography and MR angiography. All patients received heparin intravenously guided by doubling the aPTT value for 3 weeks, followed by oral anticoagulation. Partial or complete recanalization was found in 36 cases. 40 patients improved clinically, in 26 of them complete recovery was observed. One patient deteriorated and developed an apallic syndrome, one further patient died of septic multiorgan failure. Only in one patient was hemorrhagic transformation of infarcted brain tissue observed but without clinical deterioration.


HIGH-DOSE HEPARIN PLUS WARFARIN ADMINISTRATION IN NON-TRAUMATIC DURAL SINUSES THROMBOSIS. A CLINICAL AND NEURORADIOLOGICAL STUDY.


Division of Neurosurgery, Bianchi-Morelli-Melacrino Hospital, Reggio Calabria, Italy.

BACKGROUND: The management of intracranial dural sinuses thrombosis is still controversial and uncertain. The authors report the cases of 7 patients with non-traumatic thrombosis of the dural sinuses and describe the most important radiographic findings, the indication, effectiveness of antithrombotic therapy,
and outcome. METHODS: A retrospective review was conducted of 7 cases of dural sinus thrombosis admitted, between 1994 and 1996, to our division. All patients underwent full anticoagulation therapy. **Heparin was administered, using a dose of 25,000 units/day for two weeks; warfarin** was given using a dose of 5 mg twice daily. Treatment course was followed by maintenance treatment with a single administration of 5 mg/day of warfarin. All patients were submitted to close titration and coagulation profile monitoring. RESULTS: In 4 cases **Magnetic Resonance Imaging-Angiography (Angio-MRI)** was performed for following up the recanalization of the sinuses, resulting a persistent no patency of the dural sinuses. Three patients underwent contrast-enhanced CT scan, demonstrated an "empty delta sign" in the sagittal sinus, confirming no recanalization. Nevertheless, six patients had a good quality recovery, and one patient a moderate disability. **DISCUSSION:** Cerebral venous sinus thrombosis is an uncommon cause of cerebral infarction, and may be mistaken, unless specifically sought. The natural history of the disease is highly variable, with a mortality rates range from 10% to 20%. At present, in our opinion, the venous phase of Angio-MRI is the definitive examination, and a gold standard for diagnosis of dural sinus thrombosis. In our cases, antithrombotic therapy has been found to be a safe and effective treatment, despite contrast-CT scans and Angio-MRI showed no recanalization of the sinuses, in all patients.

4. HEP for Acute Stroke

(1) Lindley RI

**DRUG THERAPY FOR ACUTE ISCHAEMIC STROKE: RISKS VERSUS BENEFITS.**


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**Stroke** is a very common medical emergency that, until recently, had no specific treatment. Following the results of several major trials (including 2 'mega-trials'), **aspirin** (acetylsalicylic acid) can be recommended for the majority of patients with **acute ischaemic stroke**. While the benefit of aspirin is only modest, i.e. an increase of 11 per 1000 long term independent survivors, the public health benefit in the world will be substantial as this treatment could be given to millions of patients with **acute ischaemic stroke** each year. **Heparin is associated with a reduction in early recurrent ischaemic stroke**, but there is no net benefit because of a similar sized excess of recurrent haemorrhagic stroke (even for those in atrial fibrillation). Thrombolytic therapy has not been so widely tested and the results of the small trials to date have yielded conflicting results. The only positive publication to date (comprised of 2 related trials) evaluated the **recombinant tissue plasminogen activator** alteplase, but such treatment is probably only indicated for highly selected patients. Further trials are almost certainly required and it would be unwise to change clinical practice based on the current evidence. No other stroke treatments have been shown to be beneficial, and much larger trials will be required to confirm or refute possible moderate benefits of treatment. **A well organised stroke service and participation in clinical trials will improve the future care of patients with acute ischaemic stroke.**

(2) Sherman DG

**HEPARIN AND HEPARINOIDS IN STROKE.**

*Neurology* 1998 Sep;51(3 Suppl 3):S56-8

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**Anticoagulation with heparin has a valuable place in prevention and management of deep venous thrombosis.** However, the benefit of heparin in **acute ischemic stroke** and **transient ischemic attack** remains unclear despite its widespread use for these indications. **Heparin** also carries several risks, including unpredictable anticoagulation effects, **bleeding**, and **thrombocytopenia**. **Low-molecular-weight heparins (LMWHs)** and **heparinoids** have several advantages over heparin, such as higher bioavailability, more predictable anticoagulant effects, and less interaction with platelets. **Heparin, LMWHs**, and **heparinoids** have been studied in **acute ischemic stroke** with variable results. Of three recent, large, controlled clinical trials, only one documented a net benefit of treatment. **Fewer patients treated with an LMWH within 48 hours of stroke were dead or disabled at 6 months compared with placebo-treated patients.** The largest randomized clinical trial of **heparin in acute stroke** (the International Stroke Trial) showed that **heparin** was associated with a significant excess in bleeding.
complications but no clinical benefit at 6 months. Interim analysis of the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) study also showed an excess number of bleeding complications in the treated group without a corresponding benefit on stroke outcome at 3 months. Therefore, although heparin, LMWHs, and heparinoids continue to be used in the management of patients with acute ischemic stroke, their value in recurrent stroke prevention and in the treatment of stroke-in-progress remains unsettled. Ongoing studies may help to clarify the use of LMWHs and heparinoids in these patients.

5. HEP in Acute Myocardial Infarction (AMI)

(1) Kontny F, Dale J
LEFT VENTRICULAR THROMBUS FORMATION AND RESOLUTION IN ACUTE MYOCARDIAL INFARCTION.
*Int J Cardiol* 1998 Sep 30;66(2):169-74

Department of Cardiology, Aker University Hospital, Oslo, Norway.

Left ventricular thrombus formation and resolution were studied by serial echocardiography in 38 patients with acute anterior myocardial infarction. Twenty (52.6%) patients developed thrombus. Cumulative rates were: 12/20 (60%) at 24 h (+/-24 h), 17/20 (85%) at 72 h (+/-24 h), and 19/20 (95%) at 120 h (+/-24 h). Early thrombus formation was associated with worse left ventricular wall motion relative to those with delayed thrombus development (P=0.00016). In patients with initially normal echocardiograms, subsequent thrombus formation was associated with wall motion deterioration (P=0.016). A thrombus occurred in 16/28 (57.1%) patients given streptokinase. Heparin and warfarin were given in case of thrombus formation. Among survivors with thrombus, resolution occurred with a cumulative rate of 1/18 (5.6%) at 72 h (+/-24 h), 2/18 (11.1%) at 120 h (+/-24 h), 10/18 (55.6%) at 3 months (+/-1 week) and 16/18 (88.9%) at 6 months (+/-1 week). No embolic events occurred. Left ventricular thrombus formation occurs often and early after acute anterior myocardial infarction, even when streptokinase is given. Delayed thrombus formation is associated with wall motion deterioration. Thrombus resolution occurs frequently during anticoagulation and seems not associated with increased embolic risk.

(2) Granger CB
HEPARIN MANAGEMENT IN ACUTE MYOCARDIAL INFARCTION.

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Antithrombotic agents have been shown to be beneficial in the setting of acute coronary syndromes, and as an adjunct to thrombolysis for acute myocardial infarction (AMI). The optimal type and dosing of antithrombotic drug, however, remains elusive. Heparin, the agent most commonly used, has several limitations, the most important of which may be its inability to inhibit clot-bound thrombin. Newer, direct thrombin inhibitors (such as hirudin) provide potent and predictable thrombin inhibition and are able to inhibit clot-bound thrombin. Both heparin and hirudin can carry a substantial risk of haemorrhage, however, and thrombin activity is likely to rebound after discontinuation of either agent. Further, the relationships of antithrombotic/thrombolytic dosing, measures of anticoagulation (such as APTT), and clinical outcomes are not alway clear. Nonetheless, from the data available from large, randomised trials, intravenous heparin should remain a standard adjunct to thrombolytic therapy for AMI.

LOW MOLECULAR WEIGHT HEPARIN AS AN ADJUNCT TO THROMBOLYSIS FOR ACUTE MYOCARDIAL INFARCTION: THE FATIMA STUDY. FRAXIPARIN ANTICOAGULANT THERAPY IN MYOCARDIAL INFARCTION STUDY AMSTERDAM (FATIMA) STUDY GROUP.
*Heart* 1998 Jul;80(1):35-9

Department of Cardiology, University of Amsterdam, Netherlands.

OBJECTIVE: To investigate the feasibility of fixed dose, weight adjusted subcutaneous low molecular weight heparin (LMWH), with monitoring of anti-Xa levels and assessment of coronary patency rates
after three to five days, thereby giving an initial indication of its safety and efficacy. DESIGN: In 30 patients with acute myocardial infarction, LMWH (nadroparine) was given as a body weight adjusted intravenous bolus with thrombolysis (rt-PA infusion) and in weight adjusted subcutaneous doses at six hours, and every 12 hours thereafter for 72 hours. The target range was defined prospectively as 0.35-0.70 anti-factor Xa activity (aXa) units. The aXa level was measured every six hours. Coronary angiography was performed in all patients within five days after the start of thrombolytic treatment to determine patency (TIMI 2 and 3 flow) of the infarct related artery. RESULTS: The mean (SEM) aXa level over 72 hours was 0.52 (0.08) U/ml; from 12 hours onwards 88% of all aXa measurements were within the target range. At angiography, a patent infarct related artery was present in 24 of the 30 patients. No major bleeding complications occurred, though minor bleeding complications were observed in two patients. CONCLUSIONS: This small study indicates that LMWH is feasible as an adjunct to thrombolysis in patients with acute myocardial infarction. The aXa levels were within the target range and patency rates at three to five days were around 80%, with no major bleeding complications.

6. HEP in Acute Coronary Syndromes

(1) Trujillo TC, Nolan PE Jr
UNFRACTIONATED HEPARIN IN ACUTE CORONARY SYNDROMES: HAS ITS TIME COME AND GONE?

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(2) Turpie AG
ANTITHROMBOTIC THERAPY IN CORONARY ISCHAEMIA: THE EXPANDING ROLE OF LOW-MOLECULAR-WEIGHT HEPARIN.
Haemostasis 1998 Nov;28 Suppl S3:35-42

Department of Medicine, McMaster University, Hamilton, Ont., Canada. Low-molecular-weight heparins (LMWHs) have been rigorously evaluated in the management of acute coronary ischaemia. The results of clinical trials suggest that LMWHs are effective in reducing major ischaemic outcomes in patients with unstable angina and non-Q-wave myocardial infarction. In one study, LMWH was shown to be more effective than heparin. The clinical utility of LMWHs given subcutaneously in a fixed-dose without the need for monitoring results in major cost savings. The accumulating evidence suggests that LMWHs are safe, effective alternatives to standard heparin in unstable coronary disease and offer practical and therapeutic advantages, representing an important advance in the management of acute coronary ischaemia.

(3) Turpie AG
MANAGEMENT OF ACUTE CORONARY SYNDROMES WITH LOW MOLECULAR WEIGHT HEPARIN: TIMI 11A AND 11B.
Can J Cardiol 1998 Aug;14 Suppl E:20E-23E

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The role of antithrombotic therapy has been studied in patients with acute coronary ischemia without ST segment elevation. Unfractionated heparin (UFH) has been found to decrease the rate of myocardial infarction (MI), and to reduce overall mortality and recurrent MI in a series of trials in patients with unstable angina and non-Q wave MI. UFH is limited due to its unpredictable antithrombotic effect, poor bioavailability when given subcutaneously, requirement for hospitalization and need for frequent laboratory monitoring. Conversely, low molecular weight heparins (LMWHs) offer a number of advantages over UFH. LMWHs have a predictable antithrombotic response, good bioavailability following subcutaneous administration and longer half-life than UFH, require less frequent monitoring than UFH and can be administered in fixed or weight-adjusted subcutaneous dosages once or twice daily. The safety and efficacy of the LMWH enoxaparin are evaluated in the Thrombolysis in Myocardial Infarction (TIMI) 11 program. TIMI 11 A was designed to compare the safety and tolerability of two dosage regimens of enoxaparin in patients with
unstable angina or non-Q wave MI, whereas TIMI 11B was designed as a phase III trial, comparing the efficacy and safety of enoxaparin with those of UFH in the acute phase, and the efficacy and safety of extended administration of LMWH with those of placebo for 45 days. TIMI 11A found that the rate of major hemorrhage was significantly lower for the lower enoxaparin dose (1.0 mg/kg). The results of the published studies indicate that LMWHs are effective in reducing major ischemic outcomes in patients with unstable angina and non-Q wave MI. The results of the TIMI 11B trial will be available in late 1998.

7. HEP in Angioplasty


**COMPARISON OF ACTIVATED CLOTTING TIMES TO HEPARIN MANAGEMENT TEST FOR ADEQUACY OF HEPARIN ANTICOAGULATION IN PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY.**

*Cathet Cardiovasc Diagn* 1998 Nov;45(3):329-31

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The aim of this study was to compare the activated clotting time (ACT) obtained with the Hemochron device and the Heparin Management Test (HMT) on a new automated whole-blood coagulometer, the Thrombolytic Assessment System, in patients undergoing angioplasty. Fifty patients undergoing balloon angioplasty were prospectively enrolled. The mean ACT after a 10,000 unit bolus of heparin was 283 +/- 39 sec at the end of the procedure. The mean HMT after 10,000 units of heparin was 286 +/- 31 sec at the end of the procedure in the same patients. The correlation between the two methods was significant (r = 0.6; P < 0.01). The HMT appears to correlate well with standard values obtained with the Hemochron ACT monitor in patients undergoing percutaneous transluminal coronary angioplasty.

8. HEP in Pulmonary Embolism

a) HEP in Pulmonary Embolism General Aspects of Management

(1) Simonneau G

**NEW PERSPECTIVES FOR TREATMENT OF PULMONARY EMBOLISM.**


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Subcutaneous low-molecular-weight heparins (LMWHs) have been shown to be as safe and effective as intravenous unfractionated heparin (UFH) for the initial treatment of patients with deep vein thrombosis and acute symptomatic pulmonary embolism. In comparison with UFH, LMWHs have a longer half-life, greater bioavailability and more predictable antithrombotic effect when administered in fixed doses, thus obviating the need for laboratory monitoring. It is therefore feasible that LMWH preparations may replace UFH for the treatment of pulmonary embolism in the future. It is recommended that LMWH should be administered for 5-10 days and should overlap with oral anticoagulant therapy by at least 4 days. Surgical pulmonary embolectomy should only be considered in patients with life-threatening pulmonary embolism who have failed to respond during the first 3 h of thrombolytic therapy. The systematic use of vena cava filters is not recommended in patients presumed to be at high risk for pulmonary embolism.

(2) Haas SK

**TREATMENT OF DEEP VENOUS THROMBOSIS AND PULMONARY EMBOLISM. CURRENT RECOMMENDATIONS.**


Department of Medicine, Technical University of Munich, Germany.
The therapy of deep venous thrombosis consists of several elements and depends on the localization, the age and the extent of the thrombus. This article discusses various types of initial therapy and long-term treatment of venous thromboembolism and also reviews future perspectives of pharmacological treatment. The initial treatment regimens comprise thrombolysis, thrombectomy, inferior vena cava filters and the anticoagulation with either unfractionated heparin or low molecular weight heparins. Various thrombin-inhibitors have been tested for initial treatment of thrombosis, however, further investigations of their efficacy, safety and cost-effectiveness will have to provide firm evidence on their superiority when compared to unfractionated or low molecular weight heparins.

(3) van Beek EJ, Kuijer PM, Buller HR, Brandjes DP, Bossuyt PM, ten Cate JW
THE CLINICAL COURSE OF PATIENTS WITH SUSPECTED PULMONARY EMBOLISM.
Arch Intern Med 1997 Dec 8-22;157(22):2593-8
Center for Hemostasis, Thrombosis, Athersclerosis and Inflammation Research, Department of Radiology, Amsterdam, The Netherlands.
BACKGROUND: The outcome of patients with suspected pulmonary embolism is known to a limited extent only. OBJECTIVE: To address this limited knowledge in a cohort in whom pulmonary embolism was proved or ruled out. METHODS: Consecutive patients with clinically suspected pulmonary embolism underwent lung scintigraphy and angiography if required. Pulmonary embolism was excluded by normal results of a lung scan or angiogram, and, if so, anticoagulant therapy was withheld. Pulmonary embolism was proved with a high-probability perfusion-ventilation lung scan or a confirmatory angiogram if a nondiagnostic lung scan was obtained. These patients were treated with heparin intravenously and anticoagulants orally on a long-term basis. All patients were followed up for 6 months, with a special focus on recurrent thromboembolism, bleeding complications, and mortality. RESULTS: A total of 487 consecutive inpatients and outpatients were included. Pulmonary embolism was excluded or proved in 243 and 193 patients, respectively. In 51 patients a definite diagnosis could not be established. The overall prevalence of pulmonary embolism was 39%. In patients in whom pulmonary embolism was proved, excluded, or uncertain, recurrent venous thromboembolism was observed in 2.6%, 0.9%, and 2%, respectively. Serious bleeding complications occurred in 7 patients (3.3%; 95% confidence interval [CI], 1.8%–6.3%), 2 cases of which were fatal. The total mortality after 6 months in patients with proved or excluded pulmonary embolism was 17% (95% CI, 12%–23%) and 11% (95% CI, 7%–15%), respectively. Death was related to (recurrent) pulmonary embolism in 5% and 0% of these cases, respectively. CONCLUSIONS: During a 6-month period, recurrent pulmonary embolism occurred in approximately 5 patients (2.5%) who were treated for a previous episode. Fatal bleeding complications attributable to the use of anticoagulants were encountered in 1%. The mortality among patients with suspected pulmonary embolism was considerable. However, most deaths were unrelated to pulmonary embolism, but were the result of serious underlying illnesses.

(4) Raskob GE
ANTICOAGULANTS AND THROMBOLYSIS IN THE TREATMENT OF PULMONARY EMBOLISM.
Department of Biostatistics and Epidemiology, University of Oklahoma Health Sciences Center, Oklahoma City 73190, USA.
Intravenous heparin followed by oral warfarin sodium is effective for preventing recurrent thromboembolism in patients who have pulmonary embolism or proximal vein thrombosis. The effectiveness of intravenous heparin depends on obtaining an adequate anticoagulant response early during therapy. A validated heparin protocol should be used to ensure that an adequate anticoagulant response is obtained as soon as possible. Low molecular weight heparin has the practical advantage that it does not require monitoring and dose finding. If thrombolytic therapy is indicated, it is safer for many patients to base management on the noninvasive diagnosis rather than performing pulmonary angiography. In patients suspected to have pulmonary embolism who have nondiagnostic lung scan and adequate cardiorespiratory reserve, serial noninvasive leg testing is a practical approach that avoids pulmonary angiography, identifies patients who have proximal vein thrombosis requiring treatment, and avoids the risks of anticoagulant treatment in the majority of patients.
b) HEP in Massive Pulmonary Embolism and Mobile Thrombi of the Right Heart

(1) Kuisma M, Silfvast T, Voipio V, Malmstrom R
PREHOSPITAL THROMBOLYTIC TREATMENT OF MASSIVE PULMONARY EMBOLISM WITH RETEPLASE DURING CARDIOPULMONARY RESUSCITATION. 

Helsinki City EMS, Finland.
A 52-year-old previously healthy man experienced acute severe dyspnoea after suffering from gastroenteritis for 3 days. After arrival of the ambulance, cardiac arrest with an initial rhythm of electro mechanical dissociation occurred. Circulation was restored after 10 min of cardiopulmonary resuscitation but soon cardiac arrest reoccurred. Based on a strong clinical suspicion of massive pulmonary embolism, thrombolytic treatment with heparin 5000 IU and reteplase 20 U, given as single boluses and heparin was continued as an infusion 1000 IU h\(^{-1}\). After 7 min of continued resuscitation, circulation was restored and after 40 min the vital functions began to stabilize, thus indicating pulmonary reperfusion. The diagnosis of pulmonary embolism was confirmed by a ventilation-perfusion scan and by spiral computerised tomography. The patient was discharged from intensive care after 2 days with a cerebral performance category I. Based on previous calculations, the annual number of patients who present with massive pulmonary embolism leading to cardiac arrest (and thus who would theoretically be candidates for thrombolytic treatment) was estimated to be 0.7/100000 inhabitants in this emergency medical services system.

[MOBILE THROMBI OF THE RIGHT HEART IN PULMONARY EMBOLISM] [ARTICLE IN FRENCH].
Arch Mal Coeur Vaiss 1997 Nov;90(11):1471-6

Service de soins intensifs medicaux et de reanimation cardiaque, Leclercq, Lille.
Systematic transthoracic echocardiography in all cases of pulmonary embolism may demonstrate right heart thrombi. The results of this monocentric series of 28 consecutive cases observed between 1987 and 1996 were analysed. Twenty-four patients were in NYHA Class IV: thirteen were in cardiogenic shock. Echocardiographic signs of acute cor pulmonale were usually observed: 96.3% of patients had right ventricular dilatation, 85.2% paradoxical interventricular septal motion, 88.9% pulmonary hypertension. The thrombus was typical serpentine (27/28 cases) arising from the lower limb veins. Passage into the left heart chambers through a patent foramen ovale was observed in 3 cases. Pulmonary embolism was confirmed in all cases. This is an extreme therapeutic emergency and 13 patients (46.4%) died despite treatment: surgery (7/16), thrombolysis (2/5), heparin (3/4) or interventional radiology (1/3). After the acute phase, the prognosis was generally good, as demonstrated by the 100% survival rate at 28.6 +/- 25 months. This study confirms the gravity of mobile right heart thrombi in pulmonary embolism. The diagnosis is echocardiographic. No significant difference in mortality was observed between the different therapeutic approaches used in this series. The echocardiographic finding of these thrombi is a traditional indication for emergency surgical embolectomy. Thrombolysis is rapid and readily available and seems to provide promising results alone or before surgery. In patients with contraindications to thrombolysis, interventional radiology or simple heparin therapy may be proposed.

c) HEP in Protein C Deficiency with Pulmonary Embolisation

(1) Kogure S, Makita K, Saitoh Y, Nakazawa K, Amaha K
[ANESTHETIC MANAGEMENT OF A PATIENT WITH PROTEIN C DEFICIENCY ASSOCIATED WITH PULMONARY THROMBOEMBOLISM].
[ARTICLE IN JAPANESE]
Masui 1998 Jul;47(7):831-4

Anesthetic Division, Omori Red Cross Hospital, Tokyo.
A patient with protein C deficiency associated with massive pulmonary embolism underwent open heart tromboembolectomy. The operation was successfully performed under cardiopulmonary bypass using a usual dose of heparin 3 mg.kg-1. The effect of heparin was successfully reversed by the administration of protamine sulfate 6 mg.kg-1. Perioperative administration of fresh frozen plasma or protein C concentrates might be necessary to manage hypercoagulability in a patient with protein C deficiency.

9. HEP in Antiphospholipid Syndrome

(1) Lockshin MD
PREGNANCY LOSS AND ANTIPHOSPHOLIPID ANTIBODIES.
*Lupus* 1998;7 Suppl 2:S86-9

Barbara Volcker Center for Women and Rheumatic Disease, Hospital for Special Surgery, Cornell Medical Center, New York, NY 10021, USA.

With the use of low-dose heparin, fetal survival of aPL pregnancies is 70-80%, but prematurity and intrauterine growth restriction are common. It is likely, but not proven, that dysregulated placental coagulation and resultant vasculopathy are the cause of fetal loss. Details of dysregulated coagulation remain to be described. Opportunities remain to determine the role of coagulopathy in repeated pregnancy loss, identify a critical event or window to which intervention might be directed, identify maternal (and fetal) characteristics other than aPL that determine fetal loss, describe toxicity profiles of current treatments, develop more specific, less toxic therapies, and describe long-term fetal and maternal outcomes.

(2) Harris EN, Pierangeli SS
UTILIZATION OF INTRAVENOUS IMMUNOGLOBULIN THERAPY TO TREAT RECURRENT PREGNANCY LOSS IN THE ANTIPHOSPHOLIPID SYNDROME: A REVIEW.

Academic Affairs, Morehouse School of Medicine, Atlanta, GA 30310-1495, USA.

Although experience is still limited, intravenous immunoglobulin therapy for recurrent pregnancy loss in the Antiphospholipid Syndrome (APS) may represent a significant advance. APS was widely recognized only fifteen years ago. Pregnancy loss and thrombosis are the prominent clinical features. Initially, prednisone was used for treatment of pregnancy loss, but maternal and fetal complications stimulated searches for alternative therapy. Subcutaneous heparin and low dose aspirin was next utilized, but although efficacious, there is still a 30% failure rate, and intrauterine growth retardation, prematurity, and pre-eclampsia are relatively frequent. In the late 1980's, there were a number of case reports of successful pregnancy outcomes after treatment with intravenous immunoglobulin (IVIg) but regimens differed. Series from two centers have confirmed these initial findings and treatment regimens have become more consistent. Both centers have reported success with doses of 400 mg/kg/day for 5 days or 1 g/kg/day for two days each month initiated during the first or early second trimester. Success rates of 70-100% have been reported, and complications such as pre-eclampsia, intrauterine growth retardation, and premature births appear reduced, when compared to prednisone and low dose aspirin or heparin and low dose aspirin. Several patients who were treated with IVIg also received heparin, making it uncertain whether heparin may also need to be added to IVIg. Intravenous immunoglobulin is safe, but expensive. Despite its expense, if IVIG is shown to markedly decrease maternal and fetal morbidity, it may be the logical treatment of choice to prevent pregnancy loss in APS.

ACALCULOUS ISCHEMIC GALLBLADDER NECROSIS IN THE CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME.
*Arthritis Rheum* 1998 Jul;41(7):1318-20

Centre Hospitalier de Valenciennes, France.
A 29-year-old woman was referred for abdominal pain. Results of tests for lupus anticoagulant and antibodies to phosphatidylserine and to beta2-glycoprotein I were positive, but the patient had no features of systemic lupus erythematosus (SLE). Abdominal ultrasonography showed a thickening of the gallbladder wall without cholelithiasis. A surgical procedure revealed necrotic areas of the gallbladder wall, and a cholecystectomy was performed. Histologic examination of the gallbladder showed multiple thrombi and no vasculitis. **Despite full-dose heparin, the patient developed a catastrophic antiphospholipid syndrome (APS) and subsequently died.** Among connective tissue disorders, **acute acalculous cholecystitis** has been reported in patients with polyarteritis nodosa and/or SLE. APS should be considered as a possible cause of acalculous cholecystitis.

(4) Petrovic R, Petrovic M, Novicic-Sasic D, Cirovic L, Damjanov N, Palic D

**ANTICARDIOLIPIN ANTIBODIES AND CLINICAL SPECTRUM OF ANTIPHOSPHOLIPID SYNDROME IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS.**


University School of Medicine, Institute of Rheumatology, Belgrade.

In this paper we analyzed the clinical manifestation and course of the disease in 47 patients with systemic lupus erythematosus (SLE) and secondary antiphospholipid syndrome (APS) during prospective follow-up that lasted 2-5 years (mean 3.4). The most frequent features of APS were thrombosis (51%), thrombocytopenia (46.8%), and neuropsychiatric disorders (40.4%). These features were predominantly associated with elevated concentrations of IgG aCL isotype or with the presence of both IgG and IgM isotypes. Spectrum of neuropsychiatric disorders included mainly cerebrovascular ischemic disease (63%), but also some other, such as mental disorders and seizures, and, rarely, atypical migraine and transverse myelopathy. Thrombotic events in APS are the most significant for therapeutic and prognostic considerations. The treatment of basic disease (SLE) and conventional management of thromboembolic manifestation with heparin and/or dicoumarol (or warfarin) prevented neither the recurrent thrombosis in 9 patients (37.5%), nor the fatal outcome in 6 patients (12.8%). Further investigations and perhaps more aggressive approach to APS treatment are needed for better clinical care of these patients.

(5) Ruiz-Arguelles GJ, Guzman-Ramos J, Flores-Flores J, Garay-Martinez J

**REFRACTORY HICCough HERALDING TRANSVERSE MYELITIS IN THE PRIMARY ANTIPHOSPHOLIPID SYNDROME.**


Centro de Hematologia y Medicina Interna de Puebla, Mexico.

The case of a 32-year-old female patient with a primary form of the antiphospholipid syndrome is presented. The initial symptom was a pathological form of hiccough, refractory to conventional therapy that was followed, weeks later, by a full-blown picture of transverse myelitis. Despite the fact that transverse myelitis has been described as associated with the presence of antiphospholipid antibodies, we could not find the description of refractory hiccough as the initial manifestation of the antiphospholipid syndrome. The administration of steroids, heparin and plasmapheresis resulted in resolution of the neurological symptoms.

(6) Kutteh WH

**ANTIPHOSPHOLIPID ANTIBODIES AND REPRODUCTION.**


Health Science Center, University of Tennessee, Memphis 38163-2116, USA.

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The antiphospholipid antibodies (APA) are acquired antibodies against a phospholipid which has been associated with slow progressive thrombosis and infarction in the placenta. **Clinical features** (venous or arterial thrombosis, recurrent fetal loss, thrombocytopenia) in conjunction with **positive laboratory findings** (positive IgG or IgM anticardiolipin antibodies, or positive lupus anticoagulant tests) will satisfy criteria for diagnosis of the antiphospholipid antibody syndrome (APS). A number of studies report the **incidence of antiphospholipid antibodies** in different patient populations: normal obstetrical patients (5.3% of 7278 women), women with recurrent pregnancy loss (20% of 2226...
women), women with systemic lupus erythematosus (37% of 1579 women) and, more recently, women undergoing in vitro fertilization (24% of 3343 women). As in all autoimmune syndromes it is possible that APA are secondary to some underlying disease or that they are instrumental in the pathogenesis of the various manifestations. The most commonly proposed mechanisms of antiphospholipid antibody induced thrombosis include decreased prostacycline production by endothelial cells, increased thromboxane production by platelets, and decreased protein C activation. More recently it has been demonstrated that certain phospholipids are exposed on the endothelial surface and may alter implantation during in vitro fertilization. Treatment with subcutaneous heparin and aspirin has been shown to benefit women with recurrent pregnancy loss and APA resulting in successfully deliveries of approximately 75%. Several trials of treatment with heparin and aspirin in women with positive APA undergoing IVF have been completed. Although none of the studies were randomized, prospective, blinded trials there does not appear to be a significant difference in implantation rate, pregnancy rate, or ongoing pregnancy rate. This subject remains, however, an area of active investigation as antiphospholipid antibodies have been shown to interact with syncytiotrophoblast and cytotrophoblast layers and could theoretically affect implantation.

(7) Umesaki N, Ueda K, Tanaka T, Imanaka M, Ogita S, Okamura M
FAVORABLE RESPONSE TO HEPARIN IN A PREGNANT WOMAN WITH POSSIBLE GLOMERULAR THROMBOSIS AS A COMPLICATION OF SYSTEMIC LUPUS ERYTHEMATOSUS AND ANTI-PHOSPHOLIPID ANTIBODY SYNDROME.
Department of Obstetrics and Gynecology, Osaka City University Medical School, Japan.
A rare case of possible glomerular thrombosis during pregnancy is reported in a patient with active systemic lupus erythematosus and the presence of anti-phospholipid antibodies. Acute renal impairment was restored by administering infusions of heparin. Cesarean section was performed due to fetal distress, and resulted the live birth of a healthy infant.

(8) Piette JC, Huong DL, Wechsler B
TREATMENT OF PREGNANT WOMEN WITH RECURRENT MISCARRIAGE ASSOCIATED WITH PHOSPHOLIPID ANTIBODIES. DURING PREGNANCY, HEPARIN SHOULD BE STOPPED DURING LABOUR AND THEN RESTARTED SOON AFTER DELIVERY.
BMJ 1997 Aug 9;315(7104):372-3; discussion 373
Comment on: BMJ 1997 Jan 25;314(7076):253-7

10. HEP in Klippel Trenaunay-Weber Syndrome "Low Dose"

(1) Aronoff DM, Roshon M
SEVERE HEMORRHAGE COMPLICATING THE KLIPPEL-TRENAUNAY-WEBER SYNDROME.
Department of Internal Medicine, Vanderbilt University Medical Center, Nashville, Tenn, USA.
The Klippel-Trenaunay-Weber (KTW) syndrome is a congenital disorder of angiogenesis characterized by macular nevus, skeletal and soft tissue hypertrophy, venous varicosities, and arteriovenous fistulas. Disseminated intravascular coagulation (DIC) and the Kasabach-Merritt syndrome, a consumptive coagulopathy with thrombocytopenia, are both associated with the KTW syndrome. We describe a 30-year-old woman with KTW syndrome and Kasabach-Merritt syndrome who had DIC with severe hemorrhage after a routine gynecologic procedure. The bleeding was controlled with the use of intravenous low-dose heparin and antithrombin III.

B. Heparin induced Complications

1. HEP Complications Heparin Induced Thrombocytopenia (HIT) and HEP Antibodies
a) HEP HIT I

(1) Hale LP, Smith K, Braden GA, Owen J

ORGARAN DURING ROTATIONAL AHERECTOMY IN THE SETTING OF HEPARIN-INDUCED THROMBOCYTOPENIA.


Section on Hematology, Wake Forest University School of Medicine, Winston-Salem, North Carolina 27157, USA. phaleobi@earthlink.net

Heparin is considered necessary during percutaneous coronary interventions; however, heparin is contraindicated in patients with heparin-induced thrombocytopenia and/or heparin antibodies. We describe the successful use of the heparinoid Orgaran (danaparoid sodium) in addition to abciximab (ReoPro) in a patient with heparin antibodies who required rotational atherectomy.

(2) Burke AP, Mezzetti T, Farb A, Zech ER, Virmani R

MULTIPLE CORONARY ARTERY GRAFT OCCLUSION IN A FATAL CASE OF HEPARIN-INDUCED THROMBOCYTOPENIA.

_Chest_ 1998 Nov;114(5):1492-5

Department of Cardiovascular Pathology, Armed Forces Institute of Pathology, Washington, DC 20306-6000, USA. burke@email.afip.osd.mil

Heparin-induced thrombocytopenia (HIT) is a potentially life-threatening condition when immune-mediated platelet aggregation results in thromboembolic complications. A case is detailed of multiple saphenous vein graft thromboses and cardiac mural thrombi in a patient who died from complications of HIT.

(3) Janssens U

[ANTICOAGULATION AFTER VENOUS THROMBOSIS CAUSED BY TYPE-II HIT SYNDROME]. [ARTICLE IN GERMAN]


Medizinische Klinik I, Universitatsklinikum, Rheinisch-Westfalischen Technischen Hochschule, Aachen. UJAN@pcserver.mk1.rwth-aachen.de

(4) Wilde MI, Markham A

DANAPAROID. A REVIEW OF ITS PHARMACOLOGY AND CLINICAL USE IN THE MANAGEMENT OF HEPARIN-INDUCED THROMBOCYTOPENIA.

_Drugs_ 1997 Dec;54(6):903-924

Adis International Limited, Auckland, New Zealand. demail@adis.co.nz

Danaparoid, a low molecular weight heparinoid consisting of a mixture of heparan, dermatan and chondroitin sulfates, has well established antithrombotic activity. The drug has a high antifactor Xa to antifactor IIa (thrombin) activity ratio, a low tendency to cause bleeding and minimal effects on the fibrinolytic system. Danaparoid has a low cross-reactivity rate with heparin-associated antiplatelet antibodies (0 to 20%; mean approximately 10%). This represents a significant advantage over low molecular weight heparins (LMWHs) as a potential replacement agent for unfractionated heparin (UFH) in patients with immune-mediated (type II) heparin-induced thrombocytopenia (HIT). In a worldwide compassionate-use programme involving a total of 667 patients with HIT to date, 93% of danaparoid treatment courses were considered to be successful. Thrombocytopenia resolved in 91% of episodes. In the compassionate-use programme, danaparoid was associated with a mortality rate of 10.4% during treatment (up to 3.5 years) and 7.8% during the follow-up period (3 months). 14 of 114 deaths during the follow-up period were considered to be related to danaparoid therapy. A mortality rate of 23.5% was reported in patients accepted for but not treated with, danaparoid. Mortality rates with danaparoid, ancrod and dextran in the comparative studies were similar (7, 11 and 12%, respectively). Severe bleeding was reported in 3.1% of patients in the compassionate-use programme, persistent or recurrent thrombocytopenia in 2.6% and new thromboembolic events/extension of existing thrombosis in 1.7%. The incidence of bleeding was similar with danaparoid and dextran in a comparative trial. Although in
vitro cross-reactivity does not always translate into clinical cross-reactivity, testing is currently recommended, when possible, before initiation of danaparoid therapy. Thus, danaparoid appears to be an effective and well tolerated replacement agent for UFH in many patients with HIT who require further anticoagulation. The drug has low cross-reactivity with HIT-associated antibodies. Further comparative trials are needed to confirm these promising findings.

(5) Amiral J

[PLATELET FACTOR 4, TARGET OF ANTI-HEPARIN ANTIBODIES: APPLICATION TO BIOLOGICAL DIAGNOSIS OF HEPARIN-INDUCED THROMBOCYTOPENIA] [ARTICLE IN FRENCH].

*Ann Med Interne (Paris)* 1997;148(2):142-9

Departement Immunologie, Serbio-Laboratoire de recherche, Gennevilliers.

**Heparin-platelet factor 4 (H-PF4) complexes** are the target for heparin-dependent antibodies present in most of heparin-induced thrombocytopenias (HIT). The highest reactivity is obtained with 27 IU of heparin per mg of PF4. **Low molecular weight heparin (LMWH)** and pentosane polysulphate can also form these complexes. Antibodies to H-PF4, may be of the IgG, IgA or IgM isotypes. In some HIT, IgGs are absent and only IgMs and/or IgAs are observed. These antibodies may also develop **in heparin** (15%) or LMWH (8%) **treated patients** in the absence of thrombocytopenia. IgGs rarely develop in these cases. Presence of antibodies to H-PF4 is therefore a risk factor for developing HIT. Development of pathology requires additional factors such as: PF4 and heparin at an optimised ratio allowing formation of macromolecular complexes; presence of activated platelets exposing increased Fc gamma RII-A and heparin receptors; His. 131 phenotype of Fc gamma RI-A; pre-thrombotic and/or inflammatory clinical manifestations. **Assay of antibodies to H-PF4 improves HIT diagnosis and could be predictive for monitoring heparin-therapies.**

(6) Alving BM, Krishnamurti C

RECOGNITION AND MANAGEMENT OF HEPARIN-INDUCED THROMBOCYTOPENIA (HIT) AND THROMBOSIS.

*Semin Thromb Hemost* 1997;23(6):569-74

Department of Medicine, Washington Hospital Center, DC 20010, USA.

An immune response to heparin, which is clinically manifested by the development of thrombocytopenia with or without thrombosis, is stimulated by a complex of heparin with platelet factor 4 (PF4). The **primary thrombotic events** in patients with heparin-induced thrombocytopenia (HIT) are more frequently venous than arterial. The development of antibodies, however, does not always result in **thrombocytopenia** or in **catastrophic events**. The antibodies, which are of the IgG, IgM, and IgA isotypes, can be easily measured by an ELISA that contains a complex of heparin-platelet factor 4 (PF4). Initial antibody formation can be greatly reduced by limiting the exposure to unfractionated heparin or by the use of **low-molecular-weight heparin**. For those patients who require anticoagulation and who have antibodies to heparin-PF4, **danaparoid (Orgaran)**, a low-molecular weight heparinoid that does not react with the antibodies, is now commercially available; **argatroban**, a thrombin-specific inhibitor, can also be obtained for compassionate use. The use of these agents during anticoagulation with **warfarin** is preferable to the simple discontinuation of heparin and initiation of warfarin, because the latter treatment can result in ongoing thrombosis.

b) HEP HIT II

(1) Brenske M, Tarnow J

[HEPARIN INDUCED THROMBOCYTOPENIA]. [ARTICLE IN GERMAN]

*Anaesthesiol Intensivmed Notfallmed Schmerzther* 1998 Jul;33(7):411-6

Zentrum fur Anaesthesiologie Heinrich-Heine-Universitat Dusseldorf.

Thrombocytopenia is a known adverse reaction occurring in some of the patients receiving heparin. **Two types of heparin-induced thrombocytopenia (HIT) have been described. HIT type I is mild thrombocytopenia** probably caused by a direct proaggregating effect of heparin and occurs during the first few days of heparin treatment. **No specific treatment is necessary. HIT type II is a severe**
Thrombocytopenia mediated by an immunologic mechanism where antibodies against heparin/platelet factor 4 (PF4) complexes play a major role. Thrombocytopenia usually commences 4-14 days after the onset of heparin administration. The incidence of HIT type II is below 3% and even lower when low-molecular weight heparin is used. The possible occurrence of life-threatening thrombembolic events may complicate the course of HIT type II. Diagnosis of HIT type II by clinical features alone is often difficult. A few laboratory tests are pertinent for diagnosing HIT type II including the 14C-serotonin assay, the heparin-induced platelet activation test and the heparin/PF4 ELISA. Immediate cessation of heparin administration is essential in the treatment of patients with HIT type II, if need be even without waiting for the result of the antibody search test. Several alternatives of anticoagulation for patients with HIT type II have been investigated in the past. Danaparoid-sodium as well as recombinant hirudin have shown promising results when used for this purpose.

(2) Gupta AK, Kovacs MJ, Sauder DN

HEPARIN-INDUCED THROMBOCYTOPENIA.


Department of Medicine, University of Toronto, Sunnybrook Health Science Center, North York, Ontario, Canada.

OBJECTIVE: To highlight the importance of heparin-induced thrombocytopenia (HIT), a potentially fatal adverse effect of heparin therapy. CASE SUMMARY: There are two types of HIT with distinct etiology. Type 1 HIT is a relatively mild thrombocytopenia of early onset that generally resolves with ongoing heparin therapy. Clinical complications are uncommon. Type 2 HIT, which is more severe, is the main focus of this report. Five patients receiving heparin therapy developed type 2 HIT, which in some cases resulted in complications that required limb amputation, or eventuated in death.

DISCUSSION: In a patient receiving heparin therapy, the development of thrombocytopenia should alert the caregiver to the possible development of HIT. Prompt management of HIT can help prevent complications. HIT usually manifests 5-8 days after starting heparin therapy. The platelet count usually decreases to less than 100 x 10^3/mm^3. It generally normalizes within 5-7 days after discontinuing heparin therapy. In spite of the thrombocytopenia, thrombosis or disseminated intravascular coagulation can occur. The management may be subdivided into three clinical situations: mild-to-moderate asymptomatic thrombocytopenia, severe thrombocytopenia with a platelet count of less than 50 x 10^3/mm^3, and thrombosis or embolism complicating HIT. CONCLUSIONS: Heparin-induced thrombocytopenia is an uncommon but potentially serious, and sometimes lethal, complication of heparin therapy. Therefore, it is important to be aware of the possibility of the development of HIT with heparin therapy, to recognize it early, and to manage it appropriately before the manifestation of adverse effects.

(3) Ganzer D, Gutezeit A, Mayer G, Greinacher A, Eichler P

[PREVENTION OF THROMBOEMBOLISM AS A CAUSE OF THROMBOEMBOLIC COMPLICATIONS. A STUDY OF THE INCIDENCE OF HEPARIN-INDUCED THROMBOCYTOPENIA TYPE II]. [ARTICLE IN GERMAN]

Orthop Ihre Grenzgeb 1997 Nov-Dec;135(6):543-9

Klinik und Poliklinik fur Orthopadie, Ernst-Moritz-Arntd-Universitat Greifswald.

PROBLEM: A life-threatening complication of the thrombembolism prophylaxis with heparin is heparin-induced thrombocytopenia (HIT) type II. HIT type II is based on immunological mechanisms. Even low, subcutaneously applied doses may produce HIT type II. In those patients, continued application may cause thromboembolic complications. The most important symptom of HIT type II is a decrease of platelets. METHODS: In a prospective study, we investigated the incidence of HIT type II within the period from 01.07.95 to 30.06.96 in orthopedic patients. We also evaluated the importance of the daily platelet count from the fifth postoperative day for the early diagnosis of HIT type II and a possible reduction of the thrombosis rate. The study included 307 patients after primary implantation of hip and knee endoprosthesis and after hip endoprosthesis replacement. All patients received 3 x 5000 IU/d of unfractionated heparin subcutaneously. Whenever there was a decrease of platelets of at least 50% in relation to the preoperative value or whenever thromboembolic complications occurred, serum was analyzed by the heparin-induced platelet activation test (HIPA). RESULTS: 20 patients developed HIT type II. This corresponds to an incidence of 6.5%. 10 of the HIT type II antibody positive patients (50%) developed thromboembolic complications. 3 patients (0.9%) of the group studied developed clinically symptomatic thromboembolic complications without evidence of heparin antibodies.
The total risk of getting thrombembolic complications was 4.2% (13 patients), 3.3% (10 patients) of the entire group developed HIT type II antibody associated thrombembolic complications; 1 patient died. The lethality in the HIT type II antibody positive patient group amounted to 5%. The patients with HIT type II received LMW heparinoid Orgaran (AKZO-Organon, The Netherlands) or hirudin (as a clinical trial). The comparison group (retrospective study from 17.10.92 to 16.10.93) was composed of 262 patients with the same operations and equal thromboembolism prophylaxis. The platelet count was made only as part of routine diagnostic tests. 21 patients (8.0%) developed clinically symptomatic thrombembolic complications. The difference in the thrombosis rate between these two groups of patients is statistically significant. Unrecognized HIT type II is probably the reason for the high thrombembolic complication rate in the comparison group. CONCLUSIONS: The daily platelet count from the fifth postoperative day and from the first day in case of reexposure to heparin is an important measure for the early diagnosis of HIT type II.

(4) Hobbensiefken G, Driller B, Studtmann V, Kunz K, Lehrbach G
HEPARIN-INDUCED THROMBOCYTOPENIA TYPE II (HIT II) A FATAL COMPLICATION OF HEPARIN USE FOR THROMBOEMBOLISM PREVENTION. [ARTICLE IN GERMAN]
Unfallchirurgie 1996 Dec;22(6):248-52

Institut fur Anasthesiologie und operative Intensivmedizin, Diakoniekrankenhaus Rotenburg, Wumme.

Heparin-induced thrombocytopenia type II (HIT II) is the most severe complication during prophylactic treatment with low doses of heparin. Five cases demonstrate the life-threatening consequences of this immune-mediated thromboembolic disease. In order to improve prognosis it is most important to start therapy just before diagnosis is assured by laboratory tests. First choice treatment is the low-molecular-weight heparinoid Orgaran. In patients with an episode of HIT II both low-molecular-weight heparin and unfractionated heparin will be contraindicated for a life time.

c) HEP HIT Atypical (Type III?)

ATYPICAL HEPARIN-INDUCED THROMBOCYTOPENIA COMPLICATED BY INTRACARDIAC THROMBUS, EFFECTIVELY TREATED WITH ULTRA-LOW-DOSE RT-PA LYSIS AND RECOMBINANT HIRUDIN (LEPIRUDIN).
Blood Coagul Fibrinolysis 1998 Apr;9(3):273-7

Institute for Immunology and Transfusion Medicine, Ernst-Moritz-Arndt-University Greifswald, Germany.

A serious retroperitoneal bleeding occurred in a 56-year-old male patient receiving unfractionated heparin due to multiple pulmonary embolism. After reducing the heparin dose, the patient developed a new pulmonary embolism and a large thrombus in the right atrium. Concomitantly, the platelet count dropped to a value of 29 g/l. Heparin-induced thrombocytopenia (HIT) was confirmed by a functional assay, the heparin-induced platelet activation (HIPA) assay, whereas the results of a platelet factor 4/heparin complex ELISA were repeatedly negative. This indicated that the patient's HIT antibodies were directed towards an antigen other than platelet factor 4/heparin complexes. For treatment of the atrial thrombus, an ultra-low-dose lysis with rt-PA (2 mg/h, intravenously) was administered for a period of 52 h, overlapping with systemic treatment with recombinant hirudin (Lepirudin, Refludan, 0.06-0.14 mg/kg/h intravenously). The aim was to enhance lysis of the thrombus without increasing the haematoma, and at the same time keep the risk of fulminant pulmonary embolism due to thrombus fragmentation as low as possible. The cardiac thrombus disappeared within 48 h, without new signs of pulmonary embolism. Platelet counts normalized within nine days.

2. HEP induced Hyperkalemia Aldosterone suppression
HEPARIN-INDUCED HYPERKALEMIA IN CHRONIC HEMODIALYSIS PATIENTS: COMPARISON OF LOW MOLECULAR WEIGHT AND UNFRACTIONATED HEPARIN.

Artif Organs 1998 Jul;22(7):614-7

Service de Nephrologie, Medecine Interne, CHU Amiens, France.

Aldosterone suppression and subsequent hyperkalemia are well described reversible side effects of prolonged treatment with heparin. This study was designed to examine whether the discontinuous use of heparin three times a week to prevent thrombosis formation during hemodialysis sessions could also induce hypoaldosteronism and might contribute to increased predialysis kalemia in hemodialysis patients. Two different heparinization regimens were prospectively compared in a crossover study of 11 chronic hemodialysis patients. During 2 consecutive weeks, the patients were dialyzed each week with either their usual doses of unfractionated heparin (UH) (6,160 IU +/- 1,350 IU) or low molecular weight heparin (LMWH) (15 anti-Xa activity [aXa] U/kg + 5 aXa U/kg/h). In all but 2 patients, the predialysis level of plasma K+ was higher with UH than with LMWH, and the mean value was higher (5.66 +/-0.83 versus 5.15 +/-0.68 mM, p = 0.01) while no differences in the predialysis plasma concentrations of creatinine, phosphate, urea, and bicarbonate were observed, excluding the potential role of differences in diet and dialysis efficacy in explaining the higher plasma K+ concentration with UH. The mean plasma aldosterone to plasma renin activity (pRA) ratio was higher with LMWH than with UH (149.54 +/-123.1 versus 111.91 +/-86.22 pg/ng/h, p < 0.05). Individual plasma aldosterone values were found to be correlated to pRAs both during the UH period and the LMWH period, and the slope of the positive linear relation between plasma aldosterone and pRA was lower during the UH treatment period (63 versus 105 pg/ng/h). Finally, a negative linear correlation was found between the differences in individual predialysis plasma K+ observed during the 2 protocols and the differences in the corresponding plasma aldosterone levels, suggesting a link between the higher kalemia and the lower aldosterone responsiveness to angiotensin with unfractionated heparin. Although it cannot be concluded whether or not LMWH inhibits aldosterone synthesis, should LMWH decrease aldosterone production, this side effect is 33% less marked than that of UH so that the predialysis plasma K+ levels are 10% lower. This property makes LMWH use preferable to that of UH in patients with elevated predialysis kalemia.

3. HEP Induced Antiphospholipid Syndrome

ANTIBODY-MEDIATED THROMBOSIS: RELATION TO THE ANTIPHOSPHOLIPID SYNDROME.

Lupus 1998;7 Suppl 2:S63-6

Center for Molecular and Vascular Biology, University of Leuven, Belgium.

Various forms of antibody-mediated thrombosis are presented and the mechanisms involved in their pathogenesis are discussed. Antibody-mediated thrombosis includes heparin-induced thrombocytopenia and thrombosis, autoantibodies to von Willebrand factor mimicking an antiphospholipid syndrome, thrombosis following injection of the murine monoclonal antibody OKT3, hyperacute and acute xenograft rejection, and varicella-associated antibody against protein S. In several of these entities the pathogenesis of thrombosis is closely related to development of cellular procoagulant activity through tight occupancy of Fc receptors, or through complement activation, or through cell-cell interactions. Integrating the antiphospholipid syndrome into the more general category of antibody-mediated thrombosis may provide some hints as to how we could approach the study of those intriguing patients who have the clinical features of the antiphospholipid syndrome but lack those antibodies that currently characterize it.

4. HEP induced White Clote Syndrome

[FATAL CENTRAL PULMONARY EMBOLISM UNDER HEPARIN THERAPY: WHITE-CLOT SYNDROME] [ARTICLE IN GERMAN].

Schweiz Med Wochenschr 1997 May 3;127(18):762-5
A 75-year old female underwent coronary angiography for chest pain. Significant proximal stenosis of the left coronary artery was found. During the waiting time for bypass surgery, intravenous heparin treatment was established for several days because of recurrent unstable angina pectoris. 10 days after coronary angiography an acute event with chest pain, hypotension, tachycardia and a new right bundle branch block suspect for myocardial infarction occurred, which was treated with rt-PA. Fever, persistent hypotension, acute progressive renal failure and thrombocytopenia suggested septic shock, and the patient was transferred to our hospital. A pulmonary artery catheter could not be advanced beyond the main stem of the pulmonary artery. The patient died suddenly 24 hours later from acute right ventricular failure. Autopsy demonstrated multiple white clots in both pulmonary arteries. The histological finding of clots rich in leukocytes and fibrin was compatible with the diagnosis of heparin-induced thrombosis-thrombocytopenia or white clot syndrome. Heparin-induced thrombocytopenia may occur after about 5 days of treatment. Two distinct types have been described. The first type occurs in up to 25% of patients receiving heparin and is a result of temporary platelet aggregation, margination and peripheral sequestration. The less common second type of thrombocytopenia is thought to be mediated by a heparin-dependent IgG antibody inducing platelet aggregation and may be associated with thromboembolic events leading to the white clot syndrome, which is rarely reported in the literature. In these cases heparin should be stopped immediately and replaced by oral anticoagulation. Other therapies such as low molecular weight heparin, synthetic heparinoids, hirudin, fibrinolytic agents, plasmapheresis and intravenous immunoglobulins are discussed. Monitoring of the platelet count every 5 days in patients receiving heparin for any extended period should become standard medical practice to avoid potential fatal complications.

5. HEP Complications Haemorrhage:

(1) Cohen N, Zaidenstein R, Blatt A, Sarafian DA, Litinsky I, Modai D
UNRECOGNIZED MAJOR BLEEDING FOLLOWING THROMBOLYSIS FOR ACUTE MYOCARDIAL INFARCTION PRESENTING WITH SYNCOPES.
Clin Cardiol 1998 Aug;21(8):599-601

Department of Internal Medicine A, Assaf Harofeh Medical Center, Zerifin, Israel.

Complete atrioventricular block and syncope sometimes are the presenting signs of acute myocardial infarction. In a presyncopal attempt to assume sitting position, the patient may fall and suffer consequent trauma. Once in hospital, this sequence of events may be overlooked by both the patient and admitting physicians. Moreover, physical examination initially may not be revealing. We report on two such patients who developed massive subcutaneous bleeding following thrombolytic and heparin treatment. We conclude that these patients constitute a specific group with a relatively high risk of trauma and bleeding at the gluteal region following thrombolytic therapy. Special attention must be given to these patients.

(2) Guivarc'h M
[HEMATOMA OF THE ILIAC PSOAS MUSCLE. 29 CASES]. [ARTICLE IN FRENCH]
Chir (Paris) 1997;134(9-10):382-9

Service de Chirurgie Viscerale, C.M.C. Foch, Suresnes.

We present 29 cases of haematoma of the iliac psoas muscle, following anticoagulant treatment and review 158 cases so far published. In 60 p. 100 of cases, the anticoagulant was some form of intravenous or subcutaneous heparin; prescribed in 40 p. 100 of cases for venous thrombosis followed rapidly by pulmonary embolism, in half the cases between the 3rd and the 14th day. Hypocoagulation was excessive in 64 p. 100 of the cases. Clinically the onset is marked in all cases by a violent pain in the territory of femoral nerve, anaemia (40 p. 100) psoitis (32 p. 100) and iliac mass (51 p. 100), ecchymosis (13 p. 100) and particularly 23 among 29 cases an early or late femoral paralysis. The clinical diagnosis has been confirmed by echography 21 cases an or CT scan (7 cases). Our approach has been definitely surgical. The surgical procedure carried out in 20 p. 100 of the cases published, and in 23 of our ones, relieves the pain, provides for an early efficient physiotherapy, and a regression of the femoral paralysis, much more rapidly and completely than in the absence of surgery. The anatomical lesions, and the condition of the femoral nerve are described in the operative records, account for that evolution and explain our position. Traumatic and hemophilic have evoked.
C. Low Molecular Weight Heparin (LMWH)

A. Function and Fields of Use

1. LMWH General Aspects

(1) Pini M

[LOW MOLECULAR WEIGHT HEPARIN] [ARTICLE IN ITALIAN].

*Recenti Prog Med* 1997 Dec;88(12):594-602

Dipartimento di Medicina, Ospedale, Fidenza, Azienda USL di Parma.

Low-molecular-weight heparins (LMWHs) are obtained by depolymerization from standard heparin and show substantial advantages compared with the parent compound, by virtue of their different pharmacokinetics and lower interaction with platelets, so that they are supplanting heparin in various clinical indications. In the prophylaxis of venous thromboembolism, LMWHs are more efficacious than unfractionated heparin in patients at high thrombotic risk, and equally efficacious in patients at moderate thrombotic risk, with the benefit of once-a-day administration. In the treatment of acute deep venous thrombosis and pulmonary embolism, LMWHs administered subcutaneously in fixed dose per kg of body weight show equivalent efficacy and safety than intravenous heparin in adjusted dose, and allow home treatment in selected cases. In the treatment of deep venous thrombosis after the acute phase, LMWHs are equally effective and safer than oral anticoagulants. In unstable angina and non Q myocardial infarction, nadroparine and enoxaparin plus aspirin have been shown to be more efficacious than unfractionated heparin plus aspirin. In acute ischemic stroke, preliminary results are promising, but the evidence of efficacy must be substantiated by other studies, which are currently in progress.

(2) Sarasin FP, Bounameaux H

COST-EFFECTIVENESS OF PROPHYLACTIC ANTICOAGULATION PROLONGED AFTER HOSPITAL DISCHARGE FOLLOWING GENERAL SURGERY.

*Arch Surg* 1996 Jul;131(7):694-7; discussion 698

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OBJECTIVE: To evaluate the net clinical benefit and the economic burden of prophylactic anticoagulation prolonged after hospital discharge following general surgery. DESIGN: A cost-effective analysis representing the risks of developing symptomatic venous thromboembolism beyond the hospital stay, the risks of major bleeding, and the efficacy of treatment. Data were drawn from the literature. SUBJECTS: A hypothetical cohort of 10,000 patients discharged from the hospital after general surgery (gastrointestinal, gynecologic, urologic, or vascular surgery). INTERVENTIONS: We compared 2 strategies: (1) prolonged self-administered prophylactic low-dose low-molecular-weight heparin during 4 weeks after discharge from the hospital and (2) anticoagulant therapy with heparin started immediately after the first clinically overt venous thromboembolism. MAIN OUTCOME MEASURES: The number of venous thromboembolisms prevented, the number of major bleeding events induced, and the average direct costs. RESULTS: Prophylactic low-molecular-weight heparin was an effective therapy. Depending on the rate of venous thromboembolism (0.06% to 0.18% per week), this strategy prevented 19 to 58 venous thromboembolisms for a cohort of 10,000 patients treated, more than the number of anticoagulation-related complications (n = 10). Its marginal costs, however, exceeded $2.5 million (US dollars) for 10,000 patients. As the weekly rate of venous thromboembolism increased, prophylactic low-molecular-weight heparin became more cost-effective, with a marginal cost-effectiveness ratio per venous thromboembolism prevented ranging from $135,903 (rate of venous thromboembolism, 0.06% per week) to 45,353 (rate of venous thromboembolism, 0.18% per week). CONCLUSION: Although prolonged prophylactic anticoagulation after hospital discharge for general surgery is effective in preventing venous thromboembolism, we believe that its marginal costs are too high to recommend its indiscriminate use.

2. LMWH and Triglyceride Lowering Effect

**LONG-TERM EFFECT OF LOW MOLECULAR WEIGHT HEPARIN ON SERUM LIPIDS IN HYPERTRIGLYCERIDEDEMIC CHRONIC HEMODIALYSIS PATIENTS.**

*J Nephrol* 1997 Mar-Apr;10(2):111-4

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Although low-molecular-weight heparin (LMWH) has been reported to lower serum triglycerides and raise HDL in patients previously receiving classic heparin for hemodialysis by sparing lipoprotein lipase activation, this is not universally accepted. To evaluate this effect we studied 14 hypertriglyceridemic patients on hemodialysis for a median of 61 months (range 6-168 months); six were males and eight females, with a median age of 54 years (range 30-78). Eight patients were on bicarbonate and six on acetate HD. Eight were receiving EPO. All had been given conventional heparin, 102 +/- 5.8 IU/kg, at least for the last six months (control period) before switching to LMWH. Mean LMWH dose was 77 +/- 3.1 IU/kg. Fasting levels of total cholesterol (TC), triglycerides (TG) and HDL were measured monthly during the control period and every trimester for the next 36 months. Serum lipoproteins were measured at months 0 and 36 of the trial. TC, Lp alpha and beta showed no significant change. Serum TG and Lp pre-beta dropped significantly, to almost normal levels. EPO treatment, serum iPTH levels or dialysate buffer did not seem to influence this effect. HDL rose significantly higher in women than in men. It is concluded that LMWH substantially lowered the abnormally high serum TG and Lp pre-beta to almost normal and raised serum HDL in chronic hemodialysis patients.

3. LMWH use in Endotoxin mediated Acute Lung Injury (Experimental)


**LOW MOLECULAR WEIGHT HEPARIN PREVENTS THE PULMONARY HEMODYNAMIC AND PATHOMORPHOLOGIC EFFECTS OF ENDOTOXIN IN A PORCINE ACUTE LUNG INJURY MODEL.**

*Shock* 1998 Apr;9(4):274-81

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Tumor necrosis factor alpha (TNF-alpha) activity, platelet and neutrophil degranulation and margination, and increased vascular permeability are central to the pathophysiology of endotoxin-mediated acute lung injury. Nonanticoagulant activities of low molecular weight heparin (LMWH) include solubilization of the TNF-alpha receptor protein, inhibition of neutrophil adhesion, and regulation of thromboxane B2 (TXB2) biosynthesis. In this study, we evaluated the ability of LMWH to modulate TNF-alpha and TXB2 activity during endotoxemia and the subsequent effects on pulmonary hemodynamics. Domestic pigs 8-10 weeks old were anesthetized and catheterized for standard cardiopulmonary measurements and the lungs harvested for cuff:vessel ratio, myeloperoxidase activity, and permeability index. Pigs were randomly assigned to one of four groups: lipopolysaccharide (LPS) (n = 6), given .5 microg/kg/h Escherichia coli LPS intravenously for 6 h; saline control (n = 5); LMWH (n = 5), given .5 mg/kg LMWH for 30 min, followed by .5 mg/kg/h; and LMWH + LPS (same dosages, n = 6). Administration of LPS resulted in increased plasma TNF-alpha and TXB2 activity; increased pulmonary arterial pressure, pulmonary vascular resistance, and alveolar-arterial oxygen tension; decreased systemic arterial oxygen tension; and pulmonary edema. The cardiopulmonary parameters for the LMWH-treated pigs did not differ from those of the saline-treated control pigs. Pretreatment with LMWH attenuated the LPS-mediated TNF-alpha and TXB2 activity and attenuated LPS-mediated pulmonary hypertension, hypoxemia and neutrophil emigration, and edema formation. In conclusion, the data show that the protective effects of LMWH in this model of acute lung injury are associated with altered neutrophil adhesion and TNF-alpha and thromboxane activity.

4. LMWH and Cost effectiveness
COST EFFECTIVENESS OF LOW-MOLECULAR WEIGHT HEPARIN VERSUS WARFARIN FOLLOWING HIP REPLACEMENT SURGERY.


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Little information is available on the efficacy of low-molecular-weight heparin (enoxaparin) versus warfarin for treatment of deep vein thrombosis and pulmonary embolism following hip replacement surgery. Still less is known of the comparative cost effectiveness of these two therapies. A retrospective study was done on 56 patients who underwent elective hip surgery at an urban medical center between 1991 and 1996. All patients received enoxaparin or warfarin for purposes of thromboprophylaxis. An analysis of medication cost, therapy, laboratory monitoring, and bleeding events of the two antithrombolytic agents was undertaken. Total savings with enoxaparin averaged $1253 per patient, or $137,886 over the study period. The incidence of deep vein thrombosis or pulmonary embolism was 0% with enoxaparin and 3% with warfarin. These data indicate that enoxaparin is a more cost-effective and efficacious regimen for thromboprophylaxis following hip replacement surgery than warfarin.

5. LMWH in Deep Vein Thrombosis

CAN ALL PATIENTS WITH DEEP VEIN THROMBOSIS RECEIVE LOW-MOLECULAR-WEIGHT HEPARIN IN AN OUTPATIENT SETTING?

Haemostasis 1999 Dec;29 Suppl S1:84-8

Studies have shown subcutaneous low-molecular-weight heparin (LMWH) to be at least as safe and efficacious as intravenous unfractionated heparin (UFH) for the treatment of venous thromboembolism (VTE). Furthermore, unlike UFH, LMWH is administered on a once- or twice-daily basis without monitoring in uncomplicated cases. Consequently, it has been suggested that the large majority of patients with VTE could be treated on an outpatient basis. Exceptions include patients with an increased risk of haemorrhage, pregnant women, children and those with renal insufficiency. Outpatient management would offer economic advantages and be more convenient for both the patient and the hospital staff. Copyright 1999 S. Karger AG, Basel

THE ECONOMIC IMPACT OF TREATING DEEP VEIN THROMBOSIS WITH LOW-MOLECULAR-WEIGHT HEPARIN: OUTCOME OF THERAPY AND HEALTH ECONOMY ASPECTS. LOW-MOLECULAR-WEIGHT HEPARIN VERSUS UNFRACTIONATED HEPARIN.

Haemostasis 1998 Nov;28 Suppl S3:8-16

Subcutaneous low-molecular-weight heparin (LMWH) is at least as safe and effective as classical intravenous heparin therapy for the treatment of proximal vein thrombosis. Anticoagulant monitoring and intravenous administration are not required with LMWH treatment, therefore this therapy may offer economic advantages. An economic evaluation of these therapeutic approaches was performed comparing the costs and effectiveness. The evaluation was aimed at helping decision-makers to maximize the health of the population served, subject to available resources. The American-Canadian Thrombosis Study was a multicentre, randomized, double-blind clinical trial that compared treatment by initial continuous intravenous infusion of heparin followed by 3 months of warfarin therapy with a once-daily dose of subcutaneous LMWH, tinzaparin sodium followed by 3 months of warfarin treatment in patients with acute proximal deep vein thrombosis. In the LMWH-treated group, the cost incurred for 100 patients was $399,403 (Canadian) or $335,687 (US) with a frequency of objectively documented recurrent venous thromboembolism of 2.8%. In the intravenous heparin-treated group, the cost incurred for 100 patients was $414,655 (Canadian) or $375,836 (US), with a frequency of objectively documented recurrent venous thromboembolism of 6.9%. These results show a cost saving.
of $15,252 (Canadian) or $40,149 (US) with the use of LMWH. Multiple sensitivity analyses did not alter the findings of the study which indicated that LMWH therapy is at least as safe and effective but less costly than intravenous heparin treatment. The potential for outpatient therapy in up to 37% of patients who are receiving LMWH would substantially augment the cost-saving. The cost-effectiveness findings presented in this paper are based on the assumption that all costs are covered by a single payer. Outpatient management in many countries will shift the healthcare costs from the healthcare payer to the patient, increasing the economic burden to the patient.

(3) Bller HR

OUTPATIENT THERAPY WITH LOW-MOLECULAR-WEIGHT HEPARINS: NEW PERSPECTIVES FOR TREATMENT OF DEEP VEIN THROMBOSIS.


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Subcutaneous administration of low-molecular-weight heparin (LMWH) has been demonstrated to be as safe and effective for treatment of acute venous thrombosis as conventional treatment with unfractionated heparin, which requires intravenous infusion. In addition, LMWHs appear to provide an improved quality of life for patients with less impairment of physical activity. The ease of administration of LMWHs could be exploited in the clinical management of patients to increase the extent of LMWH outpatient therapy and reduce the number of hospitalizations for venous thrombosis, thus providing a more cost-effective therapy than conventional heparin. Efficient support services, patient education and careful follow up will be required for home treatment to be successful.

(4) Downing LJ, Strieter RM, Kadell AM, Wilke CA, Greenfield LJ, Wakefield TW

LOW-DOSE LOW-MOLECULAR-WEIGHT HEPARIN IS ANTI-INFLAMMATORY DURING VENOUS THROMBOSIS.


Section of Vascular Surgery and Jobst Vascular Research Laboratory, Department of Surgery, and the Department of Internal Medicine, University of Michigan Medical Center.

PURPOSE: Venous thrombosis results in a vein wall inflammatory response initiated by thrombus. Although anticoagulation with standard heparin (SH) and low-molecular-weight heparin (LMWH) is known to limit further thrombosis, their anti-venous thrombotic properties are poorly defined. The anti-inflammatory properties of these heparins were studied. METHODS: Sprague-Dawley rats were divided into groups and underwent inferior vena cava (IVC) ligation just below the renal level producing IVC thrombosis. One hour before ligation, animals received subcutaneous SH or LMWH at either high or low dose; normal saline (NS) was used as control. Six hours after ligation, animals were killed, and the IVCs were analyzed for clot presence, vein wall morphometrics, and vein wall permeability (VP) to define injury. RESULTS: Animals in both low-dose groups had no measurable anticoagulation, whereas those in both high-dose groups were adequately anticoagulated. There were statistically less IVC neutrophils for all groups compared with the control group, with low-dose LMWH showing the least cells (low-dose LMWH, 16 +/- 3; high-dose LMWH, 37 +/- 10; low-dose SH, 37 +/- 6; high-dose SH, 32 +/- 9; NS control, 63 +/- 2). Similar results were noted for total inflammatory cells. The lowest VP was noted for low-dose LMWH. CONCLUSION: Although both SH and LMWH inhibited vein wall neutrophils and total inflammatory cells, low-dose LMWH was most effective limiting neutrophil extravasation and was the only intervention to decrease VP below control levels. This occurred without preventing thrombus formation or causing a state of anticoagulation. Low-dose LMWH possesses anti-inflammatory properties distinct from its anticoagulant properties.

(5) Prentice C

ARE SYMPTOMATIC ENDPOINTS ACCEPTABLE IN VENOUS THROMBOPROPHYLACTIC STUDIES?


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Chemoprophylaxis with subcutaneous low-molecular-weight heparin has been shown to reduce deep vein thrombosis detected by surrogate endpoints such as fibrinogen scanning and venography.
However, there have been few trials which have assessed clinical endpoints attributed to fatal and non-fatal pulmonary embolism following surgery. As these clinical endpoints are rare, large-scale trials using vascular mortality, vascular morbidity and the incidence of haemorrhage as clinical endpoints need to be performed to assess the efficacy of chemical thromboprophylaxis. The benefit of using clinical endpoints against the risk of haemorrhage should also be evaluated.

(6) Goldhaber SZ, Morrison RB, Diran LL, Creager MA, Lee TH Jr

**ABBREVIATED HOSPITALIZATION FOR DEEP VENOUS THROMBOSIS WITH THE USE OF ARDEPARIN.**

*Arch Intern Med* 1998 Nov 23;158(21):2325-8

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BACKGROUND: Ardeparin sodium has recently received approval by the Food and Drug Administration for prophylaxis against venous thromboembolism in patients undergoing elective total knee replacement. However, this low-molecular-weight heparin has not been previously evaluated in a randomized controlled trial for treatment of established acute deep venous thrombosis. METHODS: The study included patients with ultrasound-documented acute symptomatic deep venous thrombosis of the legs. They had to be deemed appropriate for discharge home to receive subcutaneous low-molecular-weight heparin. Patients were randomized to receive ardeparin with a 2-day hospitalization or unfractionated heparin sodium with a 5-day hospitalization. Both groups received warfarin sodium. Follow-up ultrasound examinations were undertaken at 6 weeks. RESULTS: Of the 80 patients enrolled, 75 had follow-up ultrasonography. Evaluation of baseline vs 6-week venous scans demonstrated that, overall, 31 of the 39 ardeparin-treated patients improved, compared with 21 of the 36 patients assigned to receive unfractionated heparin (P=.05). The 95% confidence interval for the difference in improvement was 0.6% to 42% in favor of ardeparin. Median charges for ardeparin and unfractionated heparin were $2815 and $6500, respectively (P<.001). There were no differences in bleeding or patient satisfaction between the 2 groups. CONCLUSIONS: The results of this small preliminary trial suggest that ardeparin can be administered effectively and safely to selected patients with acute deep venous thrombosis and that, with proper nursing and home services, it can help decrease the duration of hospitalization.


**OUT-PATIENT TREATMENT OF ACUTE DEEP VEIN THROMBOSIS.**

*Int Angiol* 1998 Sep;17(3):146-50

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BACKGROUND: To assess whether uncomplicated deep vein thrombosis could be treated in an out-patient setting without increasing the frequency of complications, and to determine the proportion of patients with deep vein thrombosis, traditionally treated as in-patients at the Departments of Medicine, who are eligible for such treatment. METHODS: In a multicentre study, carried out at six hospitals of varying sizes and serving a population of about 600,000, consecutive patients over 18 years of age, with verified deep vein thrombosis, primarily presented as acute cases at the respective Departments of Medicine, were considered for treatment on an out-patient basis during a 1-year period. INTERVENTIONS: Those eligible for out-patient treatment were put on low molecular weight heparin and oral anticoagulants, and scheduled for daily attendance at the out-patient clinic of the respective Dept. of Medicine. RESULTS: Of 523 patients considered for out-patient treatment, 126 (24%) were excluded according to the defined exclusion criteria, 197 (38%) were treated entirely on an out-patient basis, and another 43 (8%) were initially treated in hospital (median two days) before being transferred to the out-patient setting. Three patients had to be hospitalized for suspected complications, but none of these turned out to be serious. No serious bleeding event or thromboembolic complication was registered. CONCLUSIONS: Uncomplicated acute deep vein thrombosis could be safely treated on an out-patients basis. At least 50% of the patients with this diagnosis, former treated as in-patients at the Depts. of Medicine, are eligible for such treatment.

6. LMWH in Coronary Stenting
THE EMERGING ROLE OF LOW-MOLECULAR-WEIGHT HEPARIN AND ANTIPLATELET THERAPIES IN THE CARDIAC CATHETERIZATION LABORATORY.

Am Heart J 1999 Dec;138(6 Pt 2):S577-85

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The advent of new pharmacotherapies and interventional devices has exponentially increased the breadth of coronary procedures in a variety of clinical settings. The low-molecular-weight heparins, a new class of antithrombins, offer several advantages over unfractionated heparin as anticoagulants. New antiplatelet agents have also been developed that block components of the platelet aggregation pathway not inhibited by aspirin. The use of these new therapies has the potential to significantly improve the outcome of percutaneous coronary interventions. One low-molecular-weight heparin, enoxaparin, was shown in the ESSENCE trial to be significantly superior to unfractionated heparin in the medical management of unstable angina. Evidence from ESSENCE suggests that enoxaparin used in conjunction with percutaneous revascularization and stenting does not cause increased bleeding. Trials directly comparing the safety and efficacy of heparin and enoxaparin as adjunctive therapies in percutaneous interventions are in progress. In addition, intramural delivery of enoxaparin to achieve a locally high concentration is being investigated for the prevention of restenosis after coronary stenting. Aspirin together with ticlopidine, which inhibits adenosine diphosphate-induced platelet activation, has been shown to be superior to aspirin plus anticoagulation in trials of patients undergoing percutaneous revascularization with stenting. Clopidogrel has emerged as a possible alternative to ticlopidine. Antiplatelet therapies directed against the glycoprotein IIb/IIIa receptor, which plays a critical role in aggregation, have been tested in several clinical trials in patients undergoing percutaneous intervention. The combination of new antiplatelet and new anticoagulant therapies may offer added benefit not seen with the individual agents alone. The safety and effectiveness of such new regimens is currently being investigated in a number of clinical trials.

LOW-MOLECULAR-WEIGHT HEPARINS IN CORONARY STENTING (THE ENTICES TRIAL). ENOXAPARIN AND TICLOPIDINE AFTER ELECTIVE STENTING.

Am J Cardiol 1998 Sep 10;82(5B):29L-32L

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The role of low-molecular-weight heparins (LMWHs) in the management of stent thrombosis, although expected to produce fewer hemorrhagic complications than warfarin anticoagulation regimens, is poorly defined. The ENoxaparin and TIClopidine after Elective Stenting (ENTICES) trial was designed to compare a combination of a LMWH (enoxaparin), ticlopidine, and aspirin with the conventional warfarin anticoagulant treatment in patients who received coronary stents, in an effort to decrease stent thrombosis and ischemic clinical events. The results show that the enoxaparin regimen produced significantly fewer clinical events and vascular complications than the conventional warfarin anticoagulant regimen.

LOW MOLECULAR WEIGHT HEPARIN IN CORONARY STENTING.


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A pilot clinical study called Enoxaparin and Ticlopidine after Elective Stenting (ENTICES) was designed to determine whether the combination of enoxaparin, ticlopidine and acetylsalicylic acid (ASA) is superior to the conventional five-drug regimen routinely used after elective stent placement (warfarin, unfractionated heparin, dextran, diprydamole and ASA). Compared with patients on conventional therapy (44), those randomly assigned to enoxaparin and ticlopidine (79) had a lower composite rate of in-hospital bleeding and vascular complications (5% versus 16%; P = 0.005), a
significantly lower composite end-point rate (death, nonfatal myocardial infarction, stent thrombosis of urgent revascularization) at 30 days (5% versus 20%; P = 0.001), a significantly lower incidence of stent thrombosis in the first 30 days (0% versus 7%; P = 0.04) and the same incidence of death or repeat angioplasty at six months. The Antiplatelet Therapy versus Lovenox plus Antiplatelet Therapy for Patients with an Increased Risk of Stent Thrombosis (ATLAST) trial was subsequently designed to compare the efficacy of the combination therapy enoxaparin. ASA and ticlopidine with that of antiplatelet therapy alone after coronary stent placement in patients at increased risk of stent thrombosis. Target enrolment of 2000 patients began in December 1996 and is expected to be complete by the end of 1998. In summary, the ENTICES pilot study demonstrated that the low molecular weight heparin enoxaparin is safe and effective for use with ASA and ticlopidine for elective stent patients. The ATLAST trial should provide results on whether enoxaparin is beneficial in patients at high risk for stent thrombosis.

(4) Knight CJ, Panesar M, Wilson DJ, Patrineli A, Chronos N, Wright C, Clarke D, Patel D, Fox K, Goodall AH

INCREASED PLATELET RESPONSIVENESS FOLLOWING CORONARY STENTING. HEPARIN AS A POSSIBLE AETIOLOGICAL FACTOR IN STENT THROMBOSIS.


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AIMS: Platelet activation may be a determinant of thrombotic and restenotic complications following intracoronary stenting. In order to measure the effect of stenting on platelet activation antigen expression we used whole blood flow cytometry in 18 patients undergoing Palmaz-Schatz stenting (treated with full anticoagulation) and compared these with a group of 18 patients undergoing elective angioplasty. The effects of low molecular weight heparin and unfractionated heparin on platelet behaviour were also studied, both in vitro and in vivo to determine the contribution of prolonged heparin therapy to platelet activation following stenting. METHODS AND RESULTS: Fibrinogen binding to activated GPIIb-IIIa, and surface expression of P-selectin, GPIb and GPIIb-IIIa antigens were measured in unstimulated peripheral blood samples (rest) and on stimulation with adenosine diphosphate (0.1-10 micromol x 1(-1)) and thrombin (0.02-0.16 U x ml(-1)). No changes were seen in resting samples following angioplasty or stenting. Agonist responsiveness was unaltered after angioplasty, but in stented patients antigen expression in response to thrombin was significantly reduced (P< or =0.04), whilst the adenosine diphosphate response was significantly increased (P=0.01). Similar effects were observed in patients with unstable angina treated with either low molecular weight heparin or unfractionated heparin in vivo. In vitro, both unfractionated and low molecular weight heparin inhibited thrombin-induced platelet activation, but stimulation of adenosine diphosphate responses was more marked with unfractionated than low molecular weight heparin. CONCLUSIONS: There was a significant increase in platelet responsiveness to adenosine diphosphate following intracoronary stenting in patients treated with conventional anticoagulants. This was probably a consequence of treatment with heparin. Activation of platelets by heparin may explain the increased rate of stent thrombosis in patients treated with anticoagulant therapy. Low molecular weight heparins stimulate platelets less than unfractionated heparin.

(5) Zidar JP

RATIONALE FOR LOW-MOLECULAR WEIGHT HEPARIN IN CORONARY STENTING.

Am Heart J 1997 Nov;134(5 Pt 2):S81-7

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Stents have been as revolutionary for the practice of coronary revascularization in recent years as was the coronary angioplasty balloon 15 years ago, but they have also been associated with a high rate of stent thrombosis. The Enoxaparin and Ticlopidine After Elective Stenting (ENTICES) trial is designed to determine the impact of a reduced anticoagulation regimen on clinical outcomes after stent deployment. Patients are randomly assigned 2:1 to enoxaparin-ticlopidine-aspirin versus the conventional warfarin regimen, and surrogate markers of platelet activation and thrombin activity are measured after 3 days. Three factors underpin ENTICES: (1) a desire to eliminate stent thrombosis, (2) a desire to reduce length of stay after stent placement by avoiding the prolonged hospitalization required with the five-drug regimen of heparin, aspirin, dipyridamole, dextran, and warfarin, and (3) a desire to reduce the bleeding complications associated with the intense anticoagulation typically used in patients
receiving stents. Patients are enrolled at seven sites in the United States and include patients with recent infarctions, restenotic lesions, and lesions as large as 30 mm in length. Other trials have also addressed issues concerning anticoagulation in patients undergoing stenting. The Stent Antithrombotic Regimen Study (STARS) trial compared aspirin, aspirin plus ticlopidine, and aspirin plus warfarin in 1650 patients receiving stents. The Aspirin/Ticlopidine vs Low-Molecular Weight Heparin/Aspirin/Ticlopidine High-Risk Stent Trial (ATLAST) is comparing aspirin plus ticlopidine with enoxaparin, aspirin, and ticlopidine in a group of patients at high risk undergoing stenting. The Intracoronary Stenting and Antithrombotic Regimen (ISAR) trial, a trial of ticlopidine, aspirin, and 12 hours of postprocedural heparin versus phenprocoumon on and aspirin after stenting in 517 patients, found a significantly lower incidence of the combined end point of death, myocardial infarction, bypass surgery, or repeated percutaneous transluminal angioplasty in the patients who received antiplatelet therapy, but the patients enrolled were not representative of the usual population undergoing stenting. New trials of stents and their sequelae should include low-molecular weight heparins and should gather cost and outcome data to satisfy capitated systems and managed care. Innovative stent designs may also permit changes in antithrombotic regimens.


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INTRODUCTION: To evaluate clinical, procedural and therapeutic predictors of in- and out-hospital events in the elderly, we analyzed 69 consecutive patients (age: 74, range: 70-87) with unstable angina who successfully underwent Palmaz Schatz coronary stenting. METHODS: Between March 1991 and March 1994, after the stenting procedure, a cohort of 38 patients (AC) was treated with iv heparin for 48 hours, warfarin (dosage titrated on INR) and dipiridamole (75 mg tid) for 3 months, aspirin (325 mg a day) chronically; between April 1994 and April 1995, after 48 hours of iv heparin, a second cohort of 31 patients (NO AC) received subcutaneous low molecular weight heparin (4000 U a day) for a week, ticlopidine (250 bid) for 1 month, and aspirin (100 mg a day) chronically. NO AC patients showed, by protocol, a higher postdilatation pressure (14 +/- 2 vs 9 +/- 3 atm, p < 0.0001). RESULTS: The 2 cohorts of patients were similar with respect to baseline clinical and angiographic findings. A shorter hospital stay (5 +/- 2 vs 10 +/- 6 days, p < 0.0001) and a lower incidence of in-hospital events were seen in the NO AC group (3.2 vs 24%, p = 0.028), both by a reduction of ischaemic events (3.2 vs 10.5%, p = ns) and hemorrhagic events (0 vs 13.2%, p = 0.03). During a mean follow-up of 21 +/- 13 months, NO AC patients did not show a significant lower rate of out-hospital events (1 year event-free survival respectively 94.7% in NO AC cohort vs 85.7% in AC cohort, p = ns). At logistic regression model, anticoagulant therapy (OR 10.89, Cl 1.39-85.28, p < 0.05) and refractory angina (Braunwald C3) (OR 5.76, Cl 1.27-26.00, p = 0.02) and multivessel disease (OR 3.31, Cl 0.89-12.20, p = 0.07) to the occurrence of late cardiac events, particularly for a higher risk of non-target site new revascularizations. Stent implantation on saphenous vein graft was also associated to a higher risk of repeating a revascularization of non-treated sites (20 vs 4%, p = 0.021). CONCLUSIONS: In elderly with unstable angina treated with Palmaz Schatz stenting, NO AC patients showed a significant reduction of in-hospital events without a subsequent higher risk of late events. In addition, refractory angina, multivessel disease and stent implantation on saphenous vein graft were the other main clinical variables predictive of out-hospital events particularly for higher risk of non-target site new revascularizations.


Department of Cardiology, Hospital Reina Sofia, Cordoba, Spain.
This study compared two consecutive antithrombotic strategies after Palmaz-Schatz stent implantation and involved 918 patients. Patients treated between May 1991 and May 1994 (group 1; n = 379) received aspirin, dipyridamole, and intravenous unfractionated heparin until oral anticoagulation was effective, between June 1994 and August 1995, 539 patients (group 2) were treated for 1 month with subcutaneous low-molecular-weight heparin (Fragmin), ticlopidine, and aspirin. There were no differences between the groups in terms of sex, clinical condition, vessel diameter, and severity and location of stenosis. Patients in group 1 were younger than those in group 2 (4% were > 70 years old compared with 12%, respectively; p < 0.01). Group 1 patients had more frequent unplanned stenting (48% vs 18%, respectively; p < 0.01) and fewer endoprostheses in the same artery than those in group 2 (1.1 +/- 0.5 vs 1.2 +/- 0.5, respectively; p < 0.01). Among group 2 patients, there was a significant reduction in thrombotic and hemorrhagic complications compared with group 1 patients. No subacute thrombosis occurred in patients in group 2 in contrast with a 5.8% incidence in patients in group 1 (p < 0.01). In addition, a lower incidence of groin and systemic bleeding was observed in patients in group 2 compared with patients in group 1 (2.6% vs 15%, respectively; p < 0.01). The association of low-molecular-weight heparin and antiplatelets provides a simpler antithrombotic strategy in patients treated with intracoronary stents and reduces the incidence of stent thrombosis and hemorrhagic complications. Our findings suggest that this antithrombotic regimen may prevent or completely avoid stent thrombosis.

(8) Fernandez-Aviles F, Alonso JJ, Duran JM, Gimeno F, Munoz JC, de la Fuente L, San Roman JA
SUBACUTE OCCLUSION, BLEEDING COMPLICATIONS, HOSPITAL STAY AND RESTENOSIS AFTER PALMAZ-SCHATZ CORONARY STENTING UNDER A NEW ANTITHROMBOTIC REGIMEN.

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OBJECTIVES. This study was designed to evaluate the effect of an antithrombotic regimen without full early anticoagulation on subacute occlusion, bleeding, hospital stay and restenosis after elective coronary stenting. BACKGROUND. Subacute occlusion is a major limitation of stenting. Aggressive antithrombotic therapy is not fully prophylactic against this complication, carries risk of bleeding, prolongs hospital stay and reduces cost-effectiveness. METHODS. We studied 110 consecutive patients (121 lesions) who underwent elective Palmaz-Schatz stenting. Intravenous heparin was given only during the procedure. After stenting, patients took aspirin, dipyridamole, dextran, warfarin and low molecular weight heparin (enoxaparin, 40 mg subcutaneously daily, stopped when an international normalized ratio of 2 to 3 was achieved). The first 52 patients (group A) underwent coronary angiography 24 h after stenting, and hospital stay was extended until an international normalized ratio of 2 to 3.5 was achieved. The remaining 58 patients (group B) were discharged 24 h after stenting. Clinical and angiographic follow-up were performed 1 and 6 months after stenting for all patients. RESULTS. In group A the activated partial thromboplastin time remained normal (30 +/- 6.2 s [mean +/- SD]) during enoxaparin administration, and hospital stay was 9.1 +/- 4.3 days. In group B hospital stay was 27 +/- 8 h. No major cardiac events occurred within the first month in patients from both groups. At 1 and 30 days all stented lesions remained patent. Only two patients (1.8%, 95% confidence interval [CI] 0.32% to 7%) developed bleeding. At 6 months, the restenosis rate was 22% (95% CI 15% to 30%). CONCLUSIONS. After coronary stenting with optimal angiographic results, this new antithrombotic regimen prevented subacute stent occlusion and bleeding, with a brief hospital stay. No detrimental effect on the previously reported restenosis rate was observed.

INTRACORONARY STENTING WITHOUT COUMADIN: ONE MONTH RESULTS OF A FRENCH MULTICENTER STUDY.

Centre Cardiologique du Nord, Saint-Denis, France.

In order to simplify post-coronary stenting treatment and to obtain a lower rate of complications, especially in bailout situations, seven French institutions treated 246 stented patients with 0.25 g/day of ticlopidine, 0.1 g/day of IV aspirin, and 2 days of heparin followed by low-molecular-weight
heparin for 1 month. Fifty percent of patients had a planned stenting procedure, and 50% had an unplanned procedure, including 29 (11.8%) in bailout situations. Subacute occlusion occurred in three (1.2%) patients (one death, two non-Q-wave infarctions). During the 1 month follow-up period, another death was reported (non-stent-related), two elective coronary artery bypass grafts were performed, and three additional patients presented with non-Q-wave myocardial infarctions. Nine (3.7%) patients had a groin complication that required blood transfusion or surgical repair. These results suggest that while waiting for the technological advancements of stents, postprocedural treatment that includes a low dosage of ticlopidine, aspirin, and low-molecular-weight heparin is a very effective alternative to conventional poststenting therapy.

7. LMWH for Unstable Angina

(1) Antman EM, Cohen M
NEWER ANTITHROMBIN AGENTS IN ACUTE CORONARY SYNDROMES.

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Thrombin, through its procoagulant and prothrombotic actions, plays a central role in the pathogenesis of unstable angina and acute myocardial infarction. Antithrombin therapy with unfractionated heparin has several important disadvantages, such as a variable anticoagulant effect, sensitivity to platelet factor 4, an inability to inhibit clot-bound thrombin, and the potential to cause thrombocytopenia. Alternative approaches have focused on novel anticoagulants, including direct antithrombins (eg, hirudin) and low-molecular-weight heparins (eg, enoxaparin). Direct antithrombins bind tightly to thrombin without requiring the cofactor antithrombin. Low-molecular-weight heparins display enriched anti-factor Xa activity, improved bioavailability, and facilitated administration versus unfractionated heparin. Recent trials demonstrate that direct antithrombins reduce rates of death and myocardial infarction early in patients without ST elevation, but the treatment effect diminishes over time. In contrast, treatment with enoxaparin shows superiority versus unfractionated heparin, and the treatment effect is durable over time. Whether thrombolysis with adjunctive treatment with low-molecular-weight heparins will show efficacy in patients with ST-segment elevation is the subject of ongoing trials.

(2) Purcell H, Fox KM
CURRENT ROLES AND FUTURE POSSIBILITIES FOR LOW-MOLECULAR-WEIGHT HEPARINS IN UNSTABLE ANGINA.
Eur Heart J 1998 Sep;19 Suppl K:K18-23

Royal Brompton & Harefield NHS Trust, London, UK.
Intravenous unfractionated heparin (UFH) is associated with several limitations, including short duration of action, poor bioavailability, unpredictable anticoagulant response, a risk of heparin-induced thrombocytopenia (HIT), and disease reactivation following early discontinuation. Because of these limitations, there is interest in the development of newer antithrombotic strategies. Low-molecular-weight heparins (LMWHs) offer potential benefits over standard heparin and allow the opportunity for subcutaneous self-administration for longer periods. In the acute phase of unstable angina, LMWHs have been shown to be superior to placebo and at least as effective as UFH in reducing death, myocardial infarction and recurrent angina. Trials of longer-term therapy with LMWHs are in progress. Although animal studies have suggested that LMWHs, by reducing neo-intimal proliferation, may prevent restenosis following coronary angioplasty, clinical trials have been disappointing. However, an initial study with the LMWH enoxaparin (Lovenox/Clexane) and ticlopidine after elective stenting (ENTICES) showed a reduction in stent thrombosis and ischaemic events. This has led to a further trial of antiplatelet therapy versus Lovenox plus antiplatelet therapy for patients with an increased risk of stent thrombosis (ATLAST). Further studies are assessing the role of diffusion and pressure-driven and mechanical devices to deliver high and sustained local intravascular concentrations of heparin.
Combination antithrombotic therapy with heparin plus aspirin decreases the risk of recurrent ischemic events in patients with acute coronary syndromes without persistent ST-segment elevation. Compared with standard unfractionated heparin, low-molecular-weight heparin (LMWH) has a more predictable antithrombotic effect, is easier to administer, and does not require coagulation monitoring.

At 176 hospitals in 3 continents, 3,171 patients with unstable angina or non-wave myocardial infarction were randomly assigned to either enoxaparin (a LMWH), 1 mg/kg twice daily subcutaneously, or to continuous intravenous unfractionated heparin, for a minimum of 48 hours to a maximum of 8 days. Trial medication was administered in a double-blind, placebo-controlled fashion. At 14 days, the primary endpoint, the composite risk of death, myocardial infarction, or recurrent angina with electrocardiographic changes or prompting intervention, was significantly lower in patients assigned to enoxaparin compared with heparin (16.6% vs 19.8%; odds ratio [OR] 1.24; 95% confidence interval [CI] 1.04-1.49; p = 0.019). At 30 days, the composite risk of death, myocardial infarction, or recurrent angina remained significantly lower in the enoxaparin group compared with the unfractionated heparin group (19.8% vs 23.3%, OR 1.23; 95% CI 1.0-1.46; p = 0.016). The rate of revascularization procedures at 30 days was also significantly lower in patients assigned to enoxaparin (27.1% vs 32.2%, p = 0.001). The 30-day incidence of major bleeding complication was 6.5% versus 7.0% (p = not significant), but the incidence of minor bleeding was significantly higher in the enoxaparin group (13.8% vs 8.8%, p <0.001) due primarily to injection-site ecchymosis. Thus, combination antithrombotic therapy with enoxaparin plus aspirin is more effective than unfractionated heparin plus aspirin in decreasing ischemic outcomes in patients with unstable angina or non-Q-wave myocardial infarction in the early (30 days) phase. The lower recurrent ischemic event rate seen with the LMWH, enoxaparin, is achieved without an increase in major bleeding, but with an increase in minor bleeding complications due mainly to injection-site ecchymosis.

Combination antithrombotic therapy with heparin plus aspirin decreases the risk of recurrent ischemic events in patients with acute coronary syndromes without persistent ST-segment elevation. Compared with standard unfractionated heparin, low-molecular-weight heparin (LMWH) has a more predictable antithrombotic effect, is easier to administer, and does not require coagulation monitoring. At 176 hospitals in 3 continents, 3,171 patients with rest unstable angina or non-wave myocardial infarction were randomly assigned to either enoxaparin (a LMWH), 1 mg/kg twice daily subcutaneously, or to continuous intravenous unfractionated heparin, for a minimum of 48 hours to a maximum of 8 days. Trial medication was administered in a double-blind, placebo-controlled fashion. At 14 days, the primary endpoint, the composite risk of death, myocardial infarction, or recurrent angina with electrocardiographic changes or prompting intervention, was significantly lower in patients assigned to enoxaparin compared with heparin (16.6% vs 19.8%; odds ratio [OR] 1.24; 95% confidence interval [CI] 1.04-1.49; p = 0.019). At 30 days, the composite risk of death, myocardial infarction, or recurrent angina remained significantly lower in the enoxaparin group compared with the unfractionated heparin group (19.8% vs 23.3%, OR 1.23; 95% CI 1.0-1.46; p = 0.016). The rate of revascularization procedures at 30 days was also significantly lower in patients assigned to enoxaparin (27.1% vs 32.2%, p = 0.001). The 30-day incidence of major bleeding complication was 6.5% versus 7.0% (p = not significant), but the incidence of minor bleeding was significantly higher in the enoxaparin group (13.8% vs 8.8%, p <0.001) due primarily to injection-site ecchymosis. Thus, combination antithrombotic therapy with enoxaparin plus aspirin is more effective than unfractionated heparin plus aspirin in decreasing ischemic outcomes in patients with unstable angina or non-Q-wave myocardial infarction in the early (30 days) phase. The lower recurrent ischemic event rate seen with the LMWH, enoxaparin, is achieved without an increase in major bleeding, but with an increase in minor bleeding complications due mainly to injection-site ecchymosis.
sustained effect at 30 days. There was no increase in the total number of hemorrhages; however, a significant increase in the rate of minor hemorrhage was observed.

(5) Cohen M

APPROACHES TO THE TREATMENT OF UNSTABLE ANGINA AND NON-Q WAVE MYOCARDIAL INFARCTION.

Can J Cardiol 1998 Aug;14 Suppl E:11E-14E

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Multiple clinical trials have been undertaken to understand better the events leading to unstable angina and non-Q wave myocardial infarction. Some of these studies focused on evaluating the role of antithrombotic therapy; others evaluated the role of more aggressive invasive treatment versus medical therapy. In the 1980s and 1990s, studies revealed that antithrombotic therapy with either acetylsalicyclic acid alone or heparin alone was more effective than placebo. The Thrombosis in Myocardial Infarction (TIMI) IIIB study attempted to compare medical therapy with early surgical intervention, reporting that early intervention did not result in any significant improvement in patient outcome over medical therapy. In the mid- to late 1990s, the thrombin hypothesis was introduced, suggesting that thrombin antagonists would arrest the coagulation and thrombotic cascade. The Global Use of Strategies To Open Occluded Coronary Arteries (GUSTO) IIb study put the thrombin hypothesis to the test, and it found that there was no significant difference between hirudin and unfractionated heparin treatments after 30 days. Glycoprotein IIb/IIIa receptor antagonists were then researched in the Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC), the c7E3 Fab Antiplatelet Therapy in Unstable Refractory angina (CAPTURE), the Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in a Global Organization Network (PARAGON) and the Platelet Receptor Inhibition of Ischemic Syndrome Management in Patients Limited to Unstable Angina Signs and Symptoms (PRISM-PLUS) studies, shifting the attention to the platelet. These studies gave contrasting results, bringing to the foreground the issues of optimal use of antithrombotic agents and proper timing of surgical intervention. Medical therapy for unstable angina and non-Q wave myocardial infarction was addressed in the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events (ESSENCE) study, which compared a low molecular weight heparin, enoxaparin, with unfractionated heparin. A significant difference in outcomes was found in favour of enoxaparin.


EARLY INCREASE OF VON WILLEBRAND FACTOR PREDICTS ADVERSE OUTCOME IN UNSTABLE CORONARY ARTERY DISEASE: BENEFICIAL EFFECTS OF ENOXAPARIN. FRENCH INVESTIGATORS OF THE ESSENCE TRIAL.


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BACKGROUND: The pathogenesis of unstable angina and non-Q-wave myocardial infarction is still poorly understood, and early evaluation of prognosis remains difficult. We therefore studied the predictive value of 5 biological indicators of inflammation, thrombogenesis, vasoconstriction, and myocardial necrosis, and we examined the effects of enoxaparin and unfractionated heparin on these markers after 48 hours of treatment. METHODS AND RESULTS: Sixty-eight patients with unstable angina or non-Q-wave myocardial infarction randomized in the international ESSENCE trial participated in this French substudy. C-reactive protein, fibrinogen, von Willebrand factor antigen, endothelin-1 and troponin I were measured on admission and 48 hours later. The composite end point of death, myocardial infarction, recurrent angina, or revascularization was significantly lower at 14 and 30 days of follow-up in patients allocated to enoxaparin compared with unfractionated heparin. All acute-phase reactant proteins were elevated on admission and increased further at 48 hours. Multivariate analysis demonstrated that the rise of von Willebrand factor over 48 hours was a significant and independent predictor of the composite end point at both 14 days and 30 days. Moreover the early increase of von Willebrand factor was more frequent and more severe with unfractionated heparin than with enoxaparin (mean change was +8.7+/−8.8% with enoxaparin versus +93.9+/−11.7% with unfractionated heparin, P<0.0001). The other clinical and biological variables did not predict outcome.
CONCLUSIONS: In patients with unstable angina or non-Q-wave myocardial infarction, the acute-phase proteins increase over the first 2 days despite medical treatment. The early rise of von Willebrand factor is an independent predictor of adverse clinical outcome at 14 days and at 30 days. Enoxaparin provides protection as evidenced by the reduced release of von Willebrand factor, which represents a favorable prognostic finding.

8. LMWH in Pulmonary Embolism

EXPANDING ELIGIBILITY FOR OUTPATIENT TREATMENT OF DEEP VENOUS THROMBOSIS AND PULMONARY EMBOLISM WITH LOW-MOLECULAR-WEIGHT HEPARIN: A COMPARISON OF PATIENT SELF-INJECTION WITH HOMECARE INJECTION.

Arch Intern Med 1998 Sep 14;158(16):1809-12

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BACKGROUND: The outpatient treatment of patients with deep vein thrombosis and pulmonary embolism using low-molecular-weight heparin has the potential to reduce health care costs, but it is unclear if most patients with deep vein thrombosis and pulmonary embolism can be treated as outpatients. PATIENTS AND METHODS: We treated as outpatients all patients with deep vein thrombosis and pulmonary embolism, except for those with massive pulmonary embolism, high risk for major bleeding or an active bleed, phlegmasia, and patients hospitalized for reasons that prevented discharge. We expanded the population of patients eligible for outpatient treatment by including many patients not treated at home in previous studies. Most patients in our study were treated with dalteparin sodium, 200 U/kg every 24 hours, for a minimum of 5 days. Therapy with warfarin sodium was started on the day of diagnosis or the following day. Patients were followed up for 3 months to determine rates of recurrent venous thromboembolism, bleeding, and death. RESULTS: In this study, 194 (83%) of 233 consecutive patients were deemed eligible and treated as outpatients. Of the 39 patients who did not receive home therapy, 20 had concomitant medical problems responsible for their admission or were already inpatients, 6 had massive pulmonary embolism, 6 refused to pay for the dalteparin therapy, 4 had active bleeding, and 3 had phlegmasia cerulea dolens, which required treatment with intravenous narcotics for pain control. More than 184 (95%) of the 194 patients were treated entirely at home. There was no significant difference (P>.99) in the rate of recurrent venous thromboembolic events between the patients who were injected by homecare nurses (3/95 [3.2%]) and those who injected themselves (4/99 [4.0%]). Combining the 2 models, the overall recurrent event rate was 3.6% (95% confidence interval, 1.5%-7.4%). Similarly, there were no significant differences in rates of major hemorrhage (2/95 vs 2/99; P=.99), minor hemorrhage (8/95 vs 2/99; P =.06), and death (6/95 vs 8/99; P =.63). The overall rate of major hemorrhage was 2.0% (95% confidence interval, 0.6%-5.2%). CONCLUSIONS: We demonstrate that more than 80% of patients at our tertiary care hospital could be treated at home using 1 of the 2 models of care we describe. Our results demonstrate that patients can safely and effectively perform home self-injection under the supervision of a hospital-based nurse. Injections at home by a homecare nurse are similarly effective. Our overall rates of recurrent venous thromboembolism, bleeding, and death are at least as favorable as those previously reported despite using 1 dose per day of dalteparin for most patients.

(2) Brewer D
SHOULD LOW-MOLECULAR-WEIGHT HEPARINS REPLACE UNFRACTIONATED HEPARIN AS THE AGENT OF CHOICE FOR ADULTS WITH DEEP VENOUS THROMBOSIS?


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BACKGROUND: Several low-molecular-weight heparins (LMWHs) are now approved for use in the United States for the prophylaxis of venous thromboembolism. They are used in Europe for the treatment of deep venous thrombosis (DVT) and pulmonary embolism. This review examines the evidence addressing the question "Should LMWHs replace unfractionated heparin (UFH) in the treatment of adults with DVT?" METHODS: We performed a MEDLINE search using the key words
"low-molecular-weight heparin" from the years 1990 to 1998, and the results were assessed using the JAMA Users' Guides to the Medical Literature system. RESULTS: Low-molecular-weight heparins are at least as safe and effective as unfractionated heparin in the treatment of patients with DVT. They are probably more effective and safer. They are more convenient to use and are associated with lower overall costs. CONCLUSIONS: Based on efficacy, safety, convenience, and cost, LMWHs are clearly superior to UFH in the treatment of DVT in primary care. Studies that confirm an expected improvement in patient-oriented outcomes (e.g., mortality and quality of life) need to be done.

(3) van Gorp EC, Brandjes DP, ten Cate JW
RATIONAL ANTITHROMBOTIC THERAPY AND PROPHYLAXIS IN ELDERLY, IMMOBILE PATIENTS.

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The aging process is associated with increased coagulation and fibrinolysis parameters, resulting in an overall 'prethrombotic state'. This probably explains the increased baseline susceptibility of elderly patients to the development of thromboembolic disease. Additional factors such as major surgery or malignant disease multiply the risk of thromboembolism in this population. Even when adequate antithrombotic therapy is instituted, the mortality associated with thromboembolic disease remains considerable; this underlines the importance of adequate thromboembolic prophylaxis. At present, the use of low molecular weight heparins (LMWHs) in elderly immobile patients appears to be the most effective approach to prophylaxis. The use of compression stockings seems to be effective in the prevention of venous thrombosis, at least in moderate risk surgical patients. In patients undergoing orthopaedic surgery, additional prophylaxis (e.g. with an LMWH) is necessary. In the management of venous thrombosis, patients can initially be treated with a bodyweight-adjusted dosage of an LMWH. In patients with deep vein leg thrombosis or pulmonary embolism, oral anticoagulant therapy should be started as soon as possible, and should be continued for 6 months. However, before starting prophylaxis or therapy, an individual risk assessment should be performed in which the benefits and disadvantages are balanced. Most of the large trials that have studied the effects of thromboembolic prophylaxis have focused on postsurgical patients. However, it will be of great interest to develop more specific prophylactic and therapeutic regimens for different nonsurgical high risk subgroups of patients, particularly the elderly.

PREVENTION OF DEEP VEIN THROMBOSIS IN KNEE ARTHROPLASTY. PRELIMINARY RESULTS FROM A RANDOMIZED CONTROLLED STUDY OF LOW MOLECULAR WEIGHT HEPARIN VS FOOT PUMP COMPRESSION.
Int Angiol 1998 Jun;17(2):93-6

Department of Orthopedic Surgery, Lund University, Sweden.
BACKGROUND: We evaluated in a randomized controlled study the possibility to use foot pump mechanical compression compared to routine LMWH as prophylaxis against deep vein thrombosis during knee arthroplasty. METHODS: Forty patients were included in this preliminary report. Eleven patients withdrew, usually during the early phase of the study. RESULTS: Among the 29 patients completing a venography, 27% in the compression group and none in the LMWH group had a DVT. This difference was statistically significant (p<0.05). One further patient in the compression group died from pulmonary embolism 17 days postsoperatively. CONCLUSIONS: With the present study protocol, mechanical foot pump compression failed to be as efficient as LMWH prophylaxis.

(5) Agnelli G, Sonaglia F
ANTICOAGULANT AGENTS IN THE MANAGEMENT OF PULMONARY EMBOLISM.
Int J Cardiol 1998 May 29;65 Suppl 1:S95-8

Istituto di Medicina Interna e Medicina Vascolare, Universita di Perugia, Italy.
The anticoagulant agents most commonly used in the prevention and treatment of pulmonary embolism (PE) are unfractionated heparin, oral anticoagulants, and low molecular weight heparins (LMWHs). Unfractionated heparin at low fixed dose is the prophylactic regimen of choice for PE in patients undergoing general surgery or with serious medical diseases (low to moderate risk patients).
In high risk patients perioperative prophylaxis with LMWHs or oral anticoagulants should be adopted. Therapy of pulmonary embolism should start with an intravenous bolus dose of 5000 U heparin followed by an infusion of 1250 U/h. Then the dose should be adjusted to maintain the aPTT < 2.5 pre-treatment value. Heparin is continued for 7-10 days and is followed by oral anticoagulants for at least 3 months. Unfractionated heparin has some pharmacological limitations, mainly due to the aspecific binding to plasma proteins that limits its anticoagulant effect and causes the heparin resistance observed in some patients with PE and the inter-subject variability of the anticoagulant effect. Other antithrombotic agents such as LMWHs and selective thrombin inhibitors (hirudin and its analogues) do not aspecifically bind to plasma proteins. They have recently been used with promising results in the prevention and treatment of PE. Their definitive value in this clinical setting will be defined by the ongoing clinical trials.

(6) Charland SL, Klinter DE
LOW-MOLECULAR-WEIGHT HEPARINS IN THE TREATMENT OF PULMONARY EMBOLISM.
Ann Pharmacother 1998 Feb;32(2):258-64
Department of Pharmacy, Saint Joseph Hospital/Kaiser Permanente-Rocky Mountain Region, Denver, CO 80218, USA.
More than 621 patients diagnosed with a PE have been treated with LMWH. This review included five randomized clinical trials (> 433 patients treated with LMWH) comparing LMWH with UFH. The remainder of the clinical studies were dose-response trials, noncomparative trials, or trials that included a subset of patients diagnosed with a PE. Additionally, 138 patients diagnosed with a PE were included in the group of 510 patients with venous thromboembolism and were subsequently treated with an LMWH. The data available suggest that LMWHs may be safe and effective in the treatment of submassive PE. However, the current data on LMWHs are limited by small sample size, inadequate patient description, and inadequate follow-up. The majority of studies fail to provide concurrent disease state information (e.g., renal disease), thus limiting their usefulness. The results of these trials must be confirmed in comparative studies using different LMWHs (since they may not be interchangeable) in various patient populations before LMWHs are considered to be a safe and effective alternative to UFH in the management of submassive PE.

(7) Szeto CC, Wang AY, Lui SF, Lai KN, Yu AW
TREATMENT OF PULMONARY EMBOLISM BY SUBCUTANEOUS LOW-MOLECULAR-WEIGHT HEPARIN IN A HEMODIALYSIS PATIENT.
Department of Medicine, Prince of Wales Hospital, Chinese University of Hong Kong, Shatin.
Low-molecular-weight heparin (LMWH) has been used in the prophylaxis and treatment of deep vein thrombosis. Data regarding the efficacy of this drug without subsequent use of oral anticoagulant in the treatment of pulmonary embolism is limited. Pulmonary embolism may complicate the use of central venous catheter in hemodialysis. We report a case of acute submassive pulmonary embolism complicating a central venous hemodialysis catheter in a dialysis patient. After the catheter was removed, the patient was treated successfully with subcutaneous injection of LMWH for three months. We conclude that LMWH is safe and effective for treatment of pulmonary embolism in patient on hemodialysis.

9. LMWH the Oncologic Setting

(1) Levine M, Rickles FR
TREATMENT OF VENOUS THROMBOEMBOLISM IN CANCER PATIENTS.
Haemostasis 1998 Nov;28 Suppl S3:66-70
Cancer Care Ontario, Hamilton Regional Cancer Centre; Department of Medicine, McMaster University, Hamilton, Ont., Canada.
The occurrence of venous thromboembolism complicates the management of the patient with malignant disease because of the need for anticoagulant therapy. Cancer patients have an ongoing thrombotic stimulus due to the underlying cancer and its associated treatments, but are also considered to be at increased risk for anticoagulant-related bleeding. In recent years, the results of clinical trials have demonstrated the safety and efficacy of bodyweight-adjusted subcutaneous low-molecular-weight heparin administered at home for patients with acute deep vein thrombosis. This approach is particularly attractive in patients with cancer, in whom quality of life is an important consideration. There are no trials to date which specifically address the question of the duration of oral anticoagulant therapy in cancer patients. However, data can be extrapolated from trials evaluating the duration of oral anticoagulant therapy in other high-risk patients. Hence, cancer patients should continue oral anticoagulant therapy for as long the cancer remains active (usually at least 6 months). There remain a number of unanswered questions regarding the clinical management of thromboembolism in the cancer patient.

(2) Kakkar AK, Williamson RC
THROMBOPROPHYLAXIS IN THE CANCER PATIENT.
Haemostasis 1998 Nov;28 Suppl S3:61-65

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Thrombosis is a common complication in patients with malignant disease resulting from tumour elaboration of procoagulants and subsequent activation of intravascular coagulation. Cancer therapies (operation, chemotherapy and the use of central venous lines) further heighten the risk of thrombosis. The risk of thrombosis in cancer operations is of sufficient magnitude to necessitate routine thromboprophylaxis, for which low-dose unfractionated heparin or the low-molecular-weight heparins (LMWHs) have been proven effective and safe. Thrombotic complications with chemotherapy have been extensively described in women receiving either adjuvant or palliative cytotoxic or hormonal therapy for breast carcinoma. The problems are common, but of all the suitable prophylactic modalities available, only oral anticoagulants have been evaluated for this indication. Thrombosis complicates the use of central venous catheters in the cancer patient and both low-dose warfarin and LMWHs are effective in protecting against line-associated thrombi. Recent evidence from the retrospective analyses of randomized studies comparing unfractionated heparin and LMWH in the treatment of deep vein thrombosis have shown a striking mortality reduction among cancer patients who received LMWH. The use of LMWHs to prolong survival in patients with advanced malignant disease is currently the subject of a prospective, randomized, placebo-controlled study.

(3) von Tempelhoff GF, Niemann F, Schneider DM, Kirkpatrick CJ, Hommel G, Heilmann L
BLOOD RHEOLOGY DURING CHEMOTHERAPY IN PATIENTS WITH OVARIAN CANCER.

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The use of platinum based chemotherapy in ovarian malignancy and other cancer types is known to be associated with deep vein thrombosis. In a prospective study of 47 patients with ovarian cancer of International Federation of Gynecology and Obstetrics stage Ib-IV, serial rheological parameters were determined (plasma viscosity, red blood cell aggregation under conditions of stasis and low shear) in addition to hemoglobin, hematocrit, leukocytes, platelets, and fibrinogen. At the same time the incidence of deep vein thrombosis was recorded before, during six cycles of first line cisplatinum/epirubicin/cyclophosphamide chemotherapy, and 2 months thereafter (two-months check-up). Only six patients with previous deep vein thrombosis concomitantly received thrombosis prophylaxis once with 3000 anti Xa Units/day subcutaneously low molecular weight heparin (Certoparin, NOVARTIS) throughout chemotherapy. Before each cycle of chemotherapy impedance plethysmography was used for deep vein thrombosis screening and when this was suspected on the basis of physical examination or a pathological result of impedance plethysmography, ascending venography of both legs was performed. During chemotherapy, the venographically proven deep vein thrombosis incidence was 10.6%; (95% CI: 3.5-23.1) with no differences in occurrence between FIGO stages. Before operation mean plasma viscosity was higher in patients who developed deep vein thrombosis
postoperatively (n = 5; 1.46 +/- 0.2 mPas) and during chemotherapy (n = 5; 1.49 +/- 0.1 mPas) as compared to those without deep vein thrombosis (1.38 +/- 0.2 mPas; p = 0.04). Postoperatively (before chemotherapy) none of the rheological variables were significantly different in patients with versus those without deep vein thrombosis during chemotherapy. Leukocyte and platelet counts decreased significantly during chemotherapy until the two-months check-up after chemotherapy while red blood cell aggregation (stasis & low shear), hemoglobin, and hematocrit showed a continuous but nonsignificant increase. The mean plasma viscosity, instead, declined into the normal range after the 4th cycle of chemotherapy (1.33 +/- 0.1 mPas) in patients without thrombosis. In contrast, mean plasma viscosity was increased to 1.48 +/- 0.1 mPas at the time of deep vein thrombosis diagnosis during chemotherapy. In the ovarian cancer patients of this study, the development of deep vein thrombosis postoperatively and during chemotherapy was associated with a hematocrit-independent increase in blood viscosity characterized by a high plasma viscosity and normal or low hematocrit, which was present before primary surgery as well as at the time of deep vein thrombosis diagnosis.

(4) Girolami A

LOW MOLECULAR WEIGHT HEPARINS IN CLINICAL PRACTICE: UNSOLVED OR PARTIALLY SOLVED PROBLEMS.

Arch Inst Cardiol Mex 1998 Jan-Feb;68(1):69-76

University of Padua Medical School, II Chair of Internal Medicine, Italy.

Low molecular weight heparins (LMWH) have been shown, in recent years, to be at least as effective as standard heparin (SH) in the prophylaxis and treatment of venous thrombosis. In spite of several studies there are still some unsolved problems to be dealt with. These may be summarized along the following lines: 1) Side effect; 2) Use in pregnancy; 3) Role in arterial thrombosis; 4) Use in severe deep venous thrombosis; 5) Use for home treatment; 6) Effect on cancer related mortality; 7) Standardization of preparations; 8) Dosage uncertainties; 9) Long term treatment. The two most important aspects are those pertaining to the potential use in arterial thrombosis and the possibility of home treatment of selected patients with venous thromboembolism. A few studies now indicate that LMWH may play an important role in several arterial thrombosis (coronary disease, ischemic stroke, etc). As far as the indications for home treatment are concerned, recent studies have given a positive answer. However, rather than home treatment it would be more appropriate to refer to early discharge from the hospital. The overall impression is that LMWH may represent an important progress in the management and prophylaxis of thrombotic disease.

(5) Levine MN

PREVENTION OF THROMBOTIC DISORDERS IN CANCER PATIENTS UNDERGOING CHEMOTHERAPY.

Thromb Haemost 1997 Jul;78(1):133-6

Department of Medicine, McMaster University, Hamilton, Ontario, Canada.

The etiology of thrombosis in malignancy is multi-factorial, and mechanisms include release of procoagulants by tumor cells, comorbid predisposing factors in anti-cancer drugs. The most reliable information on the incidence of thromboembolism in patients receiving chemotherapy comes from breast cancer. The rate of thrombosis in women with Stage II breast cancer receiving adjuvant chemotherapy is approximately 5%. The highest risk is in postmenopausal women and the addition of tamoxifen to chemotherapy increases the thrombotic risk over chemotherapy alone. The rate of thrombosis in metastatic breast cancer is likely to be much higher than that in Stage II breast cancer. Cancer patients with central venous catheters, e.g. Hickman, portacath, should receive 1 mg of warfarin daily. A recent trial has demonstrated that low molecular weight heparin can prevent catheter-related clots. There has been only one trial conducted evaluating prophylaxis in ambulatory cancer patients receiving chemotherapy. In this study, very low dose warfarin (INR 1.3-1.9) substantially reduced the risk of venous thromboembolism in breast cancer patients receiving chemotherapy.
Service de Chirurgie Thoracique, Hôpital Avicenne, Bobigny.

A French multicentre, open, randomized trial was conducted in lung cancer surgery in order to test the optimal dosage regimen. (1) Fraxiparine 3075 IU AXa (fixed dosage) and (2) Fraxiparine 4100 or 6150 IU AXa (dosage adjusted for body weight only), over a period of 8 days. 75 patients were allocated to each group. Efficacy (Doppler ultrasonography at D0 and D8, controlled by bilateral ascending phlebography when positive) and safety, i.e. perioperative blood loss and postoperative bleeding complications were the main assessment criteria. The efficacy of the two treatment regimens was confirmed = no deep vein thrombosis and/or pulmonary embolism. No significant difference of safety was observed between the two groups; nevertheless fewer patients developed major bleeding complications in the (1) Fraxiparine fixed dosage group (2 patients) than in the (2) Fraxiparine adjusted dosage group (6 patients). Blood loss was comparable in the 2 groups; a statistical difference (p = 0.09) was showed between D0 and D2 in favour of (1) Fraxiparine fixed dosage group.

The results of this trial indicate that Fraxiparine administered at fixed dosage represents an effective and safe prophylaxis against fatal thromboembolism in patients undergoing oncologic thoracic surgery.

10. LMWH in Orthopedic Surgery

(1) Leclerc JR, Gent M, Hirsh J, Geerts WH, Ginsberg JS

THE INCIDENCE OF SYMPTOMATIC VENOUS THROMBOEMBOLISM DURING AND AFTER PROPHYLAXIS WITH ENOXAPARIN: A MULTI-INSTITUTIONAL COHORT STUDY OF PATIENTS WHO UNDERWENT HIP OR KNEE ARTHROPLASTY. CANADIAN COLLABORATIVE GROUP.

Arch Intern Med 1998 Apr 27;158(8):873-8

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BACKGROUND: Despite low molecular weight heparin prophylaxis, the incidence of venographically detected, residual deep vein thrombosis after hip and knee arthroplasty remains high, at approximately 15% and 30%, respectively. Most of these thrombi are asymptomatic and of unknown clinical significance. METHODS: We studied a cohort of 1984 consecutive patients who had hip or knee arthroplasty at 1 of 28 participating hospitals. Patients received enoxaparin prophylaxis, 30 mg subcutaneously every 12 hours for up to 14 days, and underwent predischarge compression ultrasonography. Study end points were symptomatic deep vein thrombosis or pulmonary embolism during and after prophylaxis, asymptomatic venous thrombosis detected by predischarge compression ultrasonography, and major hemorrhage. The duration of follow-up was 84 days. RESULTS: Enoxaparin treatment was started a mean (+/- SD) of 17.9 +/- 10.4 hours after the completion of surgery and was given for a mean of 18.0 +/- 6.9 doses. Eighty-two patients (4.1%; 95% confidence interval, 3.3%-5.0%) developed venous thromboembolism. The rates of thromboembolic events during and after prophylaxis were 2.1% and 2.0%, respectively. Only 3 patients (0.15%) had abnormal predischarge compression ultrasonography. Three patients (0.15%) died of pulmonary embolism. Major hemorrhage occurred in 58 patients (2.9%; 95% confidence interval, 2.2%-3.7%). CONCLUSIONS: Postoperative prophylaxis with enoxaparin for a mean of 9 days is associated with a clinically acceptable rate of symptomatic venous thromboembolism and major hemorrhage. Predischarge compression ultrasonography cannot be justified.

(2) Hunt D

LOW-MOLECULAR-WEIGHT HEPARINS IN CLINICAL PRACTICE.


Section of General Internal Medicine, Baylor College of Medicine, Houston, Tex., USA.

BACKGROUND. Low-molecular-weight heparin (LMWH), because of its efficacy and ease of use, is an attractive alternative to unfractionated heparin in treatment and prophylaxis of venous
thromboembolism. METHODS. Using MEDLINE, I searched for relevant clinical trials using LMWH. I carefully reviewed these trials, allowing development of recommendations for use of LMWH in clinical practice. RESULTS. A large amount of data is available for evaluating the use of LMWH in treatment of venous thromboembolism and in prophylaxis against venous thromboembolism. Less data are available concerning the utility of these agents in cardiovascular and cerebrovascular disorders. CONCLUSIONS. Based on available literature, LMWH should be strongly considered as therapy for acute deep venous thrombosis, though Food and Drug Administration (FDA) approval for this indication is currently pending. These agents are also excellent pharmacologic prophylactic agents in orthopedic surgery patients. Recent data suggest use in unstable angina in place of heparin. Other indications for use are not as well defined at this time.


EFFICACY AND SAFETY OF PROLONGED THROMBOPROPHYLAXIS WITH A LOW MOLECULAR WEIGHT HEPARIN (DALTEPARIN) AFTER TOTAL HIP ARTHROPLASTY--THE DANISH PROLONGED PROPHYLAXIS (DAPP) STUDY.


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The aim of this study was to compare the efficacy and safety of prolonged (35 days) thromboprophylaxis with a standard length (7 days) regimen of a low molecular weight heparin in patients undergoing total hip arthroplasty. The study was multicentre, randomised, double-blind, and prospective with two groups. Following seven days on a standard length regimen of dalteparin (5000 antifactor Xa units subcutaneously once daily starting 12 h before surgery), patients were randomized to continue the prophylaxis with either subcutaneous injections of dalteparin or placebo injections for a further 28 days. Efficacy was evaluated at the end of the study (day 35) in all patients with bilateral ascending phlebography to detect deep vein thrombosis. Bleeding complications and other adverse events were registered throughout the study period. Three hundred consecutive patients agreed to participate before the operation: 281 were finally randomised and 215 completed the study; two patients died before randomisation; 17 developed deep vein thrombosis; none developed pulmonary embolism; and five of 113 patients (4.4%, 95% CI 1-10%) developed deep vein thrombosis in the dalteparin group, compared with 12 of 102 (11.8%; 95% CI 6-20%) in the placebo group (p=0.039). Deep vein thrombosis in the proximal veins was diagnosed in one patient (0.9%; 95% CI 0-5%) in the dalteparin group, and in five (5.0%; 95% CI 2-11%) in the placebo group (p=0.076). Major bleeding was observed in one patient in the placebo group; minor bleeding complications and adverse events were equally distributed between the groups. We concluded that prolonged (35 days) thrombo prophylaxis with dalteparin is more effective than a standard length (7 days) regimen without increased risk of bleeding complications or other adverse events.


EFFICACY AND SAFETY OF LOW MOLECULAR WEIGHT HEPARIN, UNFRACTIONATED HEPARIN AND WARFARIN FOR THROMBO-EMBOLISM PROPHYLAXIS IN ORTHOPAEDIC SURGERY: A META-ANALYSIS OF RANDOMISED CLINICAL TRIALS.

Haemostasis 1997 Mar-Apr;27(2):75-84

Institute for Medical Informatics and Biostatistics, Riehen, Switzerland.

The efficacy and safety of low molecular weight heparin (LMWH), unfractionated heparin (UFH) and warfarin for prophylaxis of thrombo-embolism in orthopaedic surgery were compared using meta-analysis techniques. Twenty-two studies were included, 2 of which compared LMWH to warfarin. The mean probabilities to develop deep-vein thrombosis (DVT), pulmonary embolism and major and minor bleeding using UFH were: 0.21 (95% confidence interval, CI: 0.18-0.24); 0.01 (95% CI: 0.01-0.02); 0.05 (95% CI: 0.03-0.07), and 0.19 (95% CI: 0.17-0.22), respectively. The relative risk (RR) of DVT for LMWH vs. UFH was 0.76 (95% CI: 0.60-0.91), p < 0.05 and for LMWH vs. warfarin 0.78 (95% CI: 0.69-0.87), p < 0.05. The RR of minor bleeding for LMWH vs. UFH was 0.76 (95% CI: 0.64-0.92), p < 0.05. The RR of minor bleeding for LMWH vs. warfarin was 3.28 (95% CI: 0.92-11.08).
2.21-4.70), \( p < 0.05 \). Conclusion: in orthopaedic surgery, LMWH is significantly superior to both UFH and warfarin in the prevention of DVT and results in significantly less minor bleeding complications when compared to UFH, but significantly more minor bleeding when compared to warfarin.

(5) Yoo MC, Kang CS, Kim YH, Kim SK

A PROSPECTIVE RANDOMIZED STUDY ON THE USE OF NADROPARIN CALCIUM IN THE PROPHYLAXIS OF THROMBOEMBOLISM IN KOREAN PATIENTS UNDERGOING ELECTIVE TOTAL HIP REPLACEMENT.

*Int Orthop* 1997;21(6):399-402

Department of Orthopaedic Surgery, Kyung Hee University Hospital, Seoul, Korea.

Because of the belief that post-operative deep vein thrombosis (DVT) is rare in Asian patients, thromboprophylaxis is not usually prescribed for surgical patients. This study reports an open multi-centre controlled study of the use of a low molecular weight heparin, nadroparin calcium (Fraxoparine Sanofi France), as opposed to no prophylaxis in 100 patients undergoing uncemented total hip replacement. The patients had bilateral venography performed preoperatively and 10 days after operation. Eight patients (16%) developed DVT in the control group of 50 patients and 1 (2%) in the treatment group, also of 50 patients. Pulmonary embolus occurred in 1 patient in the treatment group and in 3 in the control group. Intraoperative and postoperative blood loss did not differ significantly between the two groups. Our study suggests that the incidence of DVT in Asian patients, though somewhat less than in their Western counterparts, is still considerable. It confirms the safety and efficacy of nadroparin calcium in preventing post-operative DVT in patients undergoing elective total hip replacement.

(6) Borghi B, Bassi A, Grazia M, Feoli MA, Pignotti E

[ASSESSMENT OF COMPLICATIONS OF MAJOR ORTHOPEDIC SURGERY: COMPARISON OF INDOBUFEN, CALCIUM HEPARIN, AND LOW MOLECULAR HEPARIN]. [ARTICLE IN ITALIAN]

*Minerva Anestesiol* 1996 Mar;62(3):93-100

I Servizio di Anestesia e Rianimazione, IRCCS Istituti Ortopedici Rizzoli, Bologna.

OBJECTIVE: Evaluation of incidence of postoperative thrombotic and haemorrhagic complications in autotransfused patients undergoing blood predepositing, hemodilution, intra and postoperative blood saving and treated with indobufen, heparin calcine and low molecular weight heparin (enoxeparin). Length of follow up: 6 months. PATIENTS: 980 consecutive patients admitted to hospital from 1-1-1992 to 30-6-1994 (321 males and 159 females), aged between 20 and 90 years (mean 62 +/- 11 years), with basal haemoglobin at 13.4 +/- 1.4 g/dl (range 6.7-17.9), who had undergone antithromboembolic prophylaxis with indobufen (Indo, 668), heparin calcine (CaHe, 200) and low molecular weight heparin (LMWH). INTERVENTIONS: Total hip (714) and knee (121) arthroprosthesis and hip replacements (cup 33, stem 10, cup and stem 102). RESULTS: The absence of complications was significantly greater in patients treated with indobufen (Indo 94.3% vs CaHe 83.5% vs LMWH 85.7%, CT: \( p = 0.0001 \)); the incidence of thromboembolic complications was significantly higher in patients treated with heparin calcine and low molecular weight heparin (LMWH). Due to bleeding brought about by the use of heparin calcine, one patient with coronary heart disease suffered from anemia and severe hypotensions by myocardiac infarction and cardiogenous shock which led to the patient's death. The use of homologous transfusions was significantly higher in patients treated with heparin calcine (Indo 4.2% vs CaHe 14.5% vs LMWH 4.5%, CT: \( p = 0.0001 \)). CONCLUSIONS: In patients undergoing autotransfusion and hemodilution, indobufen has a lower of haemorrhagic complications compared to heparin calcine and low molecular weight heparin and it is more effective in the prevention of thrombotic complications at clinical evidence.

11. LMWH in Pregnancy

a) General Aspects of LMWH in Pregnancy
including the following references:


SAFETY OF LOW-MOLECULAR-WEIGHT HEPARIN IN PREGNANCY: A SYSTEMATIC REVIEW.

*Thromb Haemost* 1999 May;81(5):668-72

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Unfractionated heparin (UFH) remains the anticoagulant of choice during pregnancy. Low-molecular-weight heparins (LMWH) are an attractive alternative to UFH due to their logistic advantages and their association with a lower incidence of osteoporosis and HIT. We reviewed all published clinical reports concerning the use of LMWH during pregnancy. In addition, participants of an international interest group contributed a cohort of pregnant women treated with LMWH. Pregnancies were divided into two groups; those with and those without maternal comorbid conditions. The number of adverse fetal outcomes and the occurrence of maternal complications were evaluated in the two groups. In the group of women with comorbid conditions (n = 290), 13.4% of the pregnancies were associated with an adverse fetal outcome. In contrast, in the group of women without comorbid conditions (n = 196), 3.1% were associated with an adverse outcome, which is comparable to that seen in the normal population. We conclude that LMWH appear to be a safe alternative to unfractionated heparin as an anticoagulant during pregnancy.

2. Blomback M, Bremme K, Hellgren M, Siegbahn A, Lindberg H

THROMBOPROPHYLAXIS WITH LOW MOLECULAR MASS HEPARIN, 'FRAGMIN' (DALTEPARIN), DURING PREGNANCY--A LONGITUDINAL SAFETY STUDY.


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Twenty-five women with previous verified thromboembolic complications were treated with dalteparin (Fragmin) during pregnancy and puerperium. Women with known hereditary thrombophilia (antithrombin, protein C and protein S deficiencies) or with phospholipid antibodies were excluded. The dose at entry was calculated according to body weight and thereafter monitored by anti-FXa activity aiming at 0.20-0.40 IU/ml plasma 3 h post injection. Dalteparin or dextran was used during delivery. Twenty-two women completed the study and 14 of these could be given the same dose throughout pregnancy. There was an increased dose response postpartum. There were no thromboembolic recurrences or severe bleeding complications. The level of antithrombin activity remained normal. Our thrombosis-prone pregnant women had initially increased levels of thrombin markers but no further increase was observed during the dalteparin thromboprophylaxis. Retrospectively, three heterozygous and three homozygous individuals for the FV Leiden mutation leading to activated protein C resistance were identified. In conclusion, dalteparin could safely be used as thromboprophylaxis during pregnancy in these thrombosis-prone women. Women weighing 50-79 kg at entry could be treated with 5000 IU of dalteparin once daily during pregnancy, without monitoring. Postpartum, many of the women were given a reduced dose.

3. Bates SM, Ginsberg JS

ANTICOAGULANTS IN PREGNANCY: FETAL EFFECTS.


Department of Medicine, McMaster University, Hamilton, Ontario, Canada.

Anticoagulants are used during pregnancy to prevent venous thromboembolism in highrisk patients, to prevent systemic embolism in patients with prosthetic heart valves or native valvular heart disease, and to treat patients with acute venous thromboembolism. Neither unfractionated nor low-molecular-weight heparin cross the placenta and both appear to be safe for the fetus. Oral anticoagulants do cross the placenta and they have been associated with the development of warfarin embryopathy, central nervous system anomalies, and fetal haemorrhage. The true incidence of these
events is not known. Both heparin and oral anticoagulants can be safely administered to nursing mothers.

(4) Nelson-Piercy C, Letsky EA, de Swiet M

LOW-MOLECULAR-WEIGHT HEPARIN FOR OBSTETRIC THROMBOPROPHYLAXIS: EXPERIENCE OF SIXTY-NINE PREGNANCIES IN SIXTY-ONE WOMEN AT HIGH RISK.

*Am J Obstet Gynecol* 1997 May;176(5):1062-8

Institute of Obstetrics and Gynecology, Queen Charlotte’s Hospital, London, United Kingdom.

OBJECTIVE: Our purpose was to investigate the use of low-molecular-weight heparin (enoxaparin, Clexane) for thromboprophylaxis in pregnancy. STUDY DESIGN: A prospective consecutive cohort of 61 pregnant women at high risk of thromboembolism receiving antenatal thromboprophylaxis with enoxaparin (usually 40 mg, subcutaneously daily) in a total of 69 pregnancies was identified from the obstetric medicine clinic at Queen Charlotte’s Hospital. Bone density measurements of the hip and lumbar spine were taken in 26 women after 26 pregnancies within 16 months post partum. Nonparametric statistics were used for comparisons. RESULTS: There were no episodes of antenatal thromboembolism. One woman (1.6%) (receiving 20 mg of enoxaparin) had a pulmonary embolus post partum. Heparin levels (anti-Xa assay) were greater with the 40 mg dose (median 0.09 U/ml) than with the 20 mg dose (median 0.03 U/ml) (p = 0.0006) but were not affected by gestational age (r = -0.1, p = 0.14). Enoxaparin had no effect on platelet count or on in vitro coagulation tests. Nine (32%) women had bone density in the spine or hip > 1 SD below the mean for age- and sex-matched controls. CONCLUSION: This, the largest study to date of low-molecular-weight heparin use in pregnancy, confirms previous reports that it is a safe and effective alternative to unfractionated heparin for obstetric thromboprophylaxis in high-risk women. Effects on bone demineralization require further investigation.

b) LMWH in Antiphospholipid Syndrome

(1) Cowchock S

TREATMENT OF ANTIPHOSPHOLIPID SYNDROME IN PREGNANCY.

*Lupus* 1998;7 Suppl 2:S95-7

Department of Obstetrics and Gynecology, New York University Medical Center, New York 10016, USA.

Women with antiphospholipid antibodies (aPL = IgG anticardiolipin and/or lupus anticoagulants) and a history of either prior thrombotic events or pregnancy loss are at high risk during pregnancy for either another fetal death or thrombosis. The treatment of choice is anticoagulation with heparin. Both standard unfractionated heparin and low-molecular-weight heparin are used for prophylactic anticoagulation during pregnancy. The half-lives of either standard heparin, or low-molecular-weight heparin, and the peak values for each after subcutaneous injection, are lower than those in nonpregnant patients. Doses and injection intervals need to be adjusted when treating a pregnant woman. Clotting tests such as the activated partial thromboplastin time (aPTT) vary greatly during pregnancy, and the aPTT is often not even prolonged when antithrombotic levels of heparin are achieved. The aPTT is not a useful test when the patient has a lupus anticoagulant. Levels of plasma heparin are therefore needed to best care for pregnant women who need anticoagulation even for prophylaxis. Low-dose aspirin is often added empirically to heparin for treatment of aPL during pregnancy, but its efficacy has not been evaluated. Intravenous infusions of gamma globulins (IVGG) have been used as additional therapy when prior treatment with heparin during pregnancy failed to save the fetus, when severe and early onset preeclampsia has complicated a prior pregnancy (in such cases efficacy is unproven), or when there is an additional medical complication (such as immune thrombocytopenia) for which IVGG is an appropriate treatment. There are some situations in which treatment with corticosteroids is the best, or the only choice. However, corticosteroids should not be combined with heparin for long-term treatment during pregnancy because the risk for vertebral fracture is so high.
(2) Lockshin MD

PREGNANCY LOSS AND ANTIPHOSPHOLIPID ANTIBODIES.

Lupus 1998;7 Suppl 2:S86-9

Barbara Volcker Center for Women and Rheumatic Disease, Hospital for Special Surgery, Cornell Medical Center, New York, NY 10021, USA.

With the use of low-dose heparin, fetal survival of aPL pregnancies is 70-80%, but prematurity and intrauterine growth restriction are common. It is likely, but not proven, that dysregulated placental coagulation and resultant vasculopathy are the cause of fetal loss. Details of dysregulated coagulation remain to be described. Opportunities remain to determine the role of coagulopathy in repeated pregnancy loss, identify a critical event or window to which intervention might be directed, identify maternal (and fetal) characteristics other than aPL that determine fetal loss, describe toxicity profiles of current treatments, develop more specific, less toxic therapies, and describe long-term fetal and maternal outcomes.


THE MANAGEMENT OF ANTIPHOSPHOLIPID SYNDROME.


Clinical Center of Serbia, Institute of Hematology, Belgrade.

This paper shows 21 patients with antiphospholipid syndrome, that were diagnosed after thrombosis, recurrent fetal loss or thrombocytopenia. Lupus anticoagulant was detected in 18, anticardiolipin antibodies in 15 and VDRL test was positive in 6 patients. Nine patients had recurrent venous thrombosis, 6 pulmonary embolus, 9 recurrent fetal loss and 15 were with low platelet count. Secondary prevention with oral anticoagulants was applied according to the level of INR 2.5-3.5. Only one patient relapsed due to deficient anticoagulation. Three pregnant patients were treated with aspirin, and low molecular weight heparin, alone or in combination with prednisone. All of them had recurrent spontaneous abortions between 20 and 28 weeks of gestation. In conclusion, early diagnosis of antiphospholipid syndrome is very important. Secondary prevention of thromboembolic complications is recommended according to the level of INR > or = 3. For the prevention of fetal loss we have not agreed upon treatment of all patients. Further studies are needed to define more precisely the optimal type, intensity, and the duration of therapy.

(4) Di Simone N, Ferrazzani S, Castellani R, De Carolis S, Mancuso S, Caruso A

HEPARIN AND LOW-DOSE ASPIRIN RESTORE PLACENTAL HUMAN CHORIONIC GONADOTROPHIN SECRETION ABOLISHED BY ANTIPHOSPHOLIPID ANTIBODY-CONTAINING SERA.

Hum Reprod 1997 Sep;12(9):2061-5

Department of Obstetrics and Gynecology, Universita Cattolica S. Cuore, Rome, Italy.

This study was conducted to determine whether drugs used for conventional treatments of pregnant women with antiphospholipid syndrome might be able to restore the gonadotrophin-releasing hormone (GnRH)-induced secretion of placental human chorionic gonadotrophin (HCG) in vitro. We tested this hypothesis using a modified enzyme-linked immunosorbent assay (ELISA) and an in-vitro placental culture system. Pharmacological dose of low molecular weight heparin (20 IU/ml) significantly (P < 0.02) reduced the antiphospholipid antibody (aPL) binding in the ELISA and was able to restore GnRH-induced HCG secretion (P < 0.05) in presence of aPL-containing sera. Low-dose aspirin (0.03 M) did not modify aPL binding in the ELISA, but partially restored HCG secretion (P < 0.05). These observations may help to explain the role of these treatments in antiphospholipid syndrome.

(5) al-Sayegh FA, Ensworth S, Huang S, Stein HB, Klinkhoff AV

HEMORRHAGIC COMPLICATIONS OF LONG-TERM ANTICOAGULANT THERAPY IN 7 PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS AND ANTIPHOSPHOLIPID SYNDROME.

J Rheumatol 1997 Sep;24(9):1716-8
Department of Medicine, University of British Columbia, Vancouver, Canada.

OBJECTIVE: To describe the presentation, course, and management of serious hemorrhagic complications of anticoagulant therapy for patients with antiphospholipid syndrome (APS).

METHODS: Charts of patients identified with serious bleeding complications from anticoagulation for APS were reviewed. RESULTS: Patients included 6 women and one man with systemic lupus erythematosus (SLE) and one woman with primary APS. One patient had 3 separate hemorrhagic events. There were 6 episodes of subdural hematoma in 5 patients, one episode of pericarditis with tamponade, one episode of hemoptysis, and one episode of ovarian hemorrhage. In 2 patients, symptoms related to hemorrhage were initially attributed to active SLE. Duration of anticoagulation was between one month and 10 years at the time of bleed. International normalized ratio (INR) and prothrombin time were above the intended range in 6/9 episodes. There were no deaths and no permanent sequelae due to bleeding. Anticoagulant therapy was resumed in 6/7 patients.

CONCLUSION: The management of APS must include vigilance, patient education, and anticoagulation to maintain the INR between 3 and 3.5. To prevent hemorrhagic complications, low molecular weight heparin is an option that deserves further study.

12. LMWH in Trauma

(1) Erstad BL
VENOUS THROMBOEMBOLISM IN MULTIPLE TRAUMA PATIENTS.

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Thromboembolic complications are frequent in patients with multiple trauma. The efficacy of unfractionated heparin for venous thrombosis prophylaxis has not been established. Based on limited prospective data, low-molecular-weight heparin appears to be more effective than unfractionated heparin and at least as effective as compression devices for preventing thromboembolic complications in these patients. Vena cava filters should be considered in high-risk patients who cannot receive anticoagulant therapy, but long-term filter use without concomitant anticoagulant therapy is associated with a substantial risk of recurrent thromboembolism.

(2) Cafferata HT, Morrison S, Duer C, Depalma RG
VENOUS THROMBOEMBOLISM IN TRAUMA PATIENTS: STANDARDIZED RISK FACTORS.

Department of Surgery, University of Nevada School of Medicine, Reno, USA.

PURPOSE: This study was done to evaluate the use of published standardized risk factors for venous thromboembolism (VTE) in patients admitted to a trauma intensive care unit (ICU) and to derive guidelines for the use of low molecular weight heparin (LMWH) and surveillance venous Doppler ultrasound scanning (VDUS). METHODS: Patients were admitted to a regional trauma center ICU. Two periods were studied. Period 1 was a retrospective analysis of documented cases of VTE in the trauma registry from 1993 to 1995 (n=39). The period was also a review of all patients admitted to a trauma ICU in 1994 without VTE who met the following criteria: age greater than 11 years, ICU stay of more than 36 hours, and survival of more than 72 hours (n=227). Period 2 was a concurrent analysis of 1996 documented cases of VTE and similarly selected ICU admissions (VTE, n=10; no VTE, n=224). Risk factor scores (R1, admitting; R2, total) were calculated from the International Society for Cardiovascular Surgery/Society for Vascular Surgery reporting standards. The scores were cumulative by category and over time. The suitability of such standards was determined in period 1. The resulting therapeutic and surveillance guidelines were evaluated in period 2. RESULTS: Period 1 risk factor scores, R1 and R2, were correlated with the occurrence of VTE from chi2 test (P < .05 and P < .01, respectively). Risk categories were grouped as low, moderate, and high. VTE was not observed in the low-risk group (0 to 2). Among all VTE (n=49), 11 cases occurred in patients with moderate-risk scores and 38 in patients with high-risk scores. In 1994 and 1996, the selected groups were analyzed and the incidence rate of VTE was 4.7% in both years for the moderate-risk group and 2.5% and 4.8% for the high-risk group, respectively. Most VTE cases (78%) received some form of prophylaxis (PRx), and 26% of cases had multiple methods of prophylaxis (MPRx). This included 80% of the
cases that received unfractionated heparin. In period 2, no pulmonary emboli (PE) occurred, in contrast to period 1, in which 16 of 39 cases of VTE (41%) were first seen with PE. In period 2, no patient receiving MPRx, including compression and LMWH, had VTE develop. Surveillance VDUS discovered 60% of 1996 cases in period 2. No PE were seen in period 2.

CONCLUSION: Standard risk factors were easily applied to the trauma patient at the bedside. Patients at low risk needed no PRx. Patients at high risk did best with both compression devices and LMWH. VDUS was recommended selectively in patients at high risk in whom multiple-method PRx could not be achieved. Patients at moderate risk required further study to define optimal PRx and need for surveillance VDUS. Intracavalar devices were used prophylactically only twice.

(3) Krasuski M, Jagodzinski K, Kiwerski JE, Krzyzosiak L

[PULMONARY EMBOLISM AS ONE CAUSE OF DEATH AFTER SPINAL INJURY--THE ROLE OF CLEXANE] [ARTICLE IN POLISH].

Chir Narzadow Ruchu Ortop Pol 1998;63(2):125-31

Kliniki Rehabilitacji Akademii Medycznej w Warszawie.
The paper deals with fatal pulmonary embolism in patients treated at STOCER after spinal injuries, frequently with neurological impairment. A group of 417 patients treated between 1988 and 1989 has been compared with another one of 350 patients treated between 1995 and 1996. Antiembolic prophylactics has been employed in both groups: an Aspirin in the first group and Clexane in the second one. Forty-seven fatalities (11% of all patients) occurred in the first group (2 females, 44 males, mean age 55.1 years); 40% of them caused by pulmonary embolism (5% of all patients). Twenty-nine fatalities (8% of all patients) occurred in the second group (1 female, 28 males, mean age 60.2 years) 17% of them caused by pulmonary embolism (1.4% of all patients). A comparison between these groups indicates high efficacy of clexane antiembolic prophylactics in patients treated due to spinal injury especially if complicated neurologically.

(4) Warwick D

THROMBOEMBOLIC PROPHYLAXIS IN ORTHOPAEDIC TRAUMA PATIENTS: A COMPARISON BETWEEN FIXED DOSE AND AN INDIVIDUALLY ADJUSTED DOSE OF A LOW MOLECULAR WEIGHT HEPARIN.

Injury 1997 Apr;28(3):233-4


POSTTRAUMA THROMBOEMBOLISM PROPHYLAXIS.

J Trauma 1997 Jan;42(1):100-3

Department of Surgery, University of Michigan Medical Center, Ann Arbor, USA.

PURPOSE: The need to study methods of thromboembolism prophylaxis in high-risk trauma patients is well established. METHODS: Patients were enrolled into the study, stratified as to their ability to receive anticoagulation and randomized to low-dose unfractionated heparin, low molecular weight heparin, pneumatic compression devices, or foot pumps with or without vena caval filters. Serial ultrasound scans were performed at designated intervals for 4 weeks. Pulmonary angiograms were obtained for clinical signs or symptoms of pulmonary embolism. RESULTS: Fifty-three patients, 32 male and 21 female patients with a mean age of 44 years, completed the study. The incidence of DVT was 43% (23 of 53 patients) and significantly higher in older patients. There were no pulmonary embolisms. Color-flow duplex proved to be a sensitive method for detecting both proximal and distal thrombi. The risk assessment profile for thromboembolism (RAPT) scale identified a group of patients with a high incidence of DVT. However, the occurrence of DVT was not correlated with the magnitude of the RAPT score. CONCLUSION: The ability to identify a population with a high incidence of thromboembolism by using the RAPT score to detect asymptomatic DVT, and the suggested advantage of low molecular weight heparin, all support the need for an appropriately powered randomized clinical trial.
(6) Bouderka MA, Sadraoui A, Bouaggad A, Abassi O, Benaguida M
[DEEP VENOUS THROMBOSIS IN HEAD-INJURED PATIENTS: THERAPEUTIC PROBLEMS], [ARTICLE IN FRENCH]
Cah Anesthesiol 1996;44(6):513-8

Service d'Anesthesie-Reanimation, CHU Ibn Rochd, Casablanca, Maroc.
The incidence of thromboembolism in neurosurgery is 29% to 43%. Anticoagulant therapy is faced with some problems, particularly in the traumatized cranial patients. Indeed the risk of cerebral haemorrhage inherent both to heparins and antivitamins K makes their use still debated in this setting. The problem is even more serious for curative treatment of patent venous thrombosis: medical abstention with risk of pulmonary embolism, or heparinotherapy at anticoagulant dosage with risk of intracranial haemorrhage? In connection with seven cases of venous thrombosis observed in head trauma patients and the data of recent literature, we attempted to define the preventative measures and the management of heparin treatment for venous thrombosis in head trauma patients. From the second week after the initial trauma, heparinotherapy at effective dosage can be helpful if there is no intracranial haemorrhage and if iterative scanographic supervision is possible. Less than a week after trauma or if there is cerebromeningeal haemorrhage, the treatment will be based only on physical measures (early mobilization, intermittent pneumatic compression of the legs). In case of venous thrombosis, interruption of the vena cava inferior is indicated.

13. LMWH in Transplantation Surgery

a) LMWH in Renal Transplantation

(1) Alkhunaizi AM, Olyaei AJ, Barry JM, deMattos AM, Conlin MJ, Lemmers MJ, Bennett WM, Norman DJ
EFFICACY AND SAFETY OF LOW MOLECULAR WEIGHT HEPARIN IN RENAL TRANSPLANTATION.
Transplantation 1998 Aug 27;66(4):533-4

Department of Medicine, Oregon Health Sciences University, Portland 97201, USA.
BACKGROUND: Deep venous thrombosis (DVT) is a common problem with potentially devastating results in patients undergoing major surgical procedures. Certain renal transplant recipients are particularly at risk for allograft loss as a consequence of renal vein and artery thrombosis. Over the past few years, low molecular weight heparin has been well established as an accepted modality of treatment and prophylaxis of DVT. The efficacy and safety of low molecular weight heparin in the prophylaxis of DVT following renal transplantation in adults has not previously been reported.

METHODS: Dalteparin was administered to 120 adult renal transplant recipients postoperatively at the Oregon Health Sciences University. RESULTS: No patient developed allograft arterial or venous thrombosis. One patient developed subclavian vein thrombosis. No bleeding complications were encountered, and side effects were very minimal. CONCLUSION: Prophylaxis with dalteparin is an effective and safe modality for the prevention of thrombosis in adult patients undergoing renal transplantation.

(2) Koch Nogueira PC, Giuliani C, Rey N, Said MH, Cochat P
CALCIFYING PANNICULITIS IN A CHILD AFTER RENAL TRANSPLANTATION.

Unite de Nephrologie Pediatrique, Hopital Edouard Herriot, Lyon, France.


b) LMWH in Saphenous Vein Graft Disease

Tex Heart Inst J 1997;24(4):379-83

Department of Adult Cardiology, Texas Heart Institute, Houston, USA.

Both reoperation and alternative treatments for thrombo-occlusive disease of saphenous vein grafts have been fraught with a high rate of complications and a low rate of long-term success. We report 2 cases in which thrombo-occlusive saphenous vein graft disease was treated with the aid of abciximab during the intervention and with low-molecular-weight heparin for 7 to 12 days in an outpatient setting.

14. LMWH in Protein C Deficiency

Homozygous Protein C Deficiency: Description of a New Mutation and Successful Treatment with Low Molecular Weight Heparin.


Hamilton Civic Hospital Research Centre, Ontario, Canada.

We present a kindred with a new mutation of the protein C gene, in which the proband had an unusual clinical presentation. The relationship between warfarin induced skin necrosis and level of anticoagulation was investigated. The pharmacokinetics of protein C concentrate was assessed to determine frequency of replacement therapy. The clinical and biochemical efficacy of therapy with low molecular weight heparin (LMWH) was assessed. The effect of long-term LMWH on bone density in the growing child was monitored using whole body densitometry. Warfarin therapy required an INR of greater than 3.5 to avoid skin necrosis. If protein C replacement was to be used, doses of 100 U/kg/day would have been required to maintain protein C levels consistently at or above 0.20 U/ml. While receiving prophylactic therapy with LMWH for almost 3 years, there were no episodes of recurrent thrombosis, no skin necrosis and no bleeding. Biochemical markers of in vivo thrombin generation were suppressed and within the normal range. Bone density continued to increase at the normal rate throughout the treatment period. LMWH is an effective form of long-term therapy for homozygous protein C deficient patients with measurable protein C levels.

15. LMWH a better Reversal of Effect by Synthetic Protamine variant (+ 18RGD)

Comparison of the Hemodynamic and Hematologic Toxicity of a Protamine Variant after Reversal of Low-Molecular-Weight Heparin Anticoagulation in a Canine Model.

Lab Anim Sci 1997 Apr;47(2):153-60

Unit for Laboratory Animal Medicine, University of Michigan Medical Center, Ann Arbor, USA.

Using the dog as an animal model, we developed an experimental preparation to compare hemodynamic and hematologic toxicity of anticoagulation reversal. Currently, protamine sulfate reversal of standard unfractionated heparin and low-molecular-weight heparin (LMWH) anticoagulation causes adverse side effects, including decreased systemic mean arterial pressure (MAP), decreased cardiac output (CO), decreased oxygen consumption (VO2), and thrombocytopenia. In addition, standard protamine is only marginally effective at reversing the factor Xa inhibition induced by LMWHs. We have produced protamine-like variant peptides to decrease the adverse responses attributed to standard protamine. The hemodynamic, hematologic, and coagulation effects of standard protamine and the protamine variant (+18RGD) were assessed after reversal of LMWH anticoagulation in anesthetized dogs. Flow probes and vascular catheters were surgically implanted for measurement of hemodynamic parameters.
including MAP, CO, VO2, and heart rate (HR). Hematologic studies (platelet and white blood cell counts) and coagulation studies (activated clotting time [ACT], activated partial thromboplastin time [aPTT], thrombin cloting time [TCT], antifactor Xa and antifactor IIa values) also were performed. The protamine variant +18RGD was less toxic, induced less thrombocytopenia, and was more effective in anticoagulation reversal than was standard protamine sulfate. Results of this study indicate that the dog may be a useful model for investigating important hemodynamic, hematologic, and coagulation parameters during reversal of LMWH anticoagulation by use of synthetic protamine variants.

16. LMWH for long-term Anticoagulation

(1) Harenberg J, Huhle G, Piazolo L, Giese C, Heene DL

LONG-TERM ANTICOAGULATION OF OUTPATIENTS WITH ADVERSE EVENTS TO ORAL ANTICOAGULANTS USING LOW-MOLECULAR-WEIGHT HEPARIN.

Semin Thromb Hemost 1997;23(2):167-72

1st Department of Medicine, Faculty of Clinical Medicine Mannheim, University of Heidelberg, Germany.

Bleeding complications are one of the major risks during oral anticoagulation. If further anticoagulation is indicated, low-molecular-weight heparin (LMWH) may offer an alternative treatment in those patients. In a prospective, nonrandomized study, 120 patients have been switched from oral anticoagulants to LMWH because of bleeding complications or other severe side effects during treatment with vitamin K antagonists. Indication for further anticoagulation was prophylaxis of recurrent thromboembolism, artificial heart valve replacement, atrial fibrillation with embolism and cardiomyopathy. The treatment period ranged from 2 months to 10.8 years. No fatal embolism occurred. One major but not severe episode of gastrointestinal bleeding occurred in a patient with an as yet unknown colon carcinoma. The cumulative treatment period amounts to 250 years. No drop in platelet count occurred in any patient. No other side effects were observed. LMWH was injected subcutaneously at doses ranging from 2500 to 15,000 anti-factor Xa units per day by the patient himself. The dose was adjusted on the basis of body weight, bleeding risk and thromboembolic risk. The results indicate that LMWH may be effectively and safely used as alternative anticoagulant regimen in patients with side effects or other complications on oral anticoagulants.

17. LMWH for Heparin Induced Thrombocytopenia

(1) Tomer A, Masalunga C, Abshire TC

DETERMINATION OF HEPARIN-INDUCED THROMBOCYTOPENIA: A RAPID FLOW CYTOMETRIC ASSAY FOR DIRECT DEMONSTRATION OF ANTIBODY-MEDIATED PLATELET ACTIVATION.

Am J Hematol 1999 May;61(1):53-61

Institute of Hematology and Blood Bank, Soroka University Medical Center, Beer-Sheva, Israel.

Heparin-induced thrombocytopenia (HIT) and thrombosis are serious complications of heparin therapy. Recently, we have reported a practical and rapid functional flow cytometric assay (FCA) for the diagnosis of HIT with high specificity and sensitivity compared with the radioactive serotonin-release assay (SRA). In the present study, we added an immune-neutralization assay to directly demonstrate the antibody-mediated process, and tested the immune compatibility of low-molecular-weight heparin (LMWH) Lovenox and the heparinoid Orgaran (danaproid) using plasma from 18 patients with HIT confirmed by both FCA and SRA. The clinical utility of this modified method is demonstrated by a pediatric patient with a complex clinical presentation who developed thrombocytopenia with multiple thromboses while on heparin therapy. ELISA and SRA (performed in three independent laboratories) for diagnosis of HIT were both negative. In contrast, the FCA for detecting activated platelets expressing anionic phospholipids, was highly and reproducibly positive with both unfractionated and LMWH. Another FCA also demonstrated the surface expression of the alpha-granule membrane p-selectin (CD62p). Compatibility testing with the heparinoid Orgaran was also positive (and with plasma from 4 of the 18 patients with HIT). Heparin was discontinued, along with full recovery of the platelet count. The capacity of the patient's plasma to activate platelets in the presence of heparin gradually decreased over 4 weeks consistent with antibody clearance. The
responsible mechanism was clarified using an immune-neutralization assay, which showed a dose response neutralization of the plasma activity by antibodies against human Immunoglobulin G (IgG) and IgM. This assay was also reproducible in the 18 patients with HIT. We conclude that the functional FCA with its modification is practical, sensitive, and specific for reliable diagnosis of HIT. It can simultaneously assess the compatibility of alternative therapies and directly confirm the antibody-mediated process. Further, it is particularly useful to clarify mechanisms of thrombocytopenia and thrombosis and to direct therapy in patients with a complex presentation and confounding laboratory results who often need prompt diagnosis and treatment.

(2) Taliani MR, Agnelli G, Nenci GG, Gianese F
DERMATAN SULPHATE IN PATIENTS WITH HEPARIN-INDUCED THROMBOCYTOPENIA.
Br J Haematol 1999 Jan;104(1):87-9

Istituto di Medicina Interna e Medicina Vascolare, Universita di Perugia, Italy.

Patients with thromboembolic diseases who develop heparin-induced thrombocytopenia (HIT) type II require an alternative anticoagulation strategy. Dermatan sulphate (DS) was administered to five patients with thromboembolic diseases who developed HIT type II and showed an in vitro cross-reactivity with low molecular weight heparins. The platelet count and the extension of thrombosis were monitored during DS administration. In four of the five patients the platelet count rapidly increased after heparin was discontinued and DS started. A low platelet count persisted in the single patient with cross-reactivity to DS, up to 4 d after its discontinuation. None of the patients experienced thrombus extension, haemorrhagic side-effects or other adverse events.

(3) Cohen M
HEPARIN-INDUCED THROMBOCYTOPENIA AND THE CLINICAL USE OF LOW MOLECULAR WEIGHT Heparins IN ACUTE CORONARY SYNDROMES.
Semin Hematol 1999 Jan;36(1 Suppl 1):33-6

Allegheny University of the Health Sciences, Philadelphia, PA 19102-1192, USA.

Standard unfractionated heparin has long been the mainstay of anticoagulant therapy. Despite its significant therapeutic benefits, unfractionated heparin has disadvantages in clinical usage, including the need for continuous intravenous infusion or multiple daily injections, and close laboratory monitoring of the activated partial thromboplastin time (aPTT) and/or plasma heparin concentrations, as well as risk for bleeding complications and heparin-induced thrombocytopenia (HIT). Low-molecular-weight (LMW) heparins have shown equivalent efficacy or superiority to unfractionated heparin, while permitting easier dosage and administration, and posing less risk for bleeding complications and HIT. A review of the clinical use of LMW heparins in acute coronary syndromes reveals a low incidence of HIT. However, LMW heparins are not recommended for the treatment of established HIT due to cross-reaction with 80% of antibodies generated during exposure to unfractionated heparin.

(4) Warkentin TE
LIMITATIONS OF CONVENTIONAL TREATMENT OPTIONS FOR HEPARIN-INDUCED THROMBOCYTOPENIA.

Department of Pathology, McMaster University, Hamilton, Ontario, Canada.

Thrombosis is a common and potentially serious complication of immune-mediated heparin-induced thrombocytopenia (HIT). Discontinuation of heparin is a simple and important maneuver in patients with suspected HIT. Unfortunately, thrombosis often occurs even in those patients in whom heparin was discontinued due to thrombocytopenia alone ("isolated" HIT). It therefore is reasonable to consider prophylactic anticoagulation with an alternate anticoagulant in patients with suspected HIT, especially if their initial indication for anticoagulation persists. For patients with thrombosis complicating HIT, conventional treatment options often have important limitations. Warfarin has a slow onset of action, and its use in patients with acute HIT and deep venous thrombosis has been associated with the devastating syndrome of venous limb gangrene. Ancrod, a defibrinogenating snake venom with thrombin-like activity, has also been used to treat HIT. However, this agent does
not inhibit thrombin generation in HIT, which could explain why some patients who have been treated with this agent have developed certain adverse clinical events, such as warfarin-associated venous limb gangrene. The use of low-molecular-weight heparin (LMWH) to treat patients with HIT is limited by their high rate (up to 100%) of in vitro cross-reactivity with HIT sera, and the relatively frequent occurrence of new or recurrent thrombocytopenia or thrombosis during treatment of HIT with this class of agents. In contrast, the mixture of anticoagulant glycosaminoglycans known as danaparoid sodium has a much lower frequency of in vitro cross-reactivity with HIT sera (10% to 40%, depending upon the sensitivity of the assay). Moreover, clinically significant cross-reactivity during treatment with danaparoid appears to be uncommon, even in patients in whom in vitro cross-reactivity is demonstrable.

(5) Warkentin TE

CLINICAL PRESENTATION OF HEPARIN-INDUCED THROMBOCYTOPENIA.


Department of Pathology, McMaster University, Hamilton, Ontario, Canada.

Heparin-induced thrombocytopenia (HIT) is an immune-mediated adverse effect of heparin that is important because of its relatively high frequency and its strong association with paradoxic venous and arterial thrombosis. As confirmatory laboratory assays are not always immediately available, physicians usually must make initial diagnostic and treatment decisions based on the clinical presentation alone. Three characteristic features of HIT can be helpful in distinguishing it from other causes of thrombocytopenia: (1) timing of the onset of thrombocytopenia, namely, a platelet count decrease that begins between days 5 and 8 (inclusive) of beginning heparin treatment; (2) mild to moderate severity of the thrombocytopenia, with platelet counts only rarely less than 15 x 10(9)/L; and (3) the development of large-vessel venous or arterial thrombosis in association with thrombocytopenia, or any of a number of unusual characteristic sequelae of HIT (warfarin-associated venous limb gangrene, bilateral adrenal hemorrhagic infarction, heparin-induced skin lesions, or acute systemic reactions following intravenous heparin bolus). In contrast to other drug-induced immune thrombocytopenia syndromes, HIT rarely is associated with bleeding. HIT is relatively common, occurring in as many as 3% of patients who receive unfractionated (UF) heparin for 2 weeks. Between 30% and 75% of patients with HIT develop thrombosis; thus, about 1% of patients who receive a course of heparin develop HIT-associated thrombosis. The observation that HIT is less likely to occur with low-molecular-weight heparin (LMWH) suggests that HIT ultimately may be preventable.

(6) Scheffold N, Maitra R, Cyran J

[HEPARIN-INDUCED THROMBOCYTOPENIA. DIAGNOSIS, CLINICAL COURSE AND THERAPEUTIC ALTERNATIVES].

[ARTICLE IN GERMAN]


Medizinische Klinik I, des Stadtschen Krankenhauses Heilbronn.

Heparins are common and have been widely used in prophylaxis and therapy of thromboembolic disorders for many years. Nevertheless, the serious side effect of heparin-induced thrombocytopenia type II (HIT II) has attracted attention only recently. First evidence of HIT II is a drop in platelet count below 100,000/mm3. Subsequently, thromboembolic complications occur 6-20 days after beginning heparin therapy. Overall mortality is 20-30% of patients with HIT II. Therefore, frequent platelet counts are required for early diagnosis. However, in cases of moderate or absent thrombocytopenia the diagnosis of HIT II can be difficult. Laboratory tests such as heparin-induced platelet activation (HIPA) test or heparin/PF4-antibody-ELISA have limited sensitivity and specificity. Therefore, with typical clinical findings, divergent laboratory results should be interpreted with caution. If HIT II is suspected, all heparins should be discontinued immediately. Due to a high cross reactivity rate with the heparin-dependent antibody, subsequent therapy with low molecular weight heparins (LMWH) is contraindicated. As treatment of choice danaparoid or recombinant hirudin may be administered. Oral anticoagulation should be started cautiously with an alternative immediate-acting antithrombotic agent. More widespread use of LMWH may reduce the incidence of HIT II in the future. Nevertheless, the main and most important factor in the prevention of this life-threatening complication is the awareness and caution of the clinician.

[PREVENTION OF THROMBOEMBOLISM AS A CAUSE OF THROMBOEMBOLIC COMPLICATIONS. A STUDY OF THE INCIDENCE OF HEPARIN-INDUCED THROMBOCYTOPENIA TYPE II].

[ARTICLE IN GERMAN]

Z Orthop Ihre Grenzgeb 1997 Nov-Dec;135(6):543-9

Klinik und Poliklinik für Orthopadie, Ernst-Moritz-Arndt-Universität Greifswald.

PROBLEM: A life-threatening complication of the thrombembolism prophylaxis with heparin is heparin-induced thrombocytopenia (HIT) type II. HIT type II is based on immunological mechanisms. Even low, subcutaneously applied doses may produce HIT type II. In those patients, continued application may cause thromboembolic complications. The most important symptom of HIT type II is a decrease of platelets. METHODS: In a prospective study, we investigated the incidence of HIT type II within the period from 01.07.95 to 30.06.96 in orthopedic patients. We also evaluated the importance of the daily platelet count from the fifth postoperative day for the early diagnosis of HIT type II and a possible reduction of the thrombosis rate. The study included 307 patients after primary implantation of hip and knee endoprosthesis and after hip endoprosthesis replacement. All patients received 3 x 5000 IU/d of unfractionated heparin subcutaneously. Whenever there was a decrease of platelets of at least 50% in relation to the preoperative value or whenever thrombembolic complications occurred, serum was analyzed by the heparin-induced platelet activation test (HIPA). RESULTS: 20 patients developed HIT type II. This corresponds to an incidence of 6.5%. 10 of the HIT type II antibody positive patients (50%) developed thrombembolic complications. 3 patients (0.9%) of the group studied developed clinically symptomatic thrombembolic complications without evidence of heparin antibodies. The total risk of getting thrombembolic complications was 4.2% (13 patients). 3.3% (10 patients) of the entire group developed HIT type II antibody associated thrombembolic complications; 1 patient died. The lethality in the HIT type II antibody positive patient group amounted to 5%. The patients with HIT type II received LMW heparinoid Orgaran (AKZO-Organon, The Netherlands) or hirudin (as a clinical trial). The comparison group (retrospective study from 17.10.92 to 16.10.93) was composed of 262 patients with the same operations and equal thromboembolism prophylaxis. The platelet count was made only as part of routine diagnostic tests. 21 patients (8.0%) developed clinically symptomatic thrombembolic complications. The difference in the thrombosis rate between these two groups of patients is statistically significant. Unrecognized HIT type II is probably the reason for the high thrombembolic complication rate in the comparison group. CONCLUSIONS: The daily platelet count from the fifth postoperative day and from the first day in case of reexposure to heparin is an important measure for the early diagnosis of HIT type II.

(8) Pouplard C, Amiral J, Borg JY, Vissac AM, Delahousse B, Gruel Y

DIFFERENCES IN SPECIFICITY OF HEPARIN-DEPENDENT ANTIBODIES DEVELOPED IN HEPARIN-INDUCED THROMBOCYTOPENIA AND CONSEQUENCES ON CROSS-REACTIVITY WITH DANAPAROID SODIUM.


Laboratoire d'Hematologie-Hemostase, Hopital Trousseau, Tours, France.

Heparin-induced thrombocytopenia (HIT) is frequently associated with antibodies (Abs) to heparin-PF4 complexes (H-PF4). In order to investigate whether there are variations in specificity of Abs, we studied 63 samples from patients with suspected HIT. Two groups of samples were separated after comparing their reactivity against H-PF4 or recombinant PF4 (r-PF4) using ELISA. In group Ab1 (n = 46), Abs only or mainly bound to H-PF4 complexes and thus most of the epitopes recognized probably involved both heparin and PF4. In group Ab2 (n = 17), Abs exhibited similar reactivity to r-PF4 and H-PF4, and the antigens recognized were possibly neoepitopes mainly expressed by modified PF4 and by H-PF4 complexes. Platelet activation tests were positive with 56 samples containing high titres of Abs to H-PF4. Most samples (n = 59) contained IgG antibodies, often associated with IgA antibodies which were more frequently found in group Ab2, and/or IgM. With unfractionated heparin treatment, HIT was associated with Ab1 or Ab2 antibodies, whereas only Ab1 antibodies were detected after low-molecular-weight heparin (LMWH). Furthermore, cross-reactivity with danaparoid sodium was present only in group Ab1 and mainly involved LMWH-treated patients.
A SENSITIVE AND SPECIFIC FUNCTIONAL FLOW CYTOMETRIC ASSAY FOR THE DIAGNOSIS OF HEPARIN-INDUCED THROMBOCYTOPENIA.

*Br J Haematol* 1997 Sep;98(3):648-56

Department of Medicine, Emory University, Atlanta, Georgia, USA.

A functional flow cytometric assay (FCA) for the immediate diagnosis of heparin-induced thrombocytopenia (HIT), with simultaneous compatibility testing for alternative anticoagulant therapies, has been developed to provide rapid and reliable results which effectively support patient management. The assay provides results within 1-2 h, uses readily available non-radioactive reagents, and employs standard equipment. Using the highly sensitive annexin V protein probe, the method detects activated platelets *induced by heparin immune-complexes*, with 300-fold increased binding to activated platelets. Twenty-five samples from patients clinically-suspected of having HIT (131 tests) and 10 normal control (NG) samples (36 tests) were simultaneously tested with unfractionated heparin (UH) and low-molecular-weight heparin (LMWH), and by the radioactive serotonin-release assay (SRA) (62 and 16 tests respectively). The FCA highly correlated with the SRA, showing 100% specificity and 95% sensitivity. Moreover, the FCA exhibited higher resolution between positive and negative samples (an average value of 8.6-fold the NC versus 4.0-fold the NC by SRA). The LMWH showed concordant results with UH (*r* = 0.95). We conclude that the functional FCA for HIT is practical, specific and sensitive, thereby permitting the rapid diagnosis of HIT and the suitability of alternative therapies.

B. LMWH induced Complications

1. LMWH induced Delayed-Type-Hypersensitivity


**DELAYED-TYPE HYPERSENSITIVITY TO SUBCUTANEOUS ENOXAPARIN.**

*Allergy* 1998 Oct;53(10):999-1003

**Seccion de Alergia, Hospital del Rio Hortega, Valladolid, Spain.**

BACKGROUND: Enoxaparin and other low-molecular-weight heparins are widely used to prevent and treat thromboembolic disorders. Cutaneous reactions secondary to enoxaparin injections include delayed hypersensitivity skin reactions described as erythematous, infiltrated plaques at injection sites. We studied three cases of erythematous infiltrated plaques after enoxaparin injection in order to establish the allergenic importance of this low-molecular-weight heparin. METHODS: Patch tests were performed with sodium heparin, calcium heparin, calcium enoxaparin, and calcium nadroparin. A subcutaneous test with calcium heparin and an intravenous challenge test with sodium heparin were done. A punch biopsy was obtained from an erythematous plaque in one patient. RESULTS: Patch tests were negative to calcium heparin in all patients, positive to enoxaparin and nadroparin in two patients, and positive to sodium heparin in one patient. In two patients, the subcutaneous challenge test was positive, the intravenous challenge test was negative, and the histopathologic appearance of the biopsy resembled a delayed-type hypersensitivity reaction. CONCLUSIONS: These cases provide evidence of type IV hypersensitivity and the possibility of crossed-allergenicity among unfractionated heparin and low-molecular-weight heparins. We show that the subcutaneous challenge test is the most reliable diagnostic measure.

(2) Valdes F, Vidal C, Fernandez-Redondo V, Peteiro C, Toribio J

**ECZEMA-LIKE PLAQUES TO ENOXAPARIN.**

*Allergy* 1998 Jun;53(6):625-6

**Departamento de Dermatologia, Facultad de Medicina, Santiago de Compostela, Spain.**
2. LMWH Cholesterol Crystal Embolism

(1) Belenfant X, d’Auzac C, Bariety J, Jacquot C

[CHOLESTEROL CRYSTAL EMBOLISM DURING TREATMENT WITH LOW-MOLECULAR-WEIGHT HEPARIN]. [ARTICLE IN FRENCH]

Presse Med 1997 Sep 13;26(26):1236-7

Service de Nephrologie, Hôpital Broussais, Paris.

BACKGROUND: Cholesterol crystal embolism is often an iatrogenic complication in ulcerated atherosclerosis of the aorta. CASE REPORTS: Two cases of multi-organ embolism of cholesterol crystals were histologically proven in patients treated with low-molecular-weight heparin. Both patients had acute renal failure, hypertension with acute pulmonary edema, skin necrosis and ischemia of the digestive tract. Outcome was favorable after discontinuing anticoagulants, symptomatic treatment, definitive hemodialysis and low-dose corticosteroids. DISCUSSION: These two cases are the first reported in the literature of cholesterol crystal embolism occurring during prophylactic treatment with low-molecular-weight heparin. They demonstrate that there is a risk of severe cholesterol embolism in high-risk patients after administration of low-molecular-weight heparin as for non-fractionated heparin, fibrinolytics, arteriography and cardiovascular surgery. Low-molecular-weight heparin thus should not be used in patients with a diagnosis of cholesterol crystal embolism.

3. LMWH Dermal Necrosis and Thrombocytopenia and Antibodies to H-PF4 Complex

(1) Tietge UJ, Schmidt HH, Jackel E, Trautwein C, Manns MP

LOW MOLECULAR WEIGHT HEPARIN-INDUCED SKIN NECROSIS OCCURRING DISTANT FROM INJECTION SITES AND WITHOUT THROMBOCYTOPENIA.


Department of Gastroenterology and Hepatology, Medizinische Hochschule Hannover, Germany.

In this paper we report a case of 76-year-old white male patient with skin necrosis induced by subcutaneous prophylactic administration of low-molecular-weight heparin (LMWH). Skin necrosis occurred distant from heparin injection sites and without concomitant thrombocytopenia. This is the first reported case presenting these clinical findings.

(2) Santamaria A, Romani J, Souto JC, Lopez A, Mateo J, Fontcuberta J

SKIN NECROSIS AT THE INJECTION SITE INDUCED BY LOW-MOLECULAR-WEIGHT HEPARIN: CASE REPORT AND REVIEW.

Dermatology 1998;196(2):264-5

Departamento de Hemostasia y Trombosis, Hospital de Sant Pau, Barcelona, Espana.

Heparin-induced skin necrosis at the injection site is a rare adverse effect, more commonly associated with standard heparins than with low-molecular-weight heparins (LMWH) and its mechanism remains unclear. We report a case of LMWH-induced skin necrosis in a female during prophylactic treatment with LMWH after a surgical procedure. Determination of heparin-platelet-factor-4(PF4)-induced antibodies was positive. This case describes the occurrence of LMWH-induced skin necrosis and antibodies to heparin-PF4 complex, suggesting that this effect is more frequent than previously suspected.
SKIN NECROSIS SECONDARY TO LOW-MOLECULAR WEIGHT HEPARIN IN A PATIENT WITH ANTIPHOSPHOLIPID ANTIBODY SYNDROME.


Department of Dermatology, Mayo Clinic, Rochester, MN 55905, USA.

Skin necrosis is a rare complication of subcutaneous heparin therapy that usually occurs at injection sites. It occasionally accompanies the heparin-associated thrombocytopenia and thrombosis syndrome. We describe a patient with the antiphospholipid syndrome who had skin necrosis develop from low-molecular weight heparin therapy at sites distant from injection sites.

ENOXPARIN-ASSOCIATED DERMAL NECROSIS: A CONSEQUENCE OF CROSS-REACTIVITY WITH HEPARIN-MEDIATED ANTIBODIES.

Ann Pharmacother 1997 Mar;31(3):323-6

Department of Pharmacy, Barnes-Jewish Hospital, St Louis, MO 63110, USA.

OBJECTIVE: To describe a patient with enoxaparin-induced dermal necrosis and to review previously reported cases of skin manifestations associated with low-molecular-weight heparins. CASE SUMMARY: A 43-year-old white woman with adult respiratory distress syndrome developed localized dermal necrosis and thrombocytopenia secondary to subcutaneous administration of unfractionated heparin. Upper extremity thrombi that had developed after administration of subcutaneous heparin at an outside hospital were treated with subcutaneous enoxaparin. Although platelet counts remained stable during enoxaparin therapy, dermal necrosis developed at the injection site. Parenteral anticoagulant therapy was discontinued and the necrotic lesions secondary to enoxaparin resolved with minimal local care. DISCUSSION: Numerous cases of dermal necrosis secondary to heparin administration have been reported while this reaction secondary to enoxaparin use has been reported only briefly. It has been postulated that dermal necrosis secondary to heparin is associated with heparin-induced thrombocytopenia and is a result of heparin-mediated thrombosis in the microvasculature. Antibodies to heparin have cross-reactivity with enoxaparin; therefore, dermal necrosis secondary to enoxaparin may occur by a similar mechanism. CONCLUSIONS: Although enoxaparin-associated dermal necrosis appears to be a rare occurrence, we advise against the use of enoxaparin or other low-molecular-weight heparins in patients with a previous history of heparin-associated thrombocytopenia or heparin-induced dermal necrosis.

[ENOXPARIN-INDUCED CUTANEOUS NECROSIS LOCALIZED ON INSULIN LIPODYSTROPHIES]. [ARTICLE IN FRENCH]

Ann Dermatol Venereol 1997;124(5):397-400

Clinique Dermatologique, Hopital Claude Huriez, CHRU Lille.

INTRODUCTION: Low-molecular weight heparin-induced cutaneous necrosis is exceptional. Pathogenesis remains unclear. We report an exceptional case with elective localization of the necrotic areas in insulin lipodystrophic tissue. CASE REPORT: A 69-year old patient developed areas of skin necrosis after starting enoxaparin therapy. These areas were located far from the points of injection and focalized on skin areas where the patient had been injecting insulin daily for the last four years. These areas had an aspect of insulin lipodystrophy. Biopsy specimens showed leukocytoclastic vasculitis. There were no associated biological anomalies. One month later, prick-tests were made with different low-molecular weight heparins and calcium heparinate in a lipodystrophic area together with an enoxaparin control test in healthy skin. The only positive test was for enoxaparin in an insulin lipodystrophic area (hard erythema at 24 hours). Histology at 72 hours demonstrated leukocytoclastic vasculitis. DISCUSSION: Six cases of cutaneous necrosis induced by low-molecular weight heparin have been reported, including three cases with enoxaparin. Two pathophysiological mechanisms could be involved: (i) localized heparin-dependent platelet aggregation, or (ii) vasculitis induced by type III hypersensitivity reaction. In our case, the leukocytoclastic aspect of the vasculitis was compatible with an immune complex hypersensitivity reaction. The localization of the necrotic areas would be explained by enoxaparin-induced preferential deposit of immune complexes in the vascular turbulences present in lipodystrophic areas.
(6) Plath J, Schulze R, Barz D, Krammer B, Steiner M, Anders O, Mach J
NECROTIZING SKIN LESIONS INDUCED BY LOW-MOLECULAR-WEIGHT HEPARIN
AFTER TOTAL KNEE ARTHROPLASTY.
Arch Orthop Trauma Surg 1997;116(6-7):443-5

Department of Orthopedics, Faculty of Medicine, University of Rostock, Germany.
We report the unusual complication of focal necrotizing skin lesions accompanied by moderate thrombocytopenia in a female patient undergoing thromboprophylaxis with low-molecular-weight heparin after total knee arthroplasty. Heparin-induced thrombocytopenia was suspected and confirmed using the heparin-induced platelet activation assay. The skin lesions improved gradually after the discontinuation of heparin application. In addition to the description of this exceptionally rare adverse effect of low-molecular-weight heparin, a brief discussion of previously reported cases is provided.

4. LMWH induced Thrombocytosis

(1) Williams E
THROMBOCYTOSIS ASSOCIATED WITH LOW-MOLECULAR-WEIGHT HEPARIN.
Ann Intern Med 1997 May 1;126(9):742-3

5. LMWH Crossreactive AB HIT and Heparin associated Trombocytopenia

a) LMWH Hit 1

(1) Newman PM, Swanson RL, Chong BH
HEPARIN-INDUCED THROMBOCYTOPENIA: IGG BINDING TO PF4-HEPARIN
COMPLEXES IN THE FLUID PHASE AND CROSS-REACTIVITY WITH LOW
MOLECULAR WEIGHT HEPARIN AND HEPARINOID.

Centre for Thrombosis and Vascular Research, Department of Haematology, Prince of Wales Hospital, Randwick, NSW, Australia.
Early diagnosis of heparin-induced thrombocytopenia (HIT) is essential to reduce morbidity and mortality. We report an enzyme immunoassay which detects the binding of HIT IgG to PF4-heparin in the fluid phase. Our fluid phase assay produces consistently low background and can detect low levels of anti-PF4-heparin. It is suited to testing alternative anticoagulants because, unlike in an ELISA, a clearly defined amount of antigen is available for antibody binding. We were able to detect anti-PF4-heparin IgG in 26/28 (93%) HIT patients. We investigated cross-reactivity of anti-PF4-heparin antibodies with PF4 complexed to alternative heparin-like anticoagulants. Low molecular weight heparins cross-reacted with 23/26 (88%) of the sera from HIT patients while half of the HIT sera weakly cross-reacted with PF4-danaparoid (Orgaran). The thrombocytopenia and thrombosis of most of these patients resolved during danaparoid therapy, indicating that detection of low affinity antibodies to PF4-danaparoid by immunoassay may not be an absolute contraindication for danaparoid administration.

(2) Pouplard C, Amiral J, Borg JY, Vissac AM, Delahousse B, Gruel Y
DIFFERENCES IN SPECIFICITY OF HEPARIN-DEPENDENT ANTIBODIES
DEVELOPED IN HEPARIN-INDUCED THROMBOCYTOPENIA AND
CONSEQUENCES ON CROSS-REACTIVITY WITH DANAPAROID SODIUM.

Laboratoire d'Hematologie-Hemostase, Hopital Trousseau, Tours, France.
Heparin-induced thrombocytopenia (HIT) is frequently associated with antibodies (Abs) to heparin-PF4 complexes (H-PF4). In order to investigate whether there are variations in specificity of Abs, we studied 63 samples from patients with suspected HIT. Two groups of samples were separated after
comparing their reactivity against H-PF4 or recombinant PF4 (r-PF4) using ELISA. In *group Ab1* (n = 46), Abs only or mainly bound to H-PF4 complexes and thus most of the epitopes recognized probably involved both heparin and PF4. In *group Ab2* (n = 17), Abs exhibited similar reactivity to r-PF4 and H-PF4, and the antigens recognized were possibly neoepitopes mainly expressed by modified PF4 and by H-PF4 complexes. Platelet activation tests were positive with 56 samples containing high titres of Abs to H-PF4. Most samples (n = 59) contained IgG antibodies, often associated with IgA antibodies which were more frequently found in *group Ab2*, and/or IgM. With unfractionated heparin treatment, HIT was associated with Ab1 or Ab2 antibodies, whereas only Ab1 antibodies were detected after low-molecular-weight heparin (LMWH). Furthermore, cross-reactivity with danaparoid sodium was present only in *group Ab1* and mainly involved LMWH-treated patients.

(3) de Raucourt E, Vinsonneau C, Juvin K, Fischer AM, Meyer G  
**HEPARIN-INDUCED THROMBOCYTOPENIA WITH THROMBOTIC COMPLICATIONS DURING PROPHYLACTIC TREATMENT WITH LOW-MOLECULAR-WEIGHT HEPARIN.**  
*Blood Coagul Fibrinolysis* 1996 Nov;7(8):786-8  
Department of Haematology, Laennec Hospital, Paris, France.  
Heparin-induced thrombocytopenia is very uncommon with low-molecular-weight heparin, especially when given for prophylaxis of venous thromboembolism. In two of the four published cases, with thrombotic complications, thrombocytopenia may have been related to cross-reactivity between unfractionated heparin and low-molecular-weight heparin. We report one patient who received low-molecular-weight heparin for prophylaxis against venous thromboembolism without any previous injection of unfractionated heparin, and experienced thrombocytopenia with thrombotic complications. Heparin-induced thrombocytopenia was confirmed by several laboratory assays. This observation emphasizes the need for platelet count monitoring during low-molecular-weight heparin therapy.

(4) Elalamy I, Potevin F, Lecriubier C, Bara L, Marie JP, Samama MM  
**A FATAL LOW-MOLECULAR-WEIGHT HEPARIN-ASSOCIATED THROMBOCYTOPENIA AFTER HIP SURGERY: POSSIBLE USEFULNESS OF PF4-HEPARIN ELISA TEST.**  
*Blood Coagul Fibrinolysis* 1996 Oct;7(7):665-71  
Service d’Hematologie Biologique, Hotel-Dieu, Paris, France.  
In 37 patients undergoing total hip replacement, a prophylactic treatment by a low-molecular-weight heparin (LMWH) was conducted for 2 weeks. They belonged to a group of 499 patients included in a multicenter clinically controlled trial comparing two LMWHs. Blood was collected 1 day before surgery (D-1) and at D+1 or D+2 and D+5 or D+6 as well as D+10 through D+14 after surgery for determinations of platelets counts and anti-Xa. Bilateral venography was performed between D+10 and D+14. A fatal heparin-associated-thrombocytopenia (HAT) occurred on D+9 in one patient and was associated with a positive platelet aggregation test. This finding was confirmed with a recent ELISA test which evidenced a high concentration of PF4-heparin dependent antibodies 72 h before the detection of thrombocytopenia. This led us to study retrospectively PF4-heparin ELISA results by testing the plasma samples of 36 other surgical patients treated under the same conditions and during the same period (four measurements per patient). Among these patients, seven had a venous thrombotic event as a treatment failure. Although some authors claimed that some post-operative thromboses may be facilitated by the presence of heparin-dependent antibodies associated with or without thrombocytopenia, no thrombocytopenia and no positive PF4-heparin ELISA test was observed in this group. Out of the 144 tests performed in these 36 patients for the detection of PF4-heparin complexes dependent antibodies, 15 results were borderline in ten patients and three results in two patients were positive. No relation was evidenced between a positive ELISA test and the occurrence of venous thrombosis. This study points out the possible usefulness of the PF4-heparin ELISA test for HAT-antibodies detection. A daily platelet count in a postoperative patient under heparin therapy, showing thrombocytopenia associated with the detection of heparin-dependent antibodies could allow an earlier and more reliable diagnosis of HAT.
(1) Eder S, Hamann H
[HEPARIN-INDUCED THROMBOCYTOPENIA TYPE II].
[ARTICLE IN GERMAN]
Chirurg 1999 Oct;70(10):1149-55

Abteilung fur Gefasschirurgie, Kreiskrankenhaus Leonberg.
Heparin-induced thrombocytopenia type II (HIT type II) is an immunoglobulin-mediated, drug-induced side effect for heparin-treated patients with thromboembolic complications. With an incidence of 1-3 %, mortality of 20 % and permanent disability for another 20 % is a clinically relevant disorder. With heparin treatment or prophylaxis frequent platelet count monitoring is necessary. With HIT type II the thrombocytopenia is often a harbinger of thromboembolic complications in the venous or arterial system. If HIT type II is suspected, further heparin exposure is to be stopped immediately and another anticoagulant therapy should be started. The two anticoagulant options in Germany are discussed. At the same time the diagnosis should be confirmed by laboratory testing, including testing for cross-reactivity with danaparoid. Further therapy depends on the symptoms. In the case of clinical relevance of this disorder we should think about prophylaxis: strict indications for perioperative prophylaxis only use of low-molecular-weight heparin (LMWH) for routine prophylaxis, use of LMWH for thrombosis treatment and early change to cumarine.

THROMBOEMBOLIC COMPLICATIONS IN A PATIENT WITH HEPARIN-INDUCED THROMBOCYTOPENIA (HIT) SHOWING CROSS-REACTIVITY TO A LOW MOLECULAR WEIGHT HEPARIN-TREATMENT WITH ORG 10172 (LOMOPARAN).

Department of Internal Medicine II, University of Vienna, Austria.
Heparin-induced thrombocytopenia is an immunomediated life-threatening side effect of heparin therapy which poses difficulties in diagnosis and major therapeutic problems. Heparin must be instantly discontinued. We describe the case of a 60-year-old male patient with type II heparin-induced thrombocytopenia, complicated by progressive deep venous thrombosis and pulmonary embolism. He failed to improve when therapy was continued with a low molecular weight heparin (Fragmin) and high doses of intravenous immunoglobulins were administered. The test for heparin-dependent platelet aggregation was positive for unfractionated heparin and low molecular weight heparin, but negative for the heparinoid Org 10172. During subsequent anticoagulant therapy with Org 10172 for seven days the number of platelets increased rapidly and the patient recovered. Nine months later Org 10172 was used again in this patient for thrombosis prophylaxis without any adverse effects. In patients with heparin-induced thrombocytopenia requiring immediately acting anticoagulant therapy, Org 10172 can be considered as an effective alternative drug to unfractionated and low molecular weight heparins.

(3) Hobbensiefken G, Driller B, Studtmann V, Kunz K, Lehrbach G
[HEPARIN-INDUCED THROMBOCYTOPENIA TYPE II (HIT II) A FATAL COMPLICATION OF HEPARIN USE FOR THROMBOEMBOLISM PREVENTION].
[ARTICLE IN GERMAN]
Unfallchirurgie 1996 Dec;22(6):248-52

Institut fur Anesthesiologie und operative Intensivmedizin, Diakoniekrankenhaus Rotenburg, Wumme.
Heparin-induced thrombocytopenia type II (HIT II) is the most severe complication during prophylactic treatment with low doses of heparin. Five cases demonstrate the life-threatening consequences of this immune-mediated thromboembolic disease. In order to improve prognosis it is most important to start therapy just before diagnosis is assured by laboratory tests. First choice treatment is the low-molecular-weight heparinoid Orgaran. In patients with an episode of HIT II both low-molecular-weight heparin and unfractionated heparin will be contraindicated for a life time.
6. LMWH and Antibody induced Arterial Thromboembolism resulting in Amputation

(1) Markovich GD, Russell JM, Gagne P

ANTIBODY-INDUCED ARTERIAL THROMBOEMBOLISM RESULTING IN AMPUTATION AFTER TOTAL KNEE ARTHROPLASTY.


Department of Orthopaedic Surgery, Portsmouth Naval Medical Center, Virginia 23708, USA.

Heparin-induced thrombocytopenia is a rare drug reaction that can be associated with thrombotic complications leading to myocardial infarct, stroke, or ischemic loss of a limb. Because of the broadening indications of low-molecular-weight heparin use, the current emphasis on ambulatory care, and the difficulty in clinical diagnosis and treatment of this drug reaction, heparin-induced thrombocytopenia is the most important allergic drug reaction that physicians must manage. An antibody-mediated drug reaction to low-molecular-weight heparin that resulted in a below-knee amputation after an elective total knee arthroplasty is reported.

7. LMWH induced Haemorrhage

(1) McNally MA, Cooke EA, Harding ML, Mollan RA

ATTITUDES TO, AND UTILIZATION OF, LOW MOLECULAR WEIGHT HEPARINS IN JOINT REPLACEMENT SURGERY.


Musgrave Park Hospital, Belfast and Leicester General Hospital, UK.

A postal survey was carried out to determine the attitudes to the use of low molecular weight heparin (LMWH) in joint replacement among two representative groups of orthopaedic surgeons practising in the UK. 72% of hip surgeons and 51% of knee surgeons replying had used LMWHs for deep vein thrombosis prophylaxis in joint replacement patients. Of these, 48% had discontinued LMWH use due to bleeding complications. Among those continuing to use LMWHs, 88% had witnessed excessive bruising around the wound and 53% had experienced increased wound bleeding or haematomas. Although LMWHs have been shown to reduce post-operative thromboembolism in these groups, clinical experience has revealed an increased incidence of bleeding complications associated with their use. This has prevented their routine use in joint replacement, as was the case with unfractionated heparin in the past.

(2) Francis CW, Pellegrini VD Jr, Totterman S, Boyd AD Jr, Marder VJ, Liebert KM, Stulberg BN, Ayers DC, Rosenberg A, Kessler C, Johanson NA

PREVENTION OF DEEP-VEIN THROMBOSIS AFTER TOTAL HIP ARTHROPLASTY. COMPARISON OF WARFARIN AND DALTEPARIN.

*J Bone Joint Surg Am* 1997 Sep;79(9):1365-72

Vascular Medicine Unit, University of Rochester School of Medicine, New York 14642, USA.

The effectiveness and safety of warfarin were compared with those of a low-molecular-weight heparin (dalteparin) for the prevention of deep-vein thrombosis after total hip arthroplasty in a prospective, randomized, multi-institutional trial. Patients who were older than eighteen years of age and were scheduled to have an elective primary or revision total hip arthroplasty were eligible; 580 patients were randomized, 550 had the operation and received prophylaxis, and 382 had evaluable venograms. **Prophylaxis** was provided either with **warfarin** beginning the night before the operation or with **dalteparin** beginning two hours before the operation and was continued until venography was performed. Bleeding was assessed on the basis of intraoperative blood loss, transfusion requirements, a decrease in hematocrit, and clinically identified bleeding complications. **The prevalence of deep-vein thrombosis was found to be significantly lower in the patients who had received dalteparin than in those who had received warfarin (twenty-eight [15 per cent] of 192 patients compared with forty-nine [26 per cent] of 190 patients; p = 0.006).** Deep-vein thrombosis occurred in the calf veins of twenty-one patients (11 per cent) who had received dalteparin and of forty-three patients (23 per cent) who
had received warfarin; this difference was significant \( (p = 0.003) \). Proximal deep-vein thrombosis occurred in ten patients \((5 \text{ per cent})\) who had received dalteparin and in sixteen patients \((8 \text{ per cent})\) who had received warfarin; however, with the numbers available, no significant difference could be detected \( (p = 0.185) \). We also could not detect a significant difference with regard to the intraoperative and postoperative blood loss, the decrease in hematocrit, and the prevalence of major bleeding complications between the two groups; however, the patients who had received dalteparin had a significantly higher prevalence of bleeding complications involving the operative site \( (p = 0.03) \), and a significantly greater percentage required postoperative transfusions \( (p = 0.001) \). We concluded that preoperative prophylaxis with dalteparin is significantly more effective than that with warfarin in preventing deep-vein thrombosis after total hip arthroplasty. The greater effectiveness of dalteparin must be considered, however, in light of an increased need for postoperative transfusions and an increase in the prevalence of wound-related bleeding complications.

### Risk Factors


Service de medecine interne, Hotel-Dieu, Paris, France.

Two cases of fatal bleeding in patients treated with low molecular weight heparin for deep vein thrombosis are reported. Risk factors for bleeding were: severe underlying disease (cancer in one case, morbid obesity and cardiac failure in the other), age over 80 years and worsening of renal insufficiency in both cases, recent surgical procedure in one case. Anti-Xa activity was beyond the therapeutic range at the time of bleeding in both cases. The usefulness of biologically monitoring the treatment of deep vein thrombosis with low molecular weight heparin is discussed.

### D. Protein C concentrate (PCC)

#### A. Function and Fields of Use

1. **PC Management of Homozygous Protein C Deficient**


   LONG-TERM MANAGEMENT OF HOMOZYGOUS PROTEIN C DEFICIENCY: REPLACEMENT THERAPY WITH SUBCUTANEOUS PURIFIED PROTEIN C CONCENTRATE.


Department of Hematology, Hospital Universitario de la Princesa, Madrid, Spain.

We present the case of a full-term newborn in whom purpura fulminans developed shortly after birth. A diagnosis of homozygous protein C deficiency was established based upon undetectable plasma protein C activity and antigenemia in the newborn infant, and was later confirmed by protein C gene analysis. Specific replacement therapy with intravenous protein C concentrate was started 9 days after birth. This rapidly led to the complete regression of cutaneous lesions and consumption coagulopathy. After stabilization, oral anticoagulation was initiated in association with prophylactic treatment with intravenous protein C concentrate. However, oral anticoagulation was finally abandoned as the patient presented several thrombotic and hemorrhagic episodes clearly related to difficulties with anticoagulation. Due to the hazards related to prolonged venous access, we are currently using subcutaneous infusion of protein C concentrate for the long-term management of this condition, with satisfactory results.
2. PC in Fulminant Meningococcal Sepsis

(1) Rintala E, Seppala OP, Kotilainen P, Pettila V, Rasi V
PROTEIN C IN THE TREATMENT OF COAGULOPATHY IN MENINGOCOCCAL DISEASE.

Department of Medicine, Turku University Central Hospital, Kiinamyllynkatu, Finland.
OBJECTIVE: To evaluate the clinical and laboratory effects of the substitution of protein C (PC) as an adjunct to conventional therapy in the treatment of purpura fulminans associated with meningococcal sepsis. DESIGN: case series. SETTING: Medical and medical-surgical intensive care units of two university hospitals. PATIENTS: Three patients with purpura fulminans and multiple organ
failure caused by Neisseria meningitidis. **INTERVENTION:** Intravenous administration of PC concentrate (100 IU/kg every 6 to 8 hrs). **MEASUREMENTS AND MAIN RESULTS:** The administration of PC resulted in normal or above normal levels of the plasma PC activity in all patients. The laboratory and clinical parameters reflecting the severity of coagulopathy improved during the treatment, as did peripheral ischemia and the clinical manifestations of multiple organ failure. No adverse events were noted. **One patient died of cerebral edema.** **CONCLUSION:** The administration of PC had a beneficial effect on coagulopathy and peripheral gangrene formation associated with meningococcal disease and showed no adverse effects.

(2) Cahill M
**PROTEIN-C CONCENTRATE FOR MENINGOCOCCAL PURPURA FULMINANS.**

(3) Kreuz W, Veldman A, Escuriola-Ettingshausen C, Schneider W, Beeg
**PROTEIN-C CONCENTRATE FOR MENINGOCOCCAL PURPURA FULMINANS.**

(4) Arul GS, Sacks L, Wolf A, Gargan M, Spicer RD
**PROTEIN-C CONCENTRATE FOR MENINGOCOCCAL PURPURA FULMINANS.**

(5) Roback MG, Stack AM, Thompson C, Brugnara C, Schwarz HP, Saladino RA
**ACTIVATED PROTEIN C CONCENTRATE FOR THE TREATMENT OF MENINGOCOCCAL ENDOTOXIN SHOCK IN RABBITS.**
*Shock* 1998 Feb;9(2):138-42

Department of Medicine, Children's Hospital, Denver, Colorado 80218, USA.
To evaluate the effects of activated protein C therapy in a rabbit model of meningococcal endotoxin-induced shock, we performed a prospective, blinded, placebo-controlled animal trial. Forty New Zealand White rabbits were challenged with intravenous meningococcal endotoxin (lipooligosaccharide) 100 microg/kg. Ten minutes before endotoxin challenge, animals were administered either activated protein C 1600 microg/mL (n = 20) or an equal volume of saline (n = 20) as an initial bolus. After endotoxin challenge, activated protein C treated animals were administered a continuous infusion of activated protein C 160 microg/kg/h and saline-treated animals were administered an equal volume infusion of saline. Both activated protein C treated and saline control animals demonstrated evidence of shock after endotoxin challenge; mean arterial pressure and serum bicarbonate significantly (p < .01) declined, and heart rate significantly (p < .01) increased from baseline. In activated protein C treated animals, mean plasma activated protein C activity was 5.69 microg/mL (+/- 3.2) 1 h after challenge, whereas plasma protein C activity was not detected in controls. Mean prothrombin and activated partial thromboplastin times were significantly (p < or = .01) prolonged compared with saline-treated controls. Other hematologic and chemical measurements did not differ between groups. Fifteen of 20 (75%) animals treated with activated protein C concentrate survived to 24 h, while 9 of 20 (45%) control animals survived to 24 h (p = .05). Those animals treated with activated protein C had improved survival, which corroborates the findings of early clinical studies in which replacement of protein C improved outcome.

**USE OF PROTEIN-C CONCENTRATE, HEPARIN, AND HAEMODIAFILTRATION IN MENINGOCOCCUS-INDUCED PURPURA FULMINANS.**

Department of Paediatric Haematology, National Children's Hospital, Dublin, Ireland.
**BACKGROUND:** Inflammatory and coagulation processes are both affected in meningococcaemia. Severe acquired protein-C deficiency in meningococcaemia is usually associated with substantial mortality; in survivors, skin grafts, amputation, and end-organ failure are not uncommon. **Protein C is a natural anticoagulant and also has important anti-inflammatory activity.** We assessed the effects of early replacement therapy with protein-C concentrate together with continuous veno-venous
haemodiafiltration and conventional treatment in meningococcaemia. METHODS: 12 patients aged between 3 months and 27 years with meningococcaemia and severe acquired protein-C deficiency (mean 0.20 IU/mL) were studied. All patients had septic shock, widespread purpura, skin necrosis, and disseminated intravascular coagulopathy (DIC). After a test dose of protein-C concentrate, patients received a continuous infusion with the dose adjusted daily to keep the plasma concentration between 0.8 and 1.2 IU/mL. 11 patients were given unfractionated intravenous heparin (10-15 IU kg⁻¹ h⁻¹). Nine patients had haemodiafiltration and one had peritoneal dialysis. The Glasgow meningococcal septicaemia prognostic score and the paediatric risk of mortality score predicted a minimum mortality of 80% and 57%, respectively. FINDINGS: No patient died. No adverse reactions to the treatment were seen. Two patients had lower-limb amputations, one of whom had a thrombotic cerebrovascular accident; both patients had received the protein-C concentrate and heparin later than the rest of the group (60 h [16.97] vs 12 h [3.13]). One patient developed chronic renal failure despite receiving protein-C infusion 15 h after admission. INTERPRETATION: The acquired severe deficiency of protein C in meningococcaemia contributes to the pathogenesis of the thrombotic necrotic lesions in the skin and other organs and probably has an important role in the inflammatory response. Protein-C therapy is merely one approach to improve the host response in this syndrome. We suggest that a double-blind, randomised, controlled multicentre trial is needed to confirm our results.

3. PC in VOD

(1) Lee JH, Lee KH, Kim S, Lee JS, Kim WK, Park CJ, Chi HS, Kim SH

RELEVANCE OF PROTEINS C AND S, ANTITHROMBIN III, VON WILLEBRAND FACTOR, AND FACTOR VIII FOR THE DEVELOPMENT OF HEPATIC VENO-OCCCLUSIVE DISEASE IN PATIENTS UNDERGOING ALLOGENEIC BONE MARROW TRANSPLANTATION: A PROSPECTIVE STUDY.

Bone Marrow Transplant 1998 Nov;22(9):883-8

Department of Medicine, Asan Medical Center, University of Ulsan, Seoul, Korea.

Factors that enhance hypercoagulability following BMT may have a pathogenetic role in VOD. To investigate the relevance of hemostatic parameters for the development of VOD, we prospectively measured protein C, protein S, antithrombin III (AT III), von Willebrand factor, and factor VIII in 50 consecutive patients undergoing allogeneic BMT. Each parameter was determined before conditioning, on day 0 of BMT and weekly for 3 weeks, and patients were monitored prospectively for the occurrence of VOD. VOD occurred in 26 patients at median post-BMT day 8.5 (range, day -2 to 17). Thirteen patients had mild, 10 had moderate and three had severe VOD. No coagulation parameters were significantly different at the baseline or on day 0 of BMT between patients with no/mild VOD and moderate to severe VOD. On day 7 and thereafter, levels of protein C and AT III were significantly lower in patients with moderate to severe VOD when compared to patients with no/mild VOD. Levels of protein C and AT III decreased before the clinical onset of VOD in patients with moderate to severe VOD. Early post-BMT reduction of these parameters may indicate the development of moderate to severe VOD.

(2) Heying R, Nurnberger W, Speikerkotter U, Gobel U

HEPATIC VENO-OCCCLUSIVE DISEASE WITH SEVERE CAPILLARY LEAKAGE AFTER PERIPHERAL STEM CELL TRANSPLANTATION: TREATMENT WITH RECOMBINANT PLASMINOGEN ACTIVATOR AND C1-ESTERASE INHIBITOR CONCENTRATE.

Bone Marrow Transplant 1998 May;21(9):947-9

Department for Pediatric Hematology and Oncology, Heinrich-Heine-University Medical Center, Dusseldorf, Germany.

Severe veno-occlusive disease (VOD), characterised by elevated serum bilirubin levels, is a known complication in the first 3 weeks after peripheral blood stem cell transplantation (PBSCT). Severe VOD is associated with capillary leakage and multiple organ dysfunction and leads to high mortality. We report a 17-year-old male, who developed severe VOD with capillary leakage (CL) after allogeneic PBSCT. The patient presented with a maximum serum bilirubin of 25.4 mg/dl, weight gain (10% of baseline weight), generalized edema, cardiovascular insufficiency, complement activation, jaundice and a decreased AT and protein C functional activity. After VOD and CL were diagnosed the patient was
treated with recombinant human plasminogen activator (rt-PA) and C1 esterase-inhibitor concentrate (C1-INH-C). The clinical symptoms resolved and the patient's status stabilized. The patient was in an adequate clinical state 5 months after transplantation. We noted that the combined therapy with rt-PA and C1-INH-C in this high-risk situation led to a resolution of VOD with CL.

4. PC in Thrombophilia

a) Screening for Thrombophilia

(1) Wheeler HB

SHOULD SURGICAL PATIENTS BE SCREENED FOR THROMBOPHILIA?


University of Massachusetts Medical Center, Worcester 01655-0333, USA.

Genetic abnormalities that predispose a patient to venous thromboembolism (VTE) can now be identified. These genetic abnormalities include resistance to activated protein C and deficiencies of antithrombin, protein C, or protein S. Because the risk of VTE in surgical patients is well documented, the question naturally arises as to whether screening for genetic predisposition to VTE is indicated. This paper provides an outline of the need to prevent VTE in surgical patients and a brief review of current criteria for prophylaxis. This paper also provides an evaluation of the possible role for thrombophilia screening for surgical patients, based on perspectives gained from prophylaxis. At present, a small but well-defined group of patients, especially those with idiopathic VTE or a strong family history of the disease, should be screened for thrombophilia. Results from subsequent clinical trials may indicate the need to expand the role of thrombophilia screening.

(2) James CM

THROMBOPHILIA: SOME RECENT ADVANCES IN UNDERSTANDING.


RNH Haslar.

Thrombophilia is a term with many definitions although the majority include criteria such as thrombosis under the age of 45; recurrent thromboembolism and a positive family history. It reflects a disturbance in the normal delicate balance between pro- and anti-coagulation such as to favour inappropriate thrombosis. This review concentrates on the newly described phenomenon of activated protein C resistance while reviewing the natural anticoagulant system. It will also briefly examine the indications for 'thrombophilia' screening and the implications for individuals found to have an abnormality of their natural anticoagulants.

b) PC in Hereditary Thrombophilia

(1) Schild RL, Lobb MO, Voke JM

HEREDITARY THROMBOPHILIA IN A FAMILY WITH THREE INDEPENDENT PROTEIN S AND C MUTATIONS. A CAUSE OF ADVERSE PERINATAL OUTCOME.


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A non-related couple with two independent protein S and a protein C mutation had two of their three children suffering from severe thrombosis resulting in neonatal death of the firstborn. With prenatal testing an accurate prediction of phenotype was possible for the second child but the third infant was more severely affected than had been predicted from the genotype.

5. PC in Factor V Leiden( FVL)
(1) Hagstrom JN, Walter J, Bluebond-Langner R, Amatniek JC, Manno CS, High KA

PREVALENCE OF THE FACTOR V LEIDEN MUTATION IN CHILDREN AND NEONATES WITH THROMBOEMBOLIC DISEASE.

*J Pediatr* 1998 Dec;133(6):777-781

Division of Hematology, Department of Pediatrics, and Division of Neurology, Department of Medicine, University of Pennsylvania, Philadelphia; and The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania.

OBJECTIVE: Resistance to activated protein C (APC) has been identified as a risk factor for thrombotic disease in adults. In over 90% of cases, the basis for the APC resistance is a mutation in the coagulation factor V gene (factor V Leiden) that renders the protein more resistant to inactivation by APC. We sought to determine the prevalence of the factor V Leiden (FVL) mutation in neonates and children who had experienced an arterial or venous thromboembolic event. Study design: We retrospectively analyzed the clinical records of 33 neonates and 52 children with thromboembolic disease. Screening for the FVL mutation was performed by DNA analysis, allowing for identification of patients as normal, heterozygous, or homozygous. RESULTS: Of the 85 patients studied, 12 (14.1%) were heterozygous for FVL; none were homozygous. Of the 47 patients who had arterial central nervous system events, 8 (17%) were positive for the FVL mutation, including 6 of 22 (27%) neonates. Of those patients who had a venous thrombosis, 4 of 32 (12.5%) were FVL positive. None of the 85 patients had protein C deficiency, 3.5% had protein S deficiency, 1.2% had antithrombin III deficiency, and 16.5% had anti-phospholipid antibodies. CONCLUSION: These data suggest that the FVL mutation plays a role in the development of arterial and venous thrombotic events in neonates and children.

(2) Selzman CH, Whitehill TA, Krupski WC

THROMBOPHILIA AND ACTIVATED PROTEIN C RESISTANCE.


In addition to classic vascular insults such as inflammation, trauma, malignancy, and surgery, a number of hereditary coagulation defects predispose patients to a wide array of thrombotic complications. A novel genetic defect in factor V allowing for resistance to its cleavage by activated protein C has recently been implicated in a significant number of cases of familial thrombophilia. A brief case report and review of the literature is presented to familiarize surgeons to this important and quite frequent cause of hypercoagulability.

(3) Hakala L, Vahtera E, Krusius T, Rasi V

[APC RESISTANCE AND BLOOD COAGULATION FACTOR V MUTATION IN FINNISH THROMBOTIC PATIENTS]. [ARTICLE IN FINNISH]

*Duodecim* 1995;111(22):2143-51

SPR:n Veripalvelu, Kivihaantie 7, Helsinki.

6. PC in Endotoxin Shock

(1) Fourrier F, Jourdain M, Tournoys A, Gosset P, Mangalaboyi J, Chopin C

EFFECTS OF A COMBINED ANTITHROMBIN III AND PROTEIN C SUPPLEMENTATION IN PORCINE ACUTE ENDOXICO SHOCK.

*Shock* 1998 Nov;10(5):364-70

Reanimation Polyvalente et Equipe de recherche JE 2084, Hopital R. Salengro, Centre Hospitalier Regional Universitaire, Universite Lille 2, France.

Antithrombin III (ATIII) and protein C (PC) are major inhibitors of the coagulation cascade and might regulate the cytokine network. We tested the possibility that a combined supplementation using these two inhibitors might have synergistic effects on sepsis-induced disseminated intravascular coagulation and shock. Hemodynamics, coagulation parameters, tumor necrosis factor (TNF) alpha, and interleukin 6 levels were measured in pigs submitted to a bolus infusion of Escherichia coli endotoxin.
Four groups were studied: control lipopolysaccharide, ATIII (100 IU/kg), PC (50 IU/kg), and ATIII-PC (same doses). The endotoxin infusion resulted in a typical hypokinetic shock with disseminated intravascular coagulation in all animals. Compared with the control group, a significant improvement in mean arterial pressure and systemic vascular resistance was observed in the PC and ATIII-PC groups. The increase in lactate levels was almost completely blunted in the PC group. A significant lesser increase in TNFalpha levels was observed in the ATIII-PC group. No effects were seen on interleukin 6 levels. Coagulation and fibrinolysis parameters were not improved by ATIII and/or PC, except for a lesser decrease in prothrombin time in the ATIII-PC group. We conclude that in this acute endotoxic model, a combined supplementation using PC and ATIII concentrates has favorable effects on hemodynamic parameters and TNFalpha levels, independently from the anticoagulant actions of these inhibitors.

7. PC Resistance to Activated Protein C by Oral Contraceptives

(1) Spannagl M, Dick A, Assmann A, Heinemann L, Schramm W

RESISTANCE TO ACTIVATED PROTEIN C IN WOMEN USING ORAL CONTRACEPTIVES.


Ludwig Maximilians University Munich, Klinikum Innenstadt, Dept. of Hemostasis and Angiology, Germany.

Resistance to activated protein C (APC resistance) is an important and common risk factor for deep vein thrombosis. The majority of patients with APC resistance carry a mutation on the factor V gene at nucleotid position 1691 (G/A), called factor V Leiden mutation. Besides the factor V Leiden mutation several acquired risk factors like lupus anticoagulant, elevated levels of acute phase proteins (increased plasma levels of factor VIII and fibrinogen), pregnancy, or the use of oral contraceptives are known to induce APC resistance in plasma. We studied the effect of oral contraceptives (OC) on hemostasis variables known to be risk factors for venous thromboembolism, especially looking for acquired APC resistance and the plasmatic factors of the protein C system. We studied 821 women, who were randomly selected and enrolled in the BATER- cohort study (Bavarian Thromboembolic Risk Study), which was carried out in Bavaria (Germany) from 1996 to 1997. Current use of any OC type compared with noncurrent use showed a significantly impaired response to APC. There was no difference in APC response among women currently using OCs of different generations. Coagulation factor VIII was the only factor of the protein C pathway that was not altered under OC use. All other plasmatic factors of the protein C system changed in the expected range as described before. On the other hand, coagulation factor VIII was the only factor of the protein C system which negatively correlated with the APC response in the assays applied. Thus, APC resistance is significantly lower in OC users than in nonusers but cannot be attributed to increased factor VIII levels. Whether a decreased response to APC in OC users is of clinical relevance has to be proven in further studies.

III. THROMBIN INHIBITORS

A. Antithrombin-III (AT-III)

A. Function and Fields of Use

| Biological action: Major coagulation inhibitor in blood, most strongly inhibiting Thrombin, Factor Xa, the activated forms of Factors IX, XI and XII. |
| The normal concentration of Antithrombin in normal Human Plasma is between 0.1 and 0.2 g/l. Normal Antithrombin activity has been estimated to 80-120% |

1. AT-III General aspects
a) AT-III Concentrates

(1) Kanbak M  
**HEPARIN RESISTANCE, ANTITHROMBIN III TREATMENT, AND ACTIVATED CLOTTING TIME VALUES.**  
*Anesth Analg* 1998 Nov;87(5):1215

(2) Astermark J, Lethagen S, Berntorp E  
**[ANTITHROMBIN III CONCENTRATE SEeks ITS THERAPEUTIC ROLE. BE CAREFUL AND WAIT FOR THE RESULTS OF THE STUDIES]! [ARTICLE IN SWEDISH]**  
*Lakartidningen* 1996 Oct 23;93(43):3773-6, 3778

Kliniken for hematologi och koagulation, Universitetssjukhuset MAS, Malmo.

(3) Hellstern P, Moberg U, Ekblad M, Anders CU, Faller B, Muller S  
**IN VITRO CHARACTERIZATION OF ANTITHROMBIN III CONCENTRATES--A SINGLE-BLIND STUDY.**  

Institute of Transfusion Medicine and Immunohematology, Klinikum Ludwigshafen am Rhein, Germany.

Twenty-three lots of five antithrombin III (AT III) concentrates from four manufacturers were analyzed in a single-blind study. All the preparations had been virus-inactivated by pasteurization, and one concentrate had also been treated with solvent/detergent (S/D). AT III activities were determined using two thrombin-based and one factor Xa-based chromogenic substrate assays. AT III antigen was measured by kinetic nephelometry. All AT III assays were tested against the first international reference preparation coded 72/1. In addition, AT III was characterized by crossed immunoelectrophoresis in the presence of heparin and by gel filtration. The following were quantified: heparin cofactor II activity and antigen content, heparin activity, thrombin-AI III complexes, AT III-protease complexes, total protein, albumin, immunoglobulins, glucose and pH. The AT III concentrates differed markedly in terms of their purity and potency. The specific activities of AT III and the ratios of AT III activity to antigen content ranged from 3.4 to 6.9 and from 0.63 to 0.84, respectively. The highest values were found in five lots of the concentrate that had been treated by both pasteurization and S/D. This preparation was the only one that was virtually free of denatured AT III, as judged by crossed immunoelectrophoresis. Marked batch-to-batch variation in AT III potencies was found in two out of the five preparations analyzed. In two out of five lots from one manufacturer, the measured potencies were more than 10% lower than the declared potencies.

b) AT-III Concentrate Virus Safety

**CHARACTERIZATION AND VIRAL SAFETY VALIDATION STUDY OF A PASTEURIZED THERAPEUTIC CONCENTRATE OF ANTITHROMBIN III OBTAINED THROUGH AFFINITY CHROMATOGRAPHY.**  
*Haematologica* 1998 Apr;83(4):305-11

Research and Development Area, Instituto Grifols, Barcelona, Spain.

BACKGROUND AND OBJECTIVE: Antithrombin III (ATIII) concentrates are employed as therapy for congenital or acquired deficiencies. These concentrates are obtained from Cohn's fraction IV1. To improve yields, purity and safety, our group developed a procedure to obtain a pasteurized ATIII concentrate from the supernatant of Cohn's fraction II + III including a highly efficient heparin affinity chromatography purification and pasteurization as a viral inactivation step. DESIGN AND METHODS: Three steps of the manufacturing procedure (Cohn's fraction II + III precipitation, affinity chromatography and pasteurization) were selected to examine their efficacy in inactivating and/or removing the selected viruses. RESULTS: The industrial batches show a purity higher than 99% with approximately 95% native heparin binding ATIII. Only albumin and IgG could be detected at trace
levels (0.07% and 0.16% of the total protein present, respectively). The specific activity of the product was approximately 6.65 IU/mg protein. Five viruses were spiked into the manufacturing starting materials and samples were collected at various points to determine the infection level of virus. The study showed a reduction factor (log 10) $> or = 11.7$ for HIV-1; $> or = 8.1$ for bovine herpes virus (analyzed as a model for herpes and hepatitis B viruses); $> or = 8.1$ for bovine diarrhea virus (model for hepatitis C and G) and $> or = 6.0$ for encephalomyocarditis virus (model for hepatitis A and other non-enveloped viruses).

**INTERPRETATION AND CONCLUSIONS:** No biochemical alterations of the ATIII were detected in the final product. A high viral elimination capacity of the production process was demonstrated. So far, more than 32 million units of ATIII have been transfused in the form of this therapeutic concentrate without any detected seroconversion.

(2) Chang WS, Harper PL

**COMMERCIAL ANTITHROMBIN CONCENTRATE CONTAINS INACTIVE L-FORMS OF ANTITHROMBIN.**

_Thromb Haemost_ 1997 Feb;77(2):323-8

Department of Haematology, University of Cambridge, UK.

The preparation of antithrombin concentrate for clinical use requires a viral inactivation step. In most commercial preparations this is achieved by heat pasteurisation. This process would be expected to alter the conformation of antithrombin from the active native species to an inactive latent (L-form) state (1, 2). To determine if this occurs during commercial preparation and to identify the proportion of the product in the inactive state, we examined the various antithrombin conformations within a therapeutic concentrate. The antithrombin concentrate was separated into five fractions by heparin-Sepharose chromatography. The fraction with the highest heparin affinity retained full activity, whereas the four fractions with reduced heparin affinity (approximately 40% of the total antithrombin) had lost their inhibitory function. These inactive antithrombins were intact, monomeric, thermostable and resistant to unfolding in 8 M urea. Moreover, the protein patterns on isoelectric focusing and non-denaturing-PAGE showed that there were at least two different L-forms with isoelectric points separate from the native active species. Our findings demonstrate that approximately 40% of the antithrombin preparation examined exists as inactive L-forms. The clinical significance of administering this altered material is uncertain.

(3) Highsmith F, Xue H, Chen X, Benade L, Owens J, Shanbrom E, Drohan W

**IODINE-MEDIATED INACTIVATION OF LIPID- AND NONLIPID-ENVELOPED VIRUSES IN HUMAN ANTITHROMBIN III CONCENTRATE.**

_Blood_ 1995 Jul 15;86(2):791-6

Holland Laboratory, Plasma Derivatives Department, American Red Cross, Rockville, MD 20855, USA.

Human plasma-derived protein concentrates intended for clinical use must be treated for viral inactivation to ensure patient safety. This study explored the use of liquid iodine for inactivation of several lipid- and nonlipid-enveloped viruses in an antithrombin III (AT-III) concentrate. Iodine at levels of 0.01% to 0.02% caused between 43% and 94% loss of AT-III activity, as well as degradation of AT-III as shown by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and Western blot analysis. However, addition of up to 0.1% human albumin protected the AT-III against both inactivation and fragmentation. At albumin levels sufficient to retain greater than 75% of AT-III activity, greater than 6 logs of sindbis, encephalomyocarditis, and vesicular stomatitis viruses, greater than 4 logs of pseudorabies, and greater than 3 logs of human immunodeficiency virus were inactivated. Except with sindbis virus, this represented complete inactivation of all the viruses spiked into the AT-III concentrate.

2. AT-III in Coronary Thrombolysis

(1) Conley JC, Plunkett PF

**ANTITHROMBIN III IN CARDIAC SURGERY: AN OUTCOME STUDY.**


Maine Medical Center, Portland 04102, USA.
A retrospective study examined the impact, in heparin resistant patients (HRP), of lyophilized antithrombin III (ATIII) upon five patient outcomes: intensive care unit stay (ICU-S), 24 hour chest tube drainage (CTD in ml), blood and blood product usage (BPU), development of postoperative coagulopathy (PO-Coag), and reoperation for bleeding (Re-Op). Data was collected from the medical records of 311 patients admitted to the hospital between 12/15/95 and 10/24/96. Subjects were divided into three groups based upon heparin resistance and hemostasis medication. Group 1 (n = 109) were HRP treated with increased heparin, Group 2 (n = 100) were HRP receiving ATIII, and Group 3 (n = 102) were non-HRP and served as controls. Group 2 was also subdivided by use of aminocaproic acid and time of ATIII administration. No significant differences were found between the groups for PO-Coag. and Re-Op. However, significant reduction in CTD (p = 0.05) was seen in the aminocaproic acid patients who were treated with ATIII pre-CPB or within the first 20 minutes of CPB. The CTD in this group was (419.37, +/- 72.96) as compared to Group 1 (782.88, +/- 360.94) and Group 3 (766.67, +/- 407.56). Other Group 2 subgroups showed significant differences in BPU, ICU-S and CTD. The results of this study support the notion that early identification and treatment of HRP with ATIII and aminocaproic acid may decrease postoperative blood loss.

(2) Pislaru SV, Pislaru C, Zhu X, Arnout J, Stassen T, Vanhove P, Herbert JM, Meuleman DG, Van de Werf F

COMPARISON OF A SYNTHETIC ANTITHROMBIN III-BINDING PENTASACCHARIDE AND STANDARD HEPARIN AS AN ADJUNCT TO CORONARY THROMBOLYSIS.


Department of Cardiology, University Hospitals Leuven, Belgium.

The effects on alteplase-induced thrombolysis of the synthetic ATIII-binding pentasaccharide SR90107A/ORG 31540 (synthetic pentasaccharide, SP) and of standard heparin (SH) were compared in a copper coil model of coronary artery thrombosis in 6 groups of 10 dogs. After 1 h of occlusion, all animals received intravenously alteplase and aspirin, and were randomly assigned to a 2 h infusion of either saline, or one of two doses of SH (100 IU/kg bolus plus 50 IU/kg/h infusion, or 200 IU/kg bolus plus 100 IU/kg/h infusion), or one of three doses of SP (100 nmol/kg bolus plus 50 nmol/kg/h infusion, 200 nmol/kg bolus plus 100 nmol/kg/h infusion, or 400 nmol/kg bolus plus 200 nmol/kg/h infusion). Coronary angiography was performed every 10 min for 4 h. Appropriate doses of SP and SH enhanced alteplase-induced thrombolysis to a similar extent. In contrast, SP was devoid of any anti-IIa activity or aPTT prolongation.

3. AT-III in Ischemia-Reperfusion Injury

(1) Woodman RC, Ostrovsky L, Teoh D, Payne D, Poon MC, Kubes P

ANTITHROMBIN AND ISCHEMIA/REPERFUSION.

Blood Coagul Fibrinolysis 1998 Apr;9 Suppl 2:S7-15

Department of Medicine, University of Calgary, Alberta, Canada.

Acute inflammation, a localized response that occurs in various diseases, is characterized by neutrophil infiltration into tissues. This process requires neutrophils to initially tether and roll along the endothelium of postcapillary venules before undergoing firm adhesion and emigration out of the vasculature into the tissues. Recently, thrombin has been implicated at multiple sites in the inflammatory cascade, and may represent an important link between inflammation and thrombosis. Our recent studies demonstrate that thrombin is an important mediator of neutrophil-dependent injury in ischemia-reperfusion injury. Furthermore, antithrombin concentrate may be therapeutically efficacious in ischemia-reperfusion injury, as it is capable of attenuating the thrombin-mediated effects on neutrophil-endothelial interactions.

4. AT-III in Acute Lung Injury

a) AT-III Lung Experimental
(1) Abubakar K, Schmidt B, Monkman S, Webber C, deSA D, Roberts R

HEPARIN IMPROVES GAS EXCHANGE DURING EXPERIMENTAL ACUTE LUNG INJURY IN NEWBORN PIGLETS.

Am J Respir Crit Care Med 1998 Nov;158(5 Pt 1):1620-5

Departments of Pediatrics, Radiology, Pathology, and Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada.

Although intrapulmonary fibrin deposition is a pathognomonic feature of acute lung injury, it remains uncertain whether thrombin inhibitors affect clinically important outcomes. We hypothesized that both heparin and antithrombin (AT) concentrate improve gas exchange during experimental respiratory distress syndrome. We also tested whether combination therapy is more beneficial than monotherapy. Forty-eight newborn piglets were randomized within 12 litters to one of four groups in a factorial design: (1) AT; (2) heparin; (3) AT plus heparin; (4) untreated control animals. After lung lavage and 4 h of barovolutrauma, mechanical ventilation was continued for 24 h during which ventilator pressures and inspired oxygen were adjusted to maintain normal blood gases. The arterial/ alveolar oxygen tension ratio (a/A ratio) and the ventilator efficiency index (VEI) at 18 and 24 h were compared by repeated measures analysis of variance (ANOVA). In contrast to our hypothesis, only heparin improved gas exchange, and we found little evidence of an interaction with AT. The a/A ratio was 0.48 +/- 0.27 (mean +/- SD) in the presence of heparin versus 0.33 +/- 0.26 in its absence; p = 0.01. Corresponding VEI was 0.30 +/- 0.12 versus 0.25 +/- 0.14; p = 0.04. Hyaline membrane formation was also decreased in heparin-treated animals (p = 0.02).

(2) Schmidt B, Davis P, La Pointe H, Monkman S, Coates G, deSa D

THROMBIN INHIBITORS REDUCE INTRAPULMONARY ACCUMULATION OF FIBRINOGEN AND PROCOAGULANT ACTIVITY OF BRONCHOALVEOLAR LAVAGE FLUID DURING ACUTE LUNG INJURY INDUCED BY PULMONARY OVERDISTENTION IN NEWBORN PIGLETS.


Department of Pediatrics, McMaster University Hamilton, Ontario, Canada.

We determined whether antithrombin (AT III) or hirudin (a specific thrombin inhibitor) reduce both the accumulation of fibrinogen in lung parenchyma and the procoagulant activity of bronchoalveolar lavage (BAL) fluid during acute lung injury induced by pulmonary overdistention. Newborn piglets were randomized to six-hourly infusions of AT III concentrate, a continuous infusion of recombinant hirudin, or no anticoagulant therapy. All animals were subjected to 24 h of identical mechanical ventilation at high peak pressures (3.9 kPa or 40 cm H2O). Tidal volumes were raised to a mean of 69 mL/kg in all three groups. Mean AT III levels in supplemented piglets (n = 22) were increased to 1.46 (SD 0.24) U/mL at 24 h, compared with 0.67 (SD 0.16) U/mL in controls (n = 23). The median activated partial thromboplastin time in animals receiving hirudin (n = 18) was prolonged to 53 s versus 34 s in untreated animals. The intrapulmonary accumulation of i.v. administered 125I-fibrinogen was reduced by AT III concentrate or hirudin, compared with untreated littermates (p = 0.003). The procoagulant activity of BAL fluid was also decreased by both thrombin inhibitors (p = 0.001). Intrapulmonary accumulation of fibrinogen and the procoagulant activity of BAL fluid were reduced by AT III or hirudin during lung injury caused by pulmonary overdistention. Future investigations should determine whether tangible clinical benefits result from this reduced potential for fibrin deposition in the injured lung.

b) AT-III Newborn Clinic RDS


A PLACEBO-CONTROLLED RANDOMIZED TRIAL OF ANTITHROMBIN THERAPY IN NEONATAL RESPIRATORY DISTRESS SYNDROME.


Departments of Paediatrics, Radiology, and Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada. schmidt@fhs.mcmaster.ca
Neonatal respiratory distress syndrome (RDS) is associated with decreased plasma activity of antithrombin (AT) and increased formation of thrombin. We tested whether AT reduces thrombin formation, improves gas exchange, and decreases the duration of mechanical ventilation and supplemental oxygen. One hundred twenty-two infants were randomized to pasteurized AT concentrate or to placebo. Two ml/kg (equivalent to 100 IU AT/kg) were followed by 1 ml/kg (50 IU/kg) every 6 h for 48 h. Outcome measures included plasma AT activity, thrombin-AT (TAT) complex, prothrombin fragment (F1+2), the ratio of arterial to alveolar oxygen pressure [(a/A)PO2], and the ventilator efficiency index (VEI). In the AT group (n = 61), mean (SD) birth weight was 1,198 (301) g, mean (SD) gestational age (GA) was 28.3 (2.0) wk, 54% were male. In the placebo group (n = 61), mean (SD) birth weight was 1,201 (315) g, mean (SD) GA was 28.8 (2.3) wk, 51% were male. In treated infants, AT activity was raised to means of 1.69 and 2.25 U/ml at 24 and 48 h, respectively. Corresponding means in control infants were 0.37 and 0.44 U/ml (p < 0.0001). F1+2, but not TAT, was significantly reduced by AT (p = 0.004). VEI and (a/A)PO2 were similar in both groups throughout the first week of life. Median days receiving mechanical ventilation were 7.1 (AT) versus 4.8 (placebo), p = 0.0014. Median days receiving supplemental oxygen were 7.9 (AT) versus 5.5 (placebo), p < 0.0001. There were seven (11.5%) deaths in the AT group and three (4.9%) deaths in the placebo group. We conclude that treatment with AT cannot be recommended in premature infants with RDS.

(2) Schmidt B, Davis P, La Pointe H, Monkman S, Coates G, deSa D
THROMBIN INHIBITORS REDUCE INTRAPULMONARY ACCUMULATION OF FIBRINOGEN AND PROCOAGULANT ACTIVITY OF BRONCHOALVEOLAR LAVAGE FLUID DURING ACUTE LUNG INJURY INDUCED BY PULMONARY OVERDISTENTION IN NEWBORN PIGLETS.

We determined whether antithrombin (AT III) or hirudin (a specific thrombin inhibitor) reduce both the accumulation of fibrinogen in lung parenchyma and the procoagulant activity of bronchoalveolar lavage (BAL) fluid during acute lung injury induced by pulmonary overdistention. Newborn piglets were randomized to six-hourly infusions of AT III concentrate, a continuous infusion of recombinant hirudin, or no anticoagulant therapy. All animals were subjected to 24 h of identical mechanical ventilation at high peak pressures (3.9 kPa or 40 cm H2O). Tidal volumes were raised to a mean of 69 ml/kg in all three groups. Mean AT III levels in supplemented piglets (n = 22) were increased to 1.46 (SD 0.24) U/ml at 24 h, compared with 0.67 (SD 0.16) U/ml in controls (n = 23). The median activated partial thromboplastin time in animals receiving hirudin (n = 18) was prolonged to 53 s versus 34 s in untreated animals. The intrapulmonary accumulation of i.v. administered 125I-fibrinogen was reduced by AT III concentrate or hirudin, compared with untreated littermates (p = 0.003). The procoagulant activity of BAL fluid was also decreased by both thrombin inhibitors (p = 0.001). Intrapulmonary accumulation of fibrinogen and the procoagulant activity of BAL fluid were reduced by AT III or hirudin during lung injury caused by pulmonary overdistention. Future investigations should determine whether tangible clinical benefits result from this reduced potential for fibrin deposition in the injured lung.

(3) Schmidt BK
ANTITHROMBIN III DEFICIENCY IN NEONATAL RESPIRATORY DISTRESS SYNDROME.
Blood Coagul Fibrinolysis 1994 Jan;5 Suppl 1:S13-7; discussion S59-64

Neonatal respiratory distress syndrome (RDS) is an acute lung injury believed to result primarily from surfactant deficiency in the immature lung. Although surfactant replacement therapy has improved the outcome of this disease, RDS remains a major cause of neonatal mortality and morbidity. Preliminary experimental evidence suggests that unopposed intravascular thrombin activity may contribute to the progression of RDS by promoting high permeability pulmonary oedema and pulmonary hypertension. In the extravascular lung compartment, polymerizing fibrin may inhibit surfactant function. In addition, interstitial and alveolar thrombin formation and resulting fibrin deposition may contribute to the development of chronic lung disease through
amplification of inflammation and fibrosis. There is good evidence that extravascular coagulation occurs during the course of RDS. Fibrin is a major component of the hyaline membranes, which are a hallmark of acute lung injury, and which can be regarded as locally produced clots. It has been less certain whether neonatal RDS is also associated with intravascular activation of the coagulation system. Although low levels of antithrombin III (AT III) have been reported in infants with RDS, direct evidence of increased intravascular thrombin formation has been lacking. However, recently, plasma concentrations of thrombin-antithrombin III (TAT) complexes have been measured in infants with RDS and correlated with RDS severity. TAT formation was significantly increased in severe neonatal RDS, while free AT III activity was decreased. These data are consistent with increased thrombin generation and resulting AT III consumption. Therefore, to regulate thrombin activity, infants with severe RDS may benefit from replacement therapy with AT III concentrate. This hypothesis has been strengthened by experiments that have demonstrated the efficacy of thrombin inhibition in several animal models of acute lung injury. However, controlled clinical trials will be required to determine whether thrombin is just a coincidental marker of neonatal RDS, or whether unopposed thrombin activity exacerbates the disease process.

THROMBIN/ANTITHROMBIN III COMPLEX FORMATION IN THE NEONATAL RESPIRATORY DISTRESS SYNDROME.
Am Rev Respir Dis 1992 Apr;145(4 Pt 1):767-70

Department of Pediatrics, McMaster University, Hamilton, Ontario, Canada.
Intravascular and intra-alveolar thrombin generation may exacerbate the pulmonary hypertension and surfactant dysfunction that characterize the neonatal respiratory distress syndrome (RDS). Although low levels of the most important thrombin inhibitor, antithrombin III (AT III), have been reported in infants with RDS, direct evidence of increased intravascular thrombin generation has been lacking. Accordingly, the objective of this study was to determine whether thrombin generation is increased in severe neonatal RDS. Thirty-nine infants of 25 to 29 wk gestation with a clinical and radiologic diagnosis of RDS were enrolled in a prospective cohort study. Plasma levels of thrombin/antithrombin III complexes (TAT) and AT III activity, measured 36 to 72 h after birth, were related to RDS severity. Seventeen infants had severe RDS (mean airway pressure greater than 10 cm H2O or FlO2 greater than 0.8), and 22 had mild or moderate disease. Mean birthweight (1,017 versus 1,054 g) and mean gestational age (27.8 versus 27.4 wk) were similar in both groups. The median TAT level in infants with severe RDS was significantly higher than that in patients with mild or moderate disease (10.7 and 4.0 micrograms/L, respectively; p less than 0.001). In addition, the mean AT III activity in infants with severe RDS was significantly lower than that in less severely affected patients (0.31 and 0.46 U/ml, respectively; p less than 0.01). Considering the entire cohort, plasma TAT levels were inversely correlated with the arterial/alveolar oxygen tension ratio (r = -0.48, p = 0.0022) and the ventilator efficiency index (r = -0.51, p = 0.0011). The elevated TAT levels and reduced AT III activity in infants with severe RDS are consistent with increased thrombin generation and resulting AT III consumption. Therefore, to regulate thrombin activity, these infants may benefit from replacement therapy with AT III concentrate.

5. AT-III Concentrate in AT-III Deficiency

a) AT-III Concentrate general use in Deficiency

(1) Bucur SZ, Levy JH, Despotis GJ, Spiess BD, Hillyer CD
USES OF ANTITHROMBIN III CONCENTRATE IN CONGENITAL AND ACQUIRED DEFICIENCY STATES.

Department of Pathology and Laboratory Medicine, Emory University School of Medicine, Atlanta, Georgia, USA.

b) AT-III Concentrate in Congenital Deficiency
1. **USE OF ANTITHROMBIN III CONCENTRATES TO CORRECT ANTITHROMBIN III DEFICIENCY DURING VASCULAR SURGERY.**


Department of Surgery, Uniformed Services University of the Health Sciences, Bethesda, USA.

**Concentrate**

**Congenital deficiency of antithrombin III (AT III)** is the only inherited hypercoagulable disorder for which a concentrate of purified protein is available for replacement therapy during periods of increased thrombotic risk. This report describes how such concentrates have been used in a patient with congenital AT-III deficiency undergoing venous surgery. A 40-year-old woman with AT III deficiency was evaluated for bilateral grade 3 chronic venous insufficiency. Noninvasive venous assessment and ascending venography revealed incompetence of the lower leg perforators, a patent deep venous system, and competent greater and lesser saphenous veins. Staged subfascial ligations were performed. Pasteurized AT III was administered 1 hour before surgery and at 30 hours at a dose calculated to increase AT-III activity to at least 120%. Perioperative AT III activity levels were measured. Subcutaneous heparin and oral warfarin were initiated the evening of surgery. An infusion of AT III increased plasma AT III from the baseline activity of 51% to 180%; it was 87% 13 hours later. Two measurements of the initial half-life of AT III were 7 and 14 hours. No perioperative thrombotic complications occurred. The ulcers healed, and the patient remains symptom free. Pasteurized AT III concentrates are now commercially available, easily administered, and provide a useful adjunct to the anticoagulation regimen of patients with AT III deficiency undergoing vascular surgery.

**c) AT-III Concentrate in Acquired Deficiency**

1. **THE PLASMA TURNOVER OF TRANSFUSED ANTITHROMBIN CONCENTRATE IN PATIENTS WITH ACQUIRED ANTITHROMBIN DEFICIENCY.**


Department of Haematology, Addenbrookes Hospital, Cambridge, UK.

**Antithrombin concentrate,** prepared from human plasma, has been used as replacement therapy in 35 patients with acquired antithrombin deficiency. The inhibitory activity of the concentrate, measured by chromogenic assay, correlates well with the manufacturer's quoted activity. The mean in vivo recovery of the product was 0.0124 iu mL-1 per iu of antithrombin (AT) concentrate administered by kilogram body weight. The recovery was similar in all diagnostic groups studied and did not vary during the course of treatment. Consumption of the antithrombin concentrate was monitored by measuring the production of thrombin-antithrombin complexes and the loss of plasma antithrombin activity. The mean concentration of thrombin-antithrombin complexes was elevated (23 ng mL-1) at the time of admission to the intensive care unit and fell progressively over the next 4 days. The mean time for the decay of half the antithrombin activity was 23 h during the first 24 h of therapy and rose to 42.1 h after day 1. The recovery and half-life measurements are necessary to plan an appropriate dosage regimen for the administration of this antithrombin concentrate in acquired deficiency states.

**6. AT-III in Venous Thrombosis**

1. **ANTITHROMBIN CONCENTRATE ALONE MAY NOT PREVENT VENOUS THROMBOEMBOLISM FOLLOWING NEUROSURGERY.**

*Br J Haematol* 1998 Nov;103(2):583-4

**7. AT-III in Leukemia**
(1) Chojnowski K, Wawrzyniak E, Trelinski J, Niewiarowska J, Cierniewski C

*ASSESSMENT OF COAGULATION DISORDERS IN PATIENTS WITH ACUTE LEUKEMIA BEFORE AND AFTER CYTOSTATIC TREATMENT.*

*Leuk Lymphoma* 1999 Dec;36(1-2):77-84

Department of Hematology, Institute of Internal Medicine, Medical University of Lodz, Poland.

Coagulation disorders are often the reason for fatal bleeding in acute promyelocytic leukemia. Their occurrence as well as pathogenesis and prognostic significance in other subtypes of acute myelogenous leukemia and acute lymphoblastic leukemia is less known. Tests were carried out in 70 patients including 49 with AML and 21 with ALL. In all patients thrombin-antithrombin complexes (TAT), D-dimer (DD) and plasmin-antiplasmin complexes (PAP), antithrombin III activity, fibrinogen/fibrin degradation products, APTT and PT were determined. The tests were performed on diagnosis and after cytostatic treatment. The level of TAT, DD and PAP was elevated in 83% of the patients on diagnosis and in 90% after treatment. The highest values were observed in AML M3 patients. Among leukemic patients with normal levels of TAT, DD and PAP at diagnosis, cytostatic treatment had a negligible effect on the level of these markers. During remission the levels of these markers returned to the normal values while in patients without remission they were either elevated or returned to normal values. No correlation between the levels of activation markers and remission rate was reported. DIC was diagnosed in 13 patients including three after chemotherapy. The DIC was acute or subacute in AML and chronic in ALL patients. In the majority of acute leukemia patients there were already changes on diagnosis indicating coagulation activation. Except for AML M3, these usually had a subclinical course. The TAT, DD and PAP tests are not reliable markers of remission in acute leukemias.


*[CHANGES IN HEMOSTASIS OF DOGS WITH ACUTE LYMPHOBLASTIC LEUKEMIA]. [ARTICLE IN GERMAN]*

*Berl Munch Tierarztl Wochenschr* 1998 Feb;111(2):53-9

Klinik fur kleine Haustiere der Tierarztlichen Hochschule Hannover.

Twelve dogs suffering from acute lymphoblastic leukaemia were investigated concerning the following tests: platelet count, prothrombin time (PT, standard test, modified test), activated partial thromboplastin time (APTT), activity of the individual coagulation factors II, V, VII, X, VIII:C, IX, XI, XII, prekallikrein, and high-molecular weight kininogen, the activity of antithrombin III (AT III), protein C, plasminogen, and alpha 2-antiplasmin as well as concentration of fibrinogen, soluble fibrin and fibrin(ogen) degradation products (FDP). All patients showed a decreased platelet count due to suppression of megakaryopoesis by infiltration of the bone marrow with leukaemic cells. In addition, in most of the patients a moderate activity decrease of one or more individual coagulation factors has been found, especially regarding factor II (median, x0.50 = 51%, p = 0.0001), but also factors X (x0.50 = 71%, p = 0.0003) and XI (x0.50 = 68%, p = 0.0006). This was reflected by the APTT and the PT activity (modified test), which were prolonged or decreased, respectively, in the majority of the cases. Furthermore, the activity of AT III and of plasminogen was distinctly diminished (p < 0.001). Like the concentration of FDP, the plasma level of soluble fibrin was significantly higher than in normal dogs (p < 0.001). This indicates that besides thrombocytopenia disseminated intravascular coagulation occurs frequently in dogs with acute lymphoblastic leukaemia and is a main cause for the decreased activity of several plasmatic components of the haemostatic system. The lack of correlation between the concentration of soluble fibrin as an indicator of intravascular coagulation and the total blast cell count (rS = 0.011) shows the importance of other factors like degree of cell lysis as well as participation of organs such as the liver for generation of consumption coagulopathy in dogs with acute lymphoblastic leukaemia.


*INHIBITION OF HYPERCOAGULATION BY ANTITHROMBIN SUBSTITUTION IN E. COLI L-ASPARAGINASE-TREATED CHILDREN.*

*Eur J Haematol* 1996 Jan-Feb;56(1-2):35-8

Department of Paediatrics, University Hospital, Munster, Germany.
Acquired deficiency of antithrombin (AT), which in some patients could lead to thrombosis, has been a serious side effect of protocols which incorporate E. coli L-asparaginase (ASP) for the treatment of acute lymphoblastic leukaemia (ALL). In a longitudinal, prospective, non-randomized study children with ALL (n=27) were treated according to the protocol ALL-BFM-90. During the induction phase using prednisone, vincristine, daunorubicin and ASP, AT substitution was performed in 15/27 patients, when their plasma concentration decreased below 60% of normal with a concomitant increase of D-dimer formation. After the administration of the AT concentrate the patients, plasma concentration of AT increased and remained elevated after 18, 48, and 72 h. In addition, the plasma concentration of enhanced thrombin generation, D-dimer formation and plasminogen activator inhibitor 1 decreased towards normal levels. Although the observed laboratory findings may serve as evidence for a possible clinical benefit of AT substitution during ASP treatment, further randomized studies are requested to evaluate whether the use of prophylactic AT administration could reduce the incidence of thromboembolic events in childhood acute leukaemia.

(4) Mazzucconi MG, Gugliotta L, Leone G, Dragoni F, Belmonte MM, De Stefano V, Chistolini A, Tura S, Mandelli F

Haematology Department, University La Sapienza, Rome, Italy.

Thrombotic events have been reported in acute lymphoblastic leukaemia patients, especially during or after L-asparaginase administration. A so-called L-asparaginase associated coagulopathy has been well recognized, being characterized by a hypercoagulable state (decrease of antithrombin III, plasminogen, protein C, protein S and increase of prothrombin fragment F1 + 2, thrombin-antithrombin complexes and fibrinopeptide A). The aim of this study was to determine whether the supplementation of antithrombin III (AT-III) concentrates could improve the L-asparaginase associated coagulopathy, thereby blocking the activation of the haemostatic system. In 25 adult patients with acute lymphoblastic leukaemia (M 19, F6, mean age 34 years) antithrombin III (AT-III) concentrates were administered at daily doses of 50 U/kg for 10 consecutive days from the beginning of L-asparaginase therapy (6,000 U/m2/day s.c. for 7 days), given according to the GIMEMA ALL 0288 trial. A marked increase of antithrombin III was recorded on days IV-VIII-XI (P < 0.001). No changes in protein C, protein S, plasminogen, alpha 2-antiplasmin, factor VII and platelet count were observed and there was no increase in markers of hypercoagulability. There was no evidence of disseminated intravascular coagulation. In conclusion, AT-III concentrate supplementation during L-asparaginase therapy, by the achievement of high levels of antithrombin III, is associated with a lack of activation of the haemostatic system and appears to overcome the complex coagulopathy associated with L-asparaginase.

(5) Pogliani EM, Parma M, Baragetti I, Mostarda G, Rivolta F, Maffe P, Corneo G

Istituto di Scienze Biomediche dell'Università di Milano, Italy.

It is well known that L-asparaginase (L-Ase) treatment may cause thrombotic events in patients with acute lymphoblastic leukaemia (ALL). The mechanism of this effect is not well understood although a reduction in plasma antithrombin III (AT III) levels is observed. In our study, a group of patients treated with L-Ase received AT III concentrates as adjuvant treatment. This adjuvant treatment reduced the levels of plasma D-dimer and thrombin-antithrombin complex, which are considered as early markers of a hypercoagulability state. These preliminary data suggest that large randomized trials will have to be conducted to improve our understanding of the role of AT III concentrates in ALL therapy.
(6) Moriki T, Murata M, Kizaki M, Kawai Y, Watanabe K, Ikeda Y
ACUTE PROMYELOCYTIC LEUKEMIA DEVELOPED IN A PATIENT WITH CONGENITAL ANTITHROMBIN III DEFICIENCY.

Department of Internal Medicine, School of Medicine, Keio University, Tokyo, Japan.

A case of acute promyelocytic leukemia (AML) developed in a patient with congenital antithrombin III (AT-III) deficiency is reported. Despite the presence of disseminated intravascular coagulation (DIC), plasma AT-III activity was not decreased at the diagnosis of AML compared to the patient's baseline level (approximately 50% of normal). He was successfully treated with all-trans retinoic acid (ATRA) to achieve complete remission without the use of heparin. Although he developed phlebitis at the site of insertion of the intravenous catheter during remission-induction, no major thrombotic episode was noted. Coagulation parameters including fibrin and fibrinogen degradation products (FDP-E), thrombin-antithrombin complex (TAT), FDP-D dimer (D-D dimer), and plasmin-alpha 2 plasmin inhibitor complex (PIC) improved rapidly after initiation of ATRA. This case is a clear demonstration of the characteristics of DIC developing in AML, i.e. no or minimal decrease in the level of AT-III activity and a predominant increase in the fibrinolytic system, rather than hypercoagulability.

(7) Cetkovsky P, Koza V, Cepelak V, Vit L
THE INFLUENCE OF INDUCTION CHEMOTHERAPY AND REMISSION STATUS ON HAEMOSTASIS IN PATIENTS TREATED FOR ACUTE MYELOID LEUKAEMIA.

Department of Medicine I, Charles University Teaching Hospital, Czech Republic.

Haemostatic parameters were studied in 31 adult patients treated for acute myeloid leukaemia (AML) using the 3 + 7 regimen. Lower values of antithrombin III (AT-III), alpha 2-antiplasmin (alpha 2AP) and plasminogen were observed on days 8 and 14 (P < 0.05). Fibrinopeptide A (FpA) levels were higher at diagnosis (P < 0.05), increased again during chemotherapy on days 4 and 8 and eventually returned to the normal range. Tissue plasminogen activator, plasminogen activator inhibitor, protein C and fibrinogen degradation products were normal throughout the period of observation. Complete remission (CR) was achieved in 19 of 31 patients (61%). In order to compare haemostatic changes in CR patients with those in refractory cases, patients were divided into two groups. In patients with refractory AML (n = 12) AT-III, plasminogen and alpha 2 AP were significantly lower than in those in CR. FpA levels were increased in all patients at diagnosis. This elevation progressed in both groups during chemotherapy (on days 4 and 8) and then normalized only in patients in CR. However, in resistant patients, higher FpA values persisted or even increased further on day 14. The fact that none of our patients suffered from clinically manifest thrombotic complications suggested that haemostasis was well compensated and the observed changes were of no clinical importance, even if they were significant statistically.

ANTITHROMBIN III INFUSION SUPPRESSES THE HYPERCOAGULABLE STATE IN ADULT ACUTE LYMPHOBLASTIC LEUKAEMIA PATIENTS TREATED WITH A LOW DOSE OF ESCHERICHIA COLI L-ASPARAGINASE. A GIMEMA STUDY.

Haematology Department, University La Sapienza, Rome, Italy.

Thrombotic events have been reported in acute lymphoblastic leukaemia patients, especially during or after L-asparaginase administration. A so-called L-asparaginase associated coagulopathy has been well recognized, being characterized by a hypercoagulable state (decrease of antithrombin III, plasminogen, protein C, protein S and increase of prothrombin fragment F1 + 2, thrombin-antithrombin complexes and fibrinopeptide A). The aim of this study was to determine whether the supplementation of antithrombin III (AT-III) concentrates could improve the L-asparaginase associated coagulopathy, thereby blocking the activation of the haemostatic system. In 25 adult patients with acute lymphoblastic leukaemia (M 19, F6, mean age 34 years) antithrombin III (AT-III) concentrates were
administered at daily doses of 50 U/kg for 10 consecutive days from the beginning of L-asparaginase therapy (6,000 U/m²/day s.c. for 7 days), given according to the GIMEMA ALL 0288 trial. A marked increase of antithrombin III was recorded on days IV-VIII-XI (P < 0.001). No changes in protein C, protein S, plasminogen, alpha 2-antiplasmin, factor VII and platelet count were observed and there was no increase in markers of hypercoagulability. There was no evidence of disseminated intravascular coagulation. In conclusion, AT-III concentrate supplementation during L-asparaginase therapy, by the achievement of high levels of antithrombin III, is associated with a lack of activation of the haemostatic system and appears to overcome the complex coagulopathy associated with L-asparaginase.

(9) Rodeghiero F, Castaman G, Gugliotta L, Mattioli Belmonte M, Falanga A, Bottasso B, Barbui T, Mannucci PM
SUPRANORMAL ANTITHROMBIN III LEVELS INDUCED BY CONCENTRATE ADMINISTRATION ARE INEFFECTIVE IN QUENCHING THROMBIN GENERATION IN ACUTE PROMYELOCYTIC LEUKEMIA.

Department of Hematology, San Bortolo Hospital, Vicenza, Italy.

Coagulation abnormalities occurring in patients with acute promyelocytic leukemia (APL) are partially corrected by heparin administration. This study was undertaken to verify if "supranormal" levels of antithrombin III (AT-III) are similarly able to quench intravascular thrombin generation triggered by APL cells. Eight patients with APL were randomly assigned to receive either 50 U/kg (Group A) or 100 U/kg (Group B) of an AT-III concentrate, starting on the first day of chemotherapy and continuing for 7 days thereafter. Fibrinopeptide A (FPA), prothrombin fragment F1+2 and thrombin-AT III complexes, measured before and 15 minutes after each AT-III infusion, decreased significantly after each infusion, but the effect was minimal and short-lived, despite the achievement of post-infusion levels of AT-III activity well above 150% (Group A) or 200% (Group B). Small amounts of heparin were consistently detected in AT-III concentrates and post-infusion plasma samples. The short-lived quenching of thrombin generation after AT-III concentrate could be partially explained by the infusion of heparin, rather than by supranormal AT-III levels.

(10) Atlihan F, Karakas Z, Batun S
PROTEIN C AND ANTITHROMBIN III IN CHILDREN WITH ACUTE LEUKEMIA.

Department of Pediatrics, Dicle University Faculty of Medicine, Diyarbakir.

In this study Protein C (PC) and antithrombin III (AT III) levels in childhood acute leukemia were investigated. The mean PC activity levels in 19 newly diagnosed cases of acute leukemia were significantly lower as compared with the normal controls (p < 0.05). A significant increase was found (p < 0.01) in the patients in remission. Prior to treatment 78.8 percent of patients had decreased PC activity levels, but all patients had normal PC activity during remission. Decreased PC activity levels were found to be independent of the leukocyte count and liver function. No statistically significant difference was found in the AT III antigen levels between the untreated patients, the patients in remission and the control group. Our results indicate that apart from thrombocytopenia, low PC activity levels and alterations in fibrinolysis and coagulation may be responsible for the hemorrhagic manifestations observed in cases of acute leukemia.

[CHANGES IN BLOOD COAGULATION IN TREATMENT WITH ALL-BFM-90 AND NHL-BFM-90 PROTOCOLS]. [ARTICLE IN GERMAN]

Universitäts-Kinderklinik Freiburg.

1. Treatment according to the ALL/NHL-BFM 90 protocol I (induction phase) caused multiple and severe coagulation changes in all 14 patients of our study. Glucocorticoids alone made Fibrinogen drop to 148 mg/dl, AT III and Protein C rise to 136% or even 179% respectively. After day 12, immediately following the start of therapy with Coli-Asparaginase (ASP), Fibrinogen continued to drop to reach its lowest average value of 46 mg/dl on day 24. Anticoagulant factors like plasminogen...
(lowest average value: 36%), AT III (47%) and Protein C (93%) dropped abruptly. These alterations were reversed after discontinuation of Glucocorticoids and ASP. During consolidation (protocol II) similar alterations are observed as in protocol I when Glucocorticoids are applied alone. However, after Erwinia-ASP there is no fall in AT III, plasminogen, and Protein C as is observed in protocol I with Coli-ASP. 2. Severe hemorrhages or thromboses are uncommon as compared to the degree of coagulation changes which can be regularly observed. Complications occur more often in girls. Most of them are seen during the 2nd or 3rd week of simultaneous ASP-Glucocorticoid therapy. 3. To avoid twofold alteration of hemostasis it should be considered to apply Glucocorticoids and ASP separately and to replace Coli-ASP by Erwinia-ASP. The efficacy of prophylactic replacement of decreased coagulation factors has not yet been confirmed. Immunologic and infectious side effects have to be taken into consideration. 4. More definite recommendations can be given when each suspected bleeding and/or thrombosis is confirmed by imaging procedures, when it is documented and registered, and when coagulation studies are performed during the critical phase.

(12) Mattioli Belmonte M, Gugliotta L, Delvos U, Catani L, Vianelli N, Cascione ML, Belardinelli AR, Mottola L, Tura S

A REGIMEN FOR ANTITHROMBIN III SUBSTITUTION IN PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA UNDER TREATMENT WITH L-ASPARAGINASE.

Haematologica 1991 May-Jun;76(3):209-14

Istituto di Ematologia, L. e A. Seragnoli, Universita di Bologna, Italy.

BACKGROUND AND METHODS. Seventeen adult patients with acute lymphoblastic leukemia (ALL) treated with L-asparaginase (20,000 IU/m2 on six alternate days) were infused with antithrombin III (AT III) concentrates (Kybernin P, Behring). Substitution therapy was aimed at increasing the reduced AT III concentration usually found in these patients, since AT III deficiency is thought to be associated with an increased risk of thrombosis. Two schedules of AT III administration, different in dosage, timing and duration were evaluated. The first 7 patients (group A) received a fixed dose of 2,000 U every day for 6 times, starting with the second L-asparaginase (L-ase) infusion, independently of their plasma AT III levels. In the following 10 patients (group B), 20-25 U/Kg b.w. were administered daily for 7 times only when the plasma AT III level was lower than 60% with plasma fibrinogen higher than 100 mg/dl and platelet count higher than 50 x 10(9)/l, or when AT III was below 40%. Thirteen patients who received L-ase without AT III substitution served as controls. RESULTS AND CONCLUSIONS. Both substitution regimens resulted in mean plasma AT III nadir values significantly (p less than 0.001) higher than in the controls. Our data suggest that, in ALL patients receiving L-ase according to the L20 protocol, satisfactory plasma AT III levels may be assured with infusions of 20-25 U/Kg b.w./day for 7-10 days, starting by day 2 of L-ase treatment.

8. AT-III in DIC

(1) Hermida J, Montes R, Munoz MC, Orbe J, Paramo JA, Rocha E

EFFECTS OF LOW MOLECULAR WEIGHT HEPARIN, ALONE OR COMBINED WITH ANTITHROMBIN III, ON MORTALITY, FIBRIN DEPOSITS AND HEMOSTATIC PARAMETERS IN ENDOTOXIN-INDUCED DISSEMINATED INTRAVASCULAR COAGULATION IN RABBITS.

Am J Hematol 1999 Jan;60(1):6-11

Laboratory of Vascular Biology and Thrombosis, School of Medicine, University of Navarra, Pamplona, Spain.

The effect of low molecular weight heparin (LMWH) with or without antithrombin III (AT III) has been studied in a rabbit model of disseminated intravascular coagulation (DIC) induced by continuous infusion of 100 microg/kg/hr of Escherichia coli endotoxin for 6 hr. LMWH (5 and 10 IU/kg/hr/6 hr), alone or in combination with AT III (20 U/kg/hr/6 hr), or saline were administered simultaneously with endotoxin. Hemostatic markers at 0, 2, and 6 hr as well as kidney fibrin deposits and the mortality rate at 24 hr were determined. Rabbits receiving only endotoxin showed an impairment in hemostasis, as well as high kidney fibrin deposits and a high mortality rate. LMWH alone did not exert any effect. The simultaneous infusion of LMWH and AT III exerted a beneficial effect on the hemostatic markers and reduced the kidney fibrin deposits as well as the mortality rate in a LMWH dose-
dependent manner. Fibrinogen and protein C consumption were significantly higher and renal fibrin deposits more intense in the rabbits that had died in the first 24 hr. There was also a significant positive correlation between kidney fibrin deposits and platelets, fibrinogen, and protein C consumption, taking the whole rabbit population. It is concluded that the simultaneous infusion of LMWH and AT III is useful in this DIC model and would make it possible to reduce significantly the AT III doses used when AT III is given alone.

(2) Cohendy R, Lefrant JY, de la Coussaye JE
THE USE OF ANTITHROMBIN III (ATIII) FOR DISSEMINATED INTRAVASCULAR COAGULATION (DIC) DURING SEPTIC SHOCK.
Intensive Care Med 1998 Dec;24(12):1344

(3) de Jonge E, Levi M, Stoutenbeek CP, van Deventer SJ
CURRENT DRUG TREATMENT STRATEGIES FOR DISSEMINATED INTRAVASCULAR COAGULATION.
Drugs 1998 Jun;55(6):767-77

Department of Intensive Care, Academic Medical Center, University of Amsterdam, The Netherlands. E.dejonge@amc.uva.nl
Disseminated intravascular coagulation (DIC) can be caused by a variety of diseases. Experimental models of DIC have provided substantial insight into the pathogenesis of this disorder, which may ultimately result in improved treatment. Disseminated coagulation is the result of a complex imbalance of coagulation and fibrinolysis. Simultaneously occurring tissue factor-dependent activation of coagulation, depression of natural anticoagulant pathways and shutdown of endogenous fibrinolysis all contribute to the clinical picture of widespread thrombotic deposition in the microvasculature and subsequent multiple organ failure (MOF). Cornerstone for the treatment of DIC is the optimal management of the underlying disorder. At present, specific treatment of the coagulation disorders themselves is not based on firm evidence from controlled clinical trials. Plasma and platelet transfusion are used in patients with bleeding or at risk for bleeding and low levels of coagulation factors or thrombocytopenia. The role of heparin and low molecular weight heparin is controversial, but their use may be justified in patients with active DIC and clinical signs of extensive fibrin deposition such as those with meningococcal sepsis. There is some evidence to indicate that low molecular weight heparin is as effective as unfractionated heparin but may be associated with a decreased bleeding risk. Antithrombin III (AT III) replacement appears to be effective in decreasing the signs of DIC if high doses are administered, but effects on survival or other clinically significant parameters are at best uncertain. If AT III supplementation is used, the dosage should be selected to achieve normal or supranormal plasma levels of 100% or higher. Results of studies on protein C concentrate, thrombomodulin or inhibitors of tissue factor are promising, but the efficacy and safety of these novel strategies remains to be established in appropriate clinical trials.

(4) Penner JA
DISSEMINATED INTRAVASCULAR COAGULATION IN PATIENTS WITH MULTIPLE ORGAN FAILURE OF NON-SEPTIC ORIGIN.
Semin Thromb Hemost 1998;24(1):45-52

Department of Medicine, Michigan State University College of Human Medicine, East Lansing 48824-1315, USA.
Disseminated intravascular coagulation (DIC) and associated multi-organ failure are serious and often terminal events of a variety of non-septic conditions. For the most part, these conditions are a result of tissue factor (thromboplastin) release from damaged tissues creating situations that favor thrombin formation. Thrombin's role in this process is critical and serves to induce the coagulopathy, as well as many of the other aspects of inflammation that contribute to the associated morbidity and mortality. Clinical disorders giving rise to DIC fall into categories of trauma, obstetrical complications, malignancies and a variety of inflammatory conditions. Diagnostic patterns for these disorders are well established with an expected decrease in platelets and fibrinogen, as well as antithrombin III, in addition to elevated levels of thrombin-antithrombin III complex, prothrombin fragment 1 + 2, and D-dimer; all of which serve to identify the hypercoagulable state. Management of these coagulopathies requires attention to the bleeding diathesis and the ongoing thrombotic
complication. Supportive therapy usually is required to provide hemostasis. However, control of the coagulopathy is of equal importance and requires not only early intervention, but also administration of sufficient antithrombotic agents to reduce thrombin's ability to consume coagulation factors, as well as to stimulate inflammatory processes. Heparin has been employed effectively in many of these situations, but suffers from its potential to induce hemorrhage. Antithrombin III concentrate, however, is devoid of this risk and provides a unique alternative that has had a limited, but effective record of benefits. Further proof of its efficacy in multi-organ failure disorders is awaited.

(5) Kessler CM, Tang Z, Jacobs HM, Szymanski LM
THE SUPRAPHARMACOLOGIC DOSING OF ANTITHROMBIN CONCENTRATE FOR STAPHYLOCOCCUS AUREUS-INDUCED DISSEMINATED INTRAVASCULAR COAGULATION IN GUINEA PIGS: SUBSTANTIAL REDUCTION IN MORTALITY AND MORBIDITY.
*Blood* 1997 Jun 15;89(12):4393-401

Division of Hematology/Oncology, The George Washington University Medical Center, Washington, DC, USA.

An animal model of gram-positive septicemia was developed to evaluate the effects of antithrombin (AT) concentrates on morbidity, mortality, and laboratory consequences of disseminated intravascular coagulation (DIC). DIC was induced in guinea pigs by infusing *Staphylococcus aureus* (SA) isolated from blood cultures of patients with DIC (DIC-SA) or without DIC (non-DIC-SA). The non-DIC-SA animals and animals infused with sterile saline served as controls. Varying doses of AT were administered either 30 minutes or 24 hours after infusion of SA. DIC was confirmed within 4 hours by changes in prothrombin time, activated partial thromboplastin time, fibrinogen, fibrinogen-fibrin degradation products, and AT activity. Clinical bleeding was also evident. Mortality of untreated DIC-SA animals was 36% within 24 hours and up to 75% by 72 hours. Intervention with any dose of AT between 125 and 1,000 IU/kg 30 minutes after DIC-SA infusion was associated with 100% survival (P ≤ .05 in the 250 IU/kg group) and sustained increases in AT activity and fibrinogen concentrations (P ≤ .05).

When AT was administered in combination with low molecular weight heparin (LMWH) or if LMWH was administered alone, mortality from DIC-SA was slightly, but not significantly reduced compared with untreated DIC-SA. Gross hemorrhage was observed premortem and at autopsy in all of the DIC-SA animals but in substantially fewer animals that received AT (P ≤ .001 in the 250, 500, and 1,000 IU/kg groups). In contrast, groups treated with LMWH, alone or with AT, experienced hemorrhage and appeared to develop pathologic DIC. Fibrin formation in end-organs was detected in all guinea pigs in the untreated DIC-SA group and in the groups treated with 125 IU/kg AT and LMWH alone. AT doses between 250 and 1,000 IU/kg administered 30 minutes after DIC-SA infusion prevented fibrin formation in end-organs (P ≤ .001 in the 250 and 1,000 IU/kg groups). AT administered 24 hours after DIC-SA could not reverse pre-existing histopathologic evidence of DIC but favorably affected survival, which reached statistical significance in the 1,000 IU/kg AT group (P < .025). In summary, suprapharmacologic doses of AT concentrate significantly decreased mortality and morbidity and ameliorated adverse changes in laboratory measures induced by DIC-SA in this guinea pig model and were not associated with untoward hemorrhagic complications. These findings provide justification for studying the use of AT therapy in patients with DIC-SA.

(6) Fuse S, Tomita H, Yoshida M, Hori T, Igarashi C, Fujita S
HIGH DOSE OF INTRAVENOUS ANTITHROMBIN III WITHOUT HEPARIN IN THE TREATMENT OF DISSEMINATED INTRAVASCULAR COAGULATION AND ORGAN FAILURE IN FOUR CHILDREN.

Department of Pediatrics, Sapporo Medical University School of Medicine, Hokkaido, Japan.

In several animal experiments, high doses of antithrombin III concentrates have shown beneficial effects on mortality and reversal of coagulation abnormalities which had resulted from disseminated intravascular coagulation. Other experiments have suggested that antithrombin III infusion without heparin is effective in the treatment of organ failure. We clinically treated children suffering disseminated intravascular coagulation only with antithrombin concentrate. Four patients suffering disseminated intravascular coagulation with organ failure were selected. We started antithrombin III
concentrate infusion as soon as the diagnosis was established. The dosage of antithrombin III was 120-250 units/kg/day for 2 or 3 days. Heparin was not used. All 4 patients recovered completely and quickly without any complications within 14 days. We suggest that the high-dose antithrombin III infusion without heparin is an effective and safe therapy for disseminated intravascular coagulation with organ failure.


Consumption coagulopathy in childhood is still a serious problem. Besides treatment of the underlying diseases therapy of consumption coagulopathy was performed with heparin and nowadays with substitution of coagulation factors, especially antithrombin III concentrate, alone or in combination with heparin. We performed administration of AT III concentrates only, without additional heparin treatment in children with proven septicemia (preterm infants n = 21, children beyond the newborn period n = 18). Antithrombin III, platelet count, fibrinogen, PT, aPTT and TT were assayed. These coagulation parameters turned to be normal 48 hours after normalisation of the antithrombin III plasma level-AT III increased to normal values within 24 hours after the initial substitution in all children. Lethal outcome was not observed after sole administration of AT III as well as no other side effects have been seen. In summary, these data indicate that consumption coagulopathy in childhood can be managed successfully with early substitution of AT III concentrate.


Department of Blood Transfusion, Kyoto Prefectural University of Medicine.

Biological properties and the efficacy of AT-III concentrate for the treatment of thromboembolic disorders were evaluated in the patients with AT III deficiency. Commercially available AT III concentrates showed heterogeneity on agarose gel isoelectric focusing, however, they inhibited thrombin in the same manner. AT-III concentrates were infused to 11 patients with congenital AT III deficiency (4 with thrombosis). Pharmacokinetic parameters of infused AT III were calculated as follows; half time 61.1 +/- 23.0 hr. (58.4 +/- 22.6 hr. in the cases with thrombosis), max increase rate 1.01 +/- 0.3%/U/kg and recovery rate 95.4 +/- 33.3%. Simulation curves adjusted to the multiple administration were correlated well with the actually determined values in the patients and steady state concentration of AT III was achieved by the administration of this concentrate in 12 or 24 hour intervals. Clinically, substitution with AT III concentrate was proved to be effective for the treatment of thromboembolism in these patients. 16 patients with disseminated intravascular coagulation were treated with heparin (6,000 U/day) followed by AT III concentrate (1,500 U/day) administration. Clinical symptoms and laboratory findings were improved in 11 patients. From these results substitution with AT III concentrate was suggested to be beneficial for the prevention or the treatment of thromboembolic disorders in the patients with AT III deficiency.

9. AT-III in Nephrotic Syndrome with Thrombo-Embolic Disease


II Klinika Chorob Dzieci Instytutu Pediatrii Akademii Medycznej w Poznaniu.

Eight children with thrombo-embolic disease in the course of nephrotic syndrome were treated at II Clinic of Children's Diseases (Institute of Pediatrics, Poznan) between 1991 and 1993. The diagnosis
was established on the basis of clinical examination and noninvasive imaging techniques. Two patients had an atypical localisation of the thrombus in the left ventricle and right atrium. In laboratory tests of the coagulation system, all of the children had decreased levels of antithrombin III (AT III). All children were treated with heparin and 4 with fibrinolytic agents. AT III concentrate was administered to 3 children. Total resolution of thrombo-embolic disease was obtained in 5 patients, 3 died during treatment. Thrombo-embolic disease should be taken into account in the differential diagnosis of complications of nephrotic syndrome.

10. AT-III in Endotoxin Shock

(1) Fourrier F, Jourdain M, Tournoys A, Gosset P, Mangalaboyi J, Chopin C
EFFECTS OF A COMBINED ANTITHROMBIN III AND PROTEIN C SUPPLEMENTATION IN PORCINE ACUTE ENDOTOXIC SHOCK.
Shock 1998 Nov;10(5):364-70

Reanimation Polyvalente and Equipe de recherche JE 2084, Hopital R. Salengro, Centre Hospitalier Regional Universitaire, Universite Lille 2, France.

Antithrombin III (ATIII) and protein C (PC) are major inhibitors of the coagulation cascade and might regulate the cytokine network. We tested the possibility that a combined supplementation using these two inhibitors might have synergistic effects on sepsis-induced disseminated intravascular coagulation and shock. Hemodynamics, coagulation parameters, tumor necrosis factor (TNF) alpha, and interleukin 6 levels were measured in pigs submitted to a bolus infusion of Escherichia coli endotoxin (lipopolysaccharide). Four groups were studied: control lipopolysaccharide, ATIII (100 IU/kg), PC (50 IU/kg), and ATIII-PC (same doses). The endotoxin infusion resulted in a typical hypokinetic shock with disseminated intravascular coagulation in all animals. Compared with the control group, a significant improvement in mean arterial pressure and systemic vascular resistance was observed in the PC and ATIII-PC groups. The increase in lactate levels was almost completely blunted in the PC group. A significant lesser increase in TNFalpha levels was observed in the ATIII-PC group. No effects were seen on interleukin 6 levels. Coagulation and fibrinolysis parameters were not improved by ATIII and/or PC, except for a lesser decrease in prothrombin time in the ATIII-PC group. We conclude that in this acute endotoxic model, a combined supplementation using PC and ATIII concentrates has favorable effects on hemodynamic parameters and TNFalpha levels, independently from the anticoagulant actions of these inhibitors.

11. AT-III in Trauma probably ???

a) AT-III in Trauma General Aspects

HIGH-DOSE ANTITHROMBIN III TREATMENT OF SEVERELY INJURED PATIENTS: RESULTS OF A PROSPECTIVE STUDY.
J Trauma 1998 Nov;45(5):931-40

Department of Surgery, Klinikum Innenstadt, Ludwig-Maximilians-University, Munich, Germany.

BACKGROUND: Antithrombin III (AT III) treatment has been shown to reduce disseminated intravascular coagulation and to inhibit thrombin, which plays a central role in the activation of platelets and other inflammatory systems in conditions with severe inflammation. The objective of this study was to evaluate the influence of early and high-dose administration of AT III to patients with severe multiple injuries on the inflammatory response and outcome. METHODS: In a placebo-controlled, double-blind study, 40 consecutive patients with Injury Severity Scores of 29 or greater who met the inclusion criteria were randomized to receive either AT III or placebo within 360 minutes after trauma. Twenty patients were administered AT III for a period of 4 days, aiming to achieve AT III concentrations of 140% of normal. RESULTS: The AT III and placebo groups were comparable with respect to Injury Severity Score, age, incidence of blood pressure less than 80 mm Hg on admission, initial base deficit, and start of the test drug. The patients in the AT III group received a total of about 20,000
IU during the first 4 days. AT III levels of 130 to 140% could be achieved by this regimen, whereas in the control group the AT III concentration averaged about 70%. In the AT III group prothrombin tended to be elevated and prothrombin fragment F1+2 as well as thrombin-AT III complex tended to be lower on the first day. No differences between groups, however, could be observed with respect to partial thromboplastin time, prothrombin time, platelets, plasminogen activator inhibitor I, soluble tumor necrosis factor receptor II, neutrophil elastase, interleukin (IL)-1 receptor antagonist, IL-6, and IL-8. Mortality (15 vs. 5%), incidence of respiratory failure (55 vs. 55%), duration of mechanical ventilation (13 vs. 12 days), and length of stay in the surgical intensive care unit (19 vs. 21 days) were also similar in both treatment groups. The duration of organ failure, however, was shorter in the patients receiving AT III.

CONCLUSION: The early and high-dose administration of AT III to patients with severe blunt trauma appears not to attenuate the posttraumatic inflammatory response or to significantly improve outcome.

b) AT-III in Neurotrauma

(1) Hoots WK

EXPERIENCE WITH ANTITHROMBIN CONCENTRATES IN NEUROTRAUMA PATIENTS.

Semin Thromb Hemost 1997;23 Suppl 1:3-16

University of Texas Health Science Center/University of Texas-MD Anderson Cancer Center, Houston, USA.

Plasma coagulation results from 2,100 injured patients were sequentially and systematically evaluated in a large natural history study of neurotrauma. A significant correlation became apparent between the severity of and morbidity from head injury and the degree of abnormality in coagulation results, especially for young injured victims. Subsequent studies in the United States, Europe, and Japan have supported the significant correlation between final clinical outcome and these measurements of plasma coagulation, as well as inflammatory proteins, performed soon after injury. This discussion reviews the data from many published reports that support this conclusion, especially data that corroborate the strong clinical association between head trauma and disseminated intravascular coagulation (DIC). The data that demonstrate a high predisposition for head-injured individuals to develop DIC serve as a the rationale for therapeutic intervention with coagulation protease inhibitors, especially antithrombin (AT). A large, double-blind, placebo-controlled trial that evaluates the therapeutic use of AT concentrate for DIC in such patients has yet to be completed. Described here is the design for such a clinical trial that examined the impact of mortality as an outcome. However, this trial was terminated for nonscientific reasons soon after it began. Very truncated data collected from this aborted study support both the scientific rationale for and the feasibility of such a study in the future. Data from such a clinical trial are needed to support the use of AT concentrate to treat DIC in this and other morbid diseases.

(2) Graham JA, Daly HM, Carson PJ

ANTITHROMBIN III DEFICIENCY AND CEREBROVASCULAR ACCIDENTS IN YOUNG ADULTS.


Department of Haematology, Royal Cornwall Hospital, Treliske, Truro.

A young man with antithrombin III (AT-III) deficiency sustained a cerebellar venous infarct and recovered following treatment with AT-III concentrate. A family study showed that other members were affected. AT-III deficiency in this family was found to be due to a new variant AT-III TRURO 1. Young patients with strokes should be screened for thrombophilia.

c) AT-III in Burn Trauma

(1) Kowal-Vern A, McGill V, Walenga JM, Gamelli RL

ANTITHROMBIN III CONCENTRATE IN THE ACUTE PHASE OF THERMAL INJURY.

Department of Pathology, Loyola University Medical Center, Maywood, IL 60153, USA.

BACKGROUND: Thermal injury disrupts homeostasis by inducing subclinical disseminated intravascular coagulation, fibrinolysis, and an acquired deficiency of Antithrombin III (ATIII), a natural anticoagulant. As a result, thermally injured patients have a high incidence of hypercoagulability and thrombosis. OBJECTIVE: ATIII (Human) concentrate was given to a thermally injured patient to evaluate safety, and dosage requirements in this setting. DESIGN: The patient was a 40 yr old male with a 68% total burn surface area, right femoral comminuted fracture, and C5-C6 subluxation sustained in a vehicular crash. He received nine infusions of AT III (H) concentrate (100-50 u/kg) within the first four days of injury. RESULT: The ATIII plasma level increased from 45% on admission (normal = 100+/20%) to 120+/25% in the next four days. During the 64 day hospitalization, there were 11 grafting procedures with an estimated blood loss (EBL)/procedure: 1140 cc; and EBL/grafted surface area ratio: 0.6 cc cm2. The average time to healing of the meshed autograft was 6.4 days. CONCLUSION: ATIII (H) concentrate can be safely utilized in the acute phase of thermal injury: no excessive bleeding or prolongation of wound healing was documented.

(2) Danielsson P, Nilsson L, Nettelblad H, Sjoberg F

**IS THERE A NEED FOR ANTITHROMBIN III SUBSTITUTION EARLY AFTER BURN INJURY?**

*Burns* 1997 Jun;23(4):300-5

Department of Plastic Surgery, Hand Surgery & Burns, University Hospital Linkoping, Sweden.

The changes in antithrombin III (AT-III) levels in the blood and restitution in coagulation parameters between patients receiving and not receiving AT-III substitution were examined early after burn injury. The study was divided into two parts with a total of 14 consecutive patients (per cent total body surface area (TBSA) > or = 20 per cent). The first six patients were given AT-III substitution when AT-III levels fell below 50 per cent. The second part examined the restitution of the coagulation parameters when the patients (n = 8) obtained AT-III substitution only at extremely low values of AT-III. The decline in AT-III observed occurred in parallel to the permeability changes and the haemodilution normally seen secondarily to the initial fluid rescucitation. The observed changes in the coagulation parameters were modest and no hepatic dysfunction was noted. In addition, no differences of the restitution in these coagulation parameters were noted between the substituted and non-substituted groups. These results suggest that changes in AT-III early after burn injury depend mainly on factors other than an ongoing disseminated coagulation process. Probable causes are increased capillary leak and haemodilution. Our results suggest that substitution of AT-III in the early postburn period, on the assumption that low levels alone indicate ongoing coagulation, is not warranted.

(3) Ueyama M, Yamamoto I, Sawada Y

**[DISSEMINATED INTRAVASCULAR COAGULATION IN THE EARLY STAGE AFTER SEVERE BURN: THE ROLE OF EXCESSIVE THROMBIN GENERATION]. [ARTICLE IN JAPANESE]**


Department of Emergency and Critical Care Medicine, Kagoshima University Hospital, Japan.

The pathogenesis of disseminated intravascular coagulation (DIC) in the early stage after burn injury remains still unclear. We investigated 12 burn injured patients by serial determination of antithrombin III (AT-III) activities and thrombin-antithrombin III complex (TAT) levels. Of these patients 4 developed DIC (DIC group) and the others had no hematological complications (non-DIC group). The mean levels of TAT increased markedly and peaked at 6 hr; the increment being more pronounced in DIC group (p less than 0.001). A significant correlation was recognized between TAT and Burn Index (r = 0.871, p less than 0.001). We also observed low AT-III activities those inversely related to Burn Index (r = 0.875, p less than 0.001), whereas closely correlated with serum albumin levels (r = 0.864, p less than 0.001), suggesting that this depression might be caused by both massive infusion and shifts of plasma into the extravascular space rather than consumption. These findings suggest that massive thrombin generation and decrease of anticoagulant activity, correlated to the
severity of burns, might concurrently develop. **Non-DIC group** may remain to latent activation of coagulation cascade where anticoagulants could inactivate thrombin generated. This compensatory mechanism may fail in **severe burn patients** who have Burn Index of more than 90, developing DIC with high levels of TAT (316.3 +/- 104.5 ng/ml) and **low AT-III activities** (19.5 +/- 8.7%).

d) AT-III in Septic and Multiple Trauma Patients

1) AT-III Concentrate in Multiple Trauma


**USE OF ANTITHROMBIN III IN CRITICAL PATIENTS.**


Department of Hematology, Hospital Insular, Las Palmas de Gran Canaria, Spain.

OBJECTIVE: To evaluate the effect of the AT III concentrates upon the clinical evolution and hemostatic parameters. DESIGN: Prospective, open, randomized trial. PATIENTS AND PARTICIPANTS: Septic and multiple trauma patients admitted to our Intensive Care Unit. SETTING: Levels of AT III below 70% were used as criteria to choose 36 patients, 20 of whom received treatment with AT III and 16 did not. INTERVENTIONS: AT III concentrates were administered at an initial dose of 60 U/kg followed by 10 U/kg every six hours. RESULTS: The administration of AT III neither contributes to alterations in haemostasis, nor the clinical evolution (evaluated according to Apache II score). CONCLUSIONS: The results suggest that the administration of AT III concentrates to critical patients with acquired low levels, but without manifest DIC, may not be justified; although further studies on a larger population are required to establish definite conclusions.

(5) Miller RS, Weatherford DA, Stein D, Crane MM, Stein M

**ANTITHROMBIN III AND TRAUMA PATIENTS: FACTORS THAT DETERMINE LOW LEVELS.**

*J Trauma* 1994 Sep;37(3):442-5

Department of Surgery, Greenville Memorial Hospital, South Carolina.

A prospective (cohort) study was conducted to determine the incidence of low antithrombin III (AT III) levels and the association with selected clinical variables in adult trauma patients. One hundred sixty AT III levels were obtained on 50 consecutive trauma admissions to a community-based level I trauma center. Antithrombin III levels were drawn as soon after admission as possible and every other day thereafter. Thirty-one patients (62%) had at least one low AT III level (< 80%), whereas 15 concurrently drawn control levels were all >= 90%. Low AT III levels were more common in patients with one or more of the following: base deficit less than -4 (39% vs. 0, p = 0.002); Injury Severity Score > 15 (48% vs. 16%, p = 0.04); and blood transfusion (32% vs. 5%, p = 0.04). All other variables (shock, surgical intervention, subcutaneous heparin, and sequential compression devices) were not statistically significant, although all six patients with shock had low levels. In conclusion, over 60% of adult trauma patients had low AT III levels at some time during hospitalization and these patients were clearly more severely injured. Further studies are required to determine if these patients are more susceptible to thromboembolic phenomena.

2) AT-III in Septic Patients

(6) Sacher RA

**POTENTIAL APPLICATIONS OF ANTITHROMBIN CONCENTRATE IN SYSTEM INFLAMMATORY DISORDERS. INTRODUCTION.**

*Coagul Fibrinolysis* 1998 Apr;9 Suppl 2:S1-2

Department of Medicine, Georgetown University Medical Center, Washington, DC 20007-2197, USA.
(7) Balk R, Emerson T, Fourrier F, Kruse JA, Mammen EF, Schuster HP, Vinazzer H

**THERAPEUTIC USE OF ANTITHROMBIN CONCENTRATE IN SEPSIS.**

*Semin Thromb Hemost* 1998;24(2):183-94

Department of Internal Medicine, Rush-Presbyterian St. Luke's Medical Center, Chicago, Illinois, USA.

Sepsis and its associated complications of disseminated intravascular coagulation (DIC) and multiple organ dysfunction syndrome (MODS) continue to be a major cause of morbidity and mortality. Improved detection of all forms of DIC is essential to assure earlier diagnosis. Studies already indicate that the therapeutic use of antithrombin (AT) concentrate may produce a more positive outcome for sepsis-associated DIC. If DIC could be identified earlier and AT concentrate could then be given earlier in the sepsis continuum, study results for the use of AT concentrate in humans might reveal a statistically significant difference versus placebo, and the efficacy of AT concentrate for this syndrome is more likely to be proved. Fixed-bolus doses of AT concentrate based on body weight are currently preferred, but improved, user-friendly assays for plasma AT levels would permit more rapid turnaround time for AT results and could help fine-tune the use of AT concentrate to the specific needs of each patient. Clinical trials involving the therapeutic use of AT concentrate in sepsis should continue, and it can be hoped that their design will reflect the concepts and conclusions offered by this panel of investigators.

(8) Mesters RM, Mannucci PM, Coppola R, Keller T, Ostermann H, Kienast J

**FACTOR VIIA AND ANTITHROMBIN III ACTIVITY DURING SEVERE SEPSIS AND SEPTIC SHOCK IN NEUTROPENIC PATIENTS.**

*Blood* 1996 Aug 1;88(3):881-6

Department of Internal Medicine, University of Munster, Germany.

Septic shock and multiple organ failure may be associated with coagulation activation, disseminated fibrin formation, and consumption of coagulation inhibitors such as antithrombin III. We have evaluated prospectively coagulation measurements in patients with severe chemotherapy-induced neutropenia. This group of patients was chosen because of their high risk of developing severe septic complications, thus allowing serial prospective coagulation testing before and during evolving sepsis or septic shock. Sixty-two patients with febrile infectious events were accrued to the study. Of these, 13 patients progressed to severe sepsis and 13 additional patients to septic shock as defined according to standard diagnostic criteria. At the onset of fever, factor (F) VIIa activity, FVII antigen and antithrombin III (AT III) activity decreased from normal baseline levels and were significantly lower in the group of patients who progressed to septic shock compared with those that developed severe sepsis (medians: 0.3 v 1.4 ng/mL, 21 v 86 U/dL and 45% v 95%; P < .001). The decrease of these measurements in septic shock was accompanied by an increase in prothrombin fragment 1+2 (median: 3.6 v 1.4 nmol/L; P = .05), a marker of thrombin generation. These differences were sustained throughout the septic episode (P < .0001). FVIIa and AT III levels of < 0.8 ng/mL and < 70%, respectively, at onset of fever predicted a lethal outcome with a sensitivity of 100% and 85%, and a specificity of 75% and 85%, respectively. In contrast, FXIIa-alpha antigen levels were not different between groups at onset of fever but increased modestly during the course of septic shock (P = .001). Thus, septic shock in neutropenic patients is associated with increased thrombin generation. Furthermore, both FVIIa and AT III measurements are sensitive markers of an unfavorable prognosis.

Comment in: *Blood* 1997 May 15;89(10):3893-4

(9) Jochum M

**INFLUENCE OF HIGH-DOSE ANTITHROMBIN CONCENTRATE THERAPY ON THE RELEASE OF CELLULAR PROTEINASES, CYTOKINES, AND SOLUBLE ADHESION MOLECULES IN ACUTE INFLAMMATION.**


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van Beek EJ, von der Mohlen MA, ten Cate JW, Brandjes DP, Buller HR

ANTITHROMBIN III CONCENTRATE IN THE TREATMENT OF DIC: A RETROSPECTIVE FOLLOW-UP STUDY.


Center for Haemastasis, Thrombosis, Atherosclerosis and Inflammation Research, University of Amsterdam, Netherlands.

OBJECTIVE: To assess the clinical utility of antithrombin III (AT-III) substitution in adults with septicemia in an intensive care unit. METHODS: A retrospective follow-up study was performed in the adult intensive care unit of a large teaching hospital. Adults with septicemia and AT-III levels less than 0.45 IU/ml were identified. AT-III administration, consisting of an intravenous bolus injection of 20 IU/kg, followed by continuous infusion of 20 IU/kg per 24 h, was given to 21 patients, while this was withheld in 21 age- and sex-matched controls. The severity of diffuse intravascular coagulation (DIC), APACHE II score, and type of septicemia were analysed. The odds ratio was calculated for survival. RESULTS: The baseline characteristics with regards to severity of DIC, APACHE scores and types of sepsis were comparable for the patients who received AT-III concentrates and those who did not. Mortality in the treated and non-treated groups was 76% (95% CI: 53-92%) and 57% (95% CI: 34-78%), respectively (p = 0.24). The odds ratio for survival was 2.4 if no AT-III concentrate was administered (95% CI: 0.537-11.5; p = 0.24). CONCLUSIONS: The use of AT-III concentrates in the doses applied in adult intensive care patients with sepsis does not appear to improve outcome in terms of mortality.

12. AT-III in BM-Transplantation and VOD

(1) Lee JH, Lee KH, Kim S, Lee JS, Kim WK, Park CJ, Chi HS, Kim SH

RELEVANCE OF PROTEINS C AND S, ANTITHROMBIN III, VON WILLEBRAND FACTOR, AND FACTOR VIII FOR THE DEVELOPMENT OF HEPATIC VENO-OCLUSIVE DISEASE IN PATIENTS UNDERGOING ALLOGENEIC BONE MARROW TRANSPLANTATION: A PROSPECTIVE STUDY.

Bone Marrow Transplant 1998 Nov;22(9):883-8

Department of Medicine, Asan Medical Center, University of Ulsan, Seoul, Korea.

Factors that enhance hypercoagulability following BMT may have a pathogenetic role in VOD. To investigate the relevance of hemostatic parameters for the development of VOD, we prospectively measured protein C, protein S, antithrombin III (AT III), von Willebrand factor, and factor VIII in 50 consecutive patients undergoing allogeneic BMT. Each parameter was determined before conditioning, on day 0 of BMT and weekly for 3 weeks, and patients were monitored prospectively for the occurrence of VOD. VOD occurred in 26 patients at median post-BMT day 8.5 (range, day -2 to 17). Thirteen patients had mild, 10 had moderate and three had severe VOD. No coagulation parameters were significantly different at the baseline or on day 0 of BMT between patients with no/mild VOD and moderate to severe VOD. On day 7 and thereafter, levels of protein C and AT III were significantly lower in patients with moderate to severe VOD when compared to patients with no/mild VOD. Levels of protein C and AT III decreased before the clinical onset of VOD in patients with moderate to severe VOD. Early post-BMT reduction of these parameters may indicate the development of moderate to severe VOD.

(2) Morris JD, Harris RE, Hashmi R, Sambrano JE, Gruppo RA, Becker AT, Morris CL

ANTITHROMBIN-III FOR THE TREATMENT OF CHEMOTHERAPY-INDUCED ORGAN DYSFUNCTION FOLLOWING BONE MARROW TRANSPLANTATION.

Bone Marrow Transplant 1997 Nov;20(10):871-8

Children's Hospital Medical Center, Division of Hematology/Oncology/Stem Cell Transplantation, Cincinnati, OH 45229, USA.

A hypercoaguable state has been shown to follow high-dose chemotherapy for bone marrow transplantation (BMT). Deficiency of the natural anticoagulants, antithrombin III (AT-III), protein C and protein S correlate with organ dysfunction following BMT. We treated 10 patients with severe post-BMT organ dysfunction with AT-III concentrate. Indications for treatment included AT-III
anticoagulant level less than 88% and life-threatening single or multiorgan dysfunction. All patients were loaded with 50 units/kg AT-III every 8 h for three doses followed by 50 units/kg/day each day for 3-12 days. Clinical improvement was seen within 1-5 days of start of therapy in all patients. Patients with veno-occlusive disease (VOD) showed a decrease in platelet consumption in nine of nine patients, resolution of hepatic tenderness in six of eight patients, and reduction of severe ascites and weight gain in four of five patients. The probability of death due to VOD and life-threatening organ dysfunction was significantly less in the AT-III-treated group when compared to a historical control group receiving the same preparative regimen (P = 0.047 and P = 0.034, respectively). Significant improvements in organ dysfunction following AT-III treatment in this small study supports a causal relationship between AT-III deficiency and post-BMT chemotherapy-induced organ dysfunction.


Department for Pediatric Hematology and Oncology, Heinrich Heine University Medical Center, Dusseldorf, Germany.

Alterations of the coagulation system that may lead to coagulation activation and thrombosis are common sequelae after allogeneic bone marrow transplantation (BMT). We performed prophylactic anticoagulation by low dose heparin (50 units/kg/day) and substitution of antithrombin (AT) concentrate to sustain plasma levels above 90% of pooled normal human plasma. Conventional tests for plasmatic hemostasis and substitution of AT concentrate were recorded for 50 patients until day +50 after BMT. Incidence of sepsis, graft-versus-host-disease [GVHD], capillary leakage syndrome [CLS] and veno-occlusive disease of the liver [VOD] were investigated and compared with the results of patients without any of these complications. Patients with proven sepsis (n = 6) showed decreased activity of AT, and a prolonged activated partial thromboplastin time (aPTT), while fibrinogen levels were slightly increased. This constellation was interpreted as mild to moderate activation of the humoral coagulation cascade. Patients with VOD (n = 10) showed an increased consumption of AT concentrate at day +7 followed by a decrease of prothrombin time, of clotting factors II and VII, and a prolongation of aPTT at days +11 to +18 after BMT. This suggests, that activation of coagulation precedes decreased synthesis of coagulation factors. Patients with CLS (n = 15) or GVHD > or = II degree (n = 14) showed no major alterations of coagulation parameters. In conclusion, after BMT, two types of coagulopathy were observed: (i) an activation of the coagulation cascade (i.e. sepsis and VOD) which was followed by (ii) a diminished synthesis of coagulation factors (VOD). In order to perform timely therapeutic interventions in the coagulation system in patients with sepsis and/or VOD it appears to be important to assess the clinical value of parameters for early detection of coagulation activation as thrombin-AT complexes, D-dimers and F1 + 2 fragments.

(4) Haire WD ANTITHROMBIN III IN HEMATOPOIETIC STEM CELL TRANSPLANTATION. Semin Thromb Hemost 1997;23(6):591-601

Department of Internal Medicine, University of Nebraska Medical Center, Omaha 68198, USA.

Many of the serious, potentially fatal complications of hematopoietic stem cell transplantation have similarities to the multiple organ dysfunction syndrome (MODS) in critically ill nontransplant patients. One of these similarities is the alteration in the hemostatic system in such a way as to lower the levels of the naturally occurring anticoagulant proteins, especially antithrombin III. As in MODS, the outcome of transplant patients with these complications correlates with the degree of change in antithrombin III levels. Preliminary studies suggest that antithrombin III concentrate in pharmacologic doses along with intensive supportive care efforts can improve the clinical outcome of patients with these transplant-related complications. Further work to confirm these findings and, it is hoped, provide insight into the mechanism of action of antithrombin III in this setting is obviously warranted. Until such studies are completed, however, the preponderance of evidence suggests that when subjected to a risk-benefit analysis, patients in the early stages of transplant-related complications would be better off receiving antithrombin III supplementation.

PROTEIN C, PROTEIN S AND ANTITHROMBIN III LEVELS IN THE COURSE OF BONE MARROW AND SUBSEQUENT LIVER TRANSPLANTATION DUE TO VENO-OCCULSIVE DISEASE.


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Veno-occlusive disease (VOD) of the liver is one of the most frequent fatal complications after bone marrow transplantation (BMT). A decrease of natural anticoagulants, in particular protein C (PC), has been assumed to be involved in the pathogenesis of the disease. We determined PC and antithrombin III (AT III) levels in two patients undergoing BMT and subsequent liver transplantation due to VOD. Additionally, in one of the patients protein S (PS) levels were also measured. Normal baseline (day-8) PC levels (86 and 89%) were markedly reduced in both patients at the time of VOD manifestation on day 20 and 40, respectively (26 and 31%). PS levels lay within the normal range from day-8 (before myeloablative chemotherapy) until one week after clinical onset of VOD when substitution therapy with fresh frozen plasma (FFP) was initiated. AT III levels decreased moderately during the second and third posttransplant week, but were normal in the patient with a late clinical manifestation of VOD. In both patients PC and PS levels lay within the normal range after liver transplantation which was performed on day 41 and 79, respectively. AT III was substituted several times. Both patients died due to infectious complications on day 141 and 101, respectively. The data confirm previous reports that a decrease of PC is observed in BMT recipients and can be associated with hepatic vein occlusion. Whereas the relevance of AT III is uncertain, PS does not seem to be involved in the pathogenesis of VOD. Liver transplantation lead to normalization of PC levels, but its significance remains to be discussed in terms of ethical justifiability, medical feasibility and costs.

(6) Tabbara IA, Ghazal CD, Ghazal HH

EARLY DROP IN PROTEIN C AND ANTITHROMBIN III IS A PREDICTOR FOR THE DEVELOPMENT OF VENOOCCLUSIVE DISEASE IN PATIENTS UNDERGOING HEMATOPOIETIC STEM CELL TRANSPLANTATION.

J Hematother 1996 Feb;5(1):79-84

George Washington University, School of Medicine, Bone Marrow Transplant Program, Washington, DC 20037, USA.

Venoocclusive disease (VOD) of the liver remains one of the major obstacles for patients undergoing high-dose chemotherapy and hematopoietic stem cell transplantation (HSCT). Many factors have been associated with the development of VOD, including a hypercoagulable state secondary to a drop in protein C and antithrombin III (AT III). We conducted a prospective nonrandomized trial to try to determine whether the development of clinical VOD was associated with a drop in protein C, protein S, and AT III. A total of 42 patients undergoing high-dose chemotherapy and HSCT were enrolled in this study. Eleven patients underwent allogeneic bone marrow transplantation (BMT) following high-dose cyclophosphamide and fractionated total body irradiation (TBI). Thirty-one patients received autologous stem cell rescue following different preparative regimens. Measurements of protein C, protein S, and AT III levels were obtained prior to conditioning therapy and weekly thereafter for 2-3 weeks. A significant difference was noted in the mean levels of protein C on day 7 between those who developed VOD and those who did not (57.5 versus 72.1, p = 0.009). Similarly, there was a significant difference in the mean levels of AT III on days 7 and 14 between the two groups (day 7, 95.5 versus 80.6, p = 0.002; day 14, 99.6 versus 85.2, p = 0.01). The drop in protein S levels on days 7 and 14 was not statistically significant between the two groups. In conclusion, the degree of drop in protein C and AT III levels on day 7 was predictive for the development and severity of VOD.
TREATMENT OF VENO-OCCCLUSIVE DISEASE OF THE LIVER WITH BOLUS
TISSUE PLASMINOGEN ACTIVATOR AND CONTINUOUS INFUSION
ANTITHROMBIN III CONCENTRATE.
Bone Marrow Transplant 1996 Mar;17(3):443-7

Department of Pediatrics, University of Nebraska Medical Center, Omaha 68198-3330, USA.

Veno-occlusive disease (VOD) of the liver is a common complication of BMT and is accompanied by reduced levels of natural anticoagulants and by multi-organ dysfunction. We describe two cases of clinical VOD developing after autologous BMT and accompanied by ultrasonographic features of reversed portal venous flow. In both cases the patients had decreased levels of antithrombin (AT). Once the diagnosis of VOD was made, these patients were treated with tissue plasminogen activator (tPA) and continuous infusion AT. Each patient had radiographic and clinical resolution of VOD with the therapy. This novel treatment appears to have reversed the course of VOD without the increased risk of bleeding seen in the use of heparin therapy.

13. AT-III in End Stage Chronic Liver Disease

(1) Scherer R, Kabatnik M, Erhard J, Peters J
THE INFLUENCE OF ANTITHROMBIN III (AT III) SUBSTITUTION TO SUPRANORMAL ACTIVITIES ON SYSTEMIC PROCOAGULANT TURNOVER IN PATIENTS WITH END-STAGE CHRONIC LIVER DISEASE.
Intensive Care Med 1997 Nov;23(11):1150-8

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OBJECTIVE: Since antithrombin III (AT III) substitution to normal activities could not be shown to have major beneficial effects in patients with end-stage chronic liver disease in a variety of clinical settings, we tested the hypothesis that substitution to supranormal activities decreases systemic procoagulant turnover better in this patient group. DESIGN: Controlled prospective clinical study. SETTING: Operating rooms at a University Hospital. PATIENTS: Twenty-four patients with histologically verified liver cirrhosis consecutively scheduled for liver transplantation. INTERVENTIONS: Nineteen patients were given an antithrombin III concentrate to achieve either 100% (n = 10) or 175% (n = 9) AT III activity. Control patients (n = 5) received saline 0.9% instead. MEASUREMENTS AND RESULTS: Molecular markers of coagulation activation, platelet count and aggregability, and global coagulation variables were measured prior to AT III infusion and 60 min thereafter. In both AT III-treated groups thrombin-antithrombin III-complex increased significantly (p < 0.005), whereas prothrombin fragment F1 + 2, soluble fibrin and D-dimer concentrations, as well as other variables, did not show major changes. CONCLUSIONS: Despite thrombin inhibition by AT III in patients with end-stage chronic liver disease, systemic procoagulant turnover was not significantly decreased 60 min after AT III application even to supranormal activities. Replenishment of the inhibitory antithrombin III pool, decreased in chronic liver disease, should not be expected to slow down the baseline consumptive component of the haemostatic disorder in this patient group.

(2) Ribeiro AA, Lourenco DM, Toledo CF, Noguti MA, Borges DR
[ANTITHROMBIN III CONCENTRATE USE IN PATIENTS WITH CIRRHOSIS WITH COAGULATION DISORDERS]. [ARTICLE IN PORTUGESE]

Disciplina de Hematologia, Universidade Federal de Sao Paulo, Escola Paulista de Medicina.

BACKGROUND: Patients with severe hepatic failure present acquired deficiency of antithrombin III (ATIII) owing to reduced synthesis associated with intravascular activation of blood coagulation, which may be corrected by ATIII infusion. OBJECTIVE: The aim of this uncontrolled trial was to verify the effect of a standard dose of ATIII concentrate (Kybernin), that is, 50 U/kg of body weight per day, every 2 days, on ATIII levels in patients with severe hepatic failure and hemostatic imbalance.
PATIENTS AND METHODS: Six cirrhotic patients were studied: mean age of 44 years (14 to 63 years), who presented at least 2 abnormal coagulation tests (PT > 1.40, APTT > 1.25, Fibrinogen < 1.5 g/dL, Platelet count < 80,000/mm3). Mean serum albumin was 2.6 g/dL (1.9 to 3.8 g/dL). Blood was drawn before infusion, 4 h after the first infusion, and just before the next infusion. ATIII levels were measured by amidolytic method. RESULTS: Mean ATIII levels were: initial = 35.8%, 4th h = 56.2%*, 2nd d = 48.7%*, 4th d = 45.7%*, and 8th d = 42.3%. ATIII levels increased significantly after infusion of this standard dose in all patients, although they have not been fully corrected (Friedman test, * p < 0.02), which has been sustained till the 4th day. There was no improvement on the clinical outcome. CONCLUSIONS: These findings suggest that doses of ATIII concentrate higher than 50 U/kg/infusion must be administered to patients with severe hepatic failure, to guarantee normal levels of the inhibitor, in order to verify its influence on the hemostatic mechanism.

14. AT-III in Preterm infant

(1) Brangenberg R, Bodensohn M, Burger U
ANTITHROMBIN-III SUBSTITUTION IN PRETERM INFANTS—EFFECT ON INTRACRANIAL HEMORRHAGE AND COAGULATION PARAMETERS.
Biol Neonate 1997;72(2):76-83

Department of Pediatrics, Kreiskrankenhaus Traunstein, Academic Hospital of the University of Munich, Germany.

In preterm infants the activity of antithrombin III (AT-III), the main inhibitor of thrombin, is reduced depending on gestational age and complications such as sepsis or respiratory distress syndrome. Babies with low levels of AT-III have been shown to have a higher mortality and an increased incidence of intracranial hemorrhage (ICH). In our study we tried to show the effect of early AT-III substitution on coagulation parameters and the incidence of intraventricular hemorrhage (IVH).

One hundred three preterm infant sat a gestational age of 25-32 weeks (mean 28.9 weeks; birth weight 600-2,170 g, mean 1,285 g) received AT-III concentrate at a single dosage of 50-200 IU/kg on the day of birth and subsequently only in case of a new decrease below an AT-III activity of 50%. We measured AT-III activity, Quick's prothrombin time (PT), partial thromboplastin time (PTT) and platelet count on the day of birth, and after 1 and 5-9 days in 25 patients. AT-III activity before substitution was lower than described for term infants (20-72%, mean 40%). Within the first week of life Quick's PT and PTT reached almost term values. No significant differences of the platelet count were found within the first week of life. The incidence of IVH was lower than in current epidemiologic studies: in only 13% of the study patients. Six percent of the infants had IVH grade I, 3% grade II, 4% grade III and none grade IV. Therefore, in preterm infants AT-III substitution may reduce the incidence and progression of intracranial hemorrhage.

(2) Seguin J, Weatherstone K, Nankervis C
INHERITED ANTITHROMBIN III DEFICIENCY IN THE NEONATE.

Section of Neonatology, Children's Hospital, Columbus, Ohio.

OBJECTIVE: To describe two cases of inherited antithrombin III (AT-III) deficiency presenting at less than or equal to 28 days of age, and to review other neonatal reports. RESEARCH DESIGN: Clinical descriptions of two patients and literature review of known references to the neonatal presentation of this disorder. SETTING: Academic neonatal intensive care unit. PATIENTS: Case reports--two patients with thrombosis and family history of AT-III deficiency. Literature review--neonatal patients with thrombosis and diagnosis of AT-III deficiency or parental diagnosis of AT-III deficiency or diagnosis of AT-III deficiency alone. SELECTION PROCEDURES: Random observation (case reports) and literature search for cases of AT-III deficiency diagnosed in the neonatal period or presenting with thrombosis and a positive family history of the disorder. INTERVENTIONS: Fresh frozen plasma, heparin, and AT-III concentrate were employed in the current case reports. The cases from the literature used combinations of the above or no intervention. MEASUREMENTS/MAIN RESULTS: Twenty-three cases, including the current reports, of suspected or proved AT-III deficiency were found, with at least 11 cases of thrombosis and at least 10 deaths. CONCLUSIONS: Significant morbidity and mortality from inherited AT-III deficiency can occur in the neonatal period, and the incidence of affected neonatal patients is
probably underestimated. Careful family history, early recognition, diagnosis, and specific treatment are important for management of this disorder.

15. AT-III in Pregnancy

(1) Lockwood CJ
HERITABLE COAGULOPATHIES IN PREGNANCY.
*Obstet Gynecol Surv* 1999 Dec;54(12):754-65

Department of Obstetrics and Gynecology, New York University School of Medicine, NY 10016, USA.

Heritable coagulopathies are leading causes of *maternal thromboembolism* and are associated with an increased risk of maternal and perinatal morbidity and mortality. The most common of these disorders are antithrombin III deficiency, protein C deficiency, protein S deficiency, activated protein C resistance resulting from the factor V Leiden mutation, elevated prothrombin activity associated with a mutation in the prothrombin gene, and hyperhomocysteinemia. The maternal risk of a *thromboembolic episode* is increased by a factor of eight in the presence of any of these heritable states. In addition, the relative risk for a stillbirth in the presence of one of these disorders is 3.6. These conditions are also associated with *intrauterine growth retardation* and *preeclampsia*. Proper management of heritable coagulopathies during pregnancy is essential to reduce the risk of these serious sequelae. Patients with newly diagnosed deep-vein thromboses or pulmonary emboli should be treated with therapeutic levels of *unfractionated* or *low molecular weight heparin*, followed by subsequent *prophylactic heparin therapy*. All patients with a history of *thromboembolism* before pregnancy or evidence of any of these coagulopathies may be offered *prophylactic therapy* with low molecular weight heparin. Patients with *antithrombin III deficiency* should receive full therapeutic heparin therapy for the entire pregnancy, irrespective of their thromboembolic history. *Postpartum therapy* with either heparin or warfarin is required in all cases.

TARGET AUDIENCE:
Obstetricians & Gynecologists, Family Physicians

LEARNING OBJECTIVES: After completion of this article, the reader will be able to describe the various heritable coagulopathies that can complicate pregnancy, to state the potential adverse effects of heritable coagulopathies in pregnancy, and to explain the management of heritable coagulopathies during pregnancy.

(2) Nakabayashi M, Asami M, Nakatani A
EFFICACY OF ANTITHROMBIN REPLACEMENT THERAPY IN SEVERE EARLY-ONSET PREECLAMPSIA.

Maternal and Perinatal Center, Tokyo Women's Medical University, Japan.

It has been suggested that the *hypercoagulable state* in severe preeclampsia is strongly related to the onset of *intrauterine growth retardation* (IUGR) through the deterioration of placental circulation. In this study, one of two kinds of anticoagulants, *heparin* or *antithrombin (AT)*, was given to *severe early-onset preeclamptic women* (onset before 32 weeks of gestation) with IUGR, and the efficacies in maternal and fetal findings were compared. The mechanism of AT to improve placental circulation was discussed based on our previous study using the culture system of chorionic trophoblastic cells. The mean systolic blood pressure decreased significantly in the AT group (*AT concentrate 1,500 IU/d for 7 days, n = 15*). Fetal growth was calculated by ultrasonographic measurement, and the weight gain was higher in the AT group than it was in the heparin group. In vitro experiments showed that AT increased the *thrombomodulin* (TM) antigen on the cell surface and also increased *prostaglandin I2* (PGI2) production by cultured trophoblastic cells. This suggests that *AT replacement therapy* is useful for improving *maternal hypertension* and fetal findings in severe preeclampsia with IUGR through the increase of TM and PGI2 production in both maternal and placental circulation.

(3) Weiner CP, Herrig JE, Pelzer GD, Heilskov J
ELIMINATION OF ANTITHROMBIN III CONCENTRATE IN HEALTHY PREGNANT AND PREECLAMPTIC WOMEN WITH AN ACQUIRED ANTITHROMBIN III DEFICIENCY.
Department of Obstetrics and Gynecology, University of Iowa College of Medicine, Iowa City 52242.

The activity elimination half-life of heat-treated antithrombin III (AT III) concentrate was studied in 5 healthy pregnant and 5 preeclamptic women with a documented AT III deficiency. Healthy pregnant women received 1500 units over 20 minutes. Serial blood specimens were obtained over the next 12 hours. The mean (+/- SEM) activity elimination half-life of AT III was 29.4h +/- 3.4h. Preeclamptic subjects had a mean baseline AT III activity of 70.5 +/- 2% (range 61 to 75%). Their activity eliminator half-life after 3000 units of AT III concentrate was 8.5 +/- 1.2h. There was a direct relationship between the pre-concentrate AT III activity level and the AT III activity elimination half-life (r = 0.79, p = 0.01) for all subjects. Based upon parameters calculated from the first infusion, the AT III activity of preeclamptic subjects was maintained by a constant infusion at approximately 100% for 96h. At the conclusion of the infusion, the activity elimination half-life was again measured. A dramatic increase in the activity elimination half-life was demonstrated (433.6h). We conclude that the activity elimination half-life of AT III concentrate is increased during normal pregnancy and further increased in preeclamptic women with an acquired deficiency.

(4) Terao T, Kobayashi T, Imai N, Oda H, Karasawa T
PATHOLOGICAL STATE OF THE COAGULATORY AND FIBRINOLYTIC SYSTEM IN PREECLAMPSIA AND THE POSSIBILITY OF ITS TREATMENT WITH AT III CONCENTRATE.
Forty patients with preeclampsia were collected, and 27 of these cases were treated with AT III concentrate (1,000-2,000 units/day) for 7 days. According to an evaluation of objective clinical efficacy by the degree of improvement of GI scores in patients with preeclampsia, the number of effective cases was significantly greater among the treated groups than among the untreated groups (p less than 0.05). The rate of efficacy of the treated groups was 40%, compared with 0% in the untreated groups. In severe preeclampsia, a decrease in AT III activity was noted in 56.7%, a decrease in platelet count in 62.1%, and an increase in plasma FDP in 46.2%. A significant correlation was found between the GI score and the AT III activity. The anticoagulation therapy using AT III may normalize the chronic coagulation accelerated state in preeclampsia, and a good influence on the fetus may be expected.

16. AT in Cardiac Surgery

(1) Conley JC, Plunkett PF
ANTITHROMBIN III IN CARDIAC SURGERY: AN OUTCOME STUDY.

Maine Medical Center, Portland 04102, USA.

A retrospective study examined the impact, in heparin resistant patients (HRP), of lyophilized antithrombin III (ATIII) upon five patient outcomes: intensive care unit stay (ICU-S), 24 hour chest tube drainage (CTD in ml), blood and blood product usage (BPU), development of postoperative coagulopathy (PO-Coag), and reoperation for bleeding (Re-Op). Data was collected from the medical records of 311 patients admitted to the hospital between 12/15/95 and 10/24/96. Subjects were divided into three groups based upon heparin resistance and hemostasis medication. Group 1 (n = 109) were HRP treated with increased heparin, Group 2 (n = 100) were HRP receiving ATIII, and Group 3 (n = 102) were non-HRP and served as controls. Group 2 was also subdivided by use of aminocaproic acid and time of ATIII administration. No significant differences were found between the groups for PO-Coag. and Re-Op. However, significant reduction in CTD (p = 0.05) was seen in the aminocaproic acid patients who were treated with ATIII pre-CPB or within the first 20 minutes of CPB. The CTD in this group was (419.37, +/- 72.96) as compared to Group 1 (782.88, +/- 360.94) and Group 3 (766.67, +/- 407.56). Other Group 2 subgroups showed significant differences in BPU, ICU-S and CTD. The results of this study support the notion that early identification and treatment of HRP with ATIII and aminocaproic acid may decrease postoperative blood loss.

B. AT-III Complications
1. AT-III Concentrate induced Blood borne Diseases

(1) Preiss DU, Abdullah D, Eberspacher B, Wilhelm K
SAFETY OF VIRUS INACTIVATED ANTITHROMBIN III CONCENTRATE ANTITHROMBIN III IMMUNO (AT III).

Department of Anesthesia, Benedikt Kreutz Rehabilitation Center, Bad Krozingen, FRG.

In a prospective clinical trial the risk of infection after application of virus inactivated antithrombin III concentrate ANTITHROMBIN III IMMUNO (AT III) was investigated in patients undergoing cardiovascular surgery. The study was conducted according to the recommendations of the International Committee on Thrombosis and Hemostasis (ICTH), with the exception that most patients required additional blood products as well as AT III. Twenty-seven patients were eligible to test for the risk of acquiring hepatitis B. Twenty-six patients could be evaluated in terms of hepatitis NANB transmission considering ALT-levels whereas 20 patients could be tested for anti-HCV one year after surgery. Samples from 78 patients could be monitored for anti-HIV-1. None of these patients showed any signs of infection. AT III IMMUNO seems to be an antithrombin III concentrate with low or absent infectivity.

(2) Egbring R, Seitz R
IMPROVED PROGNOSIS OF FULMINANT HEPATIC FAILURE (FHF) AFTER PLASMA DERIVATIVE REPLACEMENT THERAPY. ENHANCED PROTEOLYSIS OF HEMOSTATIC PROTEINS CONFIRMED BY PROTEINASE-INHIBITOR COMPLEXES DETERMINATION.
*Z Gastroenterol* 1990 Feb;28(2):104-9

Department of Hematology/Oncology, Phillipps-University of Marburg, FRG.

In fulminant hepatic failure disturbances of blood coagulation are caused by both delayed synthesis and increased consumption of hemostatic proteins. The enhanced turnover of clotting factors and inhibitors may be induced by thrombin and plasmin after activation of the coagulation system by thromboplastic material and activators of plasminogen released from necrotic liver cells. Additionally, proteases such as elastase released from granulocytes, may be involved when infectious complications occur. The immunologic determination of the specific proteinase-inhibitor complexes thrombin-antithrombin III, plasmin-alpha 2 antiplasmin, and elastase-alpha 1 antitrypsin is of great diagnostic value to verify and differentiate the proteolysis of hemostatic proteins. Five patients with FHF were treated with plasma derivatives (FFP and AT III concentrates) until the liver had recovered and resumed synthesis of clotting factors and their inhibitors. The coagulation parameters normalized, bleeding complications and microcirculatory failure could be prevented. The data suggest that a comprehensive substitution of plasma components improves considerably the prognosis of acute liver failure.

2. AT-III Concentrate induced Allergic Reactions

B. Hirudin (HIR) and Hirudin Analogs

A. HIR Function and Fields of Use

1. HIR General Aspects

a) Hir General Aspects Recombinant Hirudin and Hemodialysis

(1) Fischer KG, van de Loo A, Bohler J
RECOMBINANT HIRUDIN (LEPIRUDIN) AS ANTICOAGULANT IN INTENSIVE CARE PATIENTS TREATED WITH CONTINUOUS HEMODIALYSIS.
Department of Medicine, University Hospital Freiburg, Germany. fischer@mm41.ukl.uni-freiburg.de

BACKGROUND: Recombinant hirudin (lepirudin) is a potent direct thrombin inhibitor, which has been approved for the treatment of heparin-induced thrombocytopenia type II (HIT). Because the drug is mainly eliminated by the kidneys, a single loading dose of hirudin may induce therapeutic anticoagulation for up to one week in patients with renal insufficiency. Thus, the use of hirudin in critically ill patients with renal failure could markedly increase their bleeding risk. In this study, hirudin was used in critically ill patients with suspected HIT while on continuous venovenous hemodialysis (CVVHD).

METHODS: Hirudin anticoagulation was performed in seven critically ill patients with suspected HIT. Four patients were initially anuric. Three patients had residual renal function. In all 64 CVVHD treatments (mean duration 12 hr), a polysulfone high-flux hemodialyzer (0.75 m²) with a dialysate flow rate of 1.5 liter/hr and an ultrafiltration rate of up to 200 ml/hr was used. Hirudin was given either as continuous intravenous infusion or as repetitive intravenous boli.

Monitoring of anticoagulation was performed by measurements of the systemic activated partial thromboplastin time (aPTT). RESULTS: Hirudin dosage had to be individualized according to the risk of bleeding or clotting. During CVVHD, a continuous intravenous infusion (0.006 to 0.025 mg/kg body wt/hr, N = 2) or repetitive intravenous boli (0.007 to 0.04 mg/kg, N = 5) were given. Two patients required blood transfusions prior to and during hirudin treatment. In five patients without a high bleeding risk, the hirudin dose was adjusted to achieve the target aPTT (1.5 to 2.0 x baseline) in order to prevent thrombotic complications or frequent clotting in the extracorporal circuit. Hirudin dose requirements depended on residual renal function and extracorporal clearance.

CONCLUSIONS: We conclude from these first clinical data that anticoagulation with hirudin in critically ill patients on continuous hemodialysis can be performed without excessive bleeding risk by combining close clinical and laboratory monitoring. The hirudin dose has to be reduced because of renal failure, and may require adjustment for residual or recovering renal function and extracorporal elimination.

(2) Roesken F, Vollmar B, Rucker M, Seiffge D, Menger MD

IN VIVO ANALYSIS OF ANTITHROMBOTIC EFFECTIVENESS OF RECOMBINANT HIRUDIN ON MICROVASCULAR THROMBUS FORMATION AND RECANALIZATION.


Institute for Clinical and Experimental Surgery, University of Saarland, Homburg/Saar, Germany.

PURPOSE: This study was undertaken to evaluate in vivo the effect of recombinant hirudin (r-hirudin [HBW 023]), a potent thrombin inhibitor, on the process of microvascular thrombus formation and recanalization. METHODS: Thrombosis was induced photochemically in distinct arterioles (n = 25) and venules (n = 30) of the ear of 16 hairless hr/hr mice (8 to 10 weeks old, 25 to 30 g of body weight). r-Hirudin (1 mg/kg of body weight) was administered intravenously directly before thrombus induction; saline-treated animals served as controls. RESULTS: Hirudin significantly delayed the process of thrombus formation compared with saline-treated controls in both arterioles (FPD: 381 +/- 80 vs 137 +/- 25 seconds, P < 0.05; D/2: 627 +/- 49 vs 501 +/- 71 seconds; CVO: 925 +/- 78 vs 854 +/- 60 seconds) and venules (FPD: 173 +/- 11 vs 59 +/- 4 seconds; D/2: 342 +/- 54 vs 228 +/- 27 seconds; CVO: 541 +/- 85 vs 344 +/- 43 seconds; P < 0.05). In addition, r-hirudin-treated animals showed an increased rate of vessel recanalization at 24 hours after thrombus induction (arterioles: 54% [7 of 13] vs 0% [0 of 12], P < 0.05; venules: 77% [10 of 13] vs 53% [9 of 17]), whereas microcirculatory parameters and leukocyte-endothelial cell interaction were not affected. CONCLUSION: Our data indicate that r-hirudin not only counteracts the process of thrombus formation but also promotes vessel recanalization, thus supporting its use in clinical microvascular surgery.

(3) Yamashita T, Tsuda Y, Konishi Y, Okada Y, Matsuoka A, Giddings JC, Yamamoto J

THE ANTITHROMBOTIC EFFECT OF POTENT BIFUNCTIONAL THROMBIN INHIBITORS BASED ON HIRUDIN SEQUENCE, P551 AND P532, ON HE-NE LASER-INDUCED THROMBOSIS IN RAT MESENTERIC MICROVESSELS.

Laboratory of Physiology, Faculty of Nutrition, Kobe Gakuin University, Japan. tsutomu@highway.or.jp

The antithrombotic effect of potent synthetic bifunctional non-substrate type thrombin inhibitors based on hirudin sequences, P551 and P532, on Helium-Neon laser-induced thrombosis was investigated in rat mesenteric microvessels and compared with other types of thrombin inhibitors. P551 and P532, when given intravenously, inhibited platelet-rich thrombus formation in both arterioles and venules in a dose-dependent manner. The inhibitory effect was maximal immediately after intravenous administration and persisted for 20-30 minutes in both arterioles and venules. The minimal effective doses of P551 and P532 were 1.0 mg/ kg (intravenously) in both. However, the time course of the antithrombotic effect was not in keeping with the inhibitory effect measured by an activated partial thromboplastin time and was similar to other types of inhibitors in spite of different half-lives. The current findings show that P551 and P532 had significant inhibitory effects on platelet-rich thrombus formation and suggest that these bifunctional thrombin inhibitors could be potent antithrombotic agents.

b) Direct Thrombin Inhibitors

(1) Anand S

DIRECT THROMBIN INHIBITORS.

Haemostasis 1999 Dec;29 Suppl S1:76-78

McMaster University, Hamilton General Hospital, Hamilton, Ont., Canada.

Direct thrombin inhibitors may offer advantages over indirect thrombin inhibitors in the management of patients with acute coronary syndromes (ACS). Two direct thrombin inhibitors, hirudin and bivalirudin, have been investigated in Phase II and Phase III clinical trials. Based on the results of a meta-analysis of study data from 25,000 patients, hirudin appears to be more effective than unfractionated heparin (UFH) in the treatment of patients with ACS, but it is associated with an increased rate of major bleeding. A meta-analysis of a smaller patient population has suggested that bivalirudin, too, may be more efficacious than UFH and may also be safer. Copyright 1999 S. Karger AG, Basel

(2) Catella-Lawson F

DIRECT THROMBIN INHIBITORS IN CARDIOVASCULAR DISEASE.

Coron Artery Dis 1997 Feb;8(2):105-11

Center for Experimental Therapeutics, University of Pennsylvania, Philadelphia 19104, USA.

Heparin, the most widely used antithrombin, suffers several limitations, including high inter-individual variability of anticoagulant response, a nonlinear dose-response curve, inability to inactivate clot-bound thrombin, a requirement for endogenous cofactors and inactivation by platelet factor 4 and heparinase. These shortcomings may explain its suboptimal efficacy and safety in the prevention of arterial vessel occlusion. Heparin's drawbacks may be overcome by direct thrombin inhibitors. The development of these specific antithrombins has been a major therapeutic goal of the past decade. The high expectations generated by the use of these compounds in experimental models of arterial thrombosis appeared to be confirmed by the initial phase I and II clinical studies. However, large phase III trials have been highly discouraging: three trials with hirudin have been interrupted as a result of a high incidence of serious adverse events. Two of these trials were subsequently restarted at lower doses and did not support an incremental efficacy of hirudin over heparin. Two trials in the setting of angioplasty (one with hirudin and one with hirulog) have also failed to demonstrate the superiority of these compounds over heparin. Is this the result of a very narrow therapeutic range of these agents or the consequence of poor design of the phase II studies leading to the selection of inappropriate doses for the comparative efficacy trials? This review focuses on the clinical development of two specific antithrombins: hirudin and hirulog. The experimental pharmacology and human studies of Argatroban are discussed in a review by Fitzgerald and Murphy.
(3) Pineo GF, Hull RD

HIRUDIN AND HIRUDIN ANALOGUES AS NEW ANTICOAGULANT AGENTS.


University of Calgary, Alberta, Canada.

Recombinant hirudin and hirudin analogues constitute interesting new antithrombotic agents that have distinct advantages over heparin. These agents specifically inhibit thrombin and all of its actions and also suppress further thrombin generation. As opposed to unfractionated heparin, hirudin and hirulog effectively suppress clot-bound thrombin, making these agents of particular interest in the treatment of arterial thrombosis, for example, following thrombolysis or percutaneous transcatheter angioplasty. The recent data derived from clinical trials supporting the use of hirudin and hirulog in the prevention and treatment of thrombotic diseases are reviewed here.

(4) Johnson PH

HIRUDIN: CLINICAL POTENTIAL OF A THROMBIN INHIBITOR.


Cell and Molecular Biology Laboratory, Life Sciences Division, SRI International, Menlo Park, California 94025.

Hirudin is the most potent and specific known inhibitor of thrombin, the enzyme that plays a key regulatory function in hemostasis and blood coagulation. The importance of thrombosis in cardiovascular disease has recently highlighted the limitations of existing antithrombotic drugs and the potential value of direct thrombin inhibition as an effective approach to antithrombotic therapy. Hirudin and a small peptidomimetic analog—hirulog—are being developed as alternatives to heparin for the treatment of unstable angina, for prevention of abrupt closure and restenosis following coronary angioplasty, for prevention of deep vein thrombosis after major orthopedic surgery, and as an adjunct to fibrinolytic therapy. Direct thrombin inhibitors have several potential advantages over heparin: They can inhibit thrombin bound to clots or extracellular matrices, which are relatively resistant to heparin; they do not require antithrombin III as a cofactor, which may lead to a more predictable dose response; and they are not inhibited by activated platelets, which release platelet factor 4 and other molecules that neutralize heparin. The results of early clinical studies suggest that hirudin and hirulog may be more efficacious and more predictable and may have fewer bleeding complications than heparin for several clinical indications.

c) Hirudin can be Eliminated by Hemofiltration

(1) Bucha E, Kreml R, Nowak G

IN VITRO STUDY OF R-HIRUDIN PERMEABILITY THROUGH MEMBRANES OF DIFFERENT HAEMODIALYSERS.

*Nephrol Dial Transplant* 1999 Dec;14(12):2922-6

Max-Planck-Gesellschaft, Research Unit Pharmacological Haemostaseology, Friedrich-Schiller-University, Jena, Germany.

BACKGROUND: After introducing the specific thrombin inhibitor recombinant hirudin (r-hirudin) into clinical practice in cases of heparin-induced thrombocytopenia (HIT, type II) the possibility of its use as an anticoagulant during haemodialysis treatment in HIT II patients is being discussed more frequently. On the one hand, the efficient, safe and routine use of r-hirudin during haemodialyses, including the maintenance of a therapeutic blood level, presupposes that no r-hirudin will leave the circulation by passing through the dialyser membrane. On the other hand, it is important to have dialysers whose permeability to r-hirudin allows its efficient removal from the human body because, to date, no antidote is commercially available in cases of dangerously high blood concentrations of r-hirudin. METHODS: An in vitro circulation model was used to study the r-hirudin permeability of some low- and high-flux dialysers. As r-hirudin-containing vehicles, both albumin-containing saline solution and bovine blood were circulated in the blood space of the system for 2 h. Transmembrane r-hirudin passage was tested by measuring r-hirudin concentration both in the blood and dialysate space fluids using the ecarin clotting time (ECT). RESULTS: Low-flux dialysers with membranes made from polysulfone or regenerated cellulose proved to be almost impermeable to r-hirudin. In
contrast, other low-flux membranes were partly permeable to r-hirudin (e.g. Hemophan) or even almost completely permeable (e.g. cellulose acetate). All high-flux dialysers tested were permeable to r-hirudin. CONCLUSIONS: Only low-flux dialysers with polysulfone or regenerated cellulose membranes proved to be suitable for r-hirudin use in routine haemodialysis therapy. Other low-flux, and all high-flux, capillaries are permeable to r-hirudin and offer the possibility of lowering toxic r-hirudin concentrations after overdosing.

(2) Frank RD, Farber H, Stefanidis I, Lanzmich R, Kierdorf HP
HIRUDIN ELIMINATION BY HEMOFILTRATION: A COMPARATIVE IN VITRO STUDY OF DIFFERENT MEMBRANES.

Medizinische Klinik II, Universitätsklinikum, Rheinisch-Westfälische Technische Hochschule, Aachen, Germany. dario.frank@post.klinikum.rwth-aachen.de

BACKGROUND: Recombinant hirudin (r-hirudin) is a highly specific and selective thrombin inhibitor. Since 1997, it has been approved for the treatment of heparin-induced thrombocytopenia (HIT type II). Renal function impairment drastically prolongs the elimination half-life time. In cases of bleeding or overdosage, there is currently no antidote available. Hemofiltration has been reported to be useful in r-hirudin elimination. In this study, we determined sieving coefficients (SCs) and drug clearances for two different hemofilters currently used in clinical medicine and intensive care.

METHODS: We developed an in vitro postdilution hemofiltration model using 500 ml heparinized (2 IU unfractionated heparin/ml) fresh human blood and bicarbonate substitution fluid. The investigated membranes were high-flux polysulfone F50 (1.0 m², Fresenius) and AN69 Nephral 200 (1.05 m², Hospal Cobe). After equilibration, a bolus of Lepirudin was injected into the postfilter port to achieve a r-hirudin blood level of approximately 15 microg/ml. Serial blood and ultrafiltrate samples were taken for the determination of hirudin levels (chromogenic assay) and control parameters. SC and clearances were calculated according to standard formulae. RESULTS: The observed SCs and clearances differed significantly between F50 and Nephral 200 (0.60 +/- 0.17 and 21.0 +/- 5.9 ml/min, respectively, vs. 0.44 +/- 0.09 and 15.5 +/- 3.0 ml/min, respectively; P = 0.001). The determination of prothrombin fragments showed no coagulation activation during the experiments. The hematocrit values remained stable. CONCLUSIONS: Our data show that r-hirudin can be eliminated by hemofiltration. The elimination obviously depends on the membrane material with high-flux polysulfone being more effective than AN69. These findings may be important in cases of overdosage and for r-hirudin dosage guidelines in continuous hemofiltration.

(3) Frank RD, Farber H, Stefanidis I, Lanzmich R, Kierdorf HP
HIRUDIN ELIMINATION BY HEMOFILTRATION: A COMPARATIVE IN VITRO STUDY OF DIFFERENT MEMBRANES.

Medizinische Klinik II, Universitätsklinikum, Rheinisch-Westfälische Technische Hochschule, Aachen, Germany. dario.frank@post.klinikum.rwth-aachen.de

BACKGROUND: Recombinant hirudin (r-hirudin) is a highly specific and selective thrombin inhibitor. Since 1997, it has been approved for the treatment of heparin-induced thrombocytopenia (HIT type II). Renal function impairment drastically prolongs the elimination half-life time. In cases of bleeding or overdosage, there is currently no antidote available. Hemofiltration has been reported to be useful in r-hirudin elimination. In this study, we determined sieving coefficients (SCs) and drug clearances for two different hemofilters currently used in clinical medicine and intensive care.

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experiments. The hematocrit values remained stable. **CONCLUSIONS**: Our data show that r-hirudin can be eliminated by hemofiltration. The elimination obviously depends on the membrane material with high-flux polysulfone being more effective than AN69. These findings may be important in cases of overdosage and for r-hirudin dosage guidelines in continuous hemofiltration.

2. HIR in Pulmonary Embolism

(1) Agnelli G, Sonaglia F  
**ANTICOAGULANT AGENTS IN THE MANAGEMENT OF PULMONARY EMBOLISM.**  
*Int J Cardiol* 1998 May 29;65 Suppl 1:S95-8

Istituto di Medicina Interna e Medicina Vascolare, Universita di Perugia, Italy.

The anticoagulant agents most commonly used in the prevention and treatment of pulmonary embolism (PE) are unfractionated heparin, oral anticoagulants, and low molecular weight heparins (LMWHs). Unfractionated heparin at low fixed dose is the prophylactic regimen of choice for PE in patients undergoing general surgery or with serious medical diseases (low to moderate risk patients). In high risk patients perioperative prophylaxis with LMWHs or oral anticoagulants should be adopted. Therapy of pulmonary embolism should start with an intravenous bolus dose of 5000 U heparin followed by an infusion of 1250 U/h. Then the dose should be adjusted to maintain the aPTTX2-2.5 pre-treatment value. Heparin is continued for 7-10 days and is followed by oral anticoagulants for at least 3 months. Unfractionated heparin has some pharmacological limitations, mainly due to the aspecific binding to plasma proteins that limits its anticoagulant effect and causes the heparin resistance observed in some patients with PE and the inter-subject variability of the anticoagulant effect. Other antithrombotic agents such as LMWHs and selective thrombin inhibitors (hirudin and its analogues) do not aspecifically bind to plasma proteins. They have recently been used with promising results in the prevention and treatment of PE. Their definitive value in this clinical setting will be defined by the ongoing clinical trials.

3. HIR in Orthopedic Surgery

**A COMPARISON OF RECOMBINANT HIRUDIN WITH A LOW-MOLECULAR-WEIGHT HEPARIN TO PREVENT THROMBOEMBOLIC COMPLICATIONS AFTER TOTAL HIP REPLACEMENT.**  

Department of Orthopedics, Sahlgrenska-Ostra University Hospital, Goteborg, Sweden.

BACKGROUND: Patients who undergo total hip replacement have a high risk of thromboembolic complications. Recombinant hirudin (desirudin), a specific inhibitor of thrombin, represents a new development in antithrombotic therapy. We compared the efficacy and safety of desirudin with those of a low-molecular-weight heparin (enoxaparin) for the prevention of thromboembolic complications in patients undergoing primary total hip replacement. METHODS: We started preoperatively: enoxaparin on the evening before surgery, and desirudin within 30 minutes before the start of surgery. The dose of desirudin was 15 mg subcutaneously twice daily, and the dose of enoxaparin was 40 mg subcutaneously once daily. A total of 1587 patients were included in the primary analysis of efficacy. In the desirudin group, as compared with the enoxaparin group, there was a significantly lower rate of proximal deep-vein thrombosis. The safety profiles were similar in the two treatment groups. **CONCLUSIONS**: When administered 30 minutes before total hip replacement surgery, desirudin is more effective than enoxaparin in preventing deep-vein thrombosis.  

4. HIR in Stent Thrombosis (Local Delivery of Hirulog)

(1) Muller DW, Gordon D, Topol EJ, Levy RJ, Golomb G  
**SUSTAINED-RELEASE LOCAL HIRULOG THERAPY DECREASES EARLY THROMBOSIS BUT NOT NEOINTIMAL THICKENING AFTER ARTERIAL STENTING.**  
*Heart J* 1996 Feb;131(2):211-8
Adventitial heparin delivery has been shown to inhibit thrombosis and neointimal thickening in a rat carotid injury model. To determine whether sustained, local delivery of hirulog, a potent antithrombin agent, inhibits thrombus formation and neointimal thickening after arterial stenting, silicone polymers containing hirulog were formulated at a concentration of 5.8% by weight and were tested in vitro to determine the rate of drug release. An oversized metallic stent was implanted in the carotid artery of 18 juvenile farm pigs. Hirulog-impregnated silicone polymers were placed around the adventitial surface of one stented segment of each animal and a control polymer was placed contralaterally. Intravenous hirulog (4 mg/kg/hr) was infused for the duration of the procedure to maintain the activated clotting time of > 300 sec. Ex vivo testing estimated the release of hirulog to be 1.54 micrograms/mg matrix/day with no loss of anticoagulant activity of the released peptide. In four pigs killed on days 3 through 5, macroscopic thrombus was very faintly visible on the stent struts of one arterial segment treated with sustained-release hirulog but was readily evident in all control arteries. However, electron microscopy showed platelet adhesion and microscopic thrombus formation on each stent of both treated and untreated sides. Fourteen pigs were killed 32 +/- 4 days after stenting. Histologic analysis showed no difference between hirulog-treated and control sides in the volume of neointima (540 +/- 129 units vs 357 +/- 95 units, p = 0.27) or in the average intima to media ratio (0.44 +/- 0.12 vs 0.34 +/- 0.24, p = 0.47) over the length of the stented segment. Late thrombotic occlusion occurred in two hirulog-treated and two control arteries. In this model, local adventitial hirulog delivery at the dose and delivery rate used may reduce, but does not prevent, thrombus formation and does not reduce the severity of neointimal thickening after carotid stent implantation.

5. HIR in Cardiac Surgery

(1) White HD, Ellis CJ, French JK, Aylward P
HIRUDIN (DESIRUDIN) AND HIRULOG (BIVALIRUDIN) IN ACUTE ISCHAEMIC SYNDROMES AND THE RATIONALE FOR THE HIRULOG/EARLY REPERFUSION OCCLUSION (HERO-2) STUDY.

Green Lane Hospital, Auckland, New Zealand.

Unlike unfractionated heparin, direct thrombin inhibitors such as hirudin and Hirulog inhibit clot-bound as well as fluid-phase thrombin, escape neutralisation by platelet secretion products, do not require monitoring, and are unassociated with immune thrombocytopenia. They have been shown to have modest advantages over heparin when given after thrombolytic therapy, reducing reinfarction by 14%. In the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO 2b) trial, patients treated with streptokinase and adjunctive hirudin had a reduction in death or myocardial infarction of 40% at 30 days (8.6% with hirudin versus 14.4% with heparin, p = 0.004). In the Hirulog Early Reperfusion/Occlusion (HERO 1) trial, 48% of patients who received Hirulog as adjunctive therapy with streptokinase had Thrombolysis in Myocardial Infarction (TIMI) trial grade 3 flow in the infarct-related artery, compared with 35% of patients who received heparin with streptokinase (p < 0.05). The HERO 2 study, involving 17,000 patients, will test the hypothesis that Hirulog and aspirin given before streptokinase will reduce mortality compared with aspirin plus heparin. Early administration of direct thrombin inhibitors may potentially improve the outcome of patients treated with thrombolytic therapy.

RECOMBINANT HIRUDIN AS A PERIPROCEDURAL ANTITHROMBOTIC IN CORONARY ANGIOPLASTY FOR UNSTABLE ANGINA PECTORIS.
Eur Heart J 1996 Aug;17(8):1207-1215

Institute of Clinical Chemistry and Laboratory Medicine, Johannes Gutenberg-University, Mainz, Germany.

Percutaneous transluminal coronary angioplasty is often complicated by thrombotic abrupt vessel closure in patients with unstable angina pectoris. We made a study of patients, enrolled in one of two sequential groups of r-hirudin (group 1: 0.3 mg.kg-1 i.v. bolus, 0.12 mg.kg-1.h-1 i.v. infusion; 21 patients; group 2: 0.5 mg.kg-1 i.v. bolus, 0.24 mg.kg-1.h-1 i.v. infusion; 19 patients) or in a heparin
control group (150 IU.kg-1 i.v. bolus, 20 IU.kg-1.h-1 i.v. infusion; 21 patients). There was a dose-dependent correlation between partial thromboplastin time and the r-hirudin plasma levels (r = 0.61). One major bleeding complication occurred in dose group 2. The functional assay for the estimation of r-hirudin plasma concentrations showed excellent correlations to the immunological technique (r = 0.99). Based on coagulation tests the present study showed the feasibility of a periprocedural antithrombotic regimen with r-hirudin for patients undergoing coronary angioplasty for unstable angina. In addition to the partial thromboplastin time the determination of r-hirudin plasma levels by a chromogenic substrate assay considerably improves the monitoring of therapy. The lower dose r-hirudin regimen seems to be suboptimal as periprocedural anticoagulation in coronary angioplasty patients as indicated by markers of thrombin generation and thrombin activity.

Comment in: Eur Heart J 1996 Aug;17(8):1134-6

6. HIR in Acute Myocardial Infarction


RECOMBINANT HIRUDIN (LEPIRUDIN) FOR THE IMPROVEMENT OF THROMBOLYSIS WITH STREPTOKINASE IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION: RESULTS OF THE HIT-4 TRIAL.


Stadtische Kliniken, Medizinische Klinik II, Kassel, Germany.

OBJECTIVES: The purpose of this study was to compare recombinant hirudin and heparin as adjuncts to streptokinase thrombolysis in patients with acute myocardial infarction (AMI).

BACKGROUND: Experimental studies and previous small clinical trials suggest that specific thrombin inhibition improves early patency rates and clinical outcome in patients treated with streptokinase. METHODS: In a randomized double-blind, multicenter trial, 1,208 patients with AMI < or =6 h were treated with aspirin and streptokinase and randomized to receive recombinant hirudin (lepirudin, i.v. bolus of 0.2 mg/kg, followed by subcutaneous (s.c.) injections of 0.5 mg/kg b.i.d. for 5 to 7 days) or heparin (i.v. placebo bolus, followed by s.c. injections of 12,500 IU b.i.d. for 5 to 7 days). A total of 447 patients were included in the angiographic substudy in which the primary end point, 90-min Thrombolysis in Myocardial Infarction (TIMI) flow grade 3 of the infarct-related artery, was evaluated, while the other two-thirds served as "safety group" in which only clinical end points were evaluated. As an additional efficacy parameter the ST-segment resolution at 90 and 180 min was measured in all patients. RESULTS: TIMI flow grade 3 was observed in 40.7% in the lepirudin and in 33.5% in the heparin group (p = 0.16), respectively. In the entire study population the proportion of patients with complete ST resolution at 90 min (28% vs. 22%, p = 0.05) and at 180 min (52% vs. 48%, p = 0.18) after start of therapy tended to be higher in the lepirudin group. There was no significant difference in the incidence of hemorrhagic stroke (0.2% vs. 0.3%) or total stroke (1.2% vs. 1.5%), reinfarction rate (4.6% vs. 5.1%) and total mortality rate (6.8% vs. 6.4%) at 30 days, as well as the combined end point of death, nonfatal stroke, nonfatal reinfarction, rescue-percutaneous transluminal coronary angioplasty and refractory angina (22.7 vs. 24.3%) were not statistically different between the two groups. CONCLUSIONS: Lepirudin as adjunct to thrombolysis with streptokinase did not significantly improve restoration of blood flow in the infarct vessel as assessed by angiography, but was associated with an accelerated ST resolution. There was no increase in the risk of major bleedings with lepirudin compared to heparin.

(2) Zeymer U, Neuhaus KL

CLINICAL TRIALS IN ACUTE MYOCARDIAL INFARCTION.

Curr Opin Cardiol 1999 Sep;14(5):392-402

Medizinische Klinik II, Klinikum Kassel, Germany.

Long-term follow-up of placebo-controlled thrombolysis trials has proven that the survival benefit from thrombolysis in acute myocardial infarction (AMI) is maintained for up to 10 years. Ongoing research is being conducted with the aim to further improve early restoration of blood flow in the infarct vessel and, thus, reperfusion of the infarcted myocardium in patients with AMI, with the ultimate goal to improve survival. In two recent mega-trials, two new single-bolus fibrinolytics (lanoteplase and TNK-tissue plasminogen activator) were shown to be equivalent to front-loaded
alteplase in reducing infarct mortality. The ease of application of these agents might help reduce the
time from symptom onset to start of therapy. More potent thrombin inhibitors such as hirudin and
hirulog seem to speed up thrombolysis with streptokinase and reduce the rate of reinfarctions. Very
promising results are derived from angiographic trials combining reduced doses of thrombolytics
with glycoprotein IIb/IIIa inhibitors. Advances in mechanical revascularization can be achieved with
the use of stents and better conjunctive therapies. All of these developments are expected to further
improve clinical outcome of patients with AMI in the near future.

(3) White HD
DIRECT THROMBIN INHIBITION AND THROMBOLYTIC THERAPY: RATIONALE
FOR THE HIRULOG AND EARLY REPERFUSION/OCLUSION (HERO-2) TRIAL.
_Am J Cardiol_ 1998 Oct 22;82(8B):57P-62P

Cardiology Department, Green Lane Hospital, Auckland, New Zealand.
Worldwide, streptokinase continues to be used widely in the treatment of myocardial infarction
because it is inexpensive and causes fewer intracranial hemorrhages than other thrombolytic
regimens. However, in the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO-I)
trial, the 90-minute angiographic Thrombolysis in Myocardial Infarction (TIMI) trial grade 3 flow
rate with streptokinase was 43% lower than that with accelerated tissue plasminogen activator, and
there was a higher incidence of death or disabling stroke with streptokinase (7.8% vs 6.9%, _p_ <0.01).
In the first Hirulog and Early Reperfusion/Oclusion (HERO-1) trial, 48% of patients given the
direct thrombin inhibitor bivalirudin (formerly Hirulog, The Medicines Company) after streptokinase
had TIMI 3 patency at 90 minutes, compared with 35% of patients given intravenous heparin (_p_
<0.05). Other angiographic and clinical studies and animal research have shown that early infarct artery
blood flow may be increased markedly if a direct thrombin inhibitor is administered before the
thrombolytic agent. In the HERO-2 trial, 17,000 patients presenting within 6 hours after the onset of
acute myocardial infarction will be given aspirin and randomized to receive either intravenous
heparin or bivalirudin before streptokinase is administered. The primary endpoint will be 30-day
mortality, and secondary endpoints will include death or myocardial infarction within 30 days, and death
or nonfatal disabling stroke. If the thrombin hypothesis is supported by improved clinical outcomes with
bivalirudin in the HERO-2 trial, large-scale clinical trials will be needed to evaluate the
administration of direct thrombin inhibitors before other thrombolytic regimens.

French JK, Collins R, Maraganore J, Adelman B
RANDOMIZED, DOUBLE-BLIND COMPARISON OF HIRULOG VERSUS HEPARIN IN
PATIENTS RECEIVING STREPTOKINASE AND ASPIRIN FOR ACUTE
MYOCARDIAL INFARCTION (HERO). HIRULOG EARLY
REPERFUSION/OCLUSION (HERO) TRIAL INVESTIGATORS.
_Circulation_ 1997 Oct 7;96(7):2155-61

Green Lane Hospital, Auckland, New Zealand. white002@msn.com
BACKGROUND: Thrombolytic therapy improves survival after myocardial infarction through
reperfusion of the infarct-related artery. Thrombin generated during thrombolytic administration
may reduce the efficacy of thrombolysis. A direct thrombin inhibitor may improve early patency
rates. METHODS AND RESULTS: Four hundred twelve patients presenting within 12 hours with ST-
segment elevation were given aspirin and streptokinase and randomized in a double-blind manner to
receive up to 60 hours of either heparin (5000 U bolus followed by 1000 to 1200 U/h), low-dose
hirulog (0.125 mg/kg bolus followed by 0.25 mg x kg(-1) x h(-1)) for 12 hours then 0.125 mg x kg(-1) x
h(-1), or high-dose hirulog (0.25 mg/kg bolus followed by 0.5 mg x kg(-1) x h(-1)) for 12 hours then
0.25 mg x kg(-1) x h(-1)). The primary outcome was Thrombolysis In Myocardial Infarction trial
(TIMI) grade 3 flow of the infarct-related artery at 90 to 120 minutes. _TIMI 3 flow was_ 35% (95% CI,
28% to 44%) _with heparin, 46% (95% CI, 38% to 55%) _with low-dose hirulog, and 48% (95% CI, 40% to
57%) _with high-dose hirulog_ (heparin versus hirulog, _P_ =.023; heparin versus high-dose hirulog,
_P_ =.03). At 48 hours, reocclusion had occurred in 7% of heparin, 5% of low-dose hirulog, and 1% of
high-dose hirulog patients (P=NS). By 35 days, death, cardiogenic shock, or reinfarction had
occurred in 25 heparin (17.9%), 19 low-dose hirulog (14%), and 17 high-dose hirulog patients
(12.5%) (P=NS). Two strokes occurred with heparin, none with low-dose hirulog, and two with high-
dose hirulog. Major bleeding (40% from the groin site) occurred in 28% of heparin, 14% of low-dose hirulog, and 19% of high-dose hirulog patients (heparin versus low-dose hirulog, P<.01).

CONCLUSIONS: Hirulog was more effective than heparin in producing early patency in patients treated with aspirin and streptokinase without increasing the risk of major bleeding. Direct thrombin inhibition may improve clinical outcome.

(5) Bates ER
CLINICAL TRIAL RESULTS WITH HIRUDIN AND BIVALIRUDIN FOR ACUTE CORONARY ARTERY SYNDROMES.
Semin Thromb Hemost 1997;23(6):575-81

Department of Medicine, University of Michigan, Ann Arbor, USA.

Thrombin plays a key role in the pathophysiology of acute coronary artery syndromes. The "thrombin hypothesis" states that more complete and consistent thrombin inhibition may improve clinical outcomes in acute ischemic syndromes. The direct thrombin inhibitors hirudin and bivalirudin are potentially superior agents to heparin and have been tested in several clinical trials. More predictable and less variable levels of anticoagulation have been demonstrated. Adverse clinical events have been reduced during active treatment with hirudin or bivalirudin, but increased bleeding, including intracerebral hemorrhage, can occur with excessive anticoagulation. Unfortunately, the short-term benefit has not been sustained during follow-up. The multiplicity of pathways for platelet activation, inadequate treatment duration, or the inability to block thrombin generation may explain the limited efficacy. In contrast, inhibitors of the glycoprotein IIb/IIIa platelet receptor are associated with a more dramatic and durable reduction in clinical events.

(6) Maraganore JM, Adelman BA
HIRULOG: A DIRECT THROMBIN INHIBITOR FOR MANAGEMENT OF ACUTE CORONARY SYNDROMES.
Coron Artery Dis 1996 Jun;7(6):438-48

Biogen, Inc., Cambridge, Massachusetts, USA.

Hirulog therapy has been studied extensively in numerous settings including prevention of DVT, treatment of unstable angina, treatment of acute myocardial infarction during thrombolysis, and prevention of acute complications of PTCA. Being one of the first direct thrombin inhibitors in clinical development, it has had to 'test the waters', so to speak, of the relationship between pathophysiology and clinical trial design: what are the correct indications, patient entry criteria, endpoints, frequency and duration of dosing, and so on? Our findings validate a role for thrombin in treating arterial thromboembolism and demonstrate clinical activity and tolerability of Hirulog.

A PILOT, EARLY ANGIOGRAPHIC PATENCY STUDY USING A DIRECT THROMBIN INHIBITOR AS ADJUNCTIVE THERAPY TO STREPTOKINASE IN ACUTE MYOCARDIAL INFARCTION.
Circulation 1994 Apr;89(4):1567-72

Department of Medicine, Montreal Heart Institute, Quebec, Canada.

BACKGROUND: The success of streptokinase in acute myocardial infarction is hampered by the high failure rate to achieve early reperfusion. This study evaluates the possible benefit of Hirulog (Biogen, Cambridge, Mass.), a direct thrombin inhibitor, as adjunct therapy to streptokinase to enhance early patency and prevent rethrombosis. Heparin has been shown to be of very limited benefits in this setting. METHODS AND RESULTS: Forty-five patients were randomized to Hirulog or heparin (2:1 ratio). Coronary angiography documented a TIMI 2 or 3 flow after 90 minutes in 77% of the patients treated with Hirulog and streptokinase and in 47% of patients treated with heparin and streptokinase (P < .05) and after 120 minutes in 87% and 47% of patients, respectively (P < .01). TIMI 3 flow was established in 77% of patients with Hirulog compared with 40% with heparin (P < .02). The clinical outcome and the bleeding rate was also favorable to Hirulog: no reocclusion was observed at late angiography performed 4.7 days later. CONCLUSIONS: Hirulog in this pilot study significantly improved the early patency rate of the infarct-related artery with a
favorable clinical profile. This new direct thrombin inhibitor exhibits promise as adjunctive therapy to thrombolysis.

7. HIR in Unstable Angina

(1) Anand SS

THE ORGANIZATION TO ASSESS STRATEGIES FOR ISCHEMIC SYNDROMES (OASIS) PILOT STUDY: EVALUATION OF ACUTE AND LONG-TERM THERAPIES FOR PATIENTS WITH ACUTE CORONARY SYNDROMES WITHOUT ST ELEVATION.

*Am J Cardiol* 1999 Sep 2;84(5A):13M-19M

Department of Preventive Cardiology and Therapeutics, McMaster University, Hamilton, Ontario, Canada.

The objectives of the Organization to Assess Strategies for Ischemic Syndromes (OASIS) Pilot Study (phase 2) were (1) to compare the efficacy, safety, and feasibility of recombinant hirudin versus unfractionated heparin as short-term therapy in patients with acute coronary syndromes without ST elevation and (2) to compare the efficacy and safety of long-term therapy with warfarin and aspirin versus standard therapy with aspirin alone in the same patient population. Investigators at 31 Canadian centers randomized 909 patients to receive either medium-dose hirudin, low-dose hirudin, or unfractionated heparin. The incidence of the 7-day primary composite outcome of cardiovascular death, new myocardial infarction (MI), or refractory angina was significantly lower among patients who received hirudin than among those assigned to unfractionated heparin. A subset of these patients was subsequently randomized to long-term, low-intensity (INR < 1.5) or moderate-intensity (INR 2-2.5) anticoagulant treatment with warfarin or to standard therapy. In this substudy, promising results were observed in favor of moderate-intensity warfarin. These findings provided the rationale for the design and conduct of the large-scale, phase III OASIS-2 trial.

(2) Fuchs J, Cannon CP

HIRULOG IN THE TREATMENT OF UNSTABLE ANGINA. RESULTS OF THE THROMBIN INHIBITION IN MYOCARDIAL ISCHEMIA (TIMI) 7 TRIAL.

*Circulation* 1995 Aug 15;92(4):727-33

Department of Medicine, Harvard Medical School, Brigham and Women's Hospital, Boston, MA 02115, USA.

BACKGROUND: Direct thrombin inhibitors are a new class of drugs that may offer a more effective and potentially simpler alternative to heparin. Hirulog is a synthetic peptide based on the leech-derived compound hirudin and, like hirudin, is a highly specific, direct inhibitor of free and clot-bound thrombin. METHODS AND RESULTS: TIMI 7 was a randomized, double-blind study of Hirulog, given with 325 mg/d aspirin to 410 patients with unstable angina. Patients received a constant infusion of Hirulog for 72 hours at one of four doses: 0.02 (n = 160), 0.25 (n = 81), 0.5 (n = 88), and 1.0 (n = 81) mg.kg-1.h-1. The primary efficacy end point was "unsatisfactory outcome," defined as death, nonfatal myocardial infarction (MI), rapid clinical deterioration, or recurrent ischemic pain at rest with ECG changes by 72 hours. Unsatisfactory outcome was not different among the four dose groups: 8.1%, 6.2%, 11.4%, and 6.2% (P = NS). However, the secondary end point of death or nonfatal MI through hospital discharge occurred in 10.0% of patients treated with 0.02 mg.kg-1.h-1 compared with 3.2% of patients treated with the three higher doses of Hirulog (0.25, 0.5, and 1.0 mg.kg-1.h-1, P = .008). Only 2 of 410 patients (0.5%) experienced a major hemorrhage attributed to Hirulog. CONCLUSIONS: The direct thrombin inhibitor Hirulog is a promising new antithrombotic agent that deserves further study. The results of TIMI 7 lend support to the use of an antithrombin agent with aspirin in patients with unstable angina.


USEFULNESS AND TOLERABILITY OF HIRULOG, A DIRECT THROMBIN-INHIBITOR, IN UNSTABLE ANGINA PECTORIS.

*Am J Cardiol* 1993 Dec 15;72(18):1357-60
Department of Medicine, Veterans Administration Medical Center, West Roxbury, Massachusetts 02132.

In an open-label pilot study of 20 patients with unstable angina (Braunwald class I-IIIB), hirulog was administered as a continuous intravenous infusion for 5 days in a dose of 0.2 mg/kg/hour to produce an activated partial thromboplastin time of approximately 200% of control. The primary end points of the study were: death, development of a transmural myocardial infarction, and intractable angina needing interventions such as an intraaortic balloon pump insertion, angioplasty and surgery. The secondary end points were the presence of an intracoronary thrombus detected on angiography and hemorrhagic complications during therapy. There was no death or transmural infarction in this study cohort; however, 1 patient developed intractable angina. Intracoronary thrombus was documented in 2 patients. Infusion of hirulog resulted in a steady prolongation of the activated partial thromboplastin time without any hemorrhagic or other adverse effect. Hirulog appears to be an effective antithrombotic agent that is tolerated well and may have advantages over heparin in the management of patients with unstable angina.

8. HIR in Angioplasty

(1) Bittl JA, Ahmed WH

RELATION BETWEEN ABRUPT VESSEL CLOSURE AND THE ANTI COAGULANT RESPONSE TO HEPARIN OR BIVALIRUDIN DURING CORONARY ANGIOPLASTY.

Am J Cardiol 1998 Oct 22;82(8B):50P-56P

Ocala Heart Institute, Munroe Regional Medical Center, Florida 34474, USA.

The dosing of anticoagulants during coronary angioplasty is commonly guided by measurements of activated clotting time (ACT), but the usefulness of these measurements remains uncertain. The Hirulog Angioplasty Study was a randomized, double-blind comparison of heparin versus bivalirudin in 4,312 patients undergoing angioplasty for unstable or postinfarction angina. In 4,098 of the patients randomized, the balloon was inflated. All patients had ACT measurements 5 minutes after a weight-adjusted bolus of heparin or bivalirudin, and patients undergoing complicated or prolonged angioplasty procedures lasting >45 minutes had additional ACT measurements to guide further anticoagulant therapy. The analysis presented in this article evaluated the relation between the initial or maximum ACT measurements and the risk of abrupt vessel closure during heparin or bivalirudin therapy. Abrupt vessel closure occurred in 189 of 2,039 patients (9.3%) treated with heparin, and in 189 of 2,059 patients (9.2%) treated with bivalirudin (p = not significant). An inverse relation between the risk of abrupt closure and initial ACT measurements was observed in heparin-treated patients: the probability of abrupt vessel closure decreased by 1.3% for every 10-second increase in the initial ACT response to heparin therapy (p = 0.02). Among 903 of 2,039 heparin-treated patients (44%) who received additional heparin for prolonged or complicated procedures, the likelihood of abrupt vessel closure also decreased by 1.1% for every 10-second increase in ACT (p = 0.04). In 2,059 patients treated with bivalirudin, however, no relation between the probability of abrupt vessel closure and the initial ACT measurement was observed (p = 0.88). From the results it was concluded that when heparin is used during coronary angioplasty, the risk of abrupt vessel closure is related to patient responsiveness to anticoagulation therapy. Heparin-resistant patients are more likely to experience abrupt vessel closure than patients who have high ACT values in response to initial therapy. In contrast, when bivalirudin is used during coronary angioplasty, a flat relation between the risk of abrupt vessel closure and ACT values is seen. This suggests that the direct thrombin inhibitor, bivalirudin, provides more even levels of anticoagulation and more predictable levels of risk of abrupt closure than heparin. Measurements of ACT may not be necessary when bivalirudin is used during coronary angioplasty.

(2) Bittl JA, Feit F

A RANDOMIZED COMPARISON OF BIVALIRUDIN AND HEPARIN IN PATIENTS UNDERGOING CORONARY ANGIOPLASTY FOR POSTINFARCTION ANGINA.

HIRULOG ANGIOPLASTY STUDY INVESTIGATORS.

Am J Cardiol 1998 Oct 22;82(8B):43P-49P

Ocala Heart Institute, Munroe Regional Medical Center, Florida 34474, USA.
The outcome of coronary angioplasty performed for unstable angina is determined, in part, by the acuteness and severity of the clinical presentation. The risk of abrupt vessel closure is increased in patients with postinfarction angina. The Hirulog Angioplasty Study compared the efficacy and safety of bivalirudin with weight-adjusted heparin in patients undergoing percutaneous transluminal coronary angioplasty (PTCA) for unstable or postinfarction angina. We report the results of the intent-to-treat analysis using adjudicated data for the prespecified group of 741 patients who underwent angioplasty within 2 weeks of documented myocardial infarction. Patients received either bivalirudin or heparin immediately before angioplasty. The primary efficacy endpoint was procedural failure defined as abrupt vessel closure, death, myocardial infarction, or revascularization during hospitalization. Bivalirudin significantly (p = 0.004) decreased the incidence of procedural failure compared with heparin (5.1% vs 10.8%, odds ratio 0.45; 95% CI 0.25-0.79). The improved efficacy of bivalirudin was replicated for each individual clinical endpoint. The incidence of major bleeding was significantly (p = 0.001) lower in bivalirudin-treated patients compared with heparin-treated patients (2.4% vs 11.8%, respectively). The benefits observed with bivalirudin are of similar magnitude as those reported for platelet glycoprotein (GP) IIb/IIIa inhibitors, such as abciximab. Bivalirudin may be a more effective foundation anticoagulant than heparin in patients undergoing coronary angioplasty for postinfarction angina.


EFFECT OF DIRECT THROMBIN INHIBITION WITH BIVALIRUDIN (HIRULOG) ON RESTENOSIS AFTER CORONARY ANGIOPLASTY.


Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA.

The direct antithrombin, bivalirudin, did not reduce angiographic restenosis measured either as the dichotomous restenosis rate of 62% for bivalirudin and 58% for heparin (p = 0.70), or as the late loss in lumen diameter of 0.44 +/- 0.47 mm for bivalirudin and 0.39 +/- 0.53 mm for heparin (p = 0.62). Direct thrombin inhibition with bivalirudin neither reduces angiographic restenosis nor alters the impact of several established risk factors for restenosis.

(4) Shah PB, Ahmed WH, Ganz P, Bittl JA

BIVALIRUDIN COMPARED WITH HEPARIN DURING CORONARY ANGIOPLASTY FOR THROMBUS-CONTAINING LESIONS.

Am Coll Cardiol 1997 Nov 1;30(5):1264-9

Department of Internal Medicine, Brigham and Women’s Hospital, Boston, Massachusetts, USA.

OBJECTIVES: We investigated whether bivalirudin is more effective than heparin in preventing ischemic complications in high risk patients undergoing coronary angioplasty for thrombus-containing lesions detected by angiography. BACKGROUND: Heparin is administered during coronary angioplasty to prevent closure of the dilated vessel. Bivalirudin (Hirulog) is a direct thrombin inhibitor that can be safely substituted for heparin during angioplasty. Bivalirudin has several theoretic advantages over heparin as an anticoagulant agent. METHODS: We performed an observational analysis of the Hirulog Angioplasty Study in which 4,098 patients with unstable or postinfarction angina were randomized to receive either bivalirudin or heparin during coronary angioplasty. The study group for this analysis consisted of 567 patients who had thrombus-containing lesions on angiography. The primary end point was death, myocardial infarction, emergency coronary artery bypass graft surgery or abrupt vessel closure before hospital discharge. RESULTS: Patients with thrombus-containing lesions had a higher incidence of myocardial infarction (5.1% vs. 3.2%, p = 0.03) and abrupt vessel closure (13.6% vs. 8.3%, p < 0.001) than those without thrombus. In patients with thrombus-containing lesions, however, the incidence of the primary end point was not different between the bivalirudin and heparin treatment groups. Furthermore, no difference in the incidence of ischemic events at 6 months was seen between the treatment groups. CONCLUSIONS: Bivalirudin is not more effective than heparin in preventing ischemic complications in patients undergoing coronary angioplasty for thrombus-containing lesions detected by angiography. Other approaches, perhaps involving potent anti-platelet agents, should be considered for patients with thrombus-containing lesions.

**TREATMENT WITH BIVALIRUDIN (HIRULOG) AS COMPARED WITH HEPARIN DURING CORONARY ANGIOPLASTY FOR UNSTABLE OR POSTINFARCTION ANGINA. HIRULOG ANGIOPLASTY STUDY INVESTIGATORS.**


Department of Medicine, Brigham and Women's Hospital, Boston, MA 02115, USA.

BACKGROUND. Heparin is often administered during and after coronary angioplasty to prevent closure of the dilated vessel. However, ischemic or hemorrhagic complications occur in 5 to 10 percent of treated patients. We studied whether these complications could be prevented when the direct thrombin inhibitor bivalirudin (Hirulog) was used in place of heparin. METHODS. We performed a double-blind, randomized trial in 4098 patients undergoing angioplasty for unstable or postinfarction angina. Patients were assigned to receive either heparin or bivalirudin immediately before angioplasty. The primary end point were death in the hospital, myocardial infarction, abrupt vessel closure, or rapid clinical deterioration of cardiac origin. RESULTS. In the total study group, bivalirudin did not significantly reduce the incidence of the primary end point (11.4 percent, vs. 12.2 percent for heparin) but did result in a lower incidence of bleeding (3.8 percent vs. 9.8 percent, P < 0.001). In the prospectively stratified subgroup of 704 patients with postinfarction angina, bivalirudin therapy resulted in a lower incidence of the primary end point (9.1 percent vs. 14.2 percent, P = 0.04) and a lower incidence of bleeding (3.0 percent vs. 11.1 percent, P < 0.001), but in a similar cumulative rate of death, myocardial infarction, and repeated revascularization in the six months after angioplasty (20.5 percent vs. 25.1 percent, P = 0.17). CONCLUSIONS. Bivalirudin was at least as effective as high-dose heparin in preventing ischemic complications in patients who underwent angioplasty for unstable angina, and it carried a lower risk of bleeding. Bivalirudin, as compared with heparin, reduced the risk of immediate ischemic complications in patients with postinfarction angina, but this difference was no longer apparent after six months.

(6) Cannon CP, Braunwald E

**HIRUDIN: INITIAL RESULTS IN ACUTE MYOCARDIAL INFARCTION, UNSTABLE ANGINA AND ANGIOPLASTY.**

*J Am Coll Cardiol* 1995 Jun;25(7 Suppl):30S-37S

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Hirudin, a direct thrombin inhibitor, has undergone extensive testing in experimental models and has recently been evaluated in patients in several pilot trials. Across these three indications, hirudin has been found to achieve a more consistent level of anticoagulation than heparin, as gauged by the activated parital thromboplastin timey. Initial results with clinical end points, appeared to favor hirudin over heparin. In several large phase III trials, hirudin is being compared with heparin for all three indications. In the first phases of these trials, the rate of hemorrhagic events, including intracranial hemorrhage, was higher than expected in both the hirudin and heparin arms, which demonstrated that a safety ceiling had been reached. The reformulated Thrombolysis in Myocardial Infarction (TIMI) 9 and Second Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO II) trials are using lower doses of hirudin and heparin, which should allow testing of whether the initial favorable results observed in pilot trials will translate into improved clinical outcome, with an acceptable safety profile, for patients with acute myocardial infarction or unstable angina or those undergoing angioplasty.

9. HIR in Arterial Thrombosis

(1) Bates SM, Weitz JI

**DIRECT THROMBIN INHIBITORS FOR TREATMENT OF ARTERIAL THROMBOSIS: POTENTIAL DIFFERENCES BETWEEN BIVALIRUDIN AND HIRUDIN.**

*Am J Cardiol* 1998 Oct 22;82(8B):12P-18P

McMaster University and Hamilton Civic Hospitals Research Centre, Ontario, Canada.
Given the central role of thrombin in arterial thrombogenesis, most treatment strategies for acute coronary syndromes are aimed at inhibiting its generation or blocking its activity. Although heparin has been widely used, it has limitations in the setting of arterial thrombosis. These limitations reflect the inability of heparin to inactivate thrombin bound to fibrin, a major stimulus for thrombus growth. In addition, the anticoagulant response to heparin varies from patient to patient, and heparin is neutralized by platelet Factor IV, large quantities of which are released from platelets activated at sites of plaque rupture. Consequently, heparin requires careful laboratory monitoring to ensure an adequate anticoagulant effect. Direct thrombin inhibitors, such as hirudin and bivalirudin, overcome the limitations of heparin. These agents inhibit fibrin-bound thrombin, as well as fluid-phase thrombin, and produce a predictable anticoagulant response. Bivalirudin has both safety and potential efficacy advantages over hirudin. Bivalirudin appears to have a wider therapeutic window than hirudin, possibly because bivalirudin only transiently inhibits the active site of thrombin. The better safety profile of bivalirudin permits administration of higher doses, which may give it an efficacy advantage. Hirudin prevents thrombin from activating protein C, thereby suppressing this natural anticoagulant pathway. In contrast, bivalirudin may promote protein C activation by transiently inhibiting thrombin until it can be bound by thrombomodulin. Differences between bivalirudin and hirudin, as well as other direct thrombin inhibitors, highlight the pitfalls of considering all direct thrombin inhibitors to have equivalent risk-benefit profiles.

10. HIR in Heparin Induced Thrombocytopenia (HIT)

(1) Huhle G, Geberth M, Hoffmann U, Heene DL, Harenberg J
MANAGEMENT OF HEPARIN-ASSOCIATED THROMBOCYTOPENIA IN PREGNANCY WITH SUBCUTANEOUS R-HIRUDIN.
*Gynecol Obstet Invest* 2000 Jan;49(1):67-69

1st Department of Medicine (Director: Prof. D.L. Heene), Faculty of Clinical Medicine Mannheim, Germany.

Heparin-induced thrombocytopenia type II is a serious, immune-mediated complication of heparin therapy. Due to its low cross-reactivity with heparin-associated antibodies (10-20%), danaparoid has successfully been administered in these patients. In recent studies, r-hirudin as a potent and specific thrombin inhibitor, was demonstrated to be a safe and effective anticoagulant. We report a pregnant woman with systemic lupus erythematosus and recurrent venous thromboembolism who suffered from heparin-induced thrombocytopenia type II while treated with dalteparin sodium. Positive cross-reactivities with danaparoid were found. Anticoagulation with 15 mg subcutaneous r-hirudin was performed twice daily from the 25th week of pregnancy until delivery. No thromboembolism or bleeding or fetal toxicity of r-hirudin was detected. Recombinant hirudin is a potent and specific thrombin inhibitor that can be used as a safe and effective anticoagulant in pregnancy. Copyright 2000 S. Karger AG, Basel

(2) Matthies B, Burger T, Koch B, Bock M
[HEPARIN-INDUCED THROMBOCYTOPENIA TYPE II: REEXPOSURE TO HEPARIN]. [ARTICLE IN GERMAN]
*Dtsch Med Wochenschr* 1999 Oct 29;124(43):1267-70

Klinik fur Chirurgie, Universitat Magdeburg.

HISTORY AND ADMISSION FINDINGS: At the age of 55 years a now 70-year-old man had his aortic valve replaced by a prosthetic (Bjork-Shiley) valve, and 11 years later a VDD pacemaker had been implanted. 18 months before the latest admission he had been hospitalized for treatment of staphylococcal endocarditis involving the aortic prosthesis. At that time thrombocytopenia developed during heparin administration, diagnosed clinically and with the heparin-induced platelet activity (HIPA) test as type II heparin induced thrombocytopenia. His latest admission was for the diagnosis and treatment of peripheral arterial disease of the right leg (Fontaine stage IIb).

INVESTIGATIONS: Right popliteal and pedal pulses were not palpable. He was able to walk pain-free for only 70 m. Doppler sonography demonstrated an arm-leg index on the right of 0.7. Angiography revealed marked stenosis in the right superficial femoral artery and a filiform stenosis in the right popliteal artery. TREATMENT AND COURSE: Both stenoses were relieved by percutaneous transluminal balloon angioplasty, in the course of which 5000 IU heparin were
administered as a bolus intraarterially. Postoperative anticoagulation was maintained for 2 days with recombinant hirudin. There was no evidence of platelet reduction or heparin-induced antibodies despite the renewed infusion of heparin. CONCLUSION: Single re-administration of heparin in a patient who had developed a type II heparin-induced thrombocytopenia several years before does not necessarily lead to a booster of antibodies and thus to a reduction of platelets in the peripheral blood. It is a moot point whether the course in this case was an exception or the rule.


(3) Schmidt O, Lang W

[HEPARIN-INDUCED THROMBOCYTOPENIA TYPE II. INTRA- AND POSTOPERATIVE LEPIRUDIN TREATMENT IN ACUTE ISCHEMIA OF THE EXTREMITIES]. [ARTICLE IN GERMAN]


Chirurgische Klinik mit Poliklinik, Universität Erlangen-Nürnberg.

HISTORY AND ADMISSION FINDINGS: A 60-year-old woman was admitted because of acute ischemia of the right leg. The patient had been immobilized during diagnostic procedures for a thoracic paraspinal space-occupying lesion and over 5 days had received unfractionated sodium heparin by subcutaneous injection. The pedal pulses were no longer palpable. INVESTIGATIONS, DIAGNOSIS AND TREATMENT: The thrombocyte count had fallen from 207,000/microliter to 45,000/microliter. Angiography revealed occlusion of the common femoral artery. Heparin-induced platelet aggregation (HIPA) test demonstrated type II heparin-induced thrombocytopenia. Thrombectomy was performed and intraoperatively an i.v. bolus of the recombinant hirudin, lepirudin (Refludan), was given (0.2 mg/kg body weight), continual lepirudin infusion being continued postoperatively. Normal blood flow was re-established in the limb and the pedal pulse was palpable. There were no complications. CONCLUSION: Recombinant hirudin is the only alternative licensed in Germany to heparin and seem to be suitable also for the intraoperative bolus administration in heparin-induced thromboembolic vascular occlusions.

(4) Nowak G, Bucha E, Brauns I, Czerwinski R

ANTICOAGULATION WITH R-HIRUDIN IN REGULAR HAEMODIALYSIS WITH HEPARIN-INDUCED THROMBOCYTOPENIA (HIT II). THE FIRST LONG-TERM APPLICATION OF R-HIRUDIN IN A HAEMODIALYSIS PATIENT.

Wien Klin Wochenschr 1997 May 23;109(10):354-8

Max Planck Gesellschaft, Research Unit Pharmacological Haemostaseology, Friedrich Schiller University, Jena, Federal Republic of Germany.

A 69-year-old female patient with renal failure developed heparin-induced thrombocytopenia type II (HIT II) two months after starting haemodialysis therapy with heparin as anticoagulant and a 6-week course of thromboembolism prophylaxis with enoxaparin sodium. The platelet count dropped by 50% as compared with initial values and ex vivo platelet aggregation induced by heparin antibodies (HIPA-test) was detected. Haemodialysis therapy was complicated by a massive thrombosis of dialyzer and ensuing repeated interruptions of treatment. After confirmation of the diagnosis of HIT II haemodialysis therapy was continued with hirudin as anticoagulant. Polysulfone dialyzers and an intravenous bolus of 0.14 mg/kg of recombinant hirudin (r-hirudin) achieved efficient haemodialysis therapy of 4.5 hours, with a minimum therapeutic blood level of hirudin of 0.5 micrograms/mL. More than 50 regular haemodialysis with hirudin anticoagulation were performed without additional problems. The ecarin clotting time (ECT) was used as bedside method to monitor blood levels and for dosage adjustments of hirudin. After the 34th haemodialysis, the frequency (previously 3-4 haemodialyses sessions/week) was reduced to 2 sessions/week. The creatinine clearance increased continuously from initially 2.6 to 10.4 ml/min after the 13th week of hirudin-anticoagulated haemodialysis and the platelet count normalized. In conclusion, we report the first long-term administration of r-hirudin to a patient on regular haemodialysis therapy complicated by heparin-induced thrombocytopenia. The use of hirudin as anticoagulant along with dialyzers impermeable to hirudin offers a novel alternative means of anticoagulation and, even in patients with HIT, enables performing an efficient haemodialysis therapy. Hirudin dosage must be individually adjusted by using bedside drug monitoring of plasma concentrations.

SUCCESSFUL TREATMENT OF HEPARIN-ASSOCIATED THROMBOCYTOPENIA AND THROMBOSIS USING HIRULOG.

Can J Cardiol 1995 Jun;11(6):511-4

Loyola University Medical Center, Department of Internal Medicine, Maywood, Illinois 60153, USA.

Heparin-associated thrombocytopenia is a serious medical problem, especially when the patient requires continued anticoagulation. Hirulog is an immediate-acting intravenous anticoagulant that can be substituted for heparin. A new use of Hirulog in the treatment of life-threatening heparin-associated thrombocytopenia with thrombosis (HATT) is presented. Two patients suffering from the HATT syndrome were successfully treated with Hirulog to prevent further thrombosis. A third patient had developed heparin-associated thrombocytopenia after coronary artery bypass surgery in the past and was subsequently treated with Hirulog during a peripheral angioplasty procedure. Hirulog was an effective and predictable anticoagulant for these patients and was free from adverse effects.

HIRULOG THERAPY FOR HEPARIN-ASSOCIATED THROMBOCYTOPENIA AND DEEP VENOUS THROMBOSIS.


11. HIR in Deep Vein Thrombosis

CARDIOVASCULAR CHEMOTHERAPY: ANTICOAGULANTS.


Merck Research Laboratories, West Point, PA 19486, USA. Jules_Shafer@Merck.com

Anticoagulant therapy has changed dramatically during the past two years. Low molecular weight heparin has substantially replaced unfractionated heparin as the parenteral anticoagulant of choice. The use of warfarin has substantially increased, especially for prevention of stroke in the setting of atrial fibrillation. It has become clear that warfarin cannot be administered effectively in an unmonitored fixed-dose fashion. The parenteral direct thrombin inhibitor desirudin was shown to be efficacious in the prevention of deep vein thrombosis in man. Small thrombin and factor Xa inhibitors with in vivo oral anticoagulant activity have been identified.

USE OF HIRULOG IN THE PREVENTION OF VENOUS THROMBOSIS AFTER MAJOR HIP OR KNEE SURGERY.

Circulation 1994 Nov;90(5):2385-9

Department of Medicine, McMaster University, Hamilton, Ontario, Canada.

BACKGROUND--The study objective was to determine whether Hirulog, a direct thrombin inhibitor, has potential efficacy and safety in the prevention of deep vein thrombosis (DVT) in orthopedic patients. A phase 2 open-label, dose-escalating design was used to study 222 unselected patients undergoing major hip or knee surgery in tertiary-care, university-affiliated hospitals. METHODS AND RESULTS--Subcutaneous Hirulog was initiated postoperatively. Patients were evaluated for bleeding and symptomatic pulmonary embolism, and mandatory bilateral venography was performed before discharge. Dose escalations were made on the basis of observed rates of bleeding and venous thrombosis. There were five dosage regimens used: 0.3 mg/kg every 12 hours, 0.6 mg/kg every 12 hours, 1.0 mg/kg every 12 hours for 3 days followed by 0.6 mg/kg every 12 hours for up to 11 days, 1.0 mg/kg every 12 hours, and 1.0 mg/kg every 8 hours. One hundred seventy-seven patients who had
technically adequate bilateral venography or objectively documented pulmonary embolism were included in the primary analysis of efficacy. The highest dosage regimen (1.0 mg/kg every 8 hours) provided the lowest rates of total DVT (17%) and proximal DVT (2%), both of which were significantly lower (P = .010 and P = .023, respectively) than the pooled rates of total (43%) and proximal (20%) DVT seen with the first four regimens. Bleeding rates were low (< 5%) with all regimens. CONCLUSIONS--This study demonstrates that 1.0 mg/kg Hirulog every 8 hours started postoperatively is potentially efficacious and safe for the prevention of DVT after major hip or knee surgery.

12. HIR in Intensive Care Patients and Endotoxin Shock

(1) Fischer KG, van de Loo A, Bohler J
RECOMBINANT HIRUDIN (LEPIRUDIN) AS ANTICOAGULANT IN INTENSIVE CARE PATIENTS TREATED WITH CONTINUOUS HEMODIALYSIS.


Department of Medicine, University Hospital Freiburg, Germany. fischer@mm41.ukl.uni-freiburg.de

BACKGROUND: Recombinant hirudin (lepirudin) is a potent direct thrombin inhibitor, which has been approved for the treatment of heparin-induced thrombocytopenia type II (HIT). Because the drug is mainly eliminated by the kidneys, a single loading dose of hirudin may induce therapeutic anticoagulation for up to one week in patients with renal insufficiency. Thus, the use of hirudin in critically ill patients with renal failure could markedly increase their bleeding risk. In this study, hirudin was used in critically ill patients with suspected HIT while on continuous venovenous hemodialysis (CVVHD). METHODS: Hirudin anticoagulation was performed in seven critically ill patients with suspected HIT. Four patients were initially anuric. Three patients had residual renal function. In all 64 CVVHD treatments (mean duration 12 hr), a polysulfone high-flux hemodialyzer (0.75 m2) with a dialysate flow rate of 1.5 liter/hr and an ultrafiltration rate of up to 200 ml/hr was used. Hirudin was given either as continuous intravenous infusion or as repetitive intravenous bolus. Monitoring of anticoagulation was performed by measurements of the systemic activated partial thromboplastin time (aPTT). RESULTS: Hirudin dosage had to be individualized according to the risk of bleeding or clotting. During CVVHD, a continuous intravenous infusion (0.006 to 0.025 mg/kg body wt/hr, N = 2) or repetitive intravenous bolus (0.007 to 0.04 mg/kg, N = 5) were given. Two patients required blood transfusions prior to and during hirudin treatment. In five patients without a high bleeding risk, the hirudin dose was adjusted to achieve the target aPTT (1.5 to 2.0 x baseline) in order to prevent thrombotic complications or frequent clotting in the extracorporal circuit. Hirudin dose requirements depended on residual renal function and extracorporal clearance.

CONCLUSIONS: We conclude from these first clinical data that anticoagulation with hirudin in critically ill patients on continuous hemodialysis can be performed without excessive bleeding risk by combining close clinical and laboratory monitoring. The hirudin dose has to be reduced because of renal failure, and may require adjustment for residual or recovering renal function and extracorporal elimination.

(2) Fischer KG, van de Loo A, Bohler J
RECOMBINANT HIRUDIN (LEPIRUDIN) AS ANTICOAGULANT IN INTENSIVE CARE PATIENTS TREATED WITH CONTINUOUS HEMODIALYSIS.


Department of Medicine, University Hospital Freiburg, Germany. fischer@mm41.ukl.uni-freiburg.de

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(3) Cicala C, Bucci MR, Maraganore JM, Cirino G
HIRULOG EFFECT IN RAT ENDOTOXIN SHOCK.

Biogen Inc., Cambridge, Massachusetts 02142, USA.

Hirulog is a thrombin catalytic site inhibitor which exhibits specificity for the anionic binding exosite of alpha thrombin. Here, we have evaluated the effect of Hirulog (1, 5 and 10 mg/kg, 30 min pretreatment) in a rat model of endotoxemia. Intravenous injection of lipopolysaccharide from E. coli (25 mg/kg; serotype 0127:B8) caused decreases in blood pressure which were significantly reduced (about 60%) in animals pretreated with Hirulog. Rat survival to endotoxin was significantly increased in Hirulog pretreated group (5 and 10 mg/kg) up to 24 hours. Hirulog at the dose of 10 mg/kg inhibited both endotoxin-induced leukopenia at 30 and 60 minute points and thrombocytopenia at 30 minute point but not at 90 and 120 minute points. Fibrinogen levels were significantly reduced after 2 hours following endotoxin administration. Pretreatment with Hirulog (5-10 mg/kg i.v.) 30 min prior to administration of endotoxin prevented changes in fibrinogen plasma levels. These results demonstrate that Hirulog-induced inhibition of thrombin is effective in reducing toxic and lethal effects of endotoxin.

B. HIR induced Complications Bleeding!

1. HIR Reversal of Hirudin induced bleeding by Antidote PCC

(1) Diehl KH, Romisch J, Hein B, Jessel A, Ronneberger H, Paques EP
INVESTIGATION OF ACTIVATED PROTHROMBIN COMPLEX CONCENTRATE AS POTENTIAL HIRUDIN ANTIDOTE IN ANIMAL MODELS.

Research Laboratories of Behringwerke AG, Marburg/Lahn, Germany.

The specific thrombin inhibitor r-hirudin (HBW 023) has been demonstrated to be effective in preventing thrombosis in preclinical models. Up to now, no bleeding complications have been observed using therapeutically effective doses in animals studies. However, in case of inadvertent overdosing the occurrence of undesired impairment of coagulation cannot be excluded. As a potential antidote an activated prothrombin complex concentrate (APC) was tested on its ability to normalize blood coagulation. APC given s bolus injections 5 min and 3.0 mg/kg neutralized the r-hirudin-induced prolongation and 3.0 mg/kg neutralized the r-hirudin-induced prolongation of whole blood coagulation time in rabbits completely within 5 min without any clot formation in the blood vessels or capillaries of the heart, kidneys, or lungs. Furthermore, bleeding time prolongation induced by bolus application of 3.0 and 30.0 mg/kg r-hirudin was significantly inhibited by APC within 5 min. These results suggest that administration of APC may be an effective way to reverse the effects of r-hirudin in the coagulation system in case of inadvertent overdosing of r-hirudin.
(2) Irani MS, White HJ Jr, Sexon RG
REVERSAL OF HIRUDIN-INDUCED BLEEDING DIATHESIS BY PROTHROMBIN COMPLEX CONCENTRATE.
Am J Cardiol 1995 Feb 15;75(5):422-3
Pathology Associates of Albuquerque, New Mexico 87106.

2. HIR induced Antibodies

GENERATION OF ANTI-HIRUDIN ANTIBODIES IN HEPARIN-INDUCED THROMBOCYTOPENIC PATIENTS TREATED WITH R-HIRUDIN.
Circulation 1999 Oct 5;100(14):1528-32
First Department of Medicine, Faculty of Clinical Medicine Mannheim, University of Heidelberg, Mannheim, Germany.
BACKGROUND: Hirudin is a small protein with strong thrombin inhibition that may be antigenic. The generation and disappearance of anti-hirudin antibodies were investigated in patients with heparin-induced thrombocytopenia who were treated with recombinant hirudin (r-hirudin) for >/=5 days. METHODS AND RESULTS: The IgA, IgE, IgG, and IgM isotypes of anti-hirudin antibodies were determined by ELISA before and after the start of r-hirudin therapy. A total of 56% of patients (13 of 23) developed >/=1 antibody isotype during therapy. No IgE antibodies were generated. IgA, IgG, and IgM antibodies were detected in 30% (7 of 23), 52% (12 of 23), and 17% (4 of 23) of patients, respectively. Four patients generated only IgG, 2 patients developed either IgM or IgG and IgM, 5 patients IgG and IgA, and 2 patients IgG, IgM, and IgA antibodies. IgM antibodies disappeared within 8 days of the cessation of r-hirudin. IgA and IgG antibodies disappeared within 1 year in all but 1 patient. Binding of purified IgG to r-hirudin in IgG antibody-positive patients (n=7) was demonstrated by competitive ELISA for r-hirudin. Of the 7 IgG antibody samples, 1 each neutralized or enhanced the anticoagulant activity of r-hirudin. CONCLUSIONS: R-hirudin may be antigenic in patients with heparin-induced thrombocytopenia. More comprehensive investigations will be required to determine the biological relevance of this and to establish the antibody-generation pattern in other diseases.

IMMUNOLOGIC RESPONSE TO RECOMBINANT HIRUDIN IN HIT TYPE II PATIENTS DURING LONG-TERM TREATMENT.
Department of Medicine I, Faculty of Clinical Medicine Mannheim, University of Heidelberg, Mannheim, Germany.
We prospectively investigated 27 patients with heparin-induced thrombocytopenia (HIT) type II who were subsequently treated with r-hirudin. Patients with venous or arterial thromboembolism were treated with activated partial thromboplastin time (aPTT)-controlled intravenous r-hirudin (n = 19; mean 19.3 d) followed by subcutaneous r-hirudin (n = 6; mean 22.5 d) and oral anticoagulation. Patients without thromboembolism were treated with subcutaneous r-hirudin (n = 8; mean 25.9 d). Four patients were readmitted to subcutaneous r-hirudin for a mean duration of 32 d. The incidence of r-hirudin antibodies was 84% for intravenously treated patients and 50% in subcutaneously treated patients. The patients (n = 27) showed a 74% overall incidence of r-hirudin antibodies, mainly of the IgG-subclass, without seroconversion before day 6 and after day 32 of r-hirudin treatment or during r-hirudin treatment. None of the patients showed onset or recurrence of venous or arterial thromboembolism, systemic allergic reactions or IgE-antibody development. During intravenous and subcutaneous administration of r-hirudin the aPTT and the ecarin clotting time was increased in the antibody-positive patients compared to antibody-negative patients. Therefore we assume that r-hirudin antibodies may reduce r-hirudin metabolism.
(3) Jappe U, Gollnick H

[ALLERGY TO HEPARIN, HEPARINOIDS, AND RECOMBINANT HIRUDIN. DIAGNOSTIC AND THERAPEUTIC ALTERNATIVES].

[ARTICLE IN GERMAN]


Klinik und Poliklinik fur Dermatologie und Venerologie, Otto-von-Guericke Universität Magdeburg.

The pathogenesis of allergic reactions to heparin is poorly understood. Clinically, this phenomenon is very relevant because of its increasing incidence and the resulting therapeutic difficulties. Since Plancherel’s first description in 1952, nearly 70 cases have been reported in the literature, among which female patients dominate. Heparin causes all kind of allergic reactions from type I to type IV. The most dangerous hypersensitivity reaction is heparin-induced thrombocytopenia (HIT), which is a type II antibody-mediated reaction. Heparin is a mucopolysaccharide with strong protein binding potency, which seems to play an important pathogenetic role, as the heparin molecule adheres to unknown dermal or subcutaneous proteins. The heparin group contains a variety of structures with varying molecular weights. The allergen has yet to be identified. Several cross-reactions between high- and low-molecular weight heparins have been demonstrated as well as between heparin and heparinoids so that there may be more than one epitope of the heparin molecule with allergic potency. Allergic reactions after the use of alternate drugs such as heparinoids and hirudin also causes severe therapeutic difficulties.

Risks when on Anticoagulation

1. Risks of Anticoagulation caused Haemorrhage

(1) Steffensen FH, Kristensen K, Ejlersen E, Dahlerup JF, Sorensen HT

MAJOR HAEMORRHAGIC COMPLICATIONS DURING ORAL ANTICOAGULANT THERAPY IN A DANISH POPULATION-BASED COHORT.


Danish Epidemiology Science Centre, University of Aarhus, Denmark.

OBJECTIVES: To estimate the incidence of bleeding leading to death or hospital admission in out-patients treated with oral anticoagulants. DESIGN: Population-based historical cohort study 1 January 1992 to 31 September 1994. SETTING: The County of North Jutland, Denmark (488,000 inhabitants). SUBJECTS: Six hundred and eighty-two consecutive patients commencing oral anticoagulant therapy. MAIN OUTCOME MEASURES: Fatal bleeding or bleeding demanding hospital admission. RESULTS: In 756 treatment-years of follow-up, there were 45 major haemorrhagic events (6.0 per 100 treatment-years) in 42 patients, of which seven (0.9 per 100 treatment-years) were fatal. The risk of a first major haemorrhagic episode was highest during the first 90 days of treatment compared with duration above one year (incidence rate ratio, IRR, 1.9; 95% CI, 0.8-4.1). The rate was highest above the age of 60 years, 6.8 per 100 treatment-years, compared with 2.9 per 100 treatment-years below 60 years (IRR 2.3; 95% CI, 1.0-5.6). The rate for a bleeding event was slightly higher in females than in males (IRR 1.3; 95% CI, 0.7-2.3), but did not vary according to type of anticoagulant drug. CONCLUSIONS: The reported rates of major bleeding in this routine community setting implied a higher bleeding risk than was found in randomized trials or when patients are monitored in specialist anticoagulation clinics.

2. Management of Heparin induced bleeding

(1) Smith CR

MANAGEMENT OF BLEEDING COMPLICATIONS IN REDO CARDIAC OPERATIONS.

Bleeding remains a complication of certain complex surgical procedures, particularly those cardiac operations associated with long bypass times and profound hypothermia. Clinical and novel experimental strategies to reduce bleeding and the need for blood and blood-product transfusions are the focus of this review. Preoperative assessment of the patient will identify drug-induced, acquired, or inherited coagulation defects that may contribute to this problem. The main attention is directed to the perioperative period, and broad areas discussed include the preoperative use of erythropoietin to increase red blood cell mass, autologous donation either preoperatively or before bypass, autotransfusion/hemofiltration, and acceptance of relative anemia both during the operation and into the postoperative period. A further, often overlooked, management strategy in treating major coagulopathies is the consideration of the cost and half-lives of the coagulation factors in individual blood components. Prevention of bleeding has become possible both by manipulation of the control of coagulation and inflammatory processes and by the introduction of pharmacologic agents such as aprotinin. Aprotinin is widely used and has proven efficacy in the management of excess bleeding. It is a serine protease inhibitor and has several possible mechanisms of action, including inhibition of the plasma enzyme systems activated by contact with the foreign surface of the bypass circuit and preservation of platelet function. Safety issues include the possibility of hypersensitivity and anaphylactic reaction on a second exposure. Concerns that aprotinin may induce a prothrombotic or coagulant state have no basis in theory or any good evidence in the current literature. A recent study specifically sought to identify the presence of disseminated microvascular platelet-fibrin thrombi present at autopsy in patients who had received aprotinin therapy. The study concluded that diffuse platelet-fibrin thrombi were not a direct complication of aprotinin therapy. Finally, modern molecular biology has led to the recent development of an inhibitor for factor IXa that competitively replaced IXa in the intrinsic complex and blocked the conversion of factor X to factor Xa. This compound is under investigation in animal studies. These have so far shown efficacy in reducing blood loss after bypass in comparison with standard heparin anticoagulation.

3. Predicting Risks of Warfarin induced Major Bleeding

(1) Beyth RJ, Quinn LM, Landefeld CS

PROSPECTIVE EVALUATION OF AN INDEX FOR PREDICTING THE RISK OF MAJOR BLEEDING IN OUTPATIENTS TREATED WITH WARFARIN.


Department of Medicine, Cleveland Veterans Affairs Medical Center, University Hospitals of Cleveland, and Case Western Reserve University School of Medicine, Ohio 44106-4961, USA.

PURPOSE: To evaluate the accuracy and clinical utility of the Outpatient Bleeding Risk Index for estimating the probability of major bleeding in outpatients treated with warfarin. The index was previously derived in a retrospective cohort of 556 patients from a different hospital (derivation cohort).

SUBJECTS AND METHODS: We enrolled 264 outpatients starting warfarin (validation cohort) to validate the index prospectively. All patients were identified upon hospital discharge, and physician estimates of the probability of major bleeding were obtained before discharge in the validation cohort. RESULTS: Major bleeding occurred in 87 of 820 outpatients (6.5%/yr). The index included four independent risk factors for major bleeding: age 65 years or greater; history of gastrointestinal bleeding; history of stroke; and one or more of four specific comorbid conditions. In the validation cohort, the index predicted major bleeding: the cumulative incidence at 48 months was 3% in 80 low-risk patients, 12% in 166 intermediate-risk patients, and 53% in 18 high-risk patients (c index, 0.78). The index performed better than physicians, who estimated the probability of major bleeding no better than expected by chance. Of the 18 episodes of major bleeding that occurred in high-risk patients, 17 were potentially preventable. CONCLUSIONS: The Outpatient Bleeding Risk Index prospectively classified patients according to risk of major bleeding and performed better than physicians. Major bleeding may be preventable in many high-risk patients by avoidance of over-anticoagulation and nonsteroidal anti-inflammatory agents.
(2) McMahan DA, Smith DM, Carey MA, Zhou XH

**RISK OF MAJOR HEMORRHAGE FOR OUTPATIENTS TREATED WITH WARFARIN.**


Richard L. Roudebush VAMC, Department of Medicine, Indiana University School of Medicine, Indianapolis, USA.

OBJECTIVE: To determine the incidence of major hemorrhage among outpatients started on warfarin therapy after the recommendation in 1986 for reduced-intensity anticoagulation therapy was made, and to identify baseline patient characteristics that predict those patients who will have a major hemorrhage. PATIENTS: Five hundred seventy-nine patients who were discharged from the hospital after being started on warfarin therapy. MEASUREMENTS AND MAIN RESULTS: The primary outcome variable was major hemorrhage. In our cohort of 579 patients, there were 40 first-time major hemorrhages with only one fatal bleed. The cumulative incidence was 7% at 1 year. The average monthly incidence of major hemorrhage was 0.82% during the first 3 months of treatment and decreased to 0.36% thereafter. Three independent predictors of major hemorrhage were identified: (1) a history of alcohol abuse, chronic renal insufficiency, and a previous gastrointestinal bleed. Age, comorbidities, medications known to influence prothrombin levels, and baseline laboratory values were not associated with major hemorrhage. CONCLUSIONS: The incidence of major hemorrhage in this population of outpatients treated with warfarin was lower than previous estimates of major hemorrhage measured before the recommendation for reduced-intensity anticoagulation therapy was made, but still higher than estimates reported from clinical trials. Alcohol abuse, chronic renal insufficiency, and a previous gastrointestinal bleed were associated with increased risk of major hemorrhage.

4. Reversal of Oral Warfarin Anticoagulation

(1) Baglin T

**MANAGEMENT OF WARFARIN (COUMARIN) OVERDOSE.**


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Treatment with coumarin oral anticoagulants, such as warfarin, is effective antithrombotic therapy, but patients treated with these drugs are at significant risk of bleeding. The risk of haemorrhage increases with increasing intensity of anticoagulation and overanticoagulation is common. Reversal can be achieved by: (1) stopping the coumarin drug or (2) administration of vitamin K, (3) fresh frozen plasma or (4) coagulation factor concentrates. However, there are surprisingly few studies defining the optimum dose of these products and there are no randomized studies comparing the relative benefit and risk of coagulation factor concentrates versus fresh frozen plasma. Guidelines for the management of overdose are based on level III and IV evidence and are, therefore, only grade B recommendations at best. Further studies are required to determine the most effective use of products and the dose required for safe reversal of overanticoagulation.

(2) Sie P

**[HOW DO WE MANAGE THE HEMORRHAGIC RISK ON HYPOVITAMINOSIS K AND TREATMENTS WITH ANTIVITAMIN K].**

**[ARTICLE IN FRENCH]**

*Ann Fr Anesth Reanim* 1998;17 Suppl 1:14a-17s

Laboratoire d'hematologie, hopital Purpan, Toulouse, France.

Vitamin K deficiency leads to a deficit in vitamin K-dependent factors, resulting in either hypocoagulability and a decrease in the Quick one-stage prothrombin time expressed as the prothrombin time (PT), or in an increase in INR in patients receiving oral anticoagulation. The anesthesiologist's objective is to bring these values back into the safety range before surgery, i.e., above 50% for PT and below 1.5 for INR. The method to be used will be chosen according to the urgency of the correction. Safety ranges may be reached in 6-12 h following oral or parenteral administration of vitamin K. A 5-mg dose is usually sufficient. If the deficit in vitamin K-dependent
factors requires immediate correction, intravenous administration of PPSB should be done. The minimum time during which antivitamin K treatment may be disrupted after surgery depends on both the possibility of restarting oral treatment and the risk of postoperative haemorrhage. During this period, the need for an anticoagulation treatment using heparin should be discussed according to the risk of thrombosis.

EMERGENCY ORAL ANTICOAGULANT REVERSAL: THE RELATIVE EFFICACY OF INFUSIONS OF FRESH FROZEN PLASMA AND CLOTTING FACTOR CONCENTRATE ON CORRECTION OF THE COAGULOPATHY.
Thromb Haemost 1997 Mar;77(3):477-80

University Department of Haematology, Royal Hallamshire Hospital, Sheffield, UK.
Haemorrhage, including intracranial bleeding, is a common, potentially lethal complication of warfarin therapy and rapid and complete reversal of anticoagulation may be life-saving. Fresh frozen plasma (FFP) and vitamin K are most frequently administered. Because of the variable content of vitamin K-dependent clotting factors in FFP, and the effects of dilution, the efficacy of this approach is open to doubt. We have therefore compared the effects of FFP and clotting factor concentrates on the INRs and clotting factor levels of orally anticoagulated subjects requiring rapid correction of their haemostatic defect. In many, the pre-treatment INR was considered to be dangerously above the target therapeutic range. In the 12 patients given FFP, the INR did not completely correct (range 1.6-3.8, mean 2.3) indicating an ongoing anticoagulated state in all. In contrast, the INR in 29 subjects given clotting factor concentrates was completely corrected in 28 (range 0.9-3.8, mean 1.3). Following treatment, marked differences were observed in clotting factor IX levels between the two groups. The median factor IX level was 19 u/dl (range 10-63) following FFP infusion and 68.5 u/dl (range 31-111) following concentrate. In FFP treated patients, poorer responses were also observed for each of the other vitamin K-dependent clotting factors but these were less marked than for factor IX, which was present in low concentrations in some batches of FFP. Thus, haemostatically effective levels of factor IX cannot be achieved, in most instances, by the conventional use of FFP in patients requiring reversal of their anticoagulant therapy. Clotting factor concentrates are the only effective option where complete and immediate correction of the coagulation defect is indicated in orally anticoagulated patients with life or limb-threatening haemorrhage.

(4) Steffensen FH, Kristensen K, Ejlersen E, Dahlerup JF, Sorensen HT
MAJOR HAEMORRHAGIC COMPLICATIONS DURING ORAL ANTICOAGULANT THERAPY IN A DANISH POPULATION-BASED COHORT.

Danish Epidemiology Science Centre, University of Aarhus, Denmark.
OBJECTIVES: To estimate the incidence of bleeding leading to death or hospital admission in outpatients treated with oral anticoagulants. DESIGN: Population-based historical cohort study 1 January 1992 to 31 September 1994. SETTING: The County of North Jutland, Denmark (488,000 inhabitants). SUBJECTS: Six hundred and eighty-two consecutive patients commencing oral anticoagulant therapy. MAIN OUTCOME MEASURES: Fatal bleeding or bleeding demanding hospital admission. RESULTS: In 756 treatment-years of follow-up, there were 45 major haemorrhagic events (6.0 per 100 treatment-years) in 42 patients, of which seven (0.9 per 100 treatment-years) were fatal. The risk of a first major haemorrhagic episode was highest during the first 90 days of treatment compared with duration above one year (incidence rate ratio, IRR, 1.9; 95% CI, 0.8-4.1). The rate was highest above the age of 60 years, 6.8 per 100 treatment-years, compared with 2.9 per 100 treatment-years below 60 years (IRR 2.3; 95% CI, 1.0-5.6). The rate for a bleeding event was slightly higher in females than in males (IRR 1.3; 95% CI, 0.7-2.3), but did not vary according to type of anticoagulant drug. CONCLUSIONS: The reported rates of major bleeding in this routine community setting implied a higher bleeding risk than was found in randomized trials or when patients are monitored in specialist anticoagulation clinics.
(5) Jansson JH, Boman K, Brannstrom M, Nilsson TK

HIGH CONCENTRATION OF THROMBOMODULIN IN PLASMA IS ASSOCIATED WITH HEMORRHAGE: A PROSPECTIVE STUDY IN PATIENTS RECEIVING LONG-TERM ANTICOAGULANT TREATMENT.

*Circulation* 1997 Nov 4;96(9):2938-43

Department of Medicine, Skelleftea Hospital, Sweden.

BACKGROUND: The aim of this study was to prospectively test whether the risk of bleeding complications in 212 consecutive outpatients treated with oral anticoagulants could be predicted by levels of endothelium-derived hemostatic variables.

METHODS AND RESULTS: All bleeding complications were recorded during 5 years of follow-up; serious bleeding was defined as intracranial bleeding or hemorrhage causing death or necessitating hospitalization. The relationships of bleeding complications and plasma concentrations of tissue plasminogen activator, von Willebrand factor, and thrombomodulin, plasminogen activator inhibitor activity, and other possible risk factors were studied. Twenty-two patients suffered from bleeding complications during anticoagulant treatment; in 14 patients, these were serious. We found that the numbers both of serious hemorrhages and of total hemorrhages were significantly associated with increased levels of thrombomodulin. The number of bleeding episodes increased exponentially through quartiles one to four of the thrombomodulin distribution.

CONCLUSIONS: Thrombomodulin concentrations in plasma are related to the risk of hemorrhage in patients treated with oral anticoagulants.

Comment in: *Circulation* 1997 Nov 4;96(9):2765-8

(6) Toulemonde F

THE ROLE OF INDIVIDUAL RISK FACTORS IN ANTICOAGULANT-ASSOCIATED HEMORRHAGES.

*Semin Thromb Hemost* 1996;22 Suppl 1:53-60

Hemorrhagic complications during therapy with anticoagulant drugs have long been considered as simply and directly related to overdosage. Yet, such adverse events have also been observed in patients correctly anticoagulated, i.e., within the therapeutic range, thus demonstrating that the predictive value of laboratory monitoring is, at best, unclear. There are, indeed, individual risk factors leading to bleeding, despite optimal anticoagulant therapy. They may be totally asymptomatic, but screening for such parameters may also be more or less neglected. It is possible to prevent a good number of these complications provided that individual risk factors are carefully sought. Individual risk factors characterize each patient’s destiny; to strive to detect them is the physician’s responsibility.

(7) van der Meer FJ, Rosendaal FR, Vandenbroucke JP, Briet E

BLEEDING COMPLICATIONS IN ORAL ANTICOAGULANT THERAPY. AN ANALYSIS OF RISK FACTORS.


Department of Hematology, University Hospital Leiden, The Netherlands.

BACKGROUND: Insufficient data are available about the safety of oral anticoagulant therapy. The specialized organization of thrombosis services in the Netherlands can provide important information on the bleeding risk and various risk factors for bleeding in patients receiving oral anticoagulant therapy. METHODS: In a follow-up study over a 12-month period beginning in January 1988 on all patients treated by the Leiden Thrombosis Service, the frequency of bleeding complications was assessed. A Poisson regression model was used to assess the relative contribution to the bleeding risk of age, sex, target zone (intensity of anticoagulant effect aimed at), achieved intensity of anticoagulant therapy ([International Normalized Ratio](#)), and the type of coumarin derivative used. RESULTS: Six thousand eight hundred fourteen patients experienced 1003 bleeding complications (16.5 per 100 treatment-years), 162 of which were major bleeds (2.7 per 100 treatment-years). Bleeding increased significantly with age (32% increase for all bleeding, 46% for major bleeding for every 10-year increase in age in comparison with age < 40 years). Women had more minor bleeding complications than men, whereas both sexes experienced major bleeding in an equal frequency. There was no influence of target zone, while every one-point increase in [International Normalized Ratio](#) gave 42% more major bleeding (54% more regarding all bleeding). Use of acenocoumarol resulted in fewer bleeds (26% less regarding all bleeding and 46% less regarding major bleeding) than use of
phenprocoumon. CONCLUSIONS: The risk of anticoagulant therapy in a routine, real-life situation is similar as in the setting of several well-organized clinical trials. The risk of bleeding complications rises significantly with age and with the achieved intensity of anticoagulation, and is dependent on the type of coumarin derivative that is used.

(8) DORMAN, et al.
IDENTIFICATION OF PATIENTS AT RISK FOR EXCESSIVE BLOOD LOSS
Anesth.Analg: 1993: 76: 694-700,

5. Risks of Intracerebral Haemorrhage in Warfarin Anticoagulated Patients

(1) Lacroix P, Portefaix O, Boucher M, Ramandrisoa H, Dumas M, Rayon R, Christides C, Laskar M
[THE CAUSES OF INTRACRANIAL HEMORRHAGIC COMPLICATIONS INDUCED BY ANTIVITAMINS K]. [ARTICLE IN FRENCH]
Arch Mal Coeur Vaiss 1994 Dec;87(12):1715-9

Service de CTCV et angiologie, CHRU Dupuytren, Limoges.

Cerebral haemorrhage is the main life-threatening complication of oral anticoagulant therapy. In order to identify a means of prevention, the authors undertook a retrospective study of 68 consecutive cases of anticoagulant-related intracerebral haemorrhage. The mortality was 38.5%. The respective frequency of intracerebral haemorrhage, subarachnoid haemorrhage, acute and chronic subdural haematoma was 63.2, 16.2, 10.3 and 10.3%, respectively. On admission, nearly half the patients (53%) had prothrombin ratios inferior to 25%. A predisposing factor was found in 58% of cases: hypertension (30.6%), head injury (14.5%), alcoholism or drug interaction (11.2%), and one case of intracerebral aneurysm. A history of a transient ischaemic attack or of a cerebrovascular accident was found in 10.2% of cases and 11.7% had a previous anticoagulant related extracranial haemorrhage. The initial indications for oral anticoagulation were ischaemic heart disease (32%), atrial fibrillation (20.5%), secondary prevention of venous thromboembolic disease (17.6%) and primary prevention of venous thrombosis (11.7%). The duration of treatment for isolated ischaemic heart disease was over 6 months in all cases: the average duration of treatment was 12.4 months in phlebitis and pulmonary embolism. A critical review of the indications of treatment in the light of recent recommendations showed that if inappropriate indications were rare, the sometimes unnecessary prolongation of treatment was more common. Nearly half of these cases were receiving anticoagulants when the potential benefits were questionable at the time of the haemorrhagic complication. Clinical and biological follow-up is necessary for patients on anticoagulants; minor bleeding complications may be the prelude to major haemorrhage. Biological follow-up is based on control of the international normalised ratio.

(2) De Jaegere PP, Arnold AA, Balk AH, Simoons ML
INTRACRANIAL HEMORRHAGE IN ASSOCIATION WITH THROMBOLYTIC THERAPY: INCIDENCE AND CLINICAL PREDICTIVE FACTORS.

Department of Cardiology, University Hospital Rotterdam-Dijkzigt, Erasmus University, The Netherlands.

In a period of 18 months, 2,469 patients with acute myocardial infarction treated with a thrombolytic agent were prospectively registered in 61 hospitals. Most patients (73%) were treated with streptokinase. Intracranial hemorrhage was observed in 24 patients, corresponding to an incidence rate of 1% (95% confidence interval 0.6% to 1.3%). The median time interval between the start of thrombolytic therapy and the first clinical signs of intracranial bleeding was 16 h (range 3 to 36). In total, 16 (66%) of the 24 patients died as a result of cerebral hematoma. To determine clinical predictive factors, a case-control study was conducted. For every patient with intracranial hemorrhage, two control patients who received thrombolytic therapy because of acute infarction in the same hospital and in the same period were selected. Detailed clinical characteristics of 22 of the 24 patients as well as of 7 other patients with documented intracerebral bleeding from the European Cooperative Study Group and of 2 patients who sustained intracranial hemorrhage outside the registry period were compared with 62 control patients. The results of multivariate logistic regression analysis indicate that patients taking an
oral anticoagulant before admission, patients with a body weight less than 70 kg and those greater than 65 years old are at higher risk for intracranial hemorrhage during thrombolytic therapy.


(3) Mattle H, Kohler S, Huber P, Rohner M, Steinsiepe KF
ANTICOAGULATION-RELATED INTRACRANIAL EXTRACEREBRAL HAEMORRHAGE.
J Neurol Neurosurg Psychiatry 1989 Jul;52(7):829-37

Department of Neurology, University of Bern, Switzerland.

From January 1981 to June 1986 116 patients with anticoagulation-related intracranial haemorrhage were referred to hospital. Seventy six of these haemorrhages were extracerebral, 69 were in the subdural and seven in the subarachnoid space. No epidural haemorrhages were identified. Compared with non-anticoagulation-related haematomas, the risk of haemorrhage was calculated to be increased fourfold in men and thirteenfold in women. An acute subdural haematoma, mostly due to contusion, was more frequently accompanied by an additional intracerebral haematoma than a chronic subdural haematoma. Trauma was a more important factor in acute subdural haematomas than in chronic. Almost half of the patients (48%) had a history of hypertension, more than a third (35%) had heart disease and about one fifth (18%) were diabetic. Headache was the most frequent initial symptom. Later decreased level of consciousness and focal neurological signs exceeded the frequency of headache. Three patients with subarachnoid haemorrhage and nine patients with acute subdural haematomas died, while those with chronic subdural haematomas all survived and had at the most mild, non-disabling sequelae. Myocardial infarction (22%), pulmonary embolism (20%), and arterial disease (20%) were the most frequent reasons for anticoagulant treatment. Critical review based on established criteria for anticoagulation treatment suggests there was no medical reason to treat a third of these patients. The single most useful measure that could be taken to reduce the risk of anticoagulation-induced intracranial haemorrhage would be to identify patients who are being unnecessarily treated and to discontinue anticoagulants.

(4) Levine M, Hirsh J
HEMORRHAGIC COMPLICATIONS OF LONG-TERM ANTICOAGULANT THERAPY FOR ISCHEMIC CEREBRAL VASCULAR DISEASE.
Stroke 1986 Jan-Feb;17(1):111-6

The main complication of anticoagulant therapy is bleeding. Although the use of long-term oral anticoagulants in patients with transient cerebral ischemia and/or minor stroke is controversial, anticoagulants are still used in some instances. We have carried out a literature review of the risk of hemorrhage during long-term oral anticoagulant therapy in patients with cerebrovascular disease to determine the rate of bleeding and the clinical and laboratory risk factors which predispose patients to bleeding. The risk of bleeding was substantial with major bleeding episodes ranging from 2% to 22% per year and fatal bleeds from 2% to 9% per year. Only hypertension emerged as an identifiable risk factor and its presence increased the relative risk of bleeding to more than two fold. Major bleeding was almost always intracranial, possibly because of associated hypertension or because of cerebrovascular disease per se. We could not detect a relationship between bleeding and the intensity of anticoagulant therapy, although major bleeding occurred frequently even with only moderately intense anticoagulant therapy. The net gain or loss in efficacy rate of treating patients with minor stroke with long-term oral anticoagulant therapy was examined and it was concluded that in order for such treatment to be beneficial, a risk reduction of more than 50% in stroke rate, and a major bleeding rate of less than 2% per year are required. Since the risk reduction for stroke and death with anticoagulant therapy is unlikely to be 50% and the risk of major bleeding likely to be more than 2%, the present evidence does not support the use of anticoagulant therapy in minor stroke.

(5) Wintzen AR, de Jonge H, Loeliger EA, Bots GT
THE RISK OF INTRACEREBRAL HEMORRHAGE DURING ORAL ANTICOAGULANT TREATMENT: A POPULATION STUDY.
Ann Neurol 1984 Nov;16(5):553-8

In a retrospective study of 166 patients, all admitted to the University Hospital, Leiden, The Netherlands, between January 1, 1970 and December 31, 1979, we estimated the relative risk of
intracerebral hemorrhage from oral anticoagulant therapy. The risk was more than ten times higher for patients over 50 years of age than for similarly aged untreated individuals in the general population. Within this age group the risk was influenced by neither age nor sex. Hypertension, present in 80% of the patients, was the most important predisposing condition; the risk of bleeding rose with increasing intensity of anticoagulation. There was no substantial difference in clinical condition at onset, rate of progression, mortality, or degree of recovery between patients with anticoagulant-associated hemorrhage and those with spontaneous intracranial hemorrhage.

6. Management of Anticoagulant induced Intracranial Haemorrhage

(1) Butler AC, Tait RC

MANAGEMENT OF ORAL ANTICOAGULANT-INDUCED INTRACRANIAL HAEMORRHAGE.


Beatson Institute for Cancer Research, Garscube Estate, Glasgow, UK.

Intracranial haemorrhage is an infrequent but often fatal complication of oral anticoagulant therapy which will become more common as anticoagulant use increases. The risk of anticoagulant-induced intracranial haemorrhage may be reduced by judicious prescribing, identification of patients at high risk of bleeding, and close monitoring by experienced staff. The presenting features of intracranial haemorrhage are often vague and physicians should be aware of the need for urgent investigation of all anticoagulated patients with neurological symptoms. Current guidelines for immediate reversal of anticoagulation recommend administration of vitamin K1 and factor replacement with either factor concentrates or fresh frozen plasma. In this review we discuss recent evidence suggesting prothrombin complex concentrates lead to faster, and more complete, correction of coagulation and, in the context of intracranial bleeding, may be associated with improved neurological status. Evidence for the risks of short-term cessation of anticoagulants, in the immediate period following an intracranial haemorrhage, and their subsequent reintroduction is also discussed.

(2) Cannegieter SC, Rosendaal FR, Bollen EL, Briet E

HIGH INTENSITY OF ORAL ANTICOAGULANT THERAPY IN PATIENTS WITH CEREBRAL HAEMORRHAGE: CAUSE OR CONSEQUENCE OF THE BLEEDING?

Br J Haematol 1997 Mar;96(3):497-9

Haemostasis and Thrombosis Research Centre, Department of Haematology, University Hospital Leiden, The Netherlands.

In assessing the optimal intensity of anticoagulant therapy, the International Normalized Ratio (INR) at admission is used as a basis for INR-specific incidence rates. In 47 patients suffering a haemorrhagic stroke we tested the assumption that the INR at admission is an acceptable measure for the INR that preceded the haemorrhage. We found high D-dimer levels in 70% of the patients, which indicated activated coagulation and fibrinolysis. This was not of such an extent that it could also be measured with other routine coagulation tests, with the possible exception of two patients. We found normal INRs in 33 non-anticoagulated patients, and only a mildly prolonged INR of 1.9 in one patient, which was most probably caused by a vitamin K deficiency. We concluded that the INR at admission can be used in studies to assess the optimal level of anticoagulation.

(3) Kawamata T, Takeshita M, Kubo O, Izawa M, Kagawa M, Takakura K

MANAGEMENT OF INTRACRANIAL HEMORRHAGE ASSOCIATED WITH ANTICOAGULANT THERAPY.


Department of Neurosurgery, Tokyo Women's Medical College, Japan.

BACKGROUND: Intracranial hemorrhage may be a particularly devastating complication of anticoagulant therapy. Very few accounts have reported data on the duration of anticoagulant discontinuation following intracranial hemorrhage or the intensity of anticoagulation during treatment for it, although we must adequately manage such a complication. METHODS: We analyzed the management of warfarin-related intracranial hemorrhages in 27 patients with cardiac diseases. We evaluated the
degree of anticoagulation using the thrombotest. Anticoagulants were stopped as soon as the diagnosis of intracranial hemorrhage was established by computed tomographic scan. RESULTS: Mechanical valve prosthesis patients, who required intensive long-term anticoagulant therapy, constituted the majority of our series (74.1%). Intraoperative hemostasis was brought under control despite low thrombotest values (13%-68%) at the time of surgery except for the acute subdural hematoma (SDH) patients with cerebral contusion. Early resumption of anticoagulant therapy (within 3 days) did not cause intracranial rebleeding in any operative patient. All the chronic SDH patients and some of the subcortical hematoma patients had a good outcome. All three patients with acute SDH and contusion, however, had a fatal outcome because of intracranial rebleeding within a short period of time or ineffective intraoperative hemostasis. CONCLUSIONS: The patients with anticoagulant-related intracranial hemorrhage may undergo surgery with thrombotest values approximately between 20% and 60%, and anticoagulants can be resumed after an interval of 3 days. Aggressive surgery should particularly be performed in patients with anticoagulation-related chronic SDH or subcortical hemorrhage, as in the cases of anticoagulant-unrelated intracranial hemorrhage.

(4) Fredriksson K, Norrving B, Stromblad LG
EMERGENCY REVERSAL OF ANTICOAGULATION AFTER INTRACEREBRAL HEMORRHAGE.

Stroke 1992 Jul;23(7):972-7

Department of Neurology, University Hospital, Lund, Sweden.

BACKGROUND AND PURPOSE: Although intracerebral hemorrhage is one of the most serious complications during oral anticoagulant therapy, there are no guidelines on emergency treatment with respect to reversal of anticoagulation effect in these patients. METHODS: We retrospectively compared laboratory data and clinical features in 17 cases of anticoagulant-related intracerebral hemorrhage treated with prothrombin complex concentrate (n = 10) or fresh-frozen plasma (n = 7). RESULTS: In the group of patients treated with prothrombin complex concentrate, the mean prothrombin time decreased from 2.83 to 1.22 International Normalized Ratio within 4.8 hours, compared with a decrease from 2.97 to 1.74 within 7.3 hours in those given fresh-frozen plasma (i.e., four to five times more rapidly after treatment with prothrombin complex concentrate) (p less than 0.001). Symptoms and signs of intracerebral hemorrhage, measured on an eight-graded Reaction Level Scale, progressed on average 0.2 grades in patients given prothrombin complex concentrate compared with 1.9 grades in those given fresh-frozen plasma (p less than 0.05). In patients with prothrombin values above 1.46, clinical progression within 12 hours occurred in five of six cases. CONCLUSIONS: Treatment with prothrombin complex concentrate reverses anticoagulation more rapidly than fresh-frozen plasma, which might be of importance for the prevention of further bleeding.

7. Risks of GI Haemorrhage in Anticoagulation

(1) Younossi ZM, Strum WB, Schatz RA, Teirstein PS, Cloutier DA, Spinks TJ
EFFECT OF COMBINED ANTICOAGULATION AND LOW-DOSE ASPIRIN TREATMENT ON UPPER GASTROINTESTINAL BLEEDING.


Division of Gastroenterology, General Clinical Research Center, Scripps Clinic and Research Foundation, La Jolla, California, USA.

Multiple studies link the use of nonsteroidal antiinflammatory drugs (NSAIDs) with severe upper gastrointestinal bleeding (UGIB); the incidence of such bleeding is 2-4%. One common regimen to assure patency after intracoronary stent placement requires an anticoagulant (warfarin) combined with aspirin as an antiplatelet agent. However, a 13-fold increase in the risk of UGIB occurs with long-term use of oral anticoagulants and NSAIDs. We retrospectively assessed the rate of UGIB in 138 patients who had received coronary stents (group I, receiving heparin followed by warfarin in combination with aspirin) and 109 angioplasty patients without stents (group II, receiving aspirin alone) between 1990 and 1994. UGIB was identified by hematemesi or melena, which led to gastrointestinal consultation. Patients were analyzed for multiple risk factors. UGIB occurred in 28 of 138 group I patients (20%; 95% CI 13.3-26.7%) and 0 of 109 group II patients (p < 0.0001). Esophagogastroduodenoscopy (EGD) findings on the 28 patients with UGIB included 13 patients with esophagitis or gastritis, 7 patients with gastric or duodenal ulcers, and 8 patients with no identifiable
source of bleeding. UGIB occurred within a mean of 2.5 days of initiation of combination therapy. Of patients with UGIB, 10 required blood transfusion (mean number of units = 5.3). Previous history of peptic ulcer disease, smoking, and use of antulcer medication did not significantly differ between the two groups. The concurrent use of anticoagulant and aspirin in patients with coronary stents creates a significant potential for UGIB and should be used only with extreme caution.

(2) Shah P, Kraklow W, Lamb G

UNUSUAL COMPLICATION OF COUMADIN TOXICITY.

*Wis Med J* 1994 May;93(5):212-4

Department of Medicine, Medical College of Wisconsin, Milwaukee.

Coumadin is a coumarin anticoagulant that induces a state similar to vitamin K deficiency and is routinely used for chronic oral anticoagulation. Intramural hematoma of the bowel is a rare complication of anticoagulant therapy. In this paper, we describe such a case of an anticoagulated patient who had complaints of abdominal pain and who had inadvertently been taking higher dose of coumadin. Although the diagnosis can usually be made by history and plain abdominal x-ray, we report here some radiographic signs that can be seen on a CT-scan of the abdomen and are relatively specific for this diagnosis. We stress the importance of recognizing the disorder because the management is conservative and surgery is reserved for cases in which no improvement is seen.

(3) CLEOPHAS TJM, et al.

THE RISK OF EMERGENCY INTESTINAL BLEEDING AMONG USERS OF ACENOCOUMARIN; A POPULATION-BASED COHORT STUDY

*Angiology*; 1993: Feb; 44: 85-92;

With standard doses of COUMARIN and a target PROTHROMBIN TIME of 2.7-4.5 INR (International Normalized Ratio) there is a 10-13-fold increased risk of bleeding. The incidence of bleeding was 0.6 bleeding/100 person years (RR 1.01,NS) for the patients receiving NSAIDS (Nonsteroidal anti-inflammatory drugs), 1.5 (RR 2.50 P 0.05) for ASPIRIN; and 1.6 (RR 2.67,0.05 less than P 0.1) for DIPYRIDAMOLE.

CONCLUSION: The authors conclude that in an adult population of 5% acenocoumarin users, about 25% of the emergency intestinal bleedings are connected with COUMARIN. The numbers of COUMARIN bleedings are 46 times higher than reported so far. They also demonstrated that the risk of bleeding from COUMARIN far exceeds the risks from alternative oral antithrombotic agents, such as ASPIRIN and DIPYRIDAMOLE.

SHEPHERD et al 1977 demonstrated an increased sensitivity to COUMARINS in elderly subjects. In our study also the incidence of bleeding was slightly higher in the oldest group. The present population-based study, using the same criteria, shows an incidence of intestinal bleedings of 4.3 per 100 person years compared with 0.6 gastrointestinal bleedings in the WARFARIN study and 1.0 in the Sixty Plus study.

8. Risk Calculations for Pulmonary Embolism

(1) Douketis JD, Kearon C, Bates S, Duku EK, Ginsberg JS

RISK OF FATAL PULMONARY EMBOLISM IN PATIENTS WITH TREATED VENOUS THROMBOEMBOLISM.

*JAMA* 1998 Feb 11;279(6):458-62

Department of Medicine, McMaster University, Hamilton, Ontario, Canada.

CONTEXT: The most serious complication of deep vein thrombosis (DVT) or nonfatal pulmonary embolism (PE) is fatal PE. However, reliable estimates as to the risk of fatal PE in patients with treated DVT or PE are lacking. OBJECTIVE: To provide reliable estimates of the risk of fatal PE and the case-fatality rate of recurrent DVT or PE among patients presenting with symptomatic DVT or PE, during and following 3 months of anticoagulant therapy. DATA SOURCES: A MEDLINE literature search was performed to identify prospective studies in which patients with symptomatic DVT or PE were treated with 5 to 10 days of heparin and 3 months of oral anticoagulants. We searched the years 1966 to September 1997 using the search terms thrombophlebitis, diagnosis, drug therapy, and prognosis. Current Contents and bibliographies were also scanned. DATA EXTRACTION: Of 137 retrieved studies,
25 studies satisfied predetermined methodologic criteria and were included in the analysis. DATA SYNTHESIS: Among patients presenting with DVT, the rate of fatal PE during anticoagulant therapy was 0.4% (95% confidence interval [CI], 0.2%-0.6%); following anticoagulant therapy it was 0.3 per 100 patient-years (95% CI, 0.1-0.8). The case-fatality rate of recurrent DVT or PE during anticoagulant therapy was 8.8% (95% CI, 5.0%-14.1%); following anticoagulant therapy it was 5.1% (95% CI, 1.4%-12.5%). Among patients presenting with PE, the rate of fatal PE during anticoagulant therapy was 1.5% (95% CI, 0.9%-2.2%); following anticoagulant therapy it was 0 per 265 patient-years (95% CI, 0.3-6). The case-fatality rate of recurrent DVT or PE among patients presenting with PE was 26.4% (95% CI, 16.7%-38.1%). CONCLUSION: Among patients with symptomatic PE or DVT who are treated with anticoagulants for 3 months, fatal PE is rare during and following anticoagulant therapy. Patients presenting with PE are more likely to die of recurrent PE or DVT than are patients presenting with DVT.

(2) Fender D, Harper WM, Thompson JR, Gregg PJ
MORTALITY AND FATAL PULMONARY EMBOLISM AFTER PRIMARY TOTAL HIP REPLACEMENT. RESULTS FROM A REGIONAL HIP REGISTER.

University of Leicester, England, UK.

We calculated the rates for perioperative mortality and fatal pulmonary embolism (PE) after primary total hip replacement in a single UK health region, using a regional arthroplasty register and the tracing service of the Office of National Statistics. During 1990, there were 2111 consecutive primary replacements in 2090 separate procedures. Within 42 days of operation a total of 19 patients had died (0.91%, 95% CI 0.55 to 1.42). Postmortem examination showed that four deaths (0.19%, 95% CI 0.05 to 0.49) were definitely due to PE. The overall perioperative mortality and fatal PE rates are low and in our study did not appear to be altered by the use of chemical thromboprophylaxis (perioperative mortality rate: one-tailed Fisher's exact test, p = 0.39; fatal PE rate: one-tailed Fisher's exact test, p = 0.56). The routine use of chemical thromboprophylaxis for primary THR is still controversial. The issue should be addressed by an appropriate randomised, prospective study using overall mortality and fatal PE rate as the main outcome measures, but the feasibility of such a study is questioned. Comment in: J Bone Joint Surg Br 1997 Nov;79(6):889-90

(3) Baglin TP, White K, Charles A
FATAL PULMONARY EMBOLISM IN HOSPITALISED MEDICAL PATIENTS.
Clin Pathol 1997 Jul;50(7):609-10

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This study aimed to determine the frequency of fatal pulmonary embolism in hospitalised medical patients by a retrospective necropsy review and prospective non-interventional patient follow up study. The main outcome measure, necropsy proven fatal pulmonary embolism, was determined from 400 consecutive necropsy records and 200 consecutive medical inpatient episodes. Fatal pulmonary embolism was recorded in 29 of 400 necropsies; 17 were medical patients. Thirty one of 200 consecutive medical patients died. Fourteen necropsies were performed and revealed pulmonary embolism as the cause of death in five patients. The incidence of necropsy proven fatal pulmonary embolism was therefore 2.5% (95% confidence intervals 0.8% to 5.7%). Therefore, one in 40 medical patients had pulmonary embolism recorded as the cause of death at necropsy. As the necropsy rate was only 45% the incidence of fatal pulmonary embolism may be greater. There is, therefore, a need to perform more large prospective studies to confirm the incidence of fatal pulmonary embolism in medical patients and to identify risk factors and effective antithrombotic

9. Risks involved in treating Elderly Patients

(1) Oates A, Jackson PR, Austin CA, Channer KS
A NEW REGIMEN FOR STARTING WARFARIN THERAPY IN OUT-PATIENTS.

Department of Cardiology, Royal Hallamshire Hospital, Sheffield.
AIMS: Oral anticoagulation is increasingly used in elderly patients with atrial fibrillation to prevent embolic phenomena. The use of anticoagulants in this population is prophylactic rather than therapeutic and so there is no urgency to establish anticoagulation within the desired therapeutic range. The aim of the study was to develop an out-patient regimen for initiation of oral anticoagulation with warfarin which requires only weekly monitoring of the International Normalized Ratio (INR).

METHODS: The study was undertaken in two phases. In the first phase, factors which predict the final maintenance dosage of warfarin were defined and used to build a decision tree and dosage algorithm. In the second phase the algorithm was tested. Patients were given 2 mg warfarin daily for 2 weeks and the INR at this time was used to predict the maintenance dose. Patients then attended for weekly measurements of the INR until steady state had been reached. Dosage adjustments were not made unless the INR was >4.0 or <1.5 for 2 consecutive weeks. The accuracy of the prediction was measured by calculating the mean INR of weeks 6-8 and the number of patients in the target range 2.0-3.0 was determined. RESULTS: One hundred and seven consecutive out-patients (mean age 70 years range 64-86) completed the first study. The age, sex, height, weight, alcohol intake, number of cigarettes smoked, concomitant medication, clinical evidence of right heart failure, liver failure, abnormalities in liver enzyme estimations, baseline INR and INR after 2 weeks of 2 mg warfarin daily were used in a polytomous logistic regression analysis with stepwise inclusion of factors to determine which factors influenced the eventual maintenance dosage of warfarin. The INR after 2 weeks of 2 mg warfarin therapy predicted 79% of the variability of the maintenance dosage. Of other factors only the sex of the patient had a large enough effect to be included in the prediction algorithm. One hundred and six patients (mean age 71 years range 50-85 years) completed the second study. Only one patient needed a dose adjustment in the first 2 weeks of warfarin 2 mg daily (INR 4.4). Overall, 60% patients were in the narrow target range (INR 2.0-3.0) at steady state. In five patients the INR was >4.0 at any visit after the second week and needed dosage adjustment. In four patients the INR was <1.5 at steady state.

CONCLUSIONS: We have developed a method of predicting the maintenance dose of warfarin in an elderly population based on the INR after 2 weeks of warfarin 2 mg daily, and the sex of the patient. This is a safe and convenient way of initiating warfarin therapy as an out-patient which requires only weekly INR checks.


[HEMORRHAGIC COMPLICATIONS OF ORAL ANTICOAGULANT THERAPY: RESULTS OF A PROSPECTIVE MULTICENTER STUDY ISCOAT]. [ARTICLE IN ITALIAN]

G Ital Cardiol 1997 Mar;27(3):231-43

Divisone di Angiologia e Malattie della Coagulazione, Policlinico S. Orsola-Malpighi, Bologna.

BACKGROUND: To assess the incidence of bleeding complications during oral anticoagulant therapy (OAT) in a population of patients representative of daily practice in Italian anticoagulation clinics. METHODS: Design: prospective, inception-cohort, multicentre. SETTING: Thirty-four anticoagulation clinics federated in the Italian Federation of Anticoagulation Clinics. PATIENTS: 2745 consecutive patients, included from beginning of their first OAT course. Most patients were aged between 60 and 79 y (57.8%), with 8% being ≥ or = 80 y. Venous thromboembolism was the most frequent indication for OAT (one third of all the patients), followed by non ischemic heart disease which mainly included atrial fibrillation (16.8% of patients). Warfarin (in 63.8% of patients) and acenocoumarol were the only anticoagulant drugs used. The targeted anticoagulation intensity was low (INR < or = 2.8) in 71% of patients and high (INR > 2.8) in the remainder. OUTCOMES: Fatal, major and minor bleeding events. Thrombotic events were also recorded, though not analyzed in the present report. FINDINGS: During the 2011 patient-years (pt-y) of follow-up, 153 bleeding complications (7.6% pt-y) were recorded—5 fatal (all cerebral haemorrhages, 0.25% pt-y), 23 major (1.1% pt-y) and 125 minor (6.2% pt-y). The rate of events did not vary according to sex, coumarin type, size of enrolling centre or targeted therapeutic range; it was higher in older patients (10.5% pt-y in those aged > or = 70 y, relative risk--RR--1.75, p < 0.001), in cases where indication for anticoagulant treatment was peripheral and/or cerebrovascular disease (12.5% pt-y; RR 1.80, p < 0.01) and during the first 90 days of treatment (11% pt-y, RR 1.75, p < 0.001). One fifth of bleeding events occurred at a very low anticoagulation intensity (INR < 2; the category rate being 7.7% pt-y); the rate was 4.8% pt-y in the 2.0-2.9 INR category, reaching 9.5% pt-y, 40.5% pt-y and 200% pt-y in the 3-4.4, 4.5-6.9 and > or = 7 INR categories respectively (RR for INR levels > 4.5 = 7.91, p < 0.0001).
CONCLUSIONS: The overall rate of bleeding events recorded in the present study was much lower than that recorded in other (including recent) observational and experimental studies. The risk of bleeding increased in the following cases: age > 70 y; arterial vascular disease as indication for OAT; first 3 months of treatment; INR values > or = 4.5. OAT has become safer in recent years, particularly if monitored in special anticoagulation clinics. Caution should be exercised when prescribing OAT in elderly patients and the intensity anticoagulation levels should be closely monitored to minimize incidental periods of overanticoagulation.


[RISK OF CHRONIC ORAL ANTICOAGULANT TREATMENT IN ELDERLY PATIENTS]. [ARTICLE IN SPANISH]
Rev Med Chil 1992 May;120(5):552-8

Departamento de Enfermedades Cardiovasculares, Hospital Clinico, Pontificia Universidad Catolica de Chile, Santiago.

To assess age-related risks of long term anticoagulation, the records of 348 patients followed up at our university hospital outpatient anticoagulation clinic during a seven year period were reviewed. There were 129 patients, under 56 years of age, 144 from 56 to 69 and 75 over 70 years old. The total observation period was 1089 patient-years (3.3 yrs per pt). 64% of the patients had adequate anticoagulation level (prothrombin time < 35%, INR 2.2-4.5) 70 to 100% of the observation period. Prothrombin time was slightly, but significantly higher in the elderly group. During this period 21 patients developed major bleeding complications (1.84/100 pt yrs), 8 of them with fatal intracranial hemorrhages, and 20 embolic complications (1.93/100 pt yrs), 3 of them fatal. No significant differences in the incidence of both bleeding and embolic complications were observed in the three groups. The results of this retrospective follow-up study suggest that long term anticoagulation can be carried out in elderly pts with risk of hemorrhagic and embolic complications similar to those observed in the general population.

(4) Launbjerg J, Egeblad H, Heaf J, Nielsen NH, Fugleholm AM, Ladefoged K

BLEEDING COMPLICATIONS TO ORAL ANTICOAGULANT THERAPY: MULTIVARIATE ANALYSIS OF 1010 TREATMENT YEARS IN 551 OUTPATIENTS.

Medical Department B, Central Hospital, Hillerod, Denmark.

One thousand and ten patient years of oral anticoagulant therapy with vitamin-K-antagonists were reviewed with regard to major bleeding complications. The incidence of bleeding that necessitated hospital admission was 2.7% per year (95% confidence limits, 1.7-3.7%). The major source of bleeding was the alimentary tract, whereas no cases of intracranial hemorrhages were found. Various factors with potential effects on the bleeding risk were evaluated by multivariate statistical analysis, and the following independent risk factors were identified: age greater than 75 years and hypertension increased the bleeding risk by 10.5% and 4.5%, respectively. Each recorded prothrombin value significantly below the therapeutic range increased the bleeding risk by 3.9%, and each year of treatment increased the risk by 2.0%. These figures may be used to estimate the risk of major bleeding in an individual patient. Current treatment with thiazide diuretics was found to increase the bleeding risk by 5.2%. However, this observation requires further documentation and analysis. Although no lethal episodes of bleeding occurred, the developing field of indications for oral anticoagulant therapy should be considered on the basis of a continuous substantial risk of major bleeding.


AGE-RELATED RISKS OF LONG-TERM ORAL ANTICOAGULANT THERAPY.

Division on Aging, Harvard Medical School, Boston, MA.

Long-term oral anticoagulant therapy is critical to the optimal management of various thromboembolic and vascular disorders. To determine whether age is related to the development of bleeding complications in patients who are receiving long-term oral anticoagulant therapy, the records of 321 patients who were followed up in the university hospital outpatient anticoagulation clinic during
an eight-year period were reviewed. During this period, 61 patients (19%) developed minor bleeding complications, and 14 patients (4.4%) developed major bleeding complications. In utilizing a life-table approach to adjust for varying lengths of follow-up, the risk of initial minor bleeding complications was found to be greatest within the first three months (14%). For major bleeding complications, risk increased throughout the first two years of anticoagulation clinic follow-up, with no particular period of greatest risk. No significant differences in the risk of initial minor or major bleeding complications were observed in the various age groups that were examined (less than 50, 50 to 59, 60 to 69, and greater than or equal to 70 years). A multivariate regression approach, controlling for several potentially confounding factors, confirmed the lack of an association of age with the risk of minor or major bleeding complications. The results of this retrospective follow-up study suggest that patient age, in and of itself, should not be considered a primary factor in assessing the risk of long-term oral anticoagulant therapy.

10. Monitoring Anticoagulant therapy

a) Monitoring Warfarin Anticoagulation

(1) Oertel LB
MONITORING WARFARIN THERAPY. HOW THE INR KEEPS YOUR PATIENT SAFE.
Nursing 1999 Nov;29(11):41-4; quiz 45

(2) Panneerselvam S, Baglin C, Lefort W, Baglin T
ANALYSIS OF RISK FACTORS FOR OVER-ANTICOAGULATION IN PATIENTS RECEIVING LONG-TERM WARFARIN.
Br J Haematol 1998 Nov;103(2):422-4

Department of Haematology, Addenbrooke's NHS Trust, Cambridge.

A cohort of patients with an INR >7.0 were identified prospectively and compared with a group of patients with stable anticoagulant control. During the study 15,100 INR measurements were recorded and 31 (0.2%) were >7.0. Odds ratios of patient characteristics were calculated as an estimate of relative risk for the development of a high INR. The highest risk factor was a target INR of 3.5 (OR 7.3, 95% CI 2.6-20.2). The second highest risk factor was antibiotic therapy in the 4 weeks preceding the high INR (OR 6.2, 95% CI 1.4-27.7). Bleeding was reported more frequently in the high INR group (OR 5.4, 95% CI 2.1-13.9). Five major bleeds occurred in this group compared to none in the stable group. This analysis identifies risk factors for over-anticoagulation and hence when to intensify monitoring and when to consider pre-emptive warfarin dose reductions.

(3) Nozawa T, Hayashi S, Naiki S, Niiya K, Asanoi H, Inoue H
[INTER-INSTITUTE VARIATIONS IN INTERNATIONAL NORMALIZED RATIO AND THROMBOTEST]. [ARTICLE IN JAPANESE]

Second Department of Internal Medicine, Toyama Medical and Pharmaceutical University.

Oral anticoagulant therapy is effective for reducing the risk of thromboembolic events in patients with atrial fibrillation or other heart diseases. However, the intensity of oral anticoagulation therapy required in high risk patients, especially in Japanese patients, to achieve the best balance between the prevention of thromboembolic events and bleeding complications remains unclear. The multicenter study of Toyama Warfarin Rational Dosage (TOWARD) was started in 1996 to determine the optimal level of anticoagulant therapy. This study investigated the relationship between values of thrombostest (TT) and International Normalized Ratio (INR) measured from the same samples to clarify inter-institute variations. The relationship between TT and INR was not linear but hyperbolic. Changes of INR to TT are relatively small in the TT range of more than 20% as compared with the range of 20% or less. There were considerable inter-institute variations of TT, and the coefficient of variation (CV) was 0.16 and 0.24 in the low level and high level anticoagulation samples, respectively. However, the variations became significantly small when the same reference was used. The CV of INR was 0.12 and 0.08 in the high level and low level anticoagulation samples, respectively, and very similar with the control samples without anticoagulation (0.11). The variation was small when INR
was obtained from the international sensitivity index (ISI) of thromboplastin less than 1.5. TT is widely used for monitoring oral anticoagulant therapy in Japan, and is an excellent system with little inter-institute variation when a standard reference is offered. Since INR has been established as an international monitoring system, the use of INR measured with thromboplastin of small ISI is recommended for monitoring.

(4) Kevorkian JP, Halimi C, Segrestaa JM, Drouet L, Soria C
MONITORING OF PATIENTS WITH DEEP-VEIN THROMBOSIS DURING AND AFTER ANTICOAGULATION WITH D-DIMER.

(5) Lawrie AS, Purdy G, Mackie IJ, Machin SJ
MONITORING OF ORAL ANTICOAGULANT THERAPY IN LUPUS ANTICOAGULANT POSITIVE PATIENTS WITH THE ANTI-PHOSPHOLIPID SYNDROME.
_Br J Haematol_ 1997 Sep;98(4):887-92

Department of Haematology, University College London.

_Introduction of the International Normalized Ratio (INR)_ has improved the standardization of laboratory control of oral anticoagulant therapy (OAT). However, it has been reported that misleading INR results can be obtained from OAT patients with lupus anticoagulant (LA). To investigate this claim, we studied 35 OAT patients, 14 of whom had anti-phospholipid syndrome (APS) with a documented LA. Attainment of anticoagulation was confirmed by chromogenic assay of factor VII and factor X. Prothrombin times were performed using eight thromboplastins (five derived from rabbit brain, two recombinant human tissue factor and one made from human placenta) with an International Sensitivity Index (ISI) of <1.40. When using the thromboplastin manufacturers' ISI there was a significant difference (ANOVA, P<0.0001) between INR results obtained with the eight reagents for both APS (average CV = 12.4%) and non-APS (average CV = 12.5%) patient groups. Variation using the eight thromboplastins was assessed by calculating the CV for each sample; these values were then pooled for each patient group to give the average CV for all samples with all reagents for the two patient groups. Results for both patient groups exhibited markedly reduced variation (APS group average CV = 6.5%, non-APS group average CV = 5.8%) when locally assigned ISI values were employed in the calculation of INRs. Our data does not support the suggestion that the INR may not reflect the true level of anticoagulation in the long-term warfarin-treated patient, in whom lupus anticoagulant was detected. However, there was strong evidence that thromboplastin use should be restricted to those clot detection systems for which the reagent's manufacturer has assigned an ISI, or local ISI assignment must be undertaken. The inappropriate use of a generic (i.e. optical or mechanical clot detection system without regard to specific analyser type) ISI value can lead to ambiguous results.


(6) Moll S, Ortel TL
MONITORING WARFARIN THERAPY IN PATIENTS WITH LUPUS ANTICOAGULANTS.
_Ann Intern Med 1997 Aug 1;127(3):177-85_

Department of Medicine, Duke University Medical Center, Durham, NC 27710, USA.

.BACKGROUND: Recommended therapeutic international normalized ratios (INRs) for oral anticoagulation in patients with lupus anticoagulants who sustain a thromboembolic event are controversial. Patients with lupus anticoagulants often have a prolonged prothrombin time, which may complicate management of anticoagulant therapy. OBJECTIVES: To determine the validity of the INR as a monitor for warfarin therapy in patients with lupus anticoagulants and to investigate alternate approaches to monitoring warfarin therapy in these patients. DESIGN: Prospective case series. SETTING: Tertiary care hospital. PATIENTS: 34 patients with lupus anticoagulants. MEASUREMENTS: Prothrombin times were determined by using several thromboplastins, and INRs were calculated for the patients receiving warfarin. Factor II levels, chromogenic factor X levels, and prothrombin-proconvertin times were determined for patients receiving warfarin. RESULTS: For patients with lupus anticoagulants who were not receiving warfarin, prothrombin times were often elevated and varied significantly with different thromboplastins. Individual thromboplastins differed in sensitivity to the
presence of a lupus anticoagulant. For patients receiving warfarin, INRs obtained by using different thromboplastins greatly varied and often overestimated the extent of anticoagulation. Chromogenic factor X levels and prothrombin-proconvertin times correlated well with each other and with established therapeutic ranges. CONCLUSIONS: Lupus anticoagulants can influence prothrombin times and lead to INRs that do not accurately reflect the true level of anticoagulation. Use of the INR to standardize prothrombin times is invalid for some patients with lupus anticoagulants. To prevent supratherapeutic or subtherapeutic anticoagulation, these patients must be individually monitored with a test that is insensitive to lupus anticoagulants.


(7) Yim JM, Albers GW, Vlasses PH
ANTICOAGULANT THERAPY MONITORING WITH INTERNATIONAL NORMALIZED RATIO AT US ACADEMIC HEALTH CENTERS.

Clinical Practice Advancement Center, University HealthSystem Consortium, Oak Brook, IL 60521, USA.

OBJECTIVE: To assess the extent of incorporation of international normalized ratio (INR) reporting in US academic hospitals. DESIGN: Survey of academic hospital clinical laboratories in January 1995. SETTING/PARTICIPANTS: Fifty-eight academic hospital clinical laboratories at institutions that are members of the University Health System Consortium. MAIN OUTCOME MEASURES: The methods for monitoring oral anticoagulant therapy at the surveyed laboratories were determined. The extent of reporting of prothrombin time (PT), PT ratio, INR, and INR therapeutic range was determined. RESULTS: All 58 of the responding hospital clinical laboratories reported INR in patients receiving oral anticoagulation. The median length of time that hospitals had been reporting INR was 24 months (range 3-108). A majority of hospitals continued to report PT values (95%) and PT reference ranges (93%) in addition to INR. Therapeutic INR ranges were reported by only 25 of the laboratories (43%). Of those that report INR ranges, many follow the published recommendations by the American College of Chest Physicians and the Food and Drug Administration. A majority of the hospitals (79%) do not confirm the accuracy of the international sensitivity index (ISI) for their own analyzers. CONCLUSIONS: Contrary to previous reports, academic hospital clinical laboratories have now adopted the more accurate system of reporting INR values in addition to PT values in patients receiving oral anticoagulation. However, better reporting of INR ranges, use of more sensitive thromboplastins, and confirmation of the accuracy of the ISI for local analyses would further improve the monitoring of oral anticoagulation.

(8) Lammle B, Hardegger T, Straub PW, Vock P, Furlan M
[INTERNAL BLEEDING IN PATIENTS ON ORAL ANTICOAGULANTS].
[ARTICLE IN GERMAN]
Schweiz Med Wochenshr 1993 Apr 17;123(15):701-10

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Five selected case reports of patients suffering from rather unusual bleeding complications during oral anticoagulant therapy are presented. The reported frequency of bleeding during oral anticoagulation varies greatly. An unacceptably high incidence of hemorrhages has been reported in North American studies of the early 1980ies. The therapeutic target INR of 2.5-4.9 in these series is comparable to that in European studies where bleeding occurred much less frequently. We suggest that the insensitive thromboplastin reagents used in North America are unsuited to guide coumarin dosage, because too many prothrombin time values were outside the INR target range. In contrast, most prothrombin time values in European studies where a sensitive thromboplastin reagent was used, were within the target range. A recent prospective investigation by 25 Swiss practitioners showed an acceptably low bleeding complication rate (2.1 hemorrhagic complications severe enough to necessitate hospitalization per 100 patient years). Observation of contraindications, regular control of the prothrombin time using a sensitive and correctly calibrated thromboplastin, participation of practitioners and hospital laboratories at quality control exercises and consideration of drug interferences with coumarins help to reduce the incidence of hemorrhagic side effects. In case of either a PT value outside the target range
or manifest bleeding, the necessary measures have to be tailored to the individual situation considering the Quick value as well as the severity and localization of hemorrhage.

(9) Brigden ML

**ORAL ANTICOAGULANT THERAPY. NEWER INDICATIONS AND AN IMPROVED METHOD OF MONITORING.**

*Postgrad Med* 1992 Feb 1;91(2):285-8, 293-6

Island Medical Laboratories, Victoria, BC, Canada.

Oral anticoagulants remain time-tested therapeutic agents. A number of new indications for use of these drugs have recently emerged, especially nonvalvular atrial fibrillation. New information on the factors associated with adverse reactions to oral anticoagulants is available, along with improved knowledge on how to evaluate and treat such complications. A major advance in the safer use of these drugs in North America will accompany increased application of the International Normalized Ratio in reporting prothrombin


**[PROBLEMS OF LONG-TERM THERAPY WITH ANTICOAGULANTS].**

[ARTICLE IN GERMAN]


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Oral anticoagulants are highly effective for the prevention of recurrence of venous thromboembolism and of thromboembolic complications in rheumatic and non-rheumatic atrial fibrillation, dilated cardiomyopathy and in patients with prosthetic heart valves, but less effective for prevention of arterial thrombosis. **Bleeding is the main side effect, the risk of fatal bleeding is 0.2 to 0.4% per year,** depending on the intensity of treatment. The problem of the **standardization of the prothrombin time determination** has been solved by the introduction of the international normalized ratio. Recent studies have shown that a lesser degree of anticoagulation (INR 2.0 to 3.0) is sufficient to prevent venous thromboembolism and cardiac emboli. The measurement of activation markers of coagulation will probably allow a more rational monitoring in the near future.

b) Monitoring longterm Heparin Therapy

1) **HEP Monitoring General Aspects**


**HEPTEST: A SUITABLE METHOD FOR MONITORING HEPARIN DURING PREGNANCY.**

*Clin Lab Haematol* 1999 Jun;21(3):193-9

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Methods of monitoring heparin in pregnancy are problematic. The aim of this study was to assess the plasma HEPTEST as a rapid and reliable test for heparin monitoring in pregnancy. HEPTEST, activated partial thromboplastin time (APTT) and chromogenic anti-Xa assays were performed on individual heparin-spiked plasma samples from two groups: normal non-pregnant women (n = 6) and normal pregnant women during the third trimester (n = 6). Heparin activity curves were established in plasma from both groups for low (< 0.3 IU/ml), intermediate (0.3-0.7 IU/ml) and high (> 0.7 IU/ml) heparin concentrations and validated by comparison with the anti-Xa chromogenic assay. Both the APTT and HEPTEST demonstrated **good correlation** with anti-Xa levels across all heparin concentrations in both plasma groups (r range = 0.879-0.945). In comparison with the APTT, the HEPTEST showed **better correlation** with anti-Xa levels at low concentrations of heparin (r values 0.933 vs. 0.772, respectively). For both the APTT and HEPTEST there were significant differences between the clotting times in pregnant and non-pregnant plasma at a number of heparin concentrations. This data supports the plasma HEPTEST as an acceptable alternative to the chromogenic anti-Xa assay for monitoring heparin thromboprophylaxis in pregnancy.
(12) Pabinger-Fasching I

[MONITORING BLOOD COAGULATION].
[ARTICLE IN GERMAN]

Wien Med Wochenschr 1999;149(2-4):70-1

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Standard heparin in therapeutic doses has to be monitored by the activated partial thromboplastin time. There is no need for monitoring of treatment or prophylaxis with low molecular weight heparins. Only specific clinical situations, like renal insufficiency, long-term treatment, pregnancy, high risk of bleeding or thrombosis, small children and an extremely low or high body weight demand determination of anti-factor Xa activities. Monitoring of oral anticoagulant treatment should be done by determination of prothrombin time, values should be given in International Normalized Ratio (INR). It has been shown that monitoring by specialized centers and most probably self-monitoring at home by the patient himself are able to optimize treatment.

(13) Mungall D, Lord M, Cason S, Treadwell P, Williams D, Tedrick D

DEVELOPING AND TESTING A SYSTEM TO IMPROVE THE QUALITY OF HEPARIN ANTICOAGULATION IN PATIENTS WITH ACUTE CARDIAC SYNDROMES.

Am J Cardiol 1998 Sep 1;82(5):574-9

Department of Pharmacy, TMRMC, Tallahassee, Florida 32308, USA.

We have taken a stepwise approach to improving the dosing of continuous intravenous heparin in patients with acute coronary syndromes. Our primary objective was to use computer modeling to develop a nomogram for managing heparin therapy and to put in place a continuous quality monitoring system to evaluate the nomogram's effectiveness. We prospectively collected data on 41 patients with unstable angina or myocardial infarction who were treated with heparin. Their response to heparin was computer modeled and the dose to achieve an activated partial thromboplastin time (aPTT) ratio of 2.0 was established. This dose was regressed against all demographic characteristics to establish predictors of heparin dose (phase I). The regression formula was used prospectively in 110 patients to initiate the infusion rate of heparin and a bolus dose to achieve an aPTT ratio of 2.5. Subsequent dosage adjustments were achieved by computer modeling the patient's aPTT response (phase II). A nomogram was developed that simulated the decisions achieved using computer-assisted methods. This was retrospectively tested and then prospectively tested in 50 patients using nursing staff (phase III). The nomogram was then made generally available (phase IV) and has been tested in an additional 310 patients. Phase I: Of the original 41 patients, 32% of the aPTT ratios were in the therapeutic range, 36% were supratherapeutic, and 32% were subtherapeutic after the first 24 hours. Phases II and III resulted in 85% of the aPTT ratios between 1.5 and 2.5 at 24 hours. Phase IV had similar results in 310 patients. The use of computer-assisted or a computer-generated nomogram to adjust heparin therapy results in better control of heparin therapy than using standard methods.

(14) Kher A, Al Dieri R, Hemker HC, Beguin S

LABORATORY ASSESSMENT OF ANTITHROMBOTIC THERAPY: WHAT TESTS AND IF SO WHY?

Haemostasis 1997 Sep-Oct;27(5):211-8

A critical review is given of the tests available for the assessment of the action of anticoagulants, such as heparins, oral anticoagulants and direct thrombin inhibitors, in patients under antithrombotic therapy. The principle of action and the performance of the thromboplastin time (PT), the activated partial thromboplastin time (aPTT), the whole blood clotting time, the thrombin time, the ecarin clotting time and the endogenous thrombin potential (ETP) is discussed, as well as the evidence behind the accepted therapeutic ranges. The two most common tests, PT and aPTT, respond in an essentially different way to clinically effective anticoagulation with heparin and with oral anticoagulants. This means that they covariate with, but do not themselves represent the essential parameter influenced by anticoagulation. The experimental basis for the widely accepted two times prolongation of the aPTT as an indicator for adequate anticoagulation is shown to be meagre in the case of unfractionated heparin and lacking for the other anticoagulants. Common sources for error in the interpretation of anti-factor Xa- and anti-thrombin activity of heparins are indicated. Extensive
experience with new tests like the ecarin clotting time and the ETP is still lacking. On the basis of preliminary data and in view of the importance of the enzymatic action of thrombin in the pathogenesis of thrombosis, the ETP is considered a possible candidate for a common parameter to assess different types of anticoagulants.

(15) Mackinlay N, Favaloro E, Arthur C, Smith J, Aboud M

A SURVEY OF HEPARIN MONITORING IN AUSTRALASIA.

Pathology 1996 Nov;28(4):343-7

Department of Hematology, Royal North Shore Hospital, St Leonards, NSW.

Full dose heparin therapy is monitored by a variety of laboratory methods, of which the activated partial thromboplastin time (APTT) is the most popular. A large number of APTT reagents are currently available, with different sensitivities to heparin evident in many. Within the literature it is apparent that there is a lack of consensus, and indeed some confusion, regarding the therapeutic ranges for the APTT for standard heparin therapy in the treatment of venous thromboembolic disease. Accordingly we conducted an Australasian survey to evaluate current laboratory and clinical practices in monitoring heparin therapy, to determine the extent of variation in the approach and to stimulate the process of standardisation of acceptable procedures and methodology. Results of the survey demonstrate that currently there is no uniform practice used to establish therapeutic ranges for monitoring standard heparin therapy. Furthermore, results suggest that current practice may lead to subtherapeutic anticoagulation in many laboratories.

Comment in: Pathology 1997 Nov;29(4):450

2) HEP Monitoring with a Portable Device


MONITORING THE EFFECTS OF HEPARIN: EVALUATION OF A NEW PORTABLE DEVICE.


Department of Vascular Surgery, The General Infirmary at Leeds, UK.

The aim of this study was to measure the effects of heparin therapy in patients undergoing vascular surgery, and to monitor the effectiveness of continuous intravenous heparin therapy in ward-based patients. In addition, we compared results from a new portable device with those from the standard laboratory assay. A prospective comparison of the two methods in patients undergoing peripheral vascular surgery, and in ward-based patients who were receiving intravenous heparin infusions was undertaken. Fifty patients who were undergoing vascular surgery and receiving a bolus dose of intravenous heparin, and 22 patients receiving a continuous heparin infusion, were recruited. Blood samples were taken 10 and 40 min following bolus heparin administration or after > 12 h of a continuous heparin infusion. Plasma activated partial thromboplastin times (APTTp) measured by the haematology laboratory were compared with whole blood (APTT(B)) ascertained with the CoaguChek Plus Device (Boehringer Mannheim UK Diagnostics and Biochemicals Limited) at each time point. The results from the two methods were compared using the method of Bland and Altman (Lancet, 1986, 307-310).

We found a good level of agreement between the two methods (at induction, mean bias was -0.050, limits of agreement -0.46 - 0.36; heparin infusions, mean bias was -0.283, limits of agreement -1.64 - 1.07). In addition we discovered that many of our patients appeared to be excessively anticoagulated during surgery (10 min following heparin bolus 47/50 patients had an APTT(B) > 150 s, 45/50 had an APTTp > 250 s; at 40 min 45/50 had an APTT(B) > 150 s, 39/50 had an APTTp > 250 s). In conclusion, whole blood APTT measurement allows rapid and accurate assessment of the effects of heparin therapy when compared with laboratory APTT measurement and may prevent both excessive and suboptimal anticoagulation.

3) HEP Bedside Monitoring with "aPTT test"
(17) Taylor CT, Petros WP, Ortel TL
TWO INSTRUMENTS TO DETERMINE ACTIVATED PARTIAL THROMBOPLASTIN TIME: IMPLICATIONS FOR HEPARIN MONITORING.

Department of Pharmacy Practice, Auburn University School of Pharmacy, Alabama, USA.

STUDY OBJECTIVE: To measure the difference in therapeutic ranges of activated partial thromboplastin time (APTT) between two laboratory devices. DESIGN: Prospective, controlled laboratory study. SETTING: University-affiliated hospital. PATIENTS: Thirty inpatients receiving intravenous unfractionated heparin for treatment of myocardial infarction, unstable angina, deep venous thrombosis, or pulmonary embolism. INTERVENTIONS: Therapeutic APTT ranges were determined by a portable (whole blood assay) and a central laboratory device (plasma assay) based on heparin serum concentrations. They were compared with APTT ranges equivalent to 1.5-2.5 times the mean normal determination. MEASUREMENTS AND MAIN RESULTS: The central laboratory and portable devices produced therapeutic ranges of 61-93 and 56-73 seconds, respectively. Both differed from conventional therapeutic ratios of 1.5-2.5 times the mean normal (41-68 sec). Mean absolute APTT differences between instruments were statistically significant (12 +/- 20 sec, p<0.006), and 58% of paired APTT values differed by more than 10 seconds. CONCLUSION: A fixed APTT ratio as a goal for monitoring unfractionated heparin may result in significant underanticoagulation. Individual therapeutic APTT ranges must be reported for each instrument if more than one is used for heparin monitoring.

(18) Chamuleau SA, de Winter RJ
ACTIVATED PARTIAL THROMBOPLASTIN TIME (APTT) MONITORING TO ACHIEVE THERAPEUTIC ANTICOAGULATION BEFORE AND AFTER INTRODUCING A NOMOGRAM FOR ADJUNCTIVE HEPARIN TREATMENT WITH THROMBOLYTIC THERAPY FOR ACUTE MYOCARDIAL INFARCTION.
Int J Cardiol 1998 Dec 31;67(3):241-6

In patients with acute myocardial infarction (AMI) receiving thrombolytic therapy and i.v. unfractionated heparin, anticoagulant levels are frequently outside the target range. We evaluated the effects on anticoagulant levels before (group A) and after (group B) the introduction of a heparin nomogram in consecutive AMI-patients, receiving thrombolytic therapy and adjunctive heparin treatment. The target activated partial thromboplastin time (aPTT) was defined as 60-90 s. During the first 72 h after admission, the total number of aPTTs within the target range and the time taken to achieve the range were compared. The incidence of bleeding complications was assessed. Group A consisted of 56 and group B of 55 patients. The number of patients within the target range at 72 h (44 versus 51; chi2=4.51; P=0.034) was significantly higher in group B. No difference was found between total aPTTs within the target range (26% in group A versus 30% in group B; P=ns). Bleeding complications were slightly less in group B (7 versus in group A versus 2 patients in group B; P=ns). We concluded that the introduction of a nomogram resulted in significantly more patients with aPTTs within the target range. However, a substantial number of aPTTs before and after introduction of the nomogram were outside the target range. Moreover, this retrospective study shows that previously acquired prospective data (which showed a marked improvement of anticoagulation using a heparin nomogram) are not necessarily reproduced in the real life clinical setting.

(19) Zabel KM, Granger CB, Becker RC, Bovill EG, Hirsh J, Aylward PE, Topol EJ, Califf RM
USE OF BEDSIDE ACTIVATED PARTIAL THROMBOPLASTIN TIME MONITOR TO ADJUST HEPARIN DOSING AFTER THROMBOLYSIS FOR ACUTE MYOCARDIAL INFARCTION: RESULTS OF GUSTO-I. GLOBAL UTILIZATION OF STREPTOKINASE AND TPA FOR OCCLUDED CORONARY ARTERIES.
Am Heart J 1998 Nov;136(5):868-76

Mid-America Heart Institute, Kansas City, MO, USA.
BACKGROUND: The safety and efficacy of bedside monitors of activated partial thromboplastin time (aPTT) have not been examined in a large population receiving intravenous heparin after thrombolytic treatment for acute myocardial infarction. We compared outcomes among patients monitored with these devices versus standard monitoring methods. METHODS AND RESULTS: Investigators chose the bedside device (n = 1713 patients) or their standard method (n = 26,162) for all aPTT measurements at their sites. Clinical outcomes at 30 days, 1-year mortality rate, and aPTT levels at 6, 12, and 24 hours were compared. Bedside-monitored patients had significantly less moderate/severe bleeding (10% vs 12%, P < .01), fewer transfusions (7% vs 11%, P < .001), and a smaller decrease in hematocrit (5.5% vs 6.7%, P < .001) but significantly more recurrent ischemia (22% vs 20%, P = .01). Fewer bedside-monitored patients had subtherapeutic aPTT levels at 12 and 24 hours. Among patients with subtherapeutic levels at 6 and 12 hours, more bedside-monitored patients had therapeutic levels when next monitored. After adjustment for baseline differences, no significant difference in mortality rate was observed in bedside-monitored patients at 30 days (4.3% vs 4.8%, P = .27) and at 1 year (7.1% vs 7.7%, P = .38). The groups had similar rates of reinfarction, shock, heart failure, and stroke. CONCLUSIONS: This prospective substudy supports the use of bedside monitoring of heparin anticoagulation after thrombolysis.

4) HEP Monitoring Activated Coagulation Time “ACT Test”

(20) Beholz S, Grubitzsch H, Bergmann B, Wollert HG, Eckel L
HEMOSTASIS MANAGEMENT BY USE OF HEPCON/HMS: INCREASED BLEEDING WITHOUT INCREASED NEED FOR BLOOD TRANSFUSION.

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BACKGROUND: Extracorporeal circulation forces complete anticoagulation, most frequently achieved by complete heparinization. Activated clotting time (ACT) is the gold standard for monitoring, although there is a lack of correlation between heparin plasma level and ACT. Several systems for the estimation of free heparin have been developed: in this study we focused investigating on the influence of the Hepcon/HMS system on postoperative bleeding and transfusion requirements. METHODS: 114 patients were randomly assigned to one group monitored by use of Hepcon/HMS (group hepcon) and another group by use of ACT (ACT group); 7 patients were excluded due to reexploration. 12 patients did not receive aprotinin; this part of the study was stopped early due to massive increased bleeding. 46 and 49 patients of groups hepcon and ACT, respectively, received aprotinin. RESULTS: Using aprotinin, in group hepcon total administered heparin was elevated by 13 % in contrast to group ACT while administered protamine was reduced by 20%. The ratio of antagonization was 82 +/- 17 % and 51 +/- 12 %, respectively. Coagulation parameters were not influenced except for increased postoperative ACT and PTT in the hepcon group. Bleeding of patients in that group was significantly increased during the first 6 hours, which led to an increased autologous retransfusion. Need for substitution of other blood components was not increased postoperatively. CONCLUSIONS: Use of the Hepcon/HMS-system for monitoring of heparinization during extracorporeal circulation is possible without increased risk of thromboembolism. Postoperative blood loss was slightly but significantly increased but there was no need for more heterogenous transfusion.

(21) Despotis GJ, Gravlee G, Filos K, Levy J
ANTICOAGULATION MONITORING DURING CARDIAC SURGERY: A REVIEW OF CURRENT AND EMERGING TECHNIQUES.
Anesthesiology 1999 Oct;91(4):1122-51

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The literature does not consistently support the importance of anticoagulation monitoring techniques during CPB. This is best reflected by studies that have evaluated the impact of the ACT method on blood loss and transfusion outcomes. Inconsistent findings from studies that evaluated the impact of ACT monitoring may be related to either suboptimal study design (i.e., retrospective, unblinded, nonrandomized) or possibly the diagnostic inprecision of the ACT method used in these studies.
There are a small number of well-controlled studies, some of which suggest that bleeding and transfusion outcomes can be improved by refining heparin monitoring techniques, either by sustaining better anticoagulation during CPB or by optimizing protamine doses (i.e., when empiric protocols result in excessive protamine doses). More well-controlled studies are needed to better define the importance of anticoagulation management during CPB.

(22) Voyce SJ, Heller LI, Weiner BH, Laifer LI, Greenwald LL, Carey KT, Becker RC

**CLINICAL EXPERIENCE WITH ROUTINE ACTIVATED COAGULATION TIME MONITORING DURING ELECTIVE PTCA.**

*J Thromb Thrombolysis* 1995;1(2):201-206

Division of Cardiology, Interventional Cardiology and Thrombosis Research Center, Clinical Trials Section, University of Massachusetts Medical School, Worcester, MA.

Background: Intracoronary thrombosis is an important factor in the pathogenesis of acute complications during percutaneous coronary interventions. The activated coagulation time (ACT) is a simple, reproducible bedside test that has become standard as the means of monitoring the anticoagulant effect of heparin during these procedures. To determine if ACT-adjusted heparin dosing reduces the procedure-related complications of elective PTCA, 1200 patients who underwent nomemergent percutaneous transluminal coronary angioplasty (PTCA) between January 1, 1988 and February 26, 1992 were studied.

Methods: Results: Two groups were identified based on the use of empirical heparin dosage (group 1, before July 1, 1990) vs. ACT-guided heparin administration strategies (group 2, after July 1, 1990). Group 2 patients were older, had worse left ventricular function, and were more likely to have experienced a prior myocardial infarction than patients in group 1. Patients in group 1 were more likely to have chronic stable angina and a positive exercise test, while group 2 patients were more likely to be undergoing PTCA for post-myocardial infarction (MI) angina. Angiographic characteristics were also consistent with a higher risk profile in group 2 than in group 1 (92.7% vs. 83.4%, p < 0.001). Postprocedural complications, including abrupt closure and late closure, were lower in group 2 patients. The incidence of abrupt vessel closure was decreased by approximately 50% (6.9% vs. 3.5%, p < 0.025), and delayed vessel closure was significantly reduced by over 6017,(3.2% vs. 1.0%, p < 0.05). There were no differences in femoral artery complications between the two specified groups. Conclusion: ACT-guided heparin therapy during percutaneous coronary interventions decreases acute and delayed vessel closure, even in the presence of clinical and angiographic characteristics that would predict a higher incidence of these events.

(23) Rosborough TK

**MONITORING UNFRACTIONATED HEPARIN THERAPY WITH ANTIFACTOR XA ACTIVITY RESULTS IN FEWER MONITORING TESTS AND DOSAGE CHANGES THAN MONITORING WITH THE ACTIVATED PARTIAL THROMBOPLASTIN TIME.**

*Pharmacotherapy* 1999 Jun;19(6):760-6

Medical Education Department, Abbott Northwestern Hospital, Minneapolis, Minnesota 55407, USA.

STUDY OBJECTIVE: To determine how much more costly it is to monitor unfractionated heparin (UFH) therapy by antifactor Xa heparin activity (HA) than by activated partial thromboplastin time (aPTT). DESIGN: Prospective, randomized, unmasked, cohort, single-center study. SETTING: A 625-bed, adults-only, private teaching hospital. PATIENTS: Two hundred sixty-eight patients with a variety of indications for UFH therapy. INTERVENTIONS: Patients were treated with UFH based on ideal weight (75 U/kg bolus, 20 U/kg initial infusion) and monitored by either HA or aPTT, MEASUREMENTS AND MAIN RESULTS: After adjusting for gender, groups were equivalent in patient characteristics and UFH dosage. The HA group had fewer monitoring tests and dosage changes/24 hours than the aPTT group. These reductions neutralized much of the increased cost of the HA assay itself. CONCLUSION: Monitoring UFH therapy over 96 hours with an HA assay costs $4.37 more than monitoring with aPTT. This modest increase may be acceptable given other advantages of the HA assay.

(6) HEP Monitoring with Heparin Management Test "HMT TAS Test"

THE HEPARIN MANAGEMENT TEST: A NEW DEVICE FOR MONITORING ANTICOAGULATION DURING CORONARY INTERVENTION.


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Whole blood coagulation analysers are widely used during percutaneous coronary interventions. The precise degree of anticoagulation in patients is important in this setting. The aim of this investigation was to compare the results obtained with ACT (Hemochron) and HMT, the Heparin Management Test (TAS) in patients undergoing percutaneous coronary interventions. Patients (n = 100) were enrolled prospectively. Each patient received 10,000 units of heparin. At the end of the procedure, the mean ACT was 284+/−31 seconds and the mean HMT was 292+/−33 seconds. The correlation between the two methods was highly significant (r = 0.64, p<0.001). The HMT correlates well with ACT values in patients undergoing percutaneous coronary interventions. Its use in the management of these patients should be considered.

(25) Flom-Halvorsen HI, Ovrum E, Abdelnoor M, Bjornsen S, Brosstad F

ASSESSMENT OF HEPARIN ANTICOAGULATION: COMPARISON OF TWO COMMERCIALLY AVAILABLE METHODS.

*Ann Thorac Surg* 1999 Apr;67(4):1012-6; discussion 1016-7

Research Institute for Internal Medicine, University of Oslo, Rikshospitalet, and Oslo Heart Center, Norway.

BACKGROUND: The activated clotting time is a bedside method routinely used to monitor heparin anticoagulation during operations requiring cardiopulmonary bypass. The thrombolytic assessment system heparin management test is a new bedside method for monitoring heparin effect. We compared these methods with respect to their ability to reflect the actual heparin concentration in plasma determined by an anti-FXa method. METHODS: Two studies were done, an ex vivo study on ten patients who had coronary artery bypass using non-heparin-coated cardiopulmonary bypass circuits and full systemic heparinization and an in vitro study on single donor plasma spiked with heparin 0 to 10 IU/mL. RESULTS: Ex vivo study correlation coefficients of activated clotting time and the thrombolytic assessment system heparin management test clotting times versus anti-FXa-based heparin assay were low (r = 0.53, p = 0.002/r = 0.64, p<0.001) in contrast with the corresponding correlation coefficients for the in vitro study (r = 0.98, p<0.001/r = 0.99, p<0.001). A substantial variability in duplicate activated clotting time determinations was noted, which was less pronounced with the thrombolytic assessment system heparin management test. CONCLUSIONS: The thrombolytic assessment system method does not correlate better to the actual amount of heparin during cardiopulmonary bypass procedures than the activated clotting time method, which should be performed in duplicate.

(26) Fitch JC, Geary KL, Mirto GP, Byrne DW, Hines RL

HEPARIN MANAGEMENT TEST VERSUS ACTIVATED COAGULATION TIME DURING CARDIOVASCULAR SURGERY: CORRELATION WITH ANTI-XA ACTIVITY.


Department of Anesthesiology, Yale University School of Medicine, Yale-New Haven Hospital, CT, USA.

OBJECTIVE: To compare the abilities of the heparin management test (HMT) and the activated coagulation time (ACT) to provide a measurement of heparin effect in patients undergoing cardiac or peripheral vascular surgery. These measurements of heparin effect were also compared with measurements of heparin concentrations tested by anti-Xa activity. A secondary objective was to compare the performance of the noncitrated HMT with that of the citrated HMT. DESIGN: A prospective study. SETTING: A single-center study conducted in a university hospital. PARTICIPANTS: After human investigation committee approval and informed consent were obtained, adult patients undergoing cardiac or peripheral vascular surgery were included in this study. INTERVENTIONS: In both surgical groups, blood was sampled for ACT, HMT, and anti-Xa
activity. Each HMT was performed on both noncitrated and citrated samples. MEASUREMENTS AND MAIN RESULTS: As an indicator of heparin effect, the HMT had a strong correlation with the ACT \((r = 0.899; p < 0.01)\). In addition, the HMT had a significantly stronger correlation with anti-Xa activity than the ACT \((p < 0.01)\). The correlation obtained from the noncitrated samples was identical with that obtained from the citrated samples \((r = 0.819; p < 0.001\) for both groups). CONCLUSION: The ability of the HMT and the ACT to measure heparin effect was similar. The HMT performed better than the ACT when using anti-Xa activity as a measure of heparin concentration. Noncitrated HMT results were similar to citrated HMT results, thus supporting the use of fresh whole blood for testing purposes.

c) LMWH Monitoring

(1) Katagiri H, Itoh S, Uchida T, Kawai Y, Watanabe K

[MONITORING OF PLASMA CONCENTRATION OF LOW MOLECULAR WEIGHT HEPARIN--COMPARATIVE EVALUATION WITH CHROMOGENIC AND CLOTTING ASSAYS]. [ARTICLE IN JAPANESE]

Rinsho Byori 1999 Nov;47(11):1046-51

Department of Laboratory Medicine, Keio University, School of Medicine, Tokyo.

The efficacy of low molecular weight heparin (LMWH) in the treatment of thrombosis is increasing interest in its clinical potential. However, the measurement of in vitro anticoagulant activities of LMWH has been controversial for its appropriate clinical dose. The study has been carried out to compare two methods for measurement of anti-factor Xa activity of LMWH (fragmin). One is 'HEPTEST' recently developed as a new clotting assay method and the other is an authentic chromogenic assay using S-2222. The coefficients of variation in intra-assay were 1.87-2.75% in clotting assay, and 0.61-0.89% in chromogenic assay. The sensitivity to detect minimum concentration was 0.02 IU/ml in clotting assay, and 0.04 IU/ml in chromogenic assay. The correlation between two methods was good \((r = 0.935)\), whereas clotting assay has been revealed as a very simple rapid method. LMWH (fragmin) with 75 IU/kg/day was administered to three patients with coagulopathy; two disseminated intravascular coagulopathy (DIC) and one veno-occlusive disease (VOD). Hemostatic abnormalities have been improved serially after treatment in all patients. During treatment, the plasma concentration of LMWH was measured, showing 0.05-0.23 IU/ml in DIC and 0.02-0.10 IU/ml in VOD. These results suggest that measurement of plasma concentration of LMWH using the easy and rapid clotting assay method as 'HEPTEST' is clinically useful for monitoring to detect clinical dose of LMWH for DIC and thrombosis.

(2) Gitlin SD, Deeb GM, Yann C, Schmaier AH

INTRAOPERATIVE MONITORING OF DANAPAROID SODIUM ANTICOAGULATION DURING CARDIOVASCULAR OPERATIONS.


Department of Internal Medicine, University of Michigan, Ann Arbor 48109-0640, USA.

PURPOSE: Patients with cardiovascular disorders frequently need anticoagulation for diagnostic studies, surgical procedures, and therapy. Heparin-induced thrombocytopenia is a relatively common complication of heparin therapy that can result in thrombosis and subsequent limb loss or death, necessitating use of alternative anticoagulants. METHODS: Two patients who needed cardiac surgery had thrombocytopenia induced by exposure to heparin and heparin-coated tubing. Several assays were examined for their ability to monitor intraoperative anticoagulation of a factor Xa inhibitor, danaparoid sodium. RESULTS: In vitro, celtie and kaolin activated dotting times and activated partial thromboplastin time were prolonged linearly in the presence of increasing concentrations of danaparoid sodium. Aprotinin did not alter the linearity of the response but did alter its slope. In vivo, activated clotting times and activated partial thromboplastin time were insensitive to clinically significant changes in danaparoid sodium plasma levels during cardiopulmonary bypass. Correction in activated partial thromboplastin time lagged 2 hours behind clinically important changes in anti-factor Xa levels. Only anti-factor Xa levels were adequate to monitor intraoperative danaparoid sodium levels. CONCLUSION: Anticoagulation for cardiopulmonary bypass can be successfully performed with danaparoid sodium and intraoperative anti-factor Xa monitoring.

**ACTIVATED CLOTTING TIME IS NOT A SENSITIVE PARAMETER TO MONITOR ANTICOAGULATION WITH LOW MOLECULAR WEIGHT HEPARIN IN HEMODIALYSIS.**

*Nephron* 1997;76(1):15-9

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To study whether the activated clotting time (ACT) is a sensitive parameter to monitor anticoagulation with low molecular weight heparin (LMWH) during hemodialysis, ACT, polymorphonuclear granulocyte-elastase, and anti-factor Xa activity were studied during 30 dialysis treatments with LMWH (35 IU/kg body weight bolus; 10 IU/h/kg). Twenty treatments were performed with Hemophan, ten with polysulfone dialyzers. No clinically relevant clotting of dialyzers was observed, but minimal fibrin deposition was found more often in the Hemophan group (50 vs. 30%). Despite continuously elevated anti-factor Xa levels (Hemophan 0.49 +/- 0.03, polysulfone 0.62 +/- 0.01 IU/ml), a significant increase of ACT was only demonstrated 10 min after bolus application in the Hemophan group. Elevated polymorphonuclear granulocyte-elastase levels were demonstrated in the Hemophan group but were linked to the presence of minimal fibrin deposits and not to the dialyzer material. **We conclude that ACT is not a sensitive parameter to monitor anticoagulation with standard doses of LMWH.**

d) Hirudoid Monitoring

(1) Potzsch B, Madlener K, Seelig C, Riess CF, Greinacher A, Muller-Berghaus G

**MONITORING OF R-HIRUDIN ANTICOAGULATION DURING CARDIOPULMONARY BYPASS--ASSESSMENT OF THE WHOLE BLOOD ECARIN CLOTTING TIME.**

*Thromb Haemost* 1997 May;77(5):920-5

Hemostasis Research Unit, Max-Planck-Institut fur physiologische und klinische Forschung, Kerckhoff-Klinik, Bad Nauheim, Germany.

The use of recombinant (r) hirudin as an anticoagulant in performing extracorporeal circulation systems including cardiopulmonary bypass (CPB) devices requires a specific and easy to handle monitoring system. The usefulness of the celite-induced activated clotting time (ACT) and the activated partial thromboplastin time (APTT) for r-hirudin monitoring has been tested on ex vivo blood samples obtained from eight patients treated with r-hirudin during open heart surgery. The very poor relationship between the prolongation of the ACT and APTT values and the concentration of r-hirudin as measured using a chromogenic factor IIa assay indicates that both assays are not suitable to monitor r-hirudin anticoagulation. As an alternative approach a whole blood clotting assay based on the prothrombin-activating snake venom ecarin has been tested. In vitro experiments using r-hirudin-spiked whole blood samples showed a linear relationship between the concentration of hirudin added and the prolongation of the clotting times up to a concentration of r-hirudin of 4.0 micrograms/ml. Interassay coefficients (CV) of variation between 2.1% and 5.4% demonstrate the accuracy of the ecarin clotting time (ECT) assay. Differences in the interindividual responsiveness to r-hirudin were analyzed on r-hirudin-spiked blood samples obtained from 50 healthy blood donors. CV-values between 1.8% and 6% measured at r-hirudin concentrations between 0.5 and 4 micrograms/ml indicate remarkably slight differences in r-hirudin responsiveness. ECT assay results of the ex vivo blood samples linearly correlate (r = 0.79) to the concentration of r-hirudin. Moreover, assay results were not influenced by treatment with aprotinin or heparin. These findings together with the short measuring time with less than 120 seconds warrant the whole blood ECT to be a suitable assay for monitoring of r-hirudin anticoagulation in cardiac surgery.

e) Monitoring Oral Anticoagulation in Antiphospholipid Syndrome


**CONTROL OF ORAL ANTICOAGULATION IN PATIENTS WITH THE ANTIPHOSPHOLIPID SYNDROME--INFLUENCE OF THE LUPUS ANTICOAGULANT**
The recommended therapeutic range of International Normalized Ratio (INR) for oral anticoagulant treatment in patients with the antiphospholipid syndrome remains controversial. As a part of this controversy, it has been suggested that lupus anticoagulants (LA) could interfere with the determination of prothrombin time, thus questioning the validity of monitoring the treatment of these patients using INR. To clarify this point, we compared the values of INR obtained in the plasmas of two groups of patients, one without LA ($n = 47$), and the other with LA ($n = 43$). INR were determined using 8 different thromboplastin reagents on the same automated coagulation instrument. Chromogenic factor X, which is supposed to be insensitive to the presence of LA, was also measured. The results are the following: provided INR was calculated using calibrated reference plasmas, there was no significant difference between INR values obtained with the 8 reagents, both in the non-LA and in the LA groups (CV: 5.9 and 6.7%, respectively). Closer examination revealed that INR results obtained with one reagent (the recombinant thromboplastin Innovin) diverged from those of the 7 others, leading to an overestimation of INR, to a very large extent in some instances. However this effect was restricted to a subset of the patient population with LA (6 out of 43). Finally, the relationship between INR (average value obtained using the 8 reagents) and factor X was identical in non-LA and in LA patient groups. We conclude that, provided the reagents which display the LA interference are identified and excluded for this purpose, the INR system is valid for monitoring oral anticoagulant treatment in patients with LA.

f) Computer assisted Management of Anticoagulation Therapy

(1) Chatellier G, Colombet I, Degoulet P

AN OVERVIEW OF THE EFFECT OF COMPUTER-ASSISTED MANAGEMENT OF ANTICOAGULANT THERAPY ON THE QUALITY OF ANTICOAGULATION.

Int J Med Inf 1998 May;49(3):311-20

Medical Informatics Department, Service d'Informatique Medicale, Hopital Broussais, Paris, France.

Risks and benefits of anticoagulant therapy depend directly on the quality of anticoagulation. We carried out a meta-analysis of published randomized trials to assess the overall effectiveness of computer-assisted prescription systems on the quality of anticoagulation. Randomized controlled trials were identified through electronic searches of the Medline database (1966-1997) and systematic analyses of the references of articles. Two investigators selected relevant papers and summarized data from the studies. The outcome variable was the proportion of days within the target range of anticoagulation. A pooled estimate of the common odds ratio of being in the target range and its confidence interval was obtained by the Mantel-Haenszel method. Nine trials having included 1336 patients were identified. Computer systems were based on a pharmacokinetic-pharmacodynamic model and a bayesian prediction method. Most of them concerned the oral anticoagulant warfarin. The global odds ratio of being in the target range was 1.29 [95% CI: 1.17-1.49], thus meaning that the use of a computer for anticoagulation optimization increased by 29% the proportion of visits where patients were appropriately treated. The proportion of clinical events was too low for allowing a summary analysis, but major hemorrhages tended to be less frequent among patients of the computer groups than among patients of the control groups (2.0 versus 3.9%). Evidence from randomized controlled trials supports the effectiveness of computer-aided anticoagulant prescription. Widespread use of these systems in ambulatory care could increase the benefit/risk ratio of anticoagulant treatment at a low cost.

II. THROMBOLYSIS

A. Fields of Use Selecting the Patients

1. Thrombolysis General Aspects
a) New Thrombolytic Drugs

(1) Reddy DS

**NEWER THROMBOLYTIC DRUGS FOR ACUTE MYOCARDIAL INFARCTION.**

Department of Pharmacology, University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh, India.

Arterial thrombosis is the underlying cause of a wide variety of cardiovascular diseases such as myocardial infarction, stroke and pulmonary thromboembolism. All the currently used thrombolytic agents are plasminogen activators, which are very efficient in restoring the blood flow. The fibrinolytic system comprises an *inactive proenzyme plasminogen*, that is converted by plasminogen activators to the *enzyme plasmin*, that degrades fibrin. Despite the widespread use of established thrombolytic agents such as streptokinase, tissue-plasminogen activator and urokinase, all these agents suffer from a number of inadequacies including resistance to reperfusion, occurrence of acute coronary reocclusion and bleeding complications. The quest continues for thrombolytic agents with a higher potency, specific thrombolytic activity and fibrin selectivity. Several lines of research towards improvement of thrombolytic agents are being explored including the construction of mutants and variants of plasminogen activators, chimeric plasminogen activators and conjugates of plasminogen activators with monoclonal antibodies. Newer molecules such as pro-urokinase, saruplase, alteplase, K1K2Pu and staphylokinase have shown promise in animal models of arterial and venous thrombosis and also in pilot scale clinical studies in patients with myocardial infarction. However, more clinical trials are needed to determine whether these novel recombinant thrombolytic agents shows improved efficacy and fibrin specificity with minimal bleeding tendencies.

b) Recognize the High Risk Patients

1) **Contraindications** to Thrombolytic Treatment

(2) Wald DS

**PERCEIVED CONTRAINDICATIONS TO THROMBOLYTIC TREATMENT IN ACUTE MYOCARDIAL INFARCTION. A SURVEY AT A TEACHING HOSPITAL.**

John Radcliffe Hospital, Oxford.

OBJECTIVE: To examine the use of thrombolytic treatment in acute myocardial infarction when faced with perceived contraindications to treatment and to explore the justification for withholding treatment in such clinical situations. METHODS: Interview survey of all doctors responsible administering thrombolysis to patients with acute myocardial infarction at a teaching hospital in the UK from March to May 1997. RESULTS: 20 doctors were interviewed and asked whether they would give or withhold thrombolysis in a series of 19 clinical situations. These included patients presenting with both an acute myocardial infarction and one of the following associated conditions: a confirmed gastrointestinal haemorrhage, a suspected gastrointestinal haemorrhage, a peptic ulcer, an abdominal aortic aneurysm, a recent cerebrovascular accident, a known intracranial aneurysm, a known intracranial tumour, a recent dental extraction, recent surgery, severe hypertension, proliferative diabetic retinopathy, a history of bleeding diathesis, coma, recent cardiopulmonary resuscitation, pregnancy, menstruation, and a recent central venous puncture. In all but one of the clinical situations (definite current gastrointestinal haemorrhage) there was wide variation in response as to what constitutes a contraindication to thrombolytic treatment. Overall, a substantial proportion of doctors (35%-95%) would withhold treatment on account of any one of these clinical histories. CONCLUSION: Clinicians may be withholding thrombolysis in acute myocardial infarction on account of perceived contraindications for which there is little or no evidence of increased haemorrhagic risk. An effective treatment for acute myocardial infarction is probably being underused.

**Are the Doctors afraid of inducing Hemorrhage and therefore underuse thrombolytic therapy?**
2) Clinical Predictors of Choice of Thrombolytic Regimen

(3) Lundergan CF, Reiner JS, McCarthy WF, Coyne KS, Califf RM, Ross AM

**CLINICAL PREDICTORS OF EARLY INFARCT-RELATED ARTERY PATENCY FOLLOWING THROMBOLYTIC THERAPY: IMPORTANCE OF BODY WEIGHT, SMOKING HISTORY, INFARCT-RELATED ARTERY AND CHOICE OF THROMBOLYTIC REGIMEN: THE GUSTO-I EXPERIENCE.** GLOBAL UTILIZATION OF STREPTOKINASE AND T-PA FOR OCCLUDED CORONARY ARTERIES.

*J Am Coll Cardiol* 1998 Sep;32(3):641-7

Cardiovascular Research Institute and the GUSTO-I Core Angiographic Laboratory, The George Washington University, Washington, DC, USA.

OBJECTIVES: The purpose of this study was to determine patient characteristics that are a priori predictors of early infarct-related artery patency following thrombolytic therapy, and to provide a paradigm which may identify patients who would be most likely to achieve restoration of normal (TIMI 3) coronary flow in response to thrombolytic therapy. BACKGROUND: Restoration of infarct-related artery perfusion in acute myocardial infarction is necessary for preservation of ventricular function and mortality reduction. Clinical variables that are a priori predictors of early patency with currently available thrombolytic regimens have not been fully characterized. METHODS: The probability of early infarct-related artery patency (TIMI 3 flow) was determined by multivariable logistic regression. We determined a reduced (parsimonious) model for predicting early (90 min) infarct-related artery patency (TIMI grade 3) based on data from 1,030 patients in the GUSTO-I Angiographic study. RESULTS: Predictors of 90 min TIMI 3 flow are use of an accelerated t-PA regimen (vs. streptokinase containing regimens) (chi2=39.1; p < or = 0.0001), infarct related artery (RCA/Lcx vs. LAD) (chi2=12.7; p=0.0004), body weight (chi2=10.3; p=0.001) and history of smoking (chi2=7.4; p=0.007). Time from symptom onset to treatment was not significant (p=0.71). CONCLUSIONS: The efficacy of currently available thrombolytic regimens is chiefly dependent on choice of thrombolytic regimen, body weight, infarct-related coronary artery and smoking history. Clinical variables alone correctly predict a priori TIMI 3 flow in the infarct-related artery 64% of the time. Patients with body weights greater than 85 kg are at a significant disadvantage with regard to achieving successful thrombolysis compared to those with lesser body weights.

c) Identify the Low Risk Patients

(1) Nidorf M, Parsons R, Thompson P, Jamrozik K, Hobbs M

**REFINING THE RISK-BENEFIT EQUATION FOR THROMBOLYSIS: HOW TO IDENTIFY THE LOW RISK PATIENT BEFORE ADMINISTERING THROMBOLYTIC THERAPY.**


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In view of the relative risk of intracranial haemorrhage and major bleeding with thrombolytic therapy, it is important to identify as early as possible the low risk patient who may not have a net clinical benefit from thrombolysis in the setting of acute myocardial infarction. An analysis of 5434 hospital-treated patients with myocardial infarction in the Perth MONICA study showed that age below 60 and absence of previous infarction or diabetes, shock, pulmonary oedema, cardiac arrest and Q-wave or left bundle branch block on the initial ECG identified a large group of patients with a 28 day mortality of only 1%, and one year mortality of only 2%. Identification of baseline risk in this way helps refine the risk-benefit equation for thrombolytic therapy, and may help avoid unnecessary use of thrombolysis in those unlikely to benefit.

d) Thrombolysis and the corrected TIMI fram Count (CTFC) Flow Grade
(1) Gibson CM, Cannon CP, Murphy SA, Ryan KA, Mesley R, Marble SJ, McCabe CH, Van De Werf F, Braunwald E

**RELATIONSHIP OF TIMI MYOCARDIAL PERFUSION GRADE TO MORTALITY AFTER ADMINISTRATION OF THROMBOLYTIC DRUGS.**  
*Circulation* 2000 Jan 18;101(2):125-130

Cardiovascular Divisions of the Departments of Medicine, the University of California at San Francisco, San Francisco (C.M.G., S.A.M., K.A.R., R.M., S.J.M.), University Hospitals Leuven, Leuven, Belgium (F.V.d.W.), and Brigham & Women’s Hospital, Boston, Mass (C.P.C., C.H.M., E.B.).

Background—Although improved epicardial blood flow (as assessed with either TIMI flow grades or TIMI frame count) has been related to reduced mortality after administration of thrombolytic drugs, the relationship of myocardial perfusion (as assessed on the coronary arteriogram) to mortality has not been examined. Methods and Results—A new, simple angiographic method, the TIMI myocardial perfusion (TMP) grade, was used to assess the filling and clearance of contrast in the myocardium in 762 patients in the TIMI (Thrombolysis In Myocardial Infarction) 10B trial, and its relationship to mortality was examined. TMP grade 0 was defined as no apparent tissue-level perfusion (no ground-glass appearance of blush or opacification of the myocardium) in the distribution of the culprit artery; TMP grade 1 indicates presence of myocardial blush but no clearance from the microvasculature (blush or a stain was present on the next injection); TMP grade 2 blush clears slowly (blush is strongly persistent and diminishes minimally or not at all during 3 cardiac cycles of the washout phase); and TMP grade 3 indicates that blush begins to clear during washout. There was a mortality gradient across the TMP grades, with mortality lowest in those patients with TMP grade 3 (2.0%), intermediate in TMP grade 2 (4.4%), and highest in TMP grades 0 and 1 (6.0%; 3-way P=0.05). Even among patients with TIMI grade 3 flow in the epicardial artery, the TMP grades allowed further risk stratification of 30-day mortality: 0.73% for TMP grade 3; 2.9% for TMP grade 2; 5.0% for TMP grade 0 or 1 (P=0.03 for TMP grade 3 versus grades 0, 1, and 2; 3-way P=0.066). TMP grade 3 flow was a multivariate correlate of 30-day mortality (OR 0.35, 95% CI 0.12 to 1.02, P=0.054) in a multivariate model that adjusted for the presence of TIMI flow (P=NS), the corrected TIMI frame count (OR 1.02, P=0.06), the presence of an anterior myocardial infarction (OR 2.3, P=0.03), pulse rate on admission (P=NS), female sex (P=NS), and age (OR 1.1, P=0.001). Conclusions—Impaired perfusion of the myocardium on coronary arteriography by use of the TMP grade is related to a higher risk of mortality after administration of thrombolytic drugs that is independent of flow in the epicardial artery. Patients with both normal epicardial flow (TIMI grade 3 flow) and normal tissue level perfusion (TMP grade 3) have an extremely low risk of mortality.


[NO TITLE AVAILABLE]. [ARTICLE IN SPANISH]  
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We studied 398 patients with diagnosis of acute myocardial infarction who arrived within the first six hours of symptom onset that were treated with thrombolysis or primary angioplasty, they were divided in two groups: Group 1 (n = 198), those treated with 1.5 million U of streptokinase over 60 min and Group 2 (n = 200), those treated with primary angioplasty. In Group 1 the "pain-door" time was 3.7 +/- 1.7 hs vs 3.8 +/- 2.4 hs in group 2 (p = NS). The "door-needle" time was 48 +/- 12 min. compared with the "door-balloon" time of 84 +/- 30 min (p < 0.001). In Group 1, 154 (77.6%) of the patients had clinical of reperfusion after thrombolysis, 58 of them underwent coronary angiography and had an infarct related artery (IRA) patency rate of 45.3%. In Group 2 the IRA patency rate was 85.5% (p < 0.005). Conclusion: Thrombolysis was achieved in a lesser period of time but our findings showed that primary angioplasty was more effective obtaining a TIMI 3 flow.
(3) French JK, Ellis CJ, White HD

THE CORRECTED TIMI FRAME COUNT. THE NEW GOLD STANDARD?


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Over the last decade Thrombolysis in Myocardial Infarction (TIMI) flow grades have been the gold standard for the assessment of efficacy of infarct-artery reperfusion. However, with the introduction of core angiographic laboratories, the reproducibility of TIMI flow grades has been questioned. The corrected TIMI frame count (CTFC) has been developed as a more reproducible method of quantifying infarct artery blood flow after myocardial infarction (MI). We have utilised the CTFC in two studies to examine infarct-artery blood flow. In the Hirulog in Early Reperfusion and Occlusion (HERO 1) study, the CTFC was measured at 90-120 minutes after administration of aspirin, streptokinase and either Hirulog or heparin. Only 27% of patients had a normal CTFC (< or = 27) in the infarct-related artery. Patients with a prolonged CTFC (> 27) had more abnormal left ventricular function (LVF) as measured by the mean chord score in the 'area at risk' (-2.51 vs -2.06, p = 0.02), on left ventriculography. In a second study, infarct-artery flow was examined four weeks and one year after MI. At four weeks, only 43% of patients with patient infarct-related arteries had a 'normal' CTFC of < or = 27. A prolonged CTFC at four weeks was a univariate predictor of increased reocclusion at one year (p = 0.001). CTFCs are frequently abnormal in patent infarct-related arteries, and predict reocclusion. Whether frame counting is a better predictor of late clinical outcomes than the TIMI flow grade needs to be prospectively examined in large clinical trials.

2. Thrombolysis "The Rapid Early Action" - Reducing Delay Time

a) Patient delay time


KNOWLEDGE OF HEART ATTACK SYMPTOMS IN A POPULATION SURVEY IN THE UNITED STATES: THE REACT TRIAL. RAPID EARLY ACTION FOR CORONARY TREATMENT.


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BACKGROUND: Greater use of thrombolysis for patients with myocardial infarction has been limited by patient delay in seeking care for heart attack symptoms. Deficiencies in knowledge of symptoms may contribute to delay and could be a target for intervention. We sought to characterize symptom knowledge. METHODS: Rapid Early Action for Coronary Treatment is a community trial designed to reduce this delay. At baseline, a random-digit dialed survey was conducted among 1294 adult respondents in the 20 study communities. Two open-ended questions were asked about heart attack symptom knowledge. RESULTS: Chest pain or discomfort was reported as a symptom by 89.7% of respondents and was thought to be the most important symptom by 56.6%. Knowledge of arm pain or numbness (67.3%), shortness of breath (50.8%), sweating (21.3%), and other heart attack symptoms was less common. The median number of correct symptoms reported was 3 (of 11). In a multivariable-adjusted model, significantly higher mean numbers of correct symptoms were reported by non-Hispanic whites than by other racial or ethnic groups, by middle-aged persons than by older and younger persons, by persons with higher socioeconomic status than by those with lower, and by persons with previous experience with heart attack than by those without. CONCLUSIONS: Knowledge of chest pain as an important heart attack symptom is high and relatively uniform; however, knowledge of the complex constellation of heart attack symptoms is deficient in the US population, especially in low socioeconomic and racial or ethnic minority groups. Efforts to reduce delay in seeking medical care among persons with heart attack symptoms should address these deficiencies in knowledge.

b) First Contact delay time
(1) Rawles J, Sinclair C, Jennings K, Ritchie L, Waugh N
CALL TO NEEDLE TIMES AFTER ACUTE MYOCARDIAL INFARCTION IN URBAN AND RURAL AREAS IN NORTHEAST SCOTLAND: PROSPECTIVE OBSERVATIONAL STUDY.
BMJ 1998 Aug 29;317(7518):576-8
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OBJECTIVE: To determine call to needle times and consider how best to provide timely thrombolytic treatment for patients with acute myocardial infarction.
DESIGN: Prospective observational study.
SETTING: City, suburban, and country practices referring patients to a single district general hospital in northeast Scotland.
SUBJECTS: 1046 patients with suspected acute myocardial infarction given thrombolytic treatment.
MAIN OUTCOME MEASURES: Time from patients' calls for medical help until receipt of opiate or thrombolytic treatment, measured against a call to needle time of 90 minutes or less, as proposed by the British Heart Foundation.
RESULTS: General practitioners were the first medical contact in 97% (528/544) of calls by country patients and 68% (340/502) of city and suburban patients. When opiate was given by general practitioners, median call to opiate time was about 30 minutes (95% within 90 minutes) in city, suburbs, and country; call to opiate delay was about 60 minutes in city and suburban patients calling "999" for an ambulance. One third of country patients received thrombolytic treatment from their general practitioners with a median call to thrombolysis time of 45 minutes (93% within 90 minutes); this compares with 150 minutes (5% within 90 minutes) when this treatment was deferred until after hospital admission. In the city and suburbs, no thrombolytic treatment was given outside hospital, and only a minority of patients received it within 90 minutes of calling; median call to thrombolysis time was 95 (46% within 90 minutes) minutes.
CONCLUSIONS: The first medical contact after acute myocardial infarction is most commonly with a general practitioner. This contact provides the optimum opportunity to give thrombolytic treatment within the British Heart Foundation's guideline.

(2) Coccolini S, Berti G, Maresta A
THE MAGNITUDE OF THE BENEFIT FROM PRECCU THROMBOLYSIS IN ACUTE MYOCARDIAL INFARCTION: A LONG TERM FOLLOW UP.
Int J Cardiol 1998 May 29;65 Suppl 1:S49-56
Department of Cardiology, S. Maria delle Croci Hospital, Ravenna, Italy.
OBJECTIVE: Our aim was to determine the relationship among the time saved by administration of thrombolytic therapy in prehospital versus hospital setting and long term mortality; number, duration of hospitalizations and their causes.
BACKGROUND: There is much theoretic, experimental and trial evidence to indicate that in acute myocardial infarction the earlier the thrombolytic therapy is given, the greater its efficacy. However, the clinical importance of this gain time in long term is still uncertain.
SUBJECTS: 280 patients with suspected acute myocardial infarction in perspective, controlled study with two parallel groups of consecutive patients without contraindication for thrombolysis, who were seen by general emergency physicians before hospitalization (Gr.1) or later in hospital by the attending cardiologist (Gr.2). The main outcomes measured was mortality rate at 5 years, causes, number and duration of hospitalizations. RESULTS: The median pain to needle time was 90' (25 degrees percentile:67'; 75 degrees percentile:165') in Gr.1 vs 165' in Gr.2 (25 degrees percentile:110'; 75 degrees percentile:225'). The median time difference was 75' (P<.001). The 35th day total mortality rate was 7.5% and 10.6% (p:n.s) in Gr.1 vs Gr.2 respectively, 8.6% (Gr.1) vs 19.7% (Gr.2) (P<.0015) at 1 year, and 19.2% (Gr.1) vs 47.2% (Gr.2) (P<.0015) at 5 years. The percentage of patients with a number of new hospitalizations greater than 1 during 5 years was not significantly different in Gr.1 vs Gr.2 (44.1% vs 48.35, p:n.s). The total duration of hospitalization was 479 days in Gr.1 vs 1431 days in Gr.2 (P<0.001). The 75 Gr.1 patients alive at the end of 5 years follow up had a mean hospital stay of 3.86+/-.5.92 days vs 8.05+/-.6.60 days (P<0.036) of the 94 Gr.2 patients alive after 5 years. The total duration of hospitalization for recurrence of acute MI was significantly different in Gr.1 vs Gr.2 (90 vs 425 days: P<.001; and 13+/-.6.2 days vs 25+/-.5.4: P<0.003 respectively). Cardiac failure led to the 1.16% in Gr.1 vs 9.43% of new admission (P<0.028) for a total of 57 vs 243 days in Gr.1 and Gr.2 respectively (P<0.001). Cumulative mortality rate for any cause at 5 years was 19.2% and 47.2% in prehospital and in hospital treated patients (P<.015), obtaining diverging survival curves.
CONCLUSIONS: The magnitude of the benefit from earlier thrombolysis is such that giving
thrombolytic treatment earlier is the main problem to reduce the time from onset of symptoms to reperfusion, to salvage myocardial muscle and obtain diverging survival curves.

(3) Bjoru H, Langfeldt E, Lovland A, Nordang B, Hoybjor S

**[STREPTOKINASE TREATMENT IN NORDKAPP] [ARTICLE IN NORWEGIAN].**

*Tidsskr Nor Laegeforen* 1998 Jun 30;118(17):2632-3

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Since July 1994 the primary health care service in the municipality of Nordkapp has been conducting a study on the feasibility of prehospital thrombolytic treatment of acute myocardial infarction. The diagnosis of infarction was verified in all nine patients included in the study up until February 1998. In one patient the treatment was ended because of serious complications; in the other eight the treatment was without complications. There was a significant time saving for these patients compared to being given the same treatment in hospital. The authors argue that thrombolytic treatment of acute myocardial infarction should be defined in standard procedures and administered by general practitioners.

c) Hospital delay time

(1) Berglin Blohm M, Nilsson G, Karlsson T, Herlitz J

**THE POSSIBILITY OF INFLUENCING COMPONENTS OF HOSPITAL DELAY TIME WITHIN EMERGENCY DEPARTMENTS AMONG PATIENTS WITH ST-ELEVATION IN THE INITIAL ELECTROCARDIOGRAM.**


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The aim of this study was to describe the possibility of influencing components of hospital delay time within the emergency department (ED) among patients with ST-elevation on the initial electrocardiogram (ECG). Nurses recorded seven patient time points: (1) ED admission; (2) ECG recording; (3) decision by nurse/ED physician; (4) cardiologist ED arrival; (5) decision of coronary care unit (CCU) admission; (6) ED departure; (7) CCU arrival. After special training in ECG, nurses in the ED were subsequently delegated to send patients directly to the CCU if showing ST-elevation on the admission ECG without contacting either the physician in ED or the cardiologist on call (intervention). Delay times between hospital admission and admission to the CCU were evaluated during the 9 months prior to and during the 6 months after the start of this intervention. Fifty patients (66% men) participated in the first study during 3 months (prior to intervention). Patients with suspected or confirmed acute myocardial infarction (AMI) in the ED had a median delay time from ED arrival to CCU arrival of 55.5 minutes (34.5 minutes for patients with confirmed AMI; ST elevation on admission). Time interval from decision to admit to CCU and ED departure was an average of 31% of the total delay. A mean of 21% of total delay occurred between ED decision to cardiologist arrival, and 19% during the time interval following the decision by the nurse or physician to the cardiologist ED arrival. Among patients receiving thrombolysis, the median delay time from hospital admission to CCU admission was reduced from 40 minutes during the 9 months prior to start of the intervention (nurses sending patients directly to the CCU) to 22 minutes during the 6 months thereafter (p = 0.02). The largest proportion of hospital delay components for acute coronary syndrome patients occurred between the cardiologist's decision to admit to the CCU and departure from the ED, and the interval following the decision by the nurse or physician to the cardiologist ED arrival. When nurses were delegated to transfer patients with ST-elevation on admission directly to the CCU without contacting a physician, the delay time from ED admission to CCU admission was reduced by nearly 50%.

3. Thrombolysis in Elderly Patients

(1) McMechan SR, Adgey AAJ

**AGE RELATED OUTCOME IN ACUTE MYOCARDIAL INFARCTION. ELDERLY PEOPLE BENEFIT FROM THROMBOLYSIS AND SHOULD BE INCLUDED IN TRIALS.**

*BMJ* 1998 Nov 14;317(7169):1334-5
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(2) Rich MW

THERAPY FOR ACUTE MYOCARDIAL INFARCTION IN OLDER PERSONS.


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**OBJECTIVE:** To review the early management of acute myocardial infarction (AMI) in older adults.

**METHODS:** Recently published studies relevant to the early management of AMI were systematically reviewed. When possible, the impact of older age on complication rates and clinical outcomes was evaluated. **RESULTS:** In general, AMI therapies that are effective in younger patients are also effective in older patients. Conversely, older age is associated with an increased risk of complications from therapy, implying that careful patient selection is required to optimize outcomes while minimizing risks. The principal limitation of currently available data is that relatively few patients older than the age of 80 have been enrolled in prospective randomized clinical trials. **CONCLUSIONS:** Thrombolysis and primary angioplasty are effective in establishing reperfusion and improving clinical outcomes in older patients with AMI. In the absence of contraindications, aspirin and beta blockers should be considered standard therapy in AMI patients of all ages, whereas heparin, nitrates, and angiotensin converting enzyme inhibitors are indicated in selected subgroups. At the present time, calcium channel blockers, magnesium, and antiarrhythmic agents are not recommended for routine use in the AMI setting, and the role of glycoprotein IIb/IIIa inhibitors, low molecular weight heparin, and other newer agents await the results of ongoing clinical trials.

(3) Dzavik V, Burton JR, Kee C, Teo KK, Ignaszewski A, Lucas AR, Tymchak WJ

CHANGING PRACTICE PATTERNS IN THE MANAGEMENT OF ACUTE MYOCARDIAL INFARCTION COMPPLICATED BY CARDIGENIC SHOCK: ELDERLY COMPARED WITH YOUNGER PATIENTS.

*Can J Cardiol* 1998 Jul;14(7):923-30

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**BACKGROUND:** Cardiogenic shock continues to be an ominous complication of acute myocardial infarction (AMI). Evidence from retrospective analyses, registries and observational studies suggests that aggressive management using emergent revascularization strategies can bring about significant improvement in survival in this setting. Several studies have identified age as an independent predictor of survival. **OBJECTIVE:** To study retrospectively the possible changes in practice patterns in the management of patients with AMI complicated by cardiogenic shock in a tertiary care referral centre, and to determine what effect these changes may have had on survival of the patients, stratified by age. **METHODS:** From 1989 to 1995, 115 patients fulfilled the study criteria of cardiogenic shock based on pump failure and of presenting within 48 h of onset of shock. Prespecified data were extracted from medical records. All available coronary angiograms (n = 72) were analyzed by two experienced angiographers and consensus of findings was obtained. **RESULTS:** The study revealed a significant increase in the use of cardiac catheterization, interventional procedures and intra-aortic balloon pump (IABP) support in patients in the age groups 65 years or less, 66 to 75 years, and older than 75 years in 1989 to 1990, through 1991 to 1992, to 1993 to 1995. Significantly fewer patients aged older than 75 years received cardiac catheterization, coronary intervention and IABP support throughout the study period and even in the final period analyzed. **In-hospital survival** improved from 4% in 1989-90 to 33% in 1991-92, and 44% in 1993-95 (P = 0.001). Patients aged 65 years or less improved from 10% in 1989-90 to 59% in 1993-95 (P = 0.032). Only 20% of patients aged older than 75 years survived in the 1993-95 period. By univariate analysis, use of coronary angiography (catheterization 46% versus no catheterization 5%; P < 0.0001), coronary intervention procedures (percutaneous transluminal coronary angioplasty or coronary artery bypass grafting) (intervention 48% versus no intervention 9%; P < 0.0001) and IABP support (IABP 41% versus no IABP 18%; P = 0.0096) were all associated with improved in-hospital survival. Use of thrombolytic therapy showed possible survival benefit only in patients aged older than 75 years (thrombolysis 33% versus no thrombolysis 5%; P = 0.10). Patients who underwent coronary intervention were younger (P = 0.002), had a lower incidence of previous myocardial infarction (P = 0.0002), lower heart rate (P = 0.04), higher peak creatine phosphokinase (P = 0.04) and fewer vessels with at least 70% stenosis (P < 0.0001). On
multivariate analysis only lower age, lower heart rate and presence of coronary intervention procedures were found to have an independent effect on survival. CONCLUSIONS: Use of invasive treatment strategies has increased significantly since 1989-90 in the management of patients with AMI complicated by cardiogenic shock. This increase has been associated with improved in-hospital survival in all age groups except possibly the very elderly. Patients undergoing coronary interventional procedures are significantly different in baseline clinical characteristics from patients not undergoing these procedures. These observations underscore the need for randomized trials to define the optimal treatment strategies in these patients. Efficacy of invasive treatment strategies in elderly patients aged older than 75 years deserves special attention.

4. Thrombolysis for Neonates

ENDOVASCULAR TREATMENT OF RENAL ARTERY THROMBOSIS CAUSED BY UMBILICAL ARTERY CATHETERIZATION.

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Renal arterial thrombosis, usually in association with aortic thrombosis, has been reported as a result of prolonged neonatal umbilical artery catheterization. A case of renal artery thrombosis attributable to umbilical artery catheterization, resulting in malignant renovascular hypertension, in a 15-day-old neonate, treated by catheter-directed thrombolysis through the involuting umbilical artery, was studied. Resolution of systemic hypertension and partial return of right renal function followed rapid thrombus dissolution.

5. Thrombolysis and Hyperbaric Oxygen in MI HOT

HYPERBARIC OXYGEN AND THROMBOLYSIS IN MYOCARDIAL INFARCTION: THE ‘HOT MI’ RANDOMIZED MULTICENTER STUDY.
Cardiology 1998 Oct;90(2):131-6

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In a previous pilot study, we demonstrated that adjunctive treatment with hyperbaric oxygen (HBO) appears to be feasible and safe in patients with acute myocardial infarction (AMI) and may result in an attenuated rise in creatine phosphokinase (CPK), more rapid resolution of pain and ST changes. This randomized multicenter trial was organized to further assess the safety and feasibility of this treatment in human subjects. Patients with an AMI treated with recombinant tissue plasminogen activator (rTPA) or streptokinase (STK), were randomized to treatment with HBO combined with either rTPA or STK, or rTPA or STK alone. An analysis included 112 patients, 66 of whom had inferior AMIs (p = NS). The remainder of the patients had anterior AMIs. The mean CPK at 12 and 24 h was reduced in the HBO patients by approximately 7.5% (p = NS). Time to pain relief was shorter in the HBO group. There were 2 deaths in the control and 1 in those treated with HBO. The left ventricle ejection fraction (LVEF) on discharge was 51.7% in the HBO group as compared to 48.4% in the controls (p = NS). The LVEF of the controls was 43.4 as compared to 47.6 for those treated, approximately 10% better (no significant difference). Treatment with HBO in combination with thrombolysis appears to be feasible and safe for patients with AMI and may result in an attenuated CPK rise, more rapid resolution of pain and improved ejection fractions. More studies are needed to assess the benefits of this treatment.

(2) Laden G
HOT MI PILOT STUDY. HYPERBARIC OXYGEN AND THROMBOLYSIS IN MYOCARDIAL INFARCTION.
HYPERBARIC OXYGEN AND THROMBOLYSIS IN MYOCARDIAL INFARCTION: THE "HOT MI" PILOT STUDY.
Heart J 1997 Sep;134(3):544-50

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Hyperbaric oxygen treatment (HBO) in combination with thrombolysis has been demonstrated to salvage myocardium in acute myocardial infarction in the animal model. Therefore a randomized pilot trial was undertaken to assess the safety and feasibility of this treatment in human beings. Patients with an acute myocardial infarction (AMI) who received recombinant tissue plasminogen activator (rTPA) were randomized to treatment with HBO combined with rTPA or rTPA alone. Sixty-six patients were included for analysis. Forty-three patients had inferior AMIs (difference not significant) and the remainder had anterior AMIs. The mean creatine phosphokinase level at 12 and 24 hours was reduced in the patients given HBO by approximately 35% (p = 0.03). Time to pain relief and ST segment resolution was shorter in the group given HBO. There were two deaths in the control group and none in those treated with HBO. The ejection fraction on discharge was 52.4% in the group given HBO compared with 47.3% in the control group (difference not significant). Adjunctive treatment with HBO appears to be a feasible and safe treatment for AMI and may result in an attenuated rise in creatine phosphokinase levels and more rapid resolution of pain and ST segment changes.

6. Thrombolysis and Hirudin for Improvement of Thrombolysis (HIT-4) in AMI

EFFECTS OF THROMBOLYTIC THERAPY IN ACUTE INFERIOR MYOCARDIAL INFARCTION WITH OR WITHOUT RIGHT VENTRICULAR INVOLVEMENT. HIT-4 TRIAL GROUP. HIRUDIN FOR IMPROVEMENT OF THROMBOLYSIS.

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OBJECTIVES: This study assessed the prognostic impact of right ventricular involvement (RVI) in streptokinase-treated patients with inferior acute myocardial infarction (AMI) stratified for small or large AMI. BACKGROUND: Only scant data exist from small studies about the impact of reperfusion therapy on survival in patients with RVI during inferior AMI. METHODS: Right ventricular involvement was assessed by ST-segment elevation ≥ 0.1 mV in lead V4R and infarct size by the extent of ST-segment deviation on the baseline electrocardiogram: small AMI=sum ST-segment elevation < or =0.8 mV and no precordial ST-segment depression (small ST); large AMI=presence of precordial ST-segment depression or sum ST-segment elevation >0.8 mV (large ST) in 522 inferior AMI patients of the Hirudin for Improvement of Thrombolysis (HIT-4) Trial. In 187 patients, 90-min coronary angiography was performed. RESULTS: Right ventricular involvement was present in 169 patients (32%). Higher 30-day cardiac mortality rates with RVI (5.9% vs. 2.5%) were related to larger infarct size rather than to RVI. For large ST, a proximal right coronary artery lesion was observed in 52% with and in 23% without RVI. Patency rates at 90 min were similar (54% vs. 52%). In the 28% of patients who had small ST, cardiac mortality was less than 1% irrespective of the presence of RVI. Coronary artery lesions were mostly located distally. Patency rates were 27% with and 80% without RVI. CONCLUSIONS: ST-segment elevation of > or =0.1 mV in V4R in inferior AMI patients is associated with larger infarct size and higher 30-day mortality rates. Right ventricular involvement is not an independent predictor of survival. In patients with small ST, cardiac mortality is low, even if ST V4R is > or =0.1 mV.

7. Thrombolysis vs Primary Angioplasty

(1) Ito H, Kubota I, Yokoyama K, Yasumura S, Tomoike H
ANGIoplasty BUT NOT THROMBOLYSIS IMPROVES SHORT-TERM MORTALITY OF ACUTE MYOCARDIAL INfarction. A MULTICENTER SURVEY IN YAMAGATA, JAPAN.
There are few district-based surveys to investigate the actual effects of thrombolytic therapy and percutaneous transluminal coronary angioplasty (PTCA) on short-term mortality in patients with acute myocardial infarction (AMI) in Japan. The study population comprised 974 patients (319 women and 655 men, aged 69 +/- 12 years) admitted with confirmed AMI to 41 hospitals in Yamagata Prefecture from January 1, 1994 to December 31, 1996. Thrombolysis and PTCA were performed in 262 (27%) and 428 (44%) patients, respectively, and 161 patients died within 28 days after the onset of AMI (short-term mortality 16.5%). Thirteen variables, including risk factors and clinical manifestations, were examined by bivariate and multiple logistic regression analyses to identify the predictors of short-term mortality. Multiple logistic regression analysis, incorporating variables with a p value < 0.05 in a bivariate analysis, demonstrated that advanced age, history of myocardial infarction and Killip class III or IV independently correlated with increased short-term mortality and treatment with PTCA independently correlated with decreased short-term mortality (odds ratio 0.21, 95% confidence interval [CI] 0.11-0.39). Thrombolytic therapy was not an independent predictor of short-term mortality (odds ratio 0.67, 95% CI 0.37-1.20). Treatment with PTCA but not thrombolysis significantly improved the short-term mortality in patients with AMI in our area-based study.


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In the present study we compared the outcome of primary percutaneous coronary angioplasty (PTCA) (PTCA without prior or concomitant administration of thrombolytic drugs) in 82 consecutive patients with acute myocardial infarction (AMI) with the outcome of 82 AMI patients, who were treated with intravenous thrombolysis. The thrombolysis patients were prospectively matched to the angioplasty patients regarding age, sex, duration of symptoms and infarct localisation. The in-hospital mortality was 3.7% in the PTCA group versus 4.9% in the thrombolysis group. Thrombolysis-treated patients had increased use of diuretics and ACE-inhibitors as compared to PTCA-treated patients. The mean ejection fraction was 52 +/- 11% in the PTCA group versus 47 +/- 10% (p = 0.01) in the thrombolysis group. We conclude that initial Danish experience with primary PTCA is promising, and that this treatment may favourably affect the outcome of acute myocardial infarction.


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Early and complete coronary reperfusion can improve survival in myocardial infarction. Primary angioplasty can achieve TIMI grade 3 flow (complete restoration) in over 90% of cases. In comparison thrombolysis can achieve TIMI grade 3 flow in only just over 50%. Comparative trials have shown superior rates of death and reinfarction with a low haemorrhagic risk with PTCA compared with thrombolysis. Early clinical trials showed a clear superiority of primary angioplasty over thrombolysis but larger trials with larger number of endpoints have shown less impressive superiority. Wider application in community studies has not shown the benefits promised in the earlier studies, possibly due to dilution of experience. The impact of newer stent regimens vs nonnewer thrombolytic and antithrombotic regimens can only be determined by further clinical trials.

(4) Grip L, Hartford M. [FIBRINOLYSIS OR ANGIOPLASTY IN ACUTE MYOCARDIAL INFARCTION]? [ARTICLE IN SWEDISH] Lakartidningen 1998 Aug 5;95(32-33):3425-9
Sahlgrenska Universitetssjukhuset, Goteborg.

Early reperfusion during myocardial infarction limits myocardial injury and reduces mortality. Fibrinolysis (with streptokinase, or tissue or recombinant plasminogen activators) is today an established method for the treatment of myocardial infarction patients manifesting ST-segment elevation or left bundle branch block at ECG (electrocardiography), effective reperfusion being obtained in fifty per cent of cases. Extensive developments are under way, both of fibrinolytic substances and of various adjuvant treatments. A satisfactory alternative treatment to fibrinolysis is percutaneous transluminal coronary angioplasty (PTCA), a method which can be used when fibrinolysis is contraindicated or during cardiogenic shock, or when there is no sign of reperfusion in response to fibrinolytic treatment. Provided the facilities and competence are available, PTCA can even be used as primary treatment instead of fibrinolysis.


Service de cardiologie, hopital Cochin, Paris.

The objective of the treatment of myocardial infarction is to reestablish patency of the occluded artery as soon as possible. Two methods have been validated (1) intravenous thrombolysis which is easy to perform, and (1) transluminal coronary angioplasty requiring expensive infrastructures and a skilled medical team but which has a higher success rate of restoring arterial patency. Angioplasty is indicated in cardiogenic shock and cases in which there is diagnostic uncertainty or a contraindication to thrombolysis. In addition, its superiority over thrombolysis has been clearly demonstrated in the following indications: 1) primary angioplasty if proper facilities with an experienced team are available in less than 45 minutes and 2) after failed thrombolysis (rescue angioplasty). The use of stents improves the results of primary angioplasty. Angioplasty and thrombolysis are not rival techniques: the choice depends on local conditions (proximity to a catheterization laboratory with a trained medical team) and the clinical context (presence of "high-risk" criteria). Their association (prehospital thrombolysis followed by immediate angioplasty) is the object of prospective clinical trials.

8. Thrombolysis for Basilar and Vertebral Arterial and dissection and thrombosis


Department of Clinical Neurosciences, Western General Hospitals NHS Trust, Edinburgh, Scotland.

A case of traumatic extracranial vertebral arterial dissection leading to vertebrobasilar thrombosis and respiratory compromise requiring mechanical ventilation was managed with intraarterial thrombolysis and stenting of the vertebral intimal dissection. In contrast to similar, previously reported cases, this critically ill patient made a full recovery, returning to his job as a secondary school teacher.


Department of Radiology, Washington University School of Medicine, St Louis, MO, USA.

BACKGROUND AND PURPOSE: This study was undertaken to examine the relationship between collateral flow and outcome after local intraarterial thrombolytic treatment for basilar artery thrombosis. METHODS: Twenty-four patients with symptomatic basilar thrombosis were treated with
intraarterial urokinase. Angiograms at the time of treatment were analyzed to characterize collateral flow. The number of posterior communicating arteries (PCoAs) and the degree of collateral filling of the basilar artery were then compared with symptom duration before treatment, with Glasgow Coma Scale (GCS) score at the time of treatment, with 90-day modified Rankin score, and with 90-day survival status. RESULTS: Of the 20 patients who had carotid artery injections at the time of the thrombolytic procedure, two had no PCoA, eight had one PCoA, and 10 had two PCoAs. Nine had no collateral opacification of the basilar artery, six had collateral opacification of the distal basilar artery, and five had collateral opacification of the distal and proximal basilar artery. Ninety-day survival was 38%; 25% of patients had good neurologic outcomes. No correlation was found between the number of PCoAs and symptom duration, pretreatment GCS score, survival, or neurologic outcome. Duration of symptoms before treatment was longer in patients with collateral flow to the basilar artery. Basilar artery collateral flow did not correlate with survival, but it did correlate with neurologic outcome for the 12 patients with middle or distal basilar artery thrombus in whom collateral flow to the basilar artery was assessed (83% with collateral flow had good neurologic outcomes, but only 17% without collateral flow had good outcomes). All six patients with proximal basilar artery thrombus in whom collateral flow was assessed died, independent of the collateral flow observed. CONCLUSION: In symptomatic acute basilar artery thrombosis, neurologic outcome was better after intraarterial thrombolysis in patients who had collateral filling of the basilar artery, except in cases of proximal basilar thrombosis. Patients with collateral filling of the basilar artery also tolerated longer symptom duration.

9. Thrombolysis for Internal Carotid Artery (ICA) Occlusion and Stroke

(1) Endo S, Kuwayama N, Hirashima Y, Akai T, Nishijima M, Takaku A
RESULTS OF URGENT THROMBOLYSIS IN PATIENTS WITH MAJOR STROKE AND ATEROTHROMBOTIC OCCLUSION OF THE CERVICAL INTERNAL CAROTID ARTERY.

Department of Neurosurgery, Toyama Medical and Pharmaceutical University, Sugitani, Japan.

PURPOSE: Atherothrombotic occlusion of the cervical internal carotid artery (ICA) without collateral flow is one of the most critical forms of acute ischemia. We report the results of urgent thrombolytic treatment of patients with major stroke in this clinical category. METHODS: Clinical findings and outcome in 33 patients were investigated. All patients had suffered a major stroke, with a score of 24 or higher on the NIH Stroke Scale on admission. Ischemic abnormalities were not detected on initial CT studies. Diagnoses were made at angiography, and patients were treated by intravenous or intraarterial local thrombolysis within 6 hours of stroke onset. RESULTS: Recanalization was accomplished in eight patients with intraarterial local thrombolysis; four of these patients had a good clinical outcome. Two factors characteristic of those whose treatment was successful were (1) dramatic improvement of symptoms after partial recanalization achieved within 3 hours of onset and (2) stabilized improvement after subsequent percutaneous transluminal angioplasty or carotid endarterectomy for residual atherosclerotic stenosis at the ICA origin. CONCLUSION: The results of this study suggest that urgent intraarterial local thrombolysis may be a successful treatment method for some patients in this critical clinical category if the treatment can be accomplished within 3 hours of ictus and followed by either angioplasty or endarterectomy for residual stenosis.

(2) Hicks P
THROMBOLYSIS IN ACUTE ISCHEMIC STROKE.

10. Thrombolysis in Pulmonary Embolism
(1) Hamel E, Pacouret G, Casset-Senon D, Dessenne X, Bertrand P, Pottier JM, Charbonnier B
[COMPARATIVE EFFICACY AND RISKS OF LOW MOLECULAR WEIGHT HEPARINS AND THROMBOLYSIS IN MASSIVE PULMONARY EMBOLISM WITHOUT CARDIOGENIC SHOCK] [ARTICLE IN FRENCH].

Service de cardiologie D, CHU Trousseau, Tours.
The aim of this retrospective study was to assess pulmonary reperfusion by scintigraphy, the risks of recurrent embolism and of bleeding complications at the 7th day and 3rd month in 2 groups of patients admitted to hospital for massive pulmonary embolism without cardiogenic shock treated by intravenous thrombolysis (Group I) and by subcutaneous low molecular weight heparin (Group II) paired by Miller's index. The basal characteristics of the two groups, each comprising 31 patients, were comparable with respect to the severity of the pulmonary embolism with an average global scintigraphic defect of 40.6 +/- 13.5% in Group I and 39 +/- 13.7% in Group II. The scintigraphic changes at the 7th day were comparable with a relative improvement of 55 and 51% respectively and at 3 months of 74% in both groups. There was no significant difference in terms of recurrence of embolism (3 versus 0% at the 7th day and 3% in each group at 3 months) or of bleeding complications (13 and 10% at the 7th day and 10 and 6% at 3 months respectively). Low molecular weight heparin seems to be as effective as intravenous thrombolysis for the treatment of massive pulmonary embolism without shock. This result requires confirmation by a large scale prospective randomised trial.

(2) Mikkola KM, Patel SR, Parker JA, Grodstein F, Goldhaber SZ
INCREASING AGE IS A MAJOR RISK FACTOR FOR HEMORRHAGIC COMPLICATIONS AFTER PULMONARY EMBOLISM THROMBOLYSIS.
Am Heart J 1997 Jul;134(1):69-72

School of Medicine, Lund University, Sweden.
We reviewed our database of 312 patients with pulmonary embolism who received thrombolysis in five clinical trials. At baseline, none had a history of stroke, internal bleeding within 6 months, surgery within 10 days, or occult blood in stool. Sixty-six major bleeding episodes occurred within 72 hours of administering thrombolysis in 61 (20%) patients: bleeding at the catheterization site (34 cases), gross hematuria (9), intracranial hemorrhage (5), and 18 other bleeding episodes that led to at least a 10% hematocrit decrease. Patients with a major bleeding complication were on average older than patients with no hemorrhagic complication (mean age 62.9 +/- 1.9 years vs 56.2 +/- 1.1 years; p = 0.005). In an adjusted analysis, there was a fourfold increased risk of bleeding among patients older than 70 years compared with patients younger than 50 years (relative risk [RR] 3.9; 95% confidence interval [CI] 1.7 to 8.9). By using age as a continuous variable, we found a 4% (RR 1.04; 95% CI 1.02 to 1.06) increase in risk of bleeding for each incremental year of age. In addition, patients with higher body mass index had an increased risk of bleeding. Patients who had undergone catheterization had a five times greater risk of bleeding (RR 5.2; 95% CI 1.5 to 17.8). In summary, increasing age, larger body mass index, and catheterization predisposed to bleeding complications after pulmonary embolism thrombolysis.

11. Thrombolysis for MI

(1) No Authors Listed
MULTICENTER, RANDOMIZED, COMPARATIVE STUDY OF RECOMBINANT VS. NATURAL STREPTOKINASES IN ACUTE MYOCARDIAL INFARCT (TERIMA). THE TERIMA GROUP INVESTIGATORS. THROMBOLYSIS WITH RECOMBINANT STREPTOKINASE IN ACUTE MYOCARDIAL INFARCT.
Thromb Haemost 1999 Dec;82(6):1605-9

Center for Biological Research, Clinical Trial Division, Havana, Cuba.
AIM: To compare the effects on hemostasis and coronary patency of recombinant (rSK) and natural (nSK) streptokinases in patients with acute myocardial infarct (AMI). METHODS: Patients from 7 hospitals, <70 years old, less than 12 h after the onset of AMI symptoms, with ST segment elevation or bundle branch block, without contraindications for thrombolytic therapy, were randomized to
receive 1.5 million units of nSK or rSK in a one-hour intravenous infusion. Fibrinogen, fibrinogen degradation products (FDP) and thrombin time were monitored. A coronary angiography was performed after 5-10 days in those patients who gave their consent and did not refer allergy to iodine contrasts. Images were blindly evaluated by an independent committee. RESULTS: 224 patients were randomized (113 nSK and 111 rSK). Groups were equivalent in all baseline and demographic variables except that rSK patients were 5.4 years significantly older. They were also comparable in all the clinical characteristics. Both treatments produced the same changes in hemostasis. Fibrinogen levels decreased, FDP and thrombin time increased immediately after thrombolysis and returned to baseline 2 days afterwards, but fibrinogen values continued to increase up to day 10. Coronary patency (TIMI 2-3) rates at 7.8 +/- 2.7 and 8.0 +/- 2.7 days after fibrinolysis were 70.7% and 67.1% for nSK and rSK groups, respectively (non-significant difference). Hypotension and arrhythmias were the most frequent adverse events in both groups, which did not differ in this respect either. Five patients from each group died, one of them (nSK) due to gastroduodenal bleeding probably related to treatment. Conclusions: rSK behaved similarly to nSK regarding coronary patency at 8 days after thrombolysis and the changes induced on fibrinogen, FDP and thrombin time. These results suggest that the same benefit/risk profile reported for AMI patients treated with nSK can be expected for rSK.

(2) Goldhammer E, Kharash L, Abinader EG
CIRCADIAN FLUCTUATIONS IN THE EFFICACY OF THROMBOLYSIS WITH STREPTOKINASE.
Postgrad Med J 1999 Nov;75(889):667-71
Department of Cardiology, Bnei-Zion Medical Center, Haifa, Israel.
This study was designed to investigate possible diurnal fluctuations in the efficacy of thrombolysis with streptokinase and whether they follow the circadian periodicity which has already been well documented for the time of onset of acute myocardial infarction, transient myocardial ischaemia, sudden cardiac death, thrombotic stroke, and for the efficacy of thrombolysis with tissue-type plasminogen and urokinase. A total of 156 consecutive patients treated with streptokinase were studied retrospectively; success or failure of thrombolysis was determined according to accepted clinical and angiographic criteria. A definite time peak for successful thrombolysis could be detected at the late afternoon and early evening hours; between 16.00 and 20.00 h, 30.2% of all successful thrombolysis cases were observed compared with 7.0% between 20.00 and 24.00 (p < 0.05) or 10.5% between 00.00 and 04.00 (p < 0.05). Between 16.00 and 20.00 h, 75.8% of treated patients had successful thrombolysis compared to 15.2% of failed treatments and 9% equivocal results (p < 0.001). Multiple regression analysis showed that the independent factor with the major impact on successful reperfusion was the actual time of thrombolysis (p = 0.037), followed by the time delay from pain onset to streptokinase administration (p = 0.020), while age and gender had much lesser impact (p = 0.328 and 0.215, respectively) and the individual risk factors even less. These findings may have several clinical implications; dose adjustment for the time of day may be required, with higher doses during morning hours, or preference for primary coronary angioplasty in order to avoid the increase in bleeding complications related to higher doses of thrombolytic agents.

12. Thrombolysis for Acute Stroke

(1) Hallan S, Asberg A, Indredavik B, Wideroe TE
A DECISION ANALYSIS OF THROMBOLYTIC THERAPY COMPARED WITH STANDARD THERAPY IN ACUTE ISCHAEMIC STROKE.
J Intern Med 1999 Dec;246(6):549-559
OBJECTIVES: Experts draw different conclusions on whether thrombolysis can be recommended or not for acute ischaemic stroke. A major problem is weighing the improvement in functional ability against the risk of increased mortality. We wanted to examine this uncertainty regarding thrombolysis using a systematic approach and with a strong emphasis on the patient’s point of view.
METHODS: We performed a decision analysis where the base case focused on an average stroke patient. We used published probabilities for different functional outcomes after standard supportive care and after adding tissue plasminogen activator (tPA), and we tried to estimate corresponding long-term survival. We interviewed 158 subjects with the standard gamble method to elicit their preference values (utility) for these outcomes. RESULTS: When using the baseline data for an
average stroke patient, thrombolysis with tPA was the better choice, with 48 extra quality-adjusted living days; tPA was also superior in 117 individual decision analyses, giving from 10 to 173 extra days. However, sensitivity analysis showed that these results were highly susceptible to changes in utility for major disability, probability of early death, and long-term survival after thrombolysis. To increase the gain as well as the margin of safety regarding the treatment choice, thrombolysis should be restricted to patients who assign low utility values < 0.6-0.7 to major poststroke disability (death = 0.0, good health = 1.0). CONCLUSION: Evaluated by decision analysis, thrombolysis with tPA is on average superior to standard therapy for the few patients fulfilling the strict medical inclusion criteria. Individual incorporation of the patient's point of view narrows the indication even further.

B. Thrombolysis Complications induced Hemorrhage

1. Complications Intracranial Bleeding

(1) Sloan MA, Sila CA, Mahaffey KW, Granger CB, Longstreth WT Jr, Koudstaal P, White HD, Gore JM, Simoons ML, Weaver WD, Green CL, Topol EJ, Califf RM

PREDICTION OF 30-DAY MORTALITY AMONG PATIENTS WITH THROMBOLYSIS-RELATED INTRACRANIAL HEMORRHAGE.


University of Maryland Medical System, Baltimore (M.A.S.); the Cleveland Clinic Foundation, Cleveland, Ohio (C.A.S., E.J.T.); Duke Clinical Research Institute, Durham, North Carolina (K.W.M., C.B.G., C.L.G., R.M.C.); University of Washington, Sea.

Background-Limited information exists on risk factors for mortality after thrombolysis-related intracranial hemorrhage. We wished to determine the characteristics associated with 30-day mortality after thrombolysis-related intracranial hemorrhage. Methods and Results-We performed an observational analysis within a randomized trial of 4 thrombolytic therapies, conducted in 1081 hospitals in 15 countries. Patients presented with ST-segment elevation within 6 hours of symptom onset. Our population was composed of the 268 patients who had primary intracranial hemorrhage after thrombolysis. With univariable and multivariable analyses, we identified clinical and brain imaging characteristics that would predict 30-day mortality among these patients. CT or MRI were available for 240 patients (90%). The 30-day mortality rate was 59.7%. Glasgow Coma Scale score, age, time from thrombolysis to symptoms of intracranial hemorrhage, hydrocephalus, herniation, mass effect, intraventricular extension, and volume and location of intracranial hemorrhage were significant univariable predictors. Multivariable analysis of 170 patients with complete data, 98 of whom died, identified the following independent, significant predictors: Glasgow Coma Scale score (chi2, 19.3; P<0.001), time from thrombolysis to intracranial hemorrhage (chi2, 15.8; P<0.001), volume of intracranial hemorrhage (chi2, 11.6; P<0.001), and baseline clinical predictors of mortality in the overall GUSTO-I trial (chi2, 10.3; P<0.001). The final model had a C-index of 0.931. Conclusions-This model provides excellent discrimination between patients who are likely to live and those who are likely to die after thrombolytic-related intracranial hemorrhage; this may aid in making decisions about the appropriate level of care for such patients.

I. Thrombolytic Agents

A. Streptokinase (STK)

A. Function and Fields of Use

1. STK in Deep Vein Thrombosis
(1) Ng CM, Rivera JO

**META-ANALYSIS OF STREPTOKINASE AND HEPARIN IN DEEP VEIN THROMBOSIS.**


School of Pharmacy, University of North Carolina at Chapel Hill, USA.

The efficacy and safety of streptokinase and heparin in deep vein thrombosis (DVT) were compared in a meta-analysis. Randomized trials in which streptokinase (followed by heparin) and heparin alone were compared in treating phlebographically documented acute DVT were identified from MEDLINE and other sources for a meta-analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) based on the logit method were computed for each study. A fixed-effect model was used to combine the study results, enabling differences between streptokinase recipients and recipients of heparin alone to be expressed as summary ORs with 95% CIs. Significantly more streptokinase recipients achieved thrombolysis than recipients of heparin alone (summary OR, 6.24; 95% CI, 3.62 to 10.78). One study was identified as an outlier and excluded from the analysis. The meta-analysis then showed that streptokinase recipients were significantly less likely to have postthrombotic changes (summary OR, 0.40; 95% CI, 0.18 to 0.88) and postphlebitic changes (summary OR, 0.32; 95% CI, 0.12 to 0.86) in phlebographic evaluation. The frequency of major bleeding was significantly higher among streptokinase recipients than recipients of heparin alone (summary OR, 3.78; 95% CI, 1.26 to 11.32). A meta-analysis showed that, compared with heparin alone, streptokinase therapy for DVT was associated with significantly more frequent thrombolysis and major bleeding; after exclusion of one outlying study, analysis showed that streptokinase therapy was associated less frequently than heparin alone with postthrombotic changes (assessed by phlebographic evaluation) and postphlebitic syndrome.

(2) Heinrich F, Heinrich U

**NORTH BADEN VENOUS LYSIS TRIAL (NBVL): MULTICENTRE PROSPECTIVE RANDOMIZED PHLEBOGRAPHICALLY CONTROLLED TRIAL ON THE EFFECT OF ULTRA-HIGH VERSUS CONVENTIONAL DOSES OF STREPTOKINASE IN FRESH LEG-PELVIS VENOUS THROMBOSES. PARTICIPATING WORKING GROUPS.**

*Vasc Med* 1998;3(2):87-94

Med. Clinic I. City Clinic, Karlsruhe, Germany.

Since no previous randomized comparison has been carried out between ultra-high and conventional dosage streptokinase therapy of fresh venous thromboses, the NBVL trial was carried out as a prospective, randomized, multicentre, phlebographically monitored comparison of the results and adverse effects of these two fibrinolytic treatment options. Using the normal exclusion criteria, 156 patients with a leg-pelvis venous thrombosis presumed to be a maximum of 14 days old were treated with 1.5 million U streptokinase/h for 6h daily (n = 77, group A) or conventional dosage with 100,000 U streptokinase per hour (n = 79, group B). There were 15 patients (eight in group A, seven in group B) who had to stop therapy prematurely, and eight patients (five in group A, three in group B) could not be evaluated because of incorrect monitoring times. The phlebograms were evaluated using IFP-C scores. These showed a reduction in the IFP score from 4.55 to 2.2 in the 64 patients in group A after a mean of 2.7 +/- 0.6 therapy cycles with administration of 24.4 +/- 5.7 million U streptokinase, i.e. 47% of the baseline value. The 69 patients in group B had a reduction in score from 4.2 to 2.93 after a mean of 3.7 +/- 1.2 days of treatment with administration of 8.6 +/- 3.3 million units, i.e. a fall of 30% in the baseline values (p = 0.007). There were 132 out of 281 completely occluded venous segments in group A (47%) and 81 out of 279 segments in group B (29%) that showed complete patency. Eight out of 27 three-segment occlusions in group A and only one of 26 in group B showed complete patency. The IFP score improved by 55% in the 45 men in group A, compared with only 30% in the 47 men in group B (p = 0.002). When both dosages are combined, men showed a greater improvement in IFP score than women (42 versus 29%; p = 0.02). The IFP score improved more in the 20 patients aged more than 60 years in group A than in the 19 patients aged over 60 years of age in group B (61 versus 20%; p = 0.003). No other significant differences in effect were seen on analysis of sub-groups and individual factors (sex, age, presumed age of thrombus and side of thrombosis). In the 77 patients in group A, haemorrhagic complications were less frequent than in the 79 patients in group B (22.1 versus 36.7%; p = 0.054), especially concerning urogenital haemorrhage (6.5 versus 22.8%; p = 0.004). Women were affected more frequently by haemorrhagic complications than men (35.2 versus 26.5%), and the 19 patients aged more than 65 years old were affected more than the 137 younger patients (21.1 versus 13.9%).
There were no deaths, and clinically insignificant pulmonary emboli occurred three times. Ultra-high dosage streptokinase shows better and more rapid thrombolytic treatment for popliteal-femoral-iliac venous thromboses and causes fewer haemorrhagic complications than conventional dosage streptokinase. The better effect of ultra-high dosage can be observed particularly for three-segment occlusion as well as in male patients. In older patients, accurate diagnosis is required because of the higher rate of haemorrhagic complications.

2. STK in Myocardial Infarction

a) Streptokinase Therapy Monitoring and Plasminogen Activator Inhibitor 1 (PAI-1)

(1) Sinkovic A

PRETREATMENT PLASMINOGEN ACTIVATOR INHIBITOR-1 (PAI-1) LEVELS AND THE OUTCOME OF THROMBOLYSIS WITH STREPTOKINASE IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION.

Am Heart J 1998 Sep;136(3):406-11

Department for Internal Intensive Medicine, Teaching Hospital Maribor, Slovenia.

BACKGROUND: The risk for reinfarctions and delays in reperfusion after streptokinase therapy may be caused by the antifibrinolytic effect of platelet-derived type 1 plasminogen activator inhibitor (PAI-1). This study aims to show the relation of pretreatment PAI-1 levels of patients with acute myocardial infarction treated with streptokinase therapy and the outcome of fibrinolysis, with the emphasis on reperfusion and reinfarction. METHODS: Pretreatment PAI-1 levels of 60 patients with acute myocardial infarction, treated with streptokinase, were determined by the chromogenic method. Failure of thrombolysis with streptokinase was present when reperfusion was delayed as assessed by noninvasive reperfusion criteria, or reinfarctions developed. RESULTS: Mean pretreatment PAI-1 level of patients was 6.3 +/- 1.2 U/ml; span 1.2 U/ml to 34.0 U/ml. Thrombolysis with streptokinase failed significantly in patients with pretreatment PAI-1 levels >4.0 U/ml (p < 0.05), mainly because of significant occurrence of reinfarction (p < 0.05), but less to delayed reperfusion (p > 0.05). CONCLUSION: Failure of thrombolysis with streptokinase is significantly associated with pretreatment PAI-1 levels of >4.0 U/ml.

b) Streptokinase for MI Thrombolysis

1) Streptokinase in MI


ATENOLOL USE AND CLINICAL OUTCOMES AFTER THROMBOLYSIS FOR ACUTE MYOCARDIAL INFARCTION: THE GUSTO-I EXPERIENCE. GLOBAL UTILIZATION OF STREPTOKINASE AND TPA (ALTEPLASE) FOR OCCLUDED CORONARY ARTERIES.

J Am Coll Cardiol 1998 Sep;32(3):634-40

Division of Cardiology, University Hospital Basel, Switzerland.

OBJECTIVES: We assessed the use and effects of acute intravenous and later oral atenolol treatment in a prospectively planned post hoc analysis of the GUSTO-I dataset. BACKGROUND: Early intravenous beta blockade is generally recommended after myocardial infarction, especially for patients with tachycardia and/or hypertension and those without heart failure. METHODS: Besides one of four thrombolytic strategies, patients without hypotension, bradycardia or signs of heart failure were to receive atenolol 5 mg intravenously as soon as possible, another 5 mg intravenously 10 min later and 50 to 100 mg orally daily during hospitalization. We compared the 30-day mortality of patients given no atenolol (n=10,073), any atenolol (n=30,771), any intravenous atenolol (n=18,200), only oral atenolol (n=12,545) and both intravenous and oral drug (n=16,406), after controlling for baseline differences and for early deaths (before oral atenolol could be given). RESULTS: Patients given any atenolol had a lower baseline risk than those not given atenolol. Adjusted 30-day mortality was significantly lower in atenolol-treated patients, but patients treated with intravenous and oral atenolol treatment vs. oral
treatment alone were more likely to die (odds ratio, 1.3; 95% confidence interval, 1.0 to 1.5; p=0.02). Subgroups had similar rates of stroke, intracranial hemorrhage and reinfarction, but intravenous atenolol use was associated with more heart failure, shock, recurrent ischemia and pacemaker use than oral atenolol use. CONCLUSIONS: Although atenolol appears to improve outcomes after thrombolysis for myocardial infarction, early intravenous atenolol seems of limited value. The best approach for most patients may be to begin oral atenolol once stable.

(3) Sgarbossa EB, Pinski SL, Gates KB, Wagner GS
PREDICTORS OF IN-HOSPITAL BUNDLE BRANCH BLOCK REVERSION AFTER PRESENTING WITH ACUTE MYOCARDIAL INFARCTION AND BUNDLE BRANCH BLOCK. GUSTO-I INVESTIGATORS. GLOBAL UTILIZATION OF STREPTOKINASE AND T-PA FOR OCCLUDED CORONARY ARTERIES.
Am J Cardiol 1998 Aug 1;82(3):373-4
Rush-Presbyterian Medical Center, Chicago, Illinois, USA.
Patients with acute myocardial infarction and bundle branch block have a higher mortality rate and more in-hospital complications than patients with normal intraventricular conduction. Patients whose conduction defects revert have an improved prognosis (with outcomes similar to patients who never develop bundle branch block); thus, we analyzed potential predictors of bundle branch block reversion.

(4) Andreassen AK, Gullestad L, Endresen K
[THROMBOLYTIC TREATMENT IN ACUTE MYOCARDIAL INFARCTION. CHOICE OF PREPARATIONS IN NORWEGIAN HOSPITALS]. [ARTICLE IN NORWEGIAN]
Tidsskr Nor Laegeforen 1998 Jun 30;118(17):2630-1
Medisinsk avdeling B, Rikshospitalet, Oslo.
In 1994 Statens legemiddelkontroll recommended Norwegian hospitals to increase the use of recombinant tissue plasminogen activator (r-tPA) in thrombolytic treatment of acute myocardial infarction. Using a questionnaire, which was distributed to all medical departments in Norwegian hospitals, we examined and assessed the preference of thrombolytic agents. None of the coronary care units administered r-tPA routinely as their first choice. Of 59 hospitals involved, 35 (59%) considered r-tPA on a wider indication (i.e. young age, short history of symptoms, and anterior wall infarction) than the 24 (41%) that only used r-tPA when streptokinase had recently been given. Of a total of 11,191 cases of myocardial infarction in 1996, 628 (6%) were treated with r-tPA. Closer examination of 2,818 cases of myocardial infarction in 13 hospitals revealed that thrombolytic treatment was given in 1,016 (36%) instances. In 206 cases (20%), the chosen agent was r-tPA, whereas 810 (80%) were given streptokinase. The reasons for the preference of streptokinase to r-tPA are discussed.

(5) Boersma E, Steyerberg EW, Van der Vlugt MJ, Simoons ML
REPERFUSION THERAPY FOR ACUTE MYOCARDIAL INFARCTION. WHICH STRATEGY FOR WHICH PATIENT?
Drugs 1998 Jul;56(1):31-48
University Hospital Rotterdam-Dijkzigt, The Netherlands.
Several modes of reperfusion therapy for evolving myocardial infarction (MI) have been developed, which differ in terms of effectiveness, complexity and costs. Reperfusion resources are often restricted by budgetary or logistical circumstances. To arrive at an equitable distribution of treatment options, physicians should therefore consider which treatment to apply in which patient. Two major questions which arise in this respect are discussed here: what is the treatment effect in an individual patient, and what is an equitable resource allocation? Currently, the most relevant treatment options are: streptokinase (1.5MU over 1h), reteplase (2 boluses of 10MU), alteplase (tissue plasminogen activator; t-PA) [100mg over 1.5 hours] and immediate angioplasty. In combination with aspirin, streptokinase leads to an almost 40% mortality reduction at 1 month compared with placebo [from 13.2 to 8.0%; Second International Study of Infarct Survival (ISIS-2) trial], The Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO-I) study demonstrated a further mortality reduction by early combination therapy of aspirin, intravenous heparin and alteplase vs aspirin, heparin (either intravenous or subcutaneous) plus streptokinase (from 7.3 to 6.3%). The
Clinical effects of reteplase fall somewhere between those of streptokinase and alteplase. Combined analysis of the angioplasty trials suggests that angioplasty is superior to thrombolysis, especially in patients with a high cerebral bleeding risk. The noticed gradient of efficacy runs parallel to a gradient of costs and complexity: streptokinase is the least costly treatment option while direct angioplasty is the most expensive and complex. Subgroup analyses indicate that there are neither apparent deviations in the relative effect of reperfusion therapy as compared to control treatment, nor in the additional effect of more intensive therapy (alteplase) upon ‘standard’ therapy (streptokinase). Consequently, the absolute number of deaths avoided by reperfusion therapy appears to be greatest in those groups with a high mortality risk without therapy. There is one major exception: in patients treated early after symptom onset a much greater relative mortality reduction is observed than in those treated later. Owing to the higher mortality risk, the life expectancy of a patient with MI is shorter than that of an ‘average’ person of the same community and the same age. Since mortality reduction of reperfusion therapy is maintained at long term follow-up, part of this potential loss can be regained. This ‘re-gain of lost years’ is judged to be the ultimate treatment effect in an individual patient. An equitable treatment allocation should be such that patients who will benefit most will receive the most effective therapy, while patients with similar expected benefit will be offered the same mode of therapy. The conclusion is that treatment guidelines or protocols can be very useful in clinical practice, especially if rapid decision making is of vital importance.

(6) Ross AM, Lundergan CF, Rohrbeck SC, Boyle DH, van den Brand M, Buller CH, Holmes DR Jr, Reiner JS
RESCUE ANGIOPLASTY AFTER FAILED THROMBOLYSIS: TECHNICAL AND CLINICAL OUTCOMES IN A LARGE THROMBOLYSIS TRIAL. GUSTO-1 ANGIOGRAPHIC INVESTIGATORS. GLOBAL UTILIZATION OF STREPTOKINASE AND TISSUE PLASMINOGEN ACTIVATOR FOR OCCLUDED CORONARY ARTERIES.
_J Am Coll Cardiol_ 1998 Jun;31(7):1511-7

George Washington University, Washington, DC, USA.

OBJECTIVES: We sought to assess the angiographic outcome, complication rates and clinical features of percutaneous transluminal coronary angioplasty (PTCA) after failed thrombolysis for acute myocardial infarction. BACKGROUND: "Rescue angioplasty" refers to mechanical reopening of an occluded infarct-related artery (IRA) after failed intravenous thrombolysis. Although the procedure is commonly performed, data describing its technical and clinical outcome are sparse. Early reports suggested that rescue PTCA is less often successful and produces more complications than primary PTCA. Other reports have described beneficial effects of successful rescue PTCA but adverse outcomes when PTCA is unsuccessful. METHODS: Using data from the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Ocluded Coronary Arteries (GUSTO-I) angiographic substudy, we compared clinical and angiographic outcomes of 198 patients selected for a rescue PTCA attempt with those of 266 patients with failed thrombolysis but managed conservatively and, for reference, with those of 1,058 patients with successful thrombolysis. RESULTS: Patients offered rescue PTCA had more impaired left ventricular function than those in whom closed vessels were managed conservatively. Rescue successfully opened 88.4% of closed arteries, with 68% attaining Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow. The interventions did not increase catheterization laboratory or postprocedural complication rates. Multivariate analysis identified severe heart failure to be a determinant of a failed rescue attempt. Successful rescue PTCA resulted in superior left ventricular function and 30-day mortality outcomes, comparable to outcomes in patients with closed IRAs managed conservatively, but less favorable than in patients in whom thrombolytic therapy was initially successful. The mortality rate after a failed rescue attempt was 30.4%; however, five of the seven patients who died after failed rescue PTCA were in cardiogenic shock before the procedure. CONCLUSIONS: Rescue PTCA tends to be selected for patients with clinical predictors of a poor outcome. It is effective in restoring patency. Patients who die after a failed rescue attempt are often already in extremis before the angioplasty attempt.

(7) Steg PG, Laperche T, Golmard JL, Juliard JM, Benamer H, Himbert D, Aubry P
EFFICACY OF STREPTOKINASE, BUT NOT TISSUE-TYPE PLASMINOGEN ACTIVATOR, IN ACHIEVING 90-MINUTE PATENCY AFTER THROMBOLYSIS FOR ACUTE MYOCARDIAL INFARCTION DECREASES WITH TIME TO TREATMENT.
PERM STUDY GROUP. PROSPECTIVE EVALUATION OF REPERFUSION MARKERS.


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**OBJECTIVES:** We sought to examine the relation between time to treatment and 90-min patency rates in patients receiving intravenous streptokinase (SK) or accelerated tissue-type plasminogen activator (t-PA).

**BACKGROUND:** Early patency of the infarct-related artery is a major determinant of survival after thrombolysis for acute myocardial infarction. Some data suggest that time to treatment may influence the efficacy of nonfibrin-specific thrombolytic agents in restoring early patency of the infarct-related vessel.

**METHODS:** We performed a retrospective analysis of a cohort of 481 patients receiving thrombolytic therapy for acute myocardial infarction <6 h after pain onset, all of whom underwent 90-min coronary angiography. Patency of the infarct-related artery was graded by two observers who had no knowledge of the treatment received or the time between pain and therapy.

**RESULTS:** There was no difference in baseline clinical or angiographic characteristics according to the timing or nature of treatment. Thrombolysis in Myocardial Infarction (TIMI) flow grade 2 or 3 patency rate after SK correlated negatively with the time between onset of pain and thrombolysis (r = 0.8, p = 0.05), whereas the 90-min patency rate after t-PA appeared stable as a function of time to treatment. When patients were categorized as having received treatment <3 or ≥ 3 h after pain onset, the patency rate was similar with t-PA, but significantly higher when SK was administered early rather than late, regardless of whether TIMI flow grades 2 and 3 were pooled (86.9% vs. 59.4%, p = 0.0001) or TIMI flow grade 3 alone was considered to indicate patency (81.7% vs. 53.6%, p = 0.0001).

**CONCLUSIONS:** The efficacy of streptokinase but not t-PA in restoring early coronary patency after intravenous thrombolysis is markedly lower when patients are treated later after onset of pain.


2) Streptokinase and Hirudin HIT-4 in AMI


**EFFECTS OF THROMBOLYTIC THERAPY IN ACUTE INFERIOR MYOCARDIAL INFARCTION WITH OR WITHOUT RIGHT VENTRICULAR INVOLVEMENT. HIT-4 TRIAL GROUP. HIRUDIN FOR IMPROVEMENT OF THROMBOLYSIS.**


Stadtische Kliniken, Kassel, Germany.

**OBJECTIVES:** This study assessed the prognostic impact of right ventricular involvement (RVI) in streptokinase-treated patients with inferior acute myocardial infarction (AMI) stratified for small or large AMI. BACKGROUND: Only scant data exist from small studies about the impact of reperfusion therapy on survival in patients with RVI during inferior AMI. METHODS: Right ventricular involvement was assessed by ST-segment elevation ≥ 0.1 mV in lead V4R and infarct size by the extent of ST-segment deviation on the baseline electrocardiogram: small AMI = sum ST-segment elevation < or =0.8 mV and no precordial ST-segment depression (small ST); large AMI = presence of precordial ST-segment depression or sum ST-segment elevation >0.8 mV (large ST) in 522 inferior AMI patients of the Hirudin for Improvement of Thrombolysis (HIT-4) Trial. In 187 patients, 90-min coronary angiography was performed. RESULTS: Right ventricular involvement was present in 169 patients (32%). Higher 30-day cardiac mortality rates with RVI (5.9% vs. 2.5%) were related to larger infarct size rather than to RVI. For large ST, a proximal right coronary artery lesion was observed in 52% with and in 23% without RVI. Patency rates at 90 min were similar (54% vs. 52%). In the 28% of patients who had small ST, cardiac mortality was less than 1% irrespective of the presence of RVI. Coronary artery lesions were mostly located distally. Patency rates were 27% with and 80% without RVI. CONCLUSIONS: ST-segment elevation of ≥ 0.1 mV in V4R in inferior AMI patients is associated with larger infarct size and higher 30-day mortality rates. Right ventricular involvement is not an independent predictor of survival. In patients with small ST, cardiac mortality is low, even if ST V4R is ≥ or =0.1 mV.
3) Post Thrombolytic therapy Monitoring

(9) Zabel KM, Granger CB, Becker RC, Bovill EG, Hirsh J, Aylward PE, Topol EJ, Califf RM
USE OF BEDSIDE ACTIVATED PARTIAL THROMBOPLASTIN TIME MONITOR TO ADJUST HEPARIN DOSING AFTER THROMBOLYSIS FOR ACUTE MYOCARDIAL INFARCTION: RESULTS OF GUSTO-I, GLOBAL UTILIZATION OF STREPTOKINASE AND TPA FOR OCCLUDED CORONARY ARTERIES.
Am Heart J 1998 Nov;136(5):868-76

Mid-America Heart Institute, Kansas City, MO, USA.

BACKGROUND: The safety and efficacy of bedside monitors of activated partial thromboplastin time (aPTT) have not been examined in a large population receiving intravenous heparin after thrombolytic treatment for acute myocardial infarction. We compared outcomes among patients monitored with these devices versus standard monitoring methods.

METHODS AND RESULTS: Investigators chose the bedside device (n = 1713 patients) or their standard method (n = 26,162) for all aPTT measurements at their sites. Clinical outcomes at 30 days, 1-year mortality rate, and aPTT levels at 6, 12, and 24 hours were compared. Bedside-monitored patients had significantly less moderate/severe bleeding (10% vs 12%, P < .01), fewer transfusions (7% vs 11%, P < .001), and a smaller decrease in hematocrit (5.5% vs 6.7%, P < .001) but significantly more recurrent ischemia (22% vs 20%, P = .01). Fewer bedside-monitored patients had subtherapeutic aPTT levels at 12 and 24 hours. Among patients with subtherapeutic levels at 6 and 12 hours, more bedside-monitored patients had therapeutic levels when next monitored. After adjustment for baseline differences, no significant difference in mortality rate was observed in bedside-monitored patients at 30 days (4.3% vs 4.8%, P = .27) and at 1 year (7.1% vs 7.7%, P = .38). The groups had similar rates of reinfarction, shock, heart failure, and stroke. CONCLUSIONS: This prospective substudy supports the use of bedside monitoring of heparin anticoagulation after thrombolysis.

3. STK in Neonatal Intraventricular Hemorrhage

(1) Luciano R, Tortorolo L, Chiaretti A, Piazza M, Velardi F, Polidori G
INTRAVENTRICULAR STREPTOKINASE INFUSION IN ACUTE POST-HAEMORRHAGIC HYDROCEPHALUS.

Institute of Pediatrics, Catholic University of Rome, Italy.

Neonatal post-haemorrhagic hydrocephalus is a clinical condition with a high mortality and long-term morbidity. Its clinical management is difficult and not well standardized. We describe the case of a term baby suffering from acute intracranial hypertension caused by an intraventricular and thalamic haemorrhage. In this case, the external ventricular drain inserted to control intracranial pressure was ineffective because of repeated obstructions due to blood clots. Continuous intraventricular infusion of streptokinase of 20,000 U/day allowed quick lysis of the clots, drainage of the cerebrospinal fluid and relief from the coma. Although it did not prevent a permanent ventriculoperitoneal shunt, we obtained reabsorption of the intraventricular haemorrhage without rebleeding complications. We suggest the use of low-dose fibrinolytic infusion through an external drain for the treatment of acute intracranial hypertension following intraventricular haemorrhage in term infants.

4. STK for Stroke

(1) Wittkowski AK
THE STROKE PHARMACOPEIA: CURRENT MEDICAL THERAPIES.
Pharmacotherapy 1998 May-Jun;18(3 Pt 2):94S-100S; discussion 85S-86S

University of Washington School of Pharmacy, Seattle 98195-6015, USA.

Drug therapies that inhibit or reverse thrombus formation are important components of the management of acute ischemic stroke. The role of antiplatelet and anticoagulant therapies in stroke prevention has been defined, but further research is needed to confirm the possible benefits of aspirin, heparin, and low-molecular-weight heparin products in acute ischemic stroke. Recently,
Double-blind, placebo-controlled studies have evaluated the role of the thrombolytic agents streptokinase and tissue plasminogen activator (t-PA) in patients with acute ischemic stroke. Intravenous t-PA, administered within 3 hours of symptom onset at a dose of 0.9 mg/kg, is safe and effective in carefully selected patients.

(2) Fisher M, Bogousslavsky J

FURTHER EVOLUTION TOWARD EFFECTIVE THERAPY FOR ACUTE ISCHEMIC STROKE.

*JAMA* 1998 Apr 22-29;279(16):1298-303

Department of Neurology, Memorial Health Care, University of Massachusetts Medical School, Worcester 01605, USA. fisherm@memorialhc.org

The effective treatment of acute ischemic stroke remains an important goal of modern medicine and substantive advances are occurring. Recently, thrombolytic therapy with tissue-type plasminogen activator was approved for selected patients with acute ischemic stroke when therapy is started within 3 hours of onset. Streptokinase therapy for acute ischemic stroke has not been shown to be effective and is associated with an increased risk of hemorrhage, although it was not evaluated as early after stroke onset as tissue-type plasminogen activator. Various types of neuroprotective interventions are effective in animal models, but none has yet been proven effective in patients. In the future, combinations of thrombolytic and neuroprotective drugs may be used to attempt maximum rates of recovery after acute ischemic stroke. For combination therapy to achieve its maximum potential, patients with acute ischemic stroke will have to be carefully selected and treated.

5. STK for Prosthetic Valve Thrombosis

(1) Bhargava B, Chopra AK, Agarwal R, Narang R, Chopra V, Manchanda SC

HIGH-DOSE STREPTOKINASE THERAPY FOR PROSTHETIC VALVE THROMBOSIS WITHIN 2 WEEKS OF OPEN HEART SURGERY.

*Int J Cardiol* 1998 Sep 30;66(2):143-5

Department of Cardiology, Cardiothoracic Sciences Centre, All India Institute of Medical Sciences, New Delhi.

(2) Kayali MT, Fetieh MW, Abdul salam MA, Memon F, Moinuddin M, Raffa H

THROMBOTIC OBSTRUCTION OF BILEAFLET MECHANICAL PROSTHETIC HEART VALVES: EARLY DIAGNOSIS AND MANAGEMENT.


King Fahd Heart Center, Jeddah, Saudi Arabia.

BACKGROUND: Thrombosis of mechanical prosthetic heart valves (TMPHV) is one of the major complications that accounts for the highest morbidity and mortality related to Bileaflet Mechanical Prosthetic Heart Valves (BMPHV). MATERIALS AND METHODS: During the last six years we had ten cases of bileaflet mechanical valve thrombosis. All patients had undergone emergency surgical interventions except one who developed systemic embolization and massive brain insult immediately after admission and died two months later. We divided the patients in two groups,(1) first group includes five patients who came in acute pulmonary edema and emergency operation was done either to replace the thrombosed BMPHV (in two) or successful thrombectomy was achieved (in three) and all of them have survived. (2) The second group (four patients) presented with cardiogenic shock and required emergency femoro-femoral bypass. Two patients survived after thrombectomy and the other two could not come off bypass after changing the TMPHV and in spite of Intra-aortic balloon pump, they died 24 and 48 hours after the procedure. All patients received intravenous heparin on admission. Preoperative i.v. Streptokinase was given in two cases, of which one required thrombectomy and the other had valve replacement and died 24 hours later. RESULTS: Early diagnosis and operation still had the best results in TMPHV though thrombolytic therapy was successful in few reported early presented cases. All patients who had thrombectomy of the TMPHV have survived without any morbidity. Follow up of survived patients ranged between two months and six years with a mean of 24.1 months. It is worth attempting thrombectomy of the thrombosed BMPHV rather than re-
replacement which carries higher morbidity and mortality, because of the longer ischemic arrest during operation which further depletes the energy of the myocardium. CONCLUSIONS: Though this is a small number of patients to make a definite conclusion, thrombectomy was more feasible in CarboMedics Prosthetic Heart Valves, since its in situ rotation that allows reorientation of its leaflets and declotting of valve hinge to be performed.

6. STK in Pulmonary Embolism


**COMPARATIVE EFFICACY OF A TWO-HOUR REGIMEN OF STREPTOKINASE VERSUS ALTEPLASE IN ACUTE MASSIVE PULMONARY EMBOLISM: IMMEDIATE CLINICAL AND HEMODYNAMIC OUTCOME AND ONE-YEAR FOLLOW-UP.**

*J Am Coll Cardiol* 1998 Apr;31(5):1057-63

Departrment de Cardiologie, Hopital Universitaire Saint-Jacques, Besancon, France.

OBJECTIVES: This study sought to compare the efficacy of 2-h regimens of alteplase and streptokinase in acute massive pulmonary embolism. The primary end point was immediate hemodynamic improvement, and secondary end points included early clinical efficacy and safety, as well as 1-year clinical outcome. BACKGROUND: Several thrombolytic regimens have been compared for the past 10 years in randomized studies, showing that 2-h infusion regimens of alteplase or urokinase lead to faster hemodynamic improvement than former 12- to 24-h administration protocols in acute massive pulmonary embolism. Many trials have focused on immediate hemodynamic and angiographic outcomes, but none has addressed long-term follow-up after thrombolysis. METHODS: Sixty-six patients with acute massive pulmonary embolism (Miller score > 17 and mean pulmonary artery pressure >20 mm Hg) were randomly assigned to receive either a 100-mg 2-h infusion of alteplase (n = 23) or 1.5 million IU of streptokinase over 2 h (n = 43). In both groups, heparin infusion was started at the end of thrombolytic infusion and adapted thereafter. Total pulmonary resistance was monitored over a 12-h period. Pulmonary vascular obstruction was assessed 36 to 48 h after thrombolytic therapy. One-year follow-up information included death, cause of death, recurrent pulmonary embolism, chronic thromboembolic pulmonary hypertension, stroke and bleeding. RESULTS: Both groups had similar baseline angiographic and hemodynamic characteristics of severity, with maintained cardiac output in 64 (97%) of 66 patients. The results (mean +/- SD) demonstrated that despite a faster total pulmonary resistance improvement observed at 1 h in the alteplase group compared with the streptokinase group (33+/-16% vs. 19 16%, p = 0.006), a similar hemodynamic efficacy was obtained at 2 h when both thrombolytic regimens were completed (38+/-18% vs. 31+/-19%). There was no significant difference in either pulmonary vascular obstruction at 36 to 48 h or bleeding complication rates. One-year event-free survival was similar in both groups, as most events were related to concomitant diseases. CONCLUSIONS: These results suggest that a 2-h regimen of streptokinase can be routinely used in patients with massive pulmonary embolism and maintained cardiac output without obviously compromising efficacy or safety.

(2) Petrovskii BV, Malinovskii NN

**[PULMONARY ARTERY EMBOLISM] [ARTICLE IN RUSSIAN].**

*Khirurgiia (Mosk)* 1998;(6):7-11

The authors have an experience in diagnosis and treatment of pulmonary embolism in 194 patients. Much attention is paid to diagnosis of thrombosis of the deep veins, phlebography and duplex scanning as the most informative methods. Due to regular unspecific and specific prophylaxis of deep phlebothrombosis in operated patients, pulmonary artery embolism occurred only in 2 patients for 12 years. Valid diagnosis of pulmonary artery embolism is thought possible only in application by pulmonary scanning and angio pulmonaryography. Mostly conservative method of treatment was used, only in 2 patients successful embolectomy was performed. Anticoagulation (heparin) and fibrinolytic (streptase) therapy was carried out. The results of streptase administration were superior to those of heparin injections. Recovery rate after fibrinolytic therapy made up 86.4%.
7. STK intrapleural or Intraperitoneal

(1) Worland MA, Radabaugh RS, Mueller BA
INTRAPERITONEAL THROMBOLYTIC THERAPY FOR PERITONEAL DIALYSIS-ASSOCIATED PERITONITIS.

Pharmacy Department, Deaconess Hospital, Evansville, IN, USA.
OBJECTIVE: To review the literature pertaining to the use of adjunctive thrombolytic therapy for the treatment of peritoneal dialysis-associated peritonitis (PDAP). DATA SOURCES: A MEDLINE search was conducted (January 1966-December 1997) to find articles using the terms peritonitis, peritoneal dialysis, and each thrombolytic drug. References from these articles were then reviewed to identify further sources. DATA EXTRACTION: Representative case reports and clinical trials are summarized in this report. Information regarding thrombolytic dosing, administration techniques, and reported efficacy rates are included from both case reports and clinical trials. DISCUSSION: Thrombolytic agents administered intraperitoneally appear to facilitate antibiotic penetration into the biofilm formed by certain bacteria. Numerous case reports of intraperitoneal thrombolytic adjunctive therapy for recurrent or persistent PDAP have indicated that these agents may have a role in the treatment of selected patients. Urokinase and streptokinase are the only thrombolytics that have been studied. They appear to have similar efficacy, but the adverse drug event rate with streptokinase is unacceptably high. The efficacy of therapy with urokinase is probably inferior to removal of the peritoneal dialysis catheter, but, if successful, allows for the continuation of peritoneal dialysis therapy. CONCLUSIONS: In conjunction with appropriate antibiotic therapy, intraperitoneal instillation of urokinase should be reserved for patients who develop two or more episodes of recurrent or persistent PDAP in the absence of poor compliance and in whom dialysis catheter removal should be avoided (i.e., they cannot tolerate hemodialysis).

(2) Inci I, Ozcelik C, Ulku R, Tuna A, Eren N
INTRAPLEURAL FIBRINOLYTIC TREATMENT OF TRAUMATIC CLOTTED HEMOTHORAX.

Department of Thoracic and Cardiovascular Surgery, Dicle University School of Medicine, Diyarbakir, Turkey.
STUDY OBJECTIVE: To evaluate the role of intrapleural fibrinolytic treatment (IPFT) in traumatic clotted hemothorax. DESIGN AND PATIENTS: Between August 1995 and February 1997, 24 patients with traumatic clotted hemothorax were included. Streptokinase (SK), 250,000 IU, or urokinase (UK), 100,000 IU, diluted in 100 mL of saline solution was given daily. We administered 5.0+/−1.8 (range, 2 to 9) doses of SK or 6.25+/−5.97 (range, 2 to 15) doses of UK. SETTING: Dicle University School of Medicine, Thoracic and Cardiovascular Surgery Department. RESULTS: Complete response, which was defined as resolution of symptoms with complete drainage of fluid and no residual space radiographically, occurred in 15 (62.5%) patients. Partial response, which was defined as resolution of symptoms with a small pleural cavity, occurred in seven (29.2%) patients. Two patients (8.3%) required decortication; they were defined as nonresponders. The mean period of time between the diagnosis and fibrinolytic treatment (FT) was 11.65+/−6.38 (range, 4 to 25) days. There were no complications related to IPFT. There was no mortality during the course of IPFT. CONCLUSION: The use of intrapleural fibrinolytic agents has resulted in resolution of clotted hemothorax with an overall
success rate of 91.7%. We recommend that IPFT should be added to the algorithm for management of clotted hemothorax before proceeding with minithoracotomy or pleural decortication.

(3) Porter J, Banning AP
INTRAPLEURAL STREPTOKINASE.

8. STK Mesenterial Vein Thrombosis

(1) Ryu R, Lin TC, Kumpe D, Krysl J, Durham JD, Goff JS, Everson GT, Kam I, Wachs M, Russ P, Shrestha R, Trouillot TE, Bilir BM
PERCUTANEOUS MESENTERIC VENOUS THROMBECTOMY AND THROMBOLYSIS: SUCCESSFUL TREATMENT FOLLOWED BY LIVER TRANSPLANTATION.

Department of Interventional Radiology, University of Colorado Health Sciences Center, Denver, Colorado, USA.

Mesenteric vein thrombosis (MVT) is a rare cause of intestinal ischemia. Because of its nonspecific symptoms, diagnosis is often delayed. We describe a patient with liver cirrhosis who developed acute MVT while waiting for liver transplantation. Surgical intervention carried a high risk because of her underlying cirrhosis. Mesenteric venous thrombectomy and thrombolysis were performed with an AngioJet (Possis Medical, Minneapolis, MN) thrombectomy device and streptokinase infusion through transjugular route. The patient subsequently received an orthotopic liver transplant. We also present a review of the literature about the occurrence and treatment options for MVT. Copyright 1998 W.B. Saunders Company.

9. STK in Urologic Clot Lysis

(1) Wymenga LF, van der Boon WJ
OBSTRUCTION OF THE RENAL PELVIS DUE TO AN INSOLUBLE BLOOD CLOT AFTER EPSILON-AMINOCAPROIC ACID THERAPY: RESOLUTION WITH INTRAURETERAL STREPTOKINASE INSTILLATIONS.

Department of Urology, Nij Smelinghe Hospital, Drachten, The Netherlands.

PURPOSE: We demonstrate the effectiveness of _intraureteral streptokinase instillations_ for the resolution of an _insoluble blood clot_ in the renal pelvis. MATERIALS AND METHODS: A patient with renal adenocarcinoma had prolonged _hematuria_ related to involvement of the "pyelum" by the tumor. An insoluble blood clot obstruction of the left renal collecting system developed as a consequence of epsilon aminocaproic acid therapy, which was treated with _low dose streptokinase_ through a ureteral catheter. RESULTS: Complete resolution of the clot and obstruction occurred within 3 days of therapy. CONCLUSIONS: This relatively simple approach should be used for the treatment of obstruction before radical surgery is performed.

B. STK Complications

1. STK induced Allergic and Anaphylactic Reactions

(1) Hohage H, Schulte B, Mehrens T, Kalvaram CM, Pfeiff B, Pullmann H
SERUM ANTIBODY TITERS IN A SYSTEMIC LYTIC THERAPY WITH STREPTOKINASE.

Department of Anaesthesiology and Emergency Medicine, District Hospital Ludenscheid, Germany.
BACKGROUND: Anaphylactic reactions to streptokinase are rare but potentially life-threatening complications. Gamma E immunoglobulin (IgE) mediated mechanisms, probably due to streptococcal infections, have been implicated. We investigated the value of in vitro laboratory or dermatologic tests in predicting anaphylactic reactions due to streptokinase and the value of antistreptolysin titers (ASL) in predicting the amount of specific IgE (sIgE) and specific gamma G immunoglobulin (sIgG) neutralizing antibodies to streptokinase. METHODS: We measured serum levels of total IgE, streptokinase sIgE and sIgG, and ASL in 16 patients before and 9 and 41 days after streptokinase therapy. Immediately before therapy, intracutaneous testing with 100 IU streptokinase was done. RESULTS: Dermatologic testing did not identify patients prone to allergic reactions. Moreover, not all patients with increased sIgE levels had allergic reactions. These reactions were independent of the dose of streptokinase given. In spite of steroid prophylaxis, allergic reactions occurred in 3 of 16 patients, but none showed life-threatening anaphylaxis. Streptokinase sIgE and sIgG concentrations were closely related to ASL titers. CONCLUSIONS: Plasma levels of sIgG, sIgE, and ASL titers showed a good correlation. We believe ASL titers can be used for the estimation of neutralizing antibodies instead of streptokinase sIgG antibodies. Currently, no laboratory or dermatologic test allows reliable predictions of allergic reactions to streptokinase.

(2) Stephens MB, Pepper PV
STREPTOKINASE THERAPY. RECOGNIZING AND TREATING ALLERGIC REACTIONS.

Naval Medical Center, San Diego, California 92106, USA. stephens@snd10.med.navy.mil
Streptokinase is an important component in the treatment strategy for acute myocardial infarction. However, physicians need to be aware that some patients may experience allergic reactions to this drug. Prompt recognition and appropriate management of symptoms usually result in recovery from the allergic event without further complication.

2. STK induced Cerebral Hemorrhage "Paradox effect with Low Dose"

(1) Fedeli F, Skouse D, Messina A
[CEREBRAL HEMORRHAGE INDUCED BY LOW-DOSE STREPTOKINASE: A PHARMACOLOGIC PARADOX? REPORT OF A CLINICAL CASE].
[ARTICLE IN ITALIAN]
Minerva Cardioangiol 1997 Jul-Aug;45(7-8):377-81

Divisione di Cardiologia-UCC, Azienda Ospedaliera E. Morelli, Sondalo, Sondrio.
A case of an important intracranial hemorrhage after a low dose (approx. 500,000 UI) of streptokinase in a 60 year-old woman suffering from myocardial infarction is presented. Clinical, electrocardiographic, echocardiographic, lab and tomographic findings are described. The authors suggest a pharmacokinetic mechanism which could be responsible of a "paradox effect" (a powerful and dangerous effect of the drug when given in low dose) and they wonder whether in case of allergic reactions should it be better not to stop the infusion of the thrombolytic drug and be more liberal with the "symptomatic" drugs. Tha patient is still alive and the clinical conditions slowly progressing.

B. Tissue Plasminogen Activator (tPA)

A. Function and Fields of Use

1. tPA Economic Evaluation of Thrombolysis
PITFALLS IN THE ECONOMIC EVALUATION OF THROMBOLYSIS IN MYOCARDIAL INFARCTION. THE IMPACT OF NATIONAL DIFFERENCES IN THE COST OF THROMBOLYTICS AND OF DIFFERENCES IN THE EFFICACY ACROSS PATIENT SUBGROUPS.

Istituto di Clinica Medica e Cardiologia, University of Florence, Italy. lorenzoni.r@lunet.it

BACKGROUND: The economic evaluation of the results of the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Artery (GUSTO) trial found that recombinant tissue plasminogen activator is more cost-effective than streptokinase for the treatment of acute myocardial infarction. AIM: We evaluated the impact on a cost effectiveness analysis, of the differences in the cost of thrombolytics among countries and of differences in efficacy across patient subgroups. METHODS: We considered the crude costs of streptokinase and recombinant tissue plasminogen activator in Germany, Italy, the United Kingdom, and the United States of America, and the 30-day mortality found in the GUSTO trial. We calculated the incremental costs for each life saved when streptokinase is substituted by recombinant tissue plasminogen activator. We also calculated the incremental costs for each life saved for two protocols implying a selective use of streptokinase and recombinant tissue plasminogen activator (age-selective protocol: recombinant tissue plasminogen activator in patients < or = 75 years, streptokinase in older patients; site-selective protocol: recombinant tissue plasminogen activator in anterior acute myocardial infarction, streptokinase in non-anterior acute myocardial infarction). RESULTS: The incremental costs when streptokinase is substituted by recombinant tissue plasminogen activator in all for each life saved GUSTO patients vary greatly among countries: the incremental costs for each life saved are 31%, 45%, and 97% higher in Germany, Italy, and the United States of America compared to the United Kingdom. The use of a site-selective protocol implies a halved cost-effectiveness ratio compared to the use of recombinant tissue plasminogen activator in all cases of acute myocardial infarction. CONCLUSIONS: (1) The cost-efficacy of recombinant tissue plasminogen activator vs streptokinase in acute myocardial infarction varies greatly among countries due to differences in the cost of drugs. (2) A selective use of thrombolytics for some sites of infarction is more cost-effective than the exclusive use of recombinant tissue plasminogen activator.

2. tPA in Pulmonary Embolism

(1) Schmitz-Rode T, Janssens U, Schild HH, Basche S, Hanrath P, Gunther RW
FRAGMENTATION OF MASSIVE PULMONARY EMBOLISM USING A PIGTAIL ROTATION CATHETER.
Chest 1998 Nov;114(5):1427-36

Department of Diagnostic Radiology, University of Technology, Aachen, Germany.

STUDY OBJECTIVES: The purpose of this study was the evaluation of the efficacy and safety of mechanical fragmentation of acute massive pulmonary emboli with a rotatable pigtail catheter. MATERIAL AND METHODS: Ten patients (4 female, 6 male, age 53.8+/−9.5 years) with acute massive pulmonary embolism with hemodynamic impairment were included in the study. The fragmentation catheter device (William Cook Europe A/S; Bjaerverskov, Denmark) consisted of a 5F catheter embedded in a flexible 5.5F sheath. Pulmonary emboli were fragmented by mechanical action of the recoiled rotating pigtail, while the guide wire was exiting an oval side hole proximal to the pigtail tip. In eight cases, an additional thrombolysis was performed. RESULTS: Fragmentation was successful in 7 of 10 patients. Average percentage of recanalization by fragmentation was 29.2±14.0%, and 36.0±10.0% exclusively of the seven successful cases. Average shock index decreased significantly prefragmentation to postfragmentation from 1.52 to 1.22 (p = 0.03) and to 0.81 48 h later (p < 0.001). Decrease of the average mean arterial pulmonary pressure prefragmentation to postfragmentation was insignificant (from 33 to 31 mm Hg, p = 0.14); further decrease within the 48 h follow-up was highly significant (from 31 to 21 mm Hg, p < 0.001) due to a synergy of fragmentation and thrombolysis (average dose 63+/−25 mg plasminogen activator). There were no procedure-related complications. Overall mortality rate was 20%. CONCLUSION: Fragmentation of massive pulmonary emboli with the pigtail rotation catheter achieved rapid partial recanalization in most
cases, with ease of instrumentation, and without complications. Hemodynamic stabilization was completed in synergy with thrombolysis.

(2) Konstantinides S, Tiede N, Geibel A, Olschewski M, Just H, Kasper W

COMPARISON OF ALTEPLASE VERSUS HEPARIN FOR RESOLUTION OF MAJOR PULMONARY EMBOLISM.

Am J Cardiol 1998 Oct 15;82(8):966-70

Abteilung Innere Medizin III-Kardiologie, Universitätsklinik Freiburg, Germany.

Complete resolution of major pulmonary embolism (PE) treated with heparin alone can often take > 3 weeks. Thrombolytic agents effectively resolve pulmonary artery thrombi within a few hours. However, the effect of the 2 types of treatment on recovery of right ventricular function has not yet been followed for periods of > 24 hours. We prospectively examined 40 consecutive patients with documented major PE (symptoms being present for < or = 8 weeks). After diagnosis, 27 patients (68%) were treated with alteplase plus heparin and 13 (32%) with heparin alone. There was no significant difference between the 2 groups with regard to baseline parameters. At 12 hours, systolic pulmonary artery pressure decreased from 56 +/- 20 to 37 +/- 21 mm Hg in the alteplase group, and from 50 +/- 11 to 46 +/- 12 mm Hg in the heparin group (significantly more; p = 0.016). On echocardiographic follow-up, a decrease in end-diastolic dimensions of the right ventricle and an increase in left ventricular dimensions was significantly more pronounced in the alteplase group (p <0.001 and p = 0.05, respectively). The incidence of right ventricular dilation and paradoxical septal wall motion decreased significantly only in the thrombolysis group. However, at 1-week follow-up, no difference was seen between the 2 groups regarding the overall change in right or left ventricular dimensions or the final values of other echocardiographic parameters. Thus, echocardiography is particularly useful for hemodynamic follow-up of major PE. Thrombolysis may rapidly reduce pulmonary artery pressure, but resolution of right ventricular pressure overload also occurs within 1 week in patients treated with heparin alone.

(3) Chao TH, Tsai LM, Teng JK, Li YH, Tsai WC, Lin LJ, Chen JH

SUCCESSFUL DELAYED THROMBOLYTIC THERAPY IN A PATIENT WITH MASSIVE PULMONARY EMBOLISM.

J Formos Med Assoc 1998 Sep;97(9):638-41

Department of Medicine, National Cheng Kung University Hospital, Tainan, Taiwan.

Pulmonary embolism can be a catastrophic event leading to early death or serious hemodynamic instability. Thrombolytic therapy, in addition to heparin therapy, may improve the clinical condition and reduce the chance of recurrent pulmonary embolism in some cases. However, the acceptable "time window" for thrombolytic therapy is not well documented, though it has been used successfully as late as 14 days after pulmonary embolism. Successful delayed thrombolytic therapy beyond this "time window" in patients with massive pulmonary embolism has not been reported. We report a case of massive pulmonary embolism in which thrombolytic therapy was delayed more than 1 month after symptom onset. A 56-year-old woman was taken to National Cheng Kung University Hospital because of an episode of recurrent syncope, followed by progressive shortness of breath of 1 month's duration. Hypoxemia and hemodynamic instability were noted on admission. Echocardiography and a lung perfusion scan provided strong evidence of pulmonary embolism. Subsequent pulmonary angiography confirmed the diagnosis of multiple pulmonary emboli. The patient received a standard dose of intravenous tissue plasminogen activator 7 days after admission because of persistent symptoms and hypoxemia. Her clinical condition dramatically improved after treatment. Follow-up imaging studies showed resolution of the emboli. She was discharged in good condition. This case suggests that delayed thrombolytic therapy in patients with massive pulmonary embolism can still be beneficial in selected cases, even if given more than 2 weeks after symptom onset.

(4) Schulte-Sinkus D, Standl T

[SUCCESSFUL RESUSCITATION AFTER BOLUS INJECTION OF TISSUE-TYPE PLASMINOGEN ACTIVATOR IN EMERGENCY ADMISSION].

[ARTICLE IN GERMAN]

Anesthesiol Intensivmed Notfallmed Schmerzther 1998 Feb;33(2):124-8

Abteilung fur Anesthesiologie Universitäts-Krankenhaus Eppendorf, Hamburg.
We report on a 30-year old female patient with suspected fulminant pulmonary embolism and cardiac arrest following ambulatory arthroscopy nine days before the event. After 15 minutes of unsuccessful cardiopulmonary resuscitation (CPR) on the ambulance the patient was transferred to the emergency unit of a hospital and was treated with bolus injection of 50 mg t-PA initially and 50 mg over the next two hours. Five minutes after the initial bolus the circulation could be stabilised and the patient could be extubated the next morning. The patient did not present any neurological deficit on the day of discharge nor did she show any bleeding complications. The time elapsing from notice to emergency service to arrival at hospital was about 35 minutes. DISCUSSION: In patients with massive and life-threatening pulmonary embolism thrombolysis offers an opportunity to manage this critical situation. Due to the serious prognosis of these patients the potential benefit of thrombolysis outweighs the lack of preceding diagnostic procedures and the risk of potential side-effects. CONCLUSION: In the light of an excellent outcome of this patient thrombolytic therapy with t-PA appears to be justified under continued CPR if fulminant pulmonary embolism is suspected.

3. tPA in Myocardial Infarction

(1) Gersh BJ
CURRENT ISSUES IN REPERFUSION THERAPY.
Am J Cardiol 1998 Oct 22;82(8B):3P-11P

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With the establishment of thrombosis as the cause of myocardial infarction, the pivotal role of thrombolytics and primary angioplasty has evolved. Large randomized trials with innovative methodologies have examined the role of these reperfusion therapies in the management of acute coronary syndromes. Intravenous thrombolytic therapy decreases mortality in a broad group of patients with acute myocardial infarction. The GUSTO trial established intravenous tissue plasminogen activator (tPA) used in combination with intravenous heparin as the most effective thrombolytic therapy. Importantly, the time to achieve reperfusion is crucial to the mortality benefit observed, and rapid attainment of Thrombolysis in Myocardial Infarction (TIMI) trial grade 3 flow is achieved in only approximately 55% of patients who receive thrombolytics. Reocclusion, cellular damage, and microvascular dysfunction may contribute to less than optimal results. Percutaneous transluminal coronary angioplasty (PTCA) may be the preferred method of acute reperfusion therapy based on higher rates of TIMI grade 3 flow and lower rates of reocclusion and recurrent myocardial infarction. However, marked variation exists in outcomes and utilization rates among individual institutions, and the benefits of PTCA have not been consistently maintained at 6 months. The use of stents and anticoagulants may improve results, and pre-PTCA strategies also are under investigation. Limitations remain in the efficacy of current reperfusion therapies, supporting the search for improved thrombolytic agents, primary angioplasty, stents, and antithrombotics with the goal of improving TIMI 3 flow rates and achieving reperfusion more rapidly.

(2) Hunt D
ALTEPLASE (R-TPA) VS STREPTOKINASE.

Royal Melbourne Hospital, Parkville, Vic.

The GUSTO trial and an Australian consensus meeting in 1993 led to the recommendation that recombinant tissue plasminogen activator (r-TPA) was the preferred thrombolytic in patients with acute myocardial infarction (AMI) and ST segment elevation under the age of 75, whose infarction was anterior, who could be treated within four hours of the onset of symptoms and who did not have a contraindication to thrombolysis. Available data suggest that streptokinase (SK) should not be administered in a patient who has received this drug three days or more previously. New data on the risks of stroke confirm that the use of r-TPA is associated with a higher risk of intracranial haemorrhage than SK, and those with a high risk profile for intracranial haemorrhage (hypertension and advanced age) should receive SK rather than r-TPA. It may be justified to give r-TPA to any patient with a large infarct regardless of location, within four hours of the onset of infarction in an attempt to achieve TIMI flow grade 3 (complete) reperfusion, reduce mortality and improve left
ventricular function and clinical outcomes. The focus for the future will be on how to treat more patients earlier with thrombolytic agents, rather than the choice of agent.

(3) Stringer KA
TIMI GRADE FLOW, MORTALITY, AND THE GUSTO-III TRIAL.

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Thrombolytic therapy dates back to animal studies performed in the early 1940s, although clinical trials did not begin until the early 1980s. Many large, placebo-controlled trials conclusively recorded improved survival with thrombolytics in the treatment of acute myocardial infarction. However, only recently did clinical trials compare tissue plasminogen activator (tPA) and streptokinase (SK), and only one study showed a difference in mortality between them. This discrepancy, in part, led to the open-artery hypothesis that early and sustained infarct-related artery patency improves outcome. This theory was tested in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-I) study. The angiographic substudy of GUSTO-I provided strong evidence for the relationship between 90-minute thrombolysis in myocardial infarction (TIMI) grade 3 flow and lower mortality. However, despite significantly higher 90-minute TIMI grade 3 flow (54% vs 32%) with accelerated tPA versus SK plus intravenous heparin, the absolute difference in mortality rate was less than 1%. The recently completed GUSTO-III trial compared accelerated tPA with reteplase (rPA). Based on the open-artery hypothesis and previous data showing an absolute difference of 15% in 90-minute TIMI grade 3 flow between the agents, it was anticipated that mortality would be lower with rPA than with accelerated tPA. The GUSTO-III study showed no significant difference in 30-day mortality for the agents (7.47% vs 7.24%, p=0.61), respectively. These results raise questions about the validity of the hypothesis: if 90-minute TIMI grade 3 flow is such a strong predictor of mortality, why is there not a greater difference in mortality rates for thrombolytic agents?

(4) Bizjak ED, Mauro VF
THROMBOLYTIC THERAPY: A REVIEW OF ITS USE IN ACUTE MYOCARDIAL INFARCTION.

College of Pharmacy, University of Toledo, OH 43606, USA.
OBJECTIVE: To review the literature on the use of thrombolytic agents in the pharmacotherapeutic management of acute myocardial infarction (AMI). AMI is one of the leading causes of mortality in the US. Following supportive data that the most common cause of an AMI is an intracoronary thrombus, clinical investigation has demonstrated that intravenous thrombolytic agents improve survival rates in patients who experience an AMI. At present, only the first Global Use of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-I) trial has reported any statistically significant difference in mortality rate. In this trial, "front-loaded" alteplase induced a statistically significant (p < 0.001) 1% absolute reduction in 30-day and 1-year mortality compared with streptokinase. This has led to alteplase being the preferred thrombolytic at many US institutions. However, the results of GUSTO-I have been questioned by some on the basis of either study design or clinical significance. CONCLUSIONS: Thrombolytic agents have secured a place in the treatment of AMI due to their well-proven reduction in mortality rates. In general, comparative trials have demonstrated minimal differences in efficacy among these agents. Probably just as important as choosing which thrombolytic agent to use is ensuring that a patient experiencing an AMI is administered thrombolytic therapy unless a contraindication to receive such therapy exists in the patient and/or the patient is a candidate to receive an emergent intracoronary procedure. Trials also indicate that the sooner thrombolytics can be administered, the greater the benefit to the patient.

(5) Remkova-Okrucka A
[NO TITLE AVAILABLE]. [ARTICLE IN CZECH]

I. interna klinika Lekarskej fakulty Univerzity Komenskeho v Bratislave, Slovakia.
The data gained from clinical studies in the past years have indicated that the thrombolytic therapy (TL) has favourable effect on patients with acute myocardial infarction (AMI). It is aimed at reperfusion in the ischaemic area, a decrease in the extent of infarction site and a decrease in mortality. TL administered within the initial hours after the onset of AMI leads to better results than when administered after several hours. Currently, TL is not limited by age. The patients who were given streptokinase (SK) or anistreplase (APSC) prior to more than 4 days, if necessary, urokinase or alteplase (rt-PA) should be given. There are differences in the opinions as to the optimal selection of thrombolytic drugs. However, all currently used drugs lead to a significant decrease in mortality due to AMI. The preferential use of accelerated administration of rt-PA in contrast to SK is justified in younger patients with extensive AMI of the anterior wall, in whom the therapy has begun within 4 hours since its onset. The occurrence of severe bleeding indicates that TL should be halted and coagulation factors should be replaced by freshly frozen plasma or fibrinogen concentrate, if necessary, transfusion of full blood should take place. If the severe bleeding occurs shortly after the administration of SK, the persisting plasminaeemia can be arranged by antifibrinolytic drugs. An improvement in TL results can be achieved by adjuvant antithrombotic therapy. At the same time, in addition to acetylsalicylic acid, the patient treated with rt-PA should be given heparin. Heparin administration is not necessary in patients treated with SK or APSAC. However, heparin is indicated in patients at risk due to systemic embolization in congestive heart disease, extensive infarction or atrial fibrillation. 


HBW 023 (RECOMBINANT HIRUDIN) FOR THE ACCELERATION OF THROMBOLYSIS AND PREVENTION OF CORONARY REOCCLUSION IN ACUTE MYOCARDIAL INFARCTION: RESULTS OF A DOSE-FINDING STUDY (HIT-II) BY THE ARBEITSGEMEINSCHAFT LEITENDER KARDIOLOGISCHER KRANKENHAUSARZTE.

Coron Artery Dis 1998;9(5):265-72

Medical Clinic, Stiftsklinikum Augustinum Munchen, Germany.

OBJECTIVE: To define an optimal dose of hirudin that would improve early coronary artery Thrombolysis in Myocardial Infarction grade 3 (TIMI 3) patency and prevent recurrences in patients with acute myocardial infarction treated with front-loaded recombinant tissue-type plasminogen activator (rt-PA). METHODS: Recombinant hirudin (HBW 023) was tested in a sequential dose-escalating study as adjunct to front-loaded rt-PA in 143 patients with acute myocardial infarction. The sequential model was assigned two 'decision boundaries': it triggered an increase in dosage if the 60-min TIMI 3 flow rate in a dosage group was statistically not consistent with a target patency rate of 75%, or if the deterioration in coronary blood flow (of at least one TIMI grade, from TIMI 2 or 3, from one angiography to the next) exceeded 5%. RESULTS: The decision boundary for TIMI 3 flow grade at 60 min was crossed when 18 patients were treated with 0.1/0.06 mg/kg (bolus/infusion per hour over 48 h) r-hirudin (dosage group I), 42 patients treated with 0.2/0.1 mg/kg (dosage group II), and 83 patients with 0.4/0.15 mg/kg (dosage group III). TIMI 3 flow at 60 min was 50%, 58%, and 63% in dosage groups I-III, respectively (P = 0.15). Early, complete, and sustained patency (TIMI 3 flow at 60 min, 90 min and 48 h) were 44%, 55% and 64% (P = 0.07). Reocclusion between 90-min and 48-h angiograms or reinfarction occurred in 0 to 15, two of 36, and one of 72 patients, respectively (P = 0.5). Four patients (2.8%) died in hospital and 14 patients suffered a major bleeding event, but no intracranial bleeding was encountered. CONCLUSIONS: With increasing doses of hirudin, there was a trend towards greater early and complete patency, but no clear dose--response relationship was observed. A borderline significant effect was observed with respect to early, complete, and sustained patencies. In all groups, reocclusions or reinfarctions were rare. Neither clinical nor laboratory data predicted the imbalance in haemorrhagic events observed in a subsequent, prematurely terminated, phase III trial with hirudin and rt-PA.
SIXTY-MINUTE ALTEPLASE PROTOCOL: A NEW ACCELERATED RECOMBINANT TISSUE-TYPE PLASMINOGEN ACTIVATOR REGIMEN FOR THROMBOLYSIS IN ACUTE MYOCARDIAL INFARCTION.

J Am Coll Cardiol 1997 Dec;30(7):1611-7

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OBJECTIVES: Our aim was to design and evaluate a new and easily administered recombinant tissue-type plasminogen activator (rt-PA) regimen for thrombolysis in acute myocardial infarction (AMI) based on established pharmacokinetic data that improve the reperfusion success rate.

BACKGROUND: Rapid restoration of Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow is a primary predictor of mortality after thrombolysis in AMI. However, TIMI grade 3 patency rates 90 min into thrombolysis of only 50% to 60% indicate an obvious need for improved thrombolytic regimens.

METHODS: Pharmacokinetic simulations were performed to design a new rt-PA regimen. We aimed for a plateau tissue-type plasminogen activator (t-PA) plasma level similar to that of the first plateau of the Neuhaus regimen. These aims were achieved with a 20-mg rt-PA intravenous (i.v.) bolus followed by an 80-mg i.v. infusion over 60 min (regimen A). This regimen was tested in a consecutive comparative trial in 80 patients versus 2.25 10(6) IU of streptokinase/60 min (B), and 70 mg (C) or 100 mg (D) of rt-PA over 90 min. Subsequently, a confirmation trial of regimen A in 254 consecutive patients was performed with angiographic assessment by independent investigators of patency at 90 min.

RESULTS: The comparative phase of the trial yielded, respectively, TIMI grade 3 and total patency (TIMI grades 2 and 3) of 80% and 85% (regimen A), 35% and 50% (B), 50% and 55% (C) and 60% and 70% (D). In the confirmation phase of the trial, regimen A yielded 81.1% TIMI grade 3 and 87.0% total patency. At follow-up angiography 7 (4.1%) of 169 vessels had recocluded. In-hospital mortality rate was 1.2%. Nadir levels of fibrinogen, plasminogen and alpha2-antiplasmin were 3.6 +/- 0.8 mg/ml, 60 +/- 21% and 42 +/- 16%, respectively (mean +/- SD). Fifty-seven patients (22.4%) suffered from bleeding; 3.5% needed blood transfusions. CONCLUSIONS: The 60-min alteplase thrombolysis in AMI protocol achieved a TIMI grade 3 patency rate of 81.1% at 90 min with no indication of an increased bleeding hazard; it was associated with a 1.2% overall mortality rate. These results are substantially better than those reported from all currently utilized regimens. Head to head comparison with established thrombolytic regimens in a large-scale randomized trial is warranted.

4. tPA in Coronary Arterial Disease


COMPARISON OF ENOXAPARIN, HIRULOG, AND HEPARIN AS ADJUNCTIVE ANTITHROMBOTIC THERAPY DURING THROMBOLYSIS WITH RTPA IN THE STENOSED CANINE CORONARY ARTERY.


Department of Cardiovascular Drug Discovery, Rhone-Poulenc Rorer Central Research, Collegeville, PA 19426, USA.

A canine model of electrolytic injury-induced coronary artery thrombosis and rtPA-induced thrombolysis was used to evaluate the relative antithrombotic efficacy of enoxaparin (a low molecular weight heparin), conventional therapy (heparin or heparin plus aspirin), and hirulog (a direct thrombin inhibitor), when used as adjunctive therapy during thrombolysis. After 60 min of clot aging, adjunctive therapy was begun at doses which elevated APTT approximately 2-fold over baseline. Fifteen minutes after the start of adjunctive therapy, recombinant tissue plasminogen activator (rtPA) was administered (100 microg/kg i.v. bolus + 20 microg/kg/min for 60 min). Adjunctive therapy was continued for 1 h after termination of rtPA and blood flow was monitored for two additional hours. Enoxaparin (1 mg/kg i.v. bolus + 30 microg/kg/min, n = 10 for each treatment group) was the only adjunctive treatment that significantly increased the total minutes of flow (143 +/- 25 min out of a possible 240 min, vs 54 +/- 25 min for vehicle, p <0.05) and decreased thrombus mass (6.0 +/- 1.3 mg vs 11.8 +/- 3.2 mg for vehicle). Although hirulog (2 mg/kg i.v. bolus + 40 microg/kg/min) did not
significantly increase the minutes of flow (120 +/- 27 min, p <0.06) or decrease thrombus mass (8.7 +/- 1.7 mg) compared to vehicle, these values were not significantly different than those measured in the enoxaparin group. However, the results with hirulog were achieved at the expense of a significantly greater increase in template bleeding time than that measured during enoxaparin treatment. Minutes of flow for heparin (50 U/kg iv. bolus + 0.6 U/kg/min) and heparin plus aspirin (5 mg/kg iv. bolus) were 69 +/- 20 and 60 +/- 23 min, respectively; thrombus masses were 8.2 +/- 1.3 and 7.3 +/- 1.0 mg, respectively. In summary, enoxaparin was more effective than conventional therapy in this model in terms of vessel patency and thrombus mass, and was as effective as hirulog, at least at a dose of hirulog that only modestly impaired hemostasis. Therefore, enoxaparin may prove to be a safe and effective alternative agent for adjunctive therapy during thrombolysis with rtPA.

(2) Gurbel PA, Serebruany VL, Shustov AR, Bahr RD, Carpo C, Ohman EM, Topol EJ
EFFECTS OF RETEPLASE AND ALTEPLASE ON PLATELET AGGREGATION AND MAJOR RECEPTOR EXPRESSION DURING THE FIRST 24 HOURS OF ACUTE MYOCARDIAL INFARCTION TREATMENT. GUSTO-III INVESTIGATORS. GLOBAL USE OF STRATEGIES TO OPEN OCCLUDED CORONARY ARTERIES.
J Am Coll Cardiol 1998 Jun;31(7):1466-73

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OBJECTIVES: We sought to compare platelet characteristics after reteplase and alteplase therapy in the setting of the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO)-III trial.

BACKGROUND: Platelet function may be impaired during thrombolysis in patients with an acute myocardial infarction. The effects of reteplase and alteplase on platelet aggregation and major surface antigen expression during the first 24 h of infarction therapy are unknown.

METHODS: Platelet aggregation and receptor expression by flow cytometry were determined in 23 patients before thrombolysis and thereafter at 3, 6, 12 and 24 h. RESULTS: Aggregation was higher after reteplase at 24 h when induced by 5 micromol/liter adenosine diphosphate (ADP) (p = 0.007), 10 micromol/liter ADP (p = 0.02), collagen (p = 0.003) and thrombin (p = 0.009) than after alteplase. Reteplase therapy exhibited greater glycoprotein (GP) IIb/IIIa (p = 0.04), very late antigen-2 (p = 0.04) and platelet/endothelial cell adhesion molecule-I (p = 0.002) expression at 24 h. Trends toward decreased receptor expression early (3 to 6 h), followed by a progressive increase at 12 h and especially at 24 h occurred after both agents. CONCLUSIONS: In this prospective clinical ex vivo platelet study, similar patterns of platelet aggregation and surface receptor expression occurred during the first 24 h of coronary thrombolysis with reteplase and alteplase. However, after reteplase, indicators of platelet activity were higher at 24 h after thrombolysis than after alteplase. These data suggest that GP IIb/IIIa inhibitors or other antiplatelet strategies may be particularly advantageous when used 12 to 24 h after thrombolysis, especially after reteplase therapy. It is at this time point during the first day of coronary thrombolysis that GP IIb/IIIa is markedly expressed and platelets are most active.

5. tPA in Prosthetic valve thrombosis

SHORT-COURSE THROMBOLYSIS AS THE FIRST LINE OF THERAPY FOR CARDIAC VALVE THROMBOSIS.

Thrombosis and Hemostasis Unit, Hospital de la Sta Creu i St Pau, Barcelona, Spain.

OBJECTIVE: To retrospectively evaluate the clinical and echocardiographic criteria of thrombolytic therapy for mechanical heart valve thrombosis. METHODS: Nineteen consecutive patients with 22 instances of prosthetic heart valve thrombosis (14 mitral, 2 aortic, 3 tricuspid, and 3 pulmonary) were treated with short-course thrombolytic therapy as first option of treatment in absence of contraindications. The thrombolytic therapy protocol consisted of streptokinase (1,500,000 IU in 90 minutes) (n = 18) in one (n = 7) or two (n = 11) cycles or recombinant tissue-type plasminogen activator (100 mg in 90 minutes) (n = 4). RESULTS: Overall success was seen in 82%, immediate complete success in 59%, and partial success in 23%. Six patients without total response to thrombolytic therapy underwent surgery, and pannus was observed in 83%. Six patients showed
complications: allergy, stroke, transient ischemic attack, coronary embolism, minor bleeding, and one death. At diagnosis, 10 patients evidenced atrial thrombus by transesophageal echocardiography, 3 of whom experienced peripheral embolism during thrombolysis. Four episodes of rethrombosis were observed (16%). The survivorship was 84% with a mean follow-up of 42.6 months.

CONCLUSIONS: A short-course of thrombolytic therapy may be considered first-line therapy for prosthetic heart valve thrombosis. The risk of peripheral embolism may be evaluated for the presence of atrial thrombus by transesophageal echocardiography at diagnosis.

(2) Serafini O, Bisignani G, Plastina F

[ACUTE DISFUNCTION FROM THROMBOSIS OF A PROSTHETIC MITRAL VALVE: THROMBOLYSIS WITH RT-PA IN THE CLINICAL EMERGENCY PHASE]. [ARTICLE IN ITALIAN]

G Ital Cardiol 1998 Apr;28(4):387-91

Divisione di Cardiologia, Azienda Ospedaliera, Cosenza.

Prosthetic valve thrombosis can determine different degrees of valvular insufficiency or obstruction, with a potentially fatal course. The current literature has not established whether the best treatment is thrombolysis or surgery (thrombectomy or valvular replacement). However, both treatments expose the patient to the risk of serious sequelae or death. Here we describe a case of acute thrombosis in a prosthetic mitral valve. At presentation, the patient was in pulmonary edema and had a low cardiac output. She was treated with recombinant tissue-type plasminogen activator infusion (rt-PA 100 mg in 2 hours). Both clinically as well as echocardiographically, we observed a quick regression of the obstruction, but after the treatment, the patient developed an ischemic stroke with aphasia and hemiplegia. The authors conclude that thrombolysis is a highly effective treatment in resolving prosthetic thrombosis. However, because it carries a significant risk of embolization, it should be limited to patients with hemodynamic deterioration in whom surgery could also entail a significant risk of death.

(3) Malm TK, Holmqvist C, Olsson CG, Johansson J, Olsson AK, Sandstrom S, Bennhagen R, Jogi P

SUCCESSFUL THROMBOLYSIS OF AN OCCLUDED MODIFIED BLALOCK SHUNT THREE DAYS AFTER OPERATION.


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A 10-day-old boy with pulmonary atresia received a right-sided aortopulmonary polytetrafluoroethylene shunt. Three days after the operation he became cyanotic and was reintubated. Shunt occlusion was confirmed with angiography. Recombinant tissue plasminogen activator was given locally into the proximal end of the shunt. The thrombus was completely resolved after 2 days. When administration of recombinant tissue plasminogen activator was stopped, heparin infusion was started for 5 days. Shunt patency was demonstrated by angiography at 3 months postoperatively.

6. tPA in Angioplasty for MI in CAD


[OPTIMAL REPERFUSION THERAPY IN ACUTE MYOCARDIAL INFARCTION: TIME TO REPERFUSION AND RECANALIZATION RATE].

[ARTICLE IN JAPANESE]

J Cardiol 1998 May;31(5):255-62

Critical Care and Emergency Center, Yokohama City University School of Medicine.

Rapid and complete reperfusion is important for the reduction of infarct size and mortality in acute myocardial infarction. The optimum reperfusion therapy with regard to the recanalization rate and the time elapsing between onset and complete reperfusion was evaluated. One hundred fifty-four patients with total occlusion of the infarct-related artery within 6 hours of the onset were classified into four therapy groups: PTCA group (n = 58) undergoing primary percutaneous transluminal coronary
angioplasty (PTCA), t-PA-IC group (n = 44) receiving tissue plasminogen activator (t-PA) intracoronary infusion, t-PA-IV group (n = 14) receiving intravenous t-PA infusion, and mt-PA-IV group (n = 38) receiving intravenous mutant t-PA infusion. Although the recanalization rate was high in the PTCA group, there were no differences between the four groups as a supplement to immediate or rescue PTCA. The time elapsing between initiation of thrombolysis and complete reperfusion was shorter in the mt-PA-IV group than in the t-PA-IV group. Assuming the time from hospital arrival to initiation of intravenous thrombolysis was 20 min, the recanalization rate at 60 min after arrival in hospital was higher in the mt-PA-IV group than the PTCA and t-PA-IC groups. Although additional coronary angiography and PTCA may be required to improve the low recanalization rate compared with primary PTCA, intravenous infusion of mutant t-PA was the most promising therapy to achieve early reperfusion.

7. tPA in Hyperbaric Oxygen in Myocardial Infarction "HOT MI" Study


HYPERBARIC OXYGEN AND THROMBOLYSIS IN MYOCARDIAL INFARCTION: THE "HOT MI" PILOT STUDY.

Am Heart J 1997 Sep;134(3):544-50

Department of Cardiology, Long Beach Memorial Medical Center, CA 90801, USA.

Hyperbaric oxygen treatment (HBO) in combination with thrombolysis has been demonstrated to salvage myocardium in acute myocardial infarction in the animal model. Therefore a randomized pilot trial was undertaken to assess the safety and feasibility of this treatment in human beings. Patients with an acute myocardial infarction (AMI) who received recombinant tissue plasminogen activator (rTPA) were randomized to treatment with HBO combined with rTPA or rTPA alone. Sixty-six patients were included for analysis. Forty-three patients had inferior AMIs (difference not significant) and the remainder had anterior AMIs. The mean creatine phosphokinase level at 12 and 24 hours was reduced in the patients given HBO by approximately 35% (p = 0.03). Time to pain relief and ST segment resolution was shorter in the group given HBO. There were two deaths in the control group and none in those treated with HBO. The ejection fraction on discharge was 52.4% in the group given HBO compared with 47.3% in the control group (difference not significant). Adjunctive treatment with HBO appears to be a feasible and safe treatment for AMI and may result in an attenuated rise in creatine phosphokinase levels and more rapid resolution of pain and ST segment changes.

8. tPA in Sinus Thrombosis

(1) Ekseth K, Bostrom S, Vegfors M

REVERSIBILITY OF SEVERE SAGITTAL SINUS THROMBOSIS WITH OPEN SURGICAL THROMBECTOMY COMBINED WITH LOCAL INFUSION OF TISSUE PLASMINOGEN ACTIVATOR: TECHNICAL CASE REPORT.


Department of Neurosurgery, University Hospital, Linkoping, Sweden.

OBJECTIVE: To explore the controversial issue of anticoagulant therapy and indications for surgery in association with severe sinus thrombosis. METHODS: During the last 4 years, we have treated three patients with severe sinus thrombosis of the dural sinuses. All three patients received systemic anticoagulant therapy and, after experiencing neurological deterioration, underwent open thrombectomy and local thrombolysis. After the operation, aggressive intensive care was given and included cerebral perfusion monitoring, barbiturate administration, hyperventilation, and osmotherapy. The treatment was guided by repeated neuroradiological investigations. RESULTS: All three patients returned to their normal lives. CONCLUSION: Intracranial sinus thrombosis, even in the worst neurological state, should be treated aggressively. A cornerstone in treatment is systemic anticoagulant therapy and repeated neuroradiological studies. When, despite adequate anticoagulant therapy and intensive care, neurological deterioration occurs, a combination of open thrombectomy and local thrombolytic therapy should be considered.
(2) Niwa J, Ohyama H, Matumura S, Maeda Y, Shimizu T
TREATMENT OF ACUTE SUPERIOR SAGITTAL SINUS THROMBOSIS BY T-PA INFUSION VIA VENOGRAPHY--DIRECT THROMBOLYTIC THERAPY IN THE ACUTE PHASE.

Department of Neurosurgery, Hakodate City Hospital, Hokkaido, Japan.

BACKGROUND: Dural sinus thrombosis is a relatively rare syndrome, often with a very poor prognosis. Systemic anticoagulant therapy has produced poor results; therefore rapid recanalization of the affected vessels is essential. The recent advancements in angiographic technique and catheter technology enable us to perform direct selective venography. CASE REPORT: We observed a case of acute superior sagittal sinus thrombosis in a pregnant woman. The patient's consciousness level and motor function gradually deteriorated. Direct thrombolysis was performed via venography. RESULTS: The patient was treated successfully by thrombolysis with infusion of t-PA via selective venography within 2 days of rapid clinical deterioration and sustained a dramatic improvement of her neurologic deficits. CONCLUSIONS: Direct thrombolysis via selective venography is considered a safe and useful treatment for dural sinus thrombosis in the acute phase.

9. tPA in Stroke

a) Stroke Angioplasty and Thrombolysis

(1) Ueda T, Sakaki S, Nochide I, Kumon Y, Kohno K, Ohta S
ANGIOPLASTY AFTER INTRA-ARTERIAL THROMBOLYSIS FOR ACUTE OCCLUSION OF INTRACRANIAL ARTERIES.
Stroke 1998 Dec;29(12):2568-74

Department of Neurological Surgery, Ehime University School of Medicine, Ehime, Japan.

Background and Purpose--The purpose of this study was to report our experience with percutaneous transluminal angioplasty (PTA) of intracranial arteries in acute stroke patients who were resistant to intra-arterial thrombolysis alone. Methods--PTA was performed within 6 hours from symptom onset in 13 acute stroke patients in whom no hypodensity areas were observed on initial CT. PTA was classified into 3 categories: immediate (3 patients), delayed (3 patients), and rescue (7 patients) angioplasty. Treatment results in the PTA group for 9 cases of middle cerebral artery (MCA) occlusion were compared with those in the thrombolysis alone group for 12 cases of thrombotic MCA occlusion. Results--Technical success rates for immediate, delayed, and rescue angioplasty were 100%, 100%, and 71%, respectively, and that of angioplasty for the MCA was 100%. Ten patients (77%) showed improvement in the National Institutes of Health (NIH) stroke score after treatment. Improvement in NIH stroke scores in the PTA group for MCA occlusion was greater than that in the thrombolysis alone group (P<0.01). Nine patients (69%) had an excellent, good, or fair outcome 3 months after treatment. In 9 patients who had follow-up angiography 1 month after treatment, no restenosis or reocclusion was demonstrated. There were no symptomatic complications during or after treatment. Conclusions--This limited study demonstrates the technical feasibility of angioplasty for intracranial arteries in acute ischemic stroke and suggests that angioplasty may be an effective option for improving the success rate of recanalization and preventing reocclusion of the MCA. The present results encourage us to perform further clinical trials in a larger number of patients to assess the efficacy of this procedure.

(2) Brint SU
ACUTE STROKE THERAPIES.
Surg Neurol 1996 Nov;46(5):446-9

Department of Neurology, University of Illinois at Chicago, USA.

It is likely that thrombolytic agents will play a role in the management of acute ischemic stroke in well-selected patients, intravenous administration is most practicable. However, intra-arterial administration via superselective catheterization is an alternative option that may offer advantages to certain settings (e.g., angiography suite, intraoperatively). Tissue plasminogen activators appear safer than
streptokinase. Fibrinolytic agents offer the unproven potential for improving stroke outcome with less risk of intracranial bleeding. LMWHs can be administered subcutaneously with minimal blood monitoring. These agents may prove more useful for secondary stroke prevention rather than acute treatment. Introduction of other agents like monoclonal antibodies directed against leukocyte adhesion molecules, aspirin, or ticlopidine offer other potential approaches to improving stroke outcome.

b) Canadian Geographic Access for Thrombolysis within 3 hours

(1) Scott PA, Temovsky CJ, Lawrence K, Gudaitis E, Lowell MJ

ANALYSIS OF CANADIAN POPULATION WITH POTENTIAL GEOGRAPHIC ACCESS TO INTRAVENOUS THROMBOLYSIS FOR ACUTE ISCHEMIC STROKE.

*Stroke* 1998 Nov;29(11):2304-10

Section of Emergency Medicine, Department of Surgery, University of Michigan Medical Center, Ann Arbor, Mich (P.A.S., M.J.L.), and Hoffmann-La Roche, Ltd (Canada), Toronto, Canada (C.J.T., K.L., E.G.).

Background and Purpose--We sought to identify the Canadian population with potential access to intravenous tissue plasminogen activator within 3 hours of onset of acute ischemic stroke. Methods--Assuming that 60 minutes is needed for stroke recognition, emergency room evaluation, and administration of tissue plasminogen activator, 120 minutes remain for transport, using a 3-hour treatment window. Ambulance databases were analyzed for transport times of 60, 90, and 120 minutes and were found to correspond to transport distances of 32, 64, and 105 kilometers (20, 40, and 65 miles), respectively. Using Geographical Information System (GIS) software, these radii were overlaid on thematic maps of Canadian hospitals identified as having a third- or fourth-generation CT and with a neurologist and an emergency physician on staff. Analysis was then performed on complete Canadian census data from 1991 and the interim 1996 census count. Results--67.3%, 78.2%, and 85.3% of the total Canadian population were within 32, 64, and 105 kilometers, respectively, of an identified hospital. For individuals >/=65 years of age, 64.4%, 77.0%, and 85.7% were within the respective radii. Complete analysis by age, ethnic origin, and gender are detailed. Conclusions--In the model described, a substantial percentage of the Canadian population has geographic access to a hospital potentially capable of delivering intravenous thrombolysis for acute ischemic stroke. GIS analysis can identify both population groups and rural areas with limited access to thrombolytic stroke treatment. A coordinated emergency medical service response for stroke is advocated to maximize coverage, as a 60-minute delay in emergency room arrival eliminated 5.1 million people from potential treatment.


CANADIAN GUIDELINES FOR INTRAVENOUS THROMBOLYTIC TREATMENT IN ACUTE STROKE. A CONSENSUS STATEMENT OF THE CANADIAN STROKE CONSORTIUM.


Sunnybrook Health Science Centre, Toronto, Ontario, Canada.

BACKGROUND: The thrombolytic drug, tissue plasminogen activator (tPA) has been approved in the United States for the treatment of acute ischemic stroke amid controversy and concern about the balance of risk and benefit. The Canadian Stroke Consortium (CSC), a national network of neurologists who collaborate on joint projects in stroke medicine, including clinical trials and consensus statements, has developed guidelines for the use of tPA in Canada. METHODS AND RESULTS: The CSC Board of Directors wrote a preliminary report based on existing publications, including randomized drug trials and the report of a special committee struck by the Stroke Council of the American Heart Association. This draft was circulated to the CSC membership-at-large for suggestions or amendments, to produce this final draft. CONCLUSIONS: The present guidelines have been devised to represent a Canadian viewpoint of management. The Health Protection Branch of the Ministry of Health of Canada has not yet produced an evaluation. Further modification of these guidelines may be necessary when more data from clinical trials and experience with the drug become available.
c) European-Australasian Study


RANDOMISED DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL OF THROMBOLYTIC THERAPY WITH INTRAVENOUS ALTEPLASE IN ACUTE ISCHAEMIC STROKE (ECASS II). SECOND EUROPEAN-AUSTRALASIAN ACUTE STROKE STUDY INVESTIGATORS.


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BACKGROUND: Thrombolytic therapy for acute ischaemic stroke has been investigated in several clinical trials, with variable results. We have assessed the safety and efficacy of intravenous thrombolysis with alteplase (0.9 mg/kg bodyweight) within 6 h of stroke onset. METHODS: This non-angiographic, randomised, double-blind, trial enrolled 800 patients in Europe, Australia, and New Zealand. Computed tomography was used to exclude patients with signs of major infarction. Alteplase (n=409) and placebo (n=391) were randomly assigned with stratification for time since symptom onset (0-3 h or 3-6 h). The primary endpoint was the modified Rankin scale (mRS) at 90 days, dichotomised for favourable (score 0-1) and unfavourable (score 2-6) outcome. Analyses were by intention to treat.

FINDINGS: 165 (40.3%) alteplase-group patients and 143 (36.6%) placebo-group patients had favourable mRS outcomes (absolute difference 3.7%, p=0.277). In a posthoc analysis of mRS scores dichotomised for death or dependency, 222 (54.3%) alteplase-group and 180 (46.0%) placebo-group patients had favourable outcomes (score 0-2; absolute difference 8.3%, p=0.024). Treatment differences were similar whether patients were treated within 3 h or 3-6 h. 85 (10.6%) patients died, with no difference between treatment groups at day 90 +/- 14 days (43 alteplase, 42 placebo). Symptomatic intracranial haemorrhage occurred in 36 (8.8%) alteplase-group patients and 13 (3.4%) placebo-group patients. INTERPRETATION: The results do not confirm a statistical benefit for alteplase. However, we believe the trend towards efficacy should be interpreted in the light of evidence from previous trials. Despite the increased risk of intracranial haemorrhage, thrombolysis with alteplase at a dose of 0.9 mg/kg in selected patients may lead to a clinically relevant improvement in outcome.

(2) Spranger M, Steiner T, Schwab S, Hacke W

ACUTE ISCHAEMIC STROKE: REVASCULARIZING THERAPY.

J Neurol 1998 Sep;245(9):567-72

Department of Neurology, University of Heidelberg, Germany.

The principal goals of thrombolytic therapy for stroke are early restitution of cerebral blood flow, reduction of ischaemia, and attenuation of neurological disability through lysis of an occluding thrombus and consequent rapid restoration of circulation in the affected territory. Therapy should be initiated as soon as possible, at least within 4-6 h of stroke onset, to prevent major infarction and to salvage the hypoperfused but potentially viable zone adjacent to the central ischaemic area known as the ischaemic penumbra. This survey focuses on the safety and efficacy of thrombolytic therapy in acute ischaemic stroke in clinical trials. The results of two successful major randomized studies using tissue plasminogen activator (t-PA) were recently published. Intravenous thrombolysis seemed to be effective in improving functional and neurological outcome in a clearly defined subgroup of patients meeting the inclusion criteria of the studies. However, the identification of those patients proved to be difficult and depended on expertise in recognizing the early infarction signs on initial computed tomography. Since treating ineligible patients is associated with an unacceptable risk of intracranial bleeding complications and death, intravenous thrombolysis should only be performed at selected centres in selected patients.

**EARLY INTRAVENOUS THROMBOLYSIS FOR ACUTE ISCHEMIC STROKE IN A COMMUNITY-BASED APPROACH.**

*Stroke* 1998 Aug;29(8):1544-9

Klinik fur Neurologie der Universität zu Köln, Germany.

**BACKGROUND AND PURPOSE:** Controlled multicenter studies have demonstrated the efficacy of systemic recombinant tissue-type plasminogen activator (rtPA) treatment in selected cases of acute ischemic stroke. The feasibility of this therapeutic option in clinical practice was assessed in a community-based approach. **METHODS:** We offered rtPA treatment to stroke patients in a prospective open-label monocenter study applying inclusion criteria similar to those of the National Institute of Neurological Disorders, and Stroke study. **RESULTS:** Of 453 consecutive patients with a presumed diagnosis of acute stroke referred to our department between March 1996 and August 1997, 100 patients (22%) were treated with intravenous thrombolysis, 26% of them within 90 minutes of symptom onset. The average time from stroke onset to arrival at our department was 78 minutes, and from arrival to treatment 48 minutes. After 3 months, 53 patients recovered to fully independent function. The rates of total, symptomatic, and fatal intracerebral hemorrhage were 11%, 5%, and 1%, respectively. Overall mortality was 12%. **CONCLUSIONS:** Thrombolysis with rtPA was effectively applied in routine management of stroke patients in a community-based approach with acceptable efforts and without additional costs. Under these circumstances, outcome and complication rates were comparable to those of multicenter trials.


**[THROMBOLYSIS CHANGES THE CARE OF STROKE]. [ARTICLE IN SWEDISH]**

*Lakartidningen* 1998 Jul 8;95(28-29):3202-11

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**Thrombolysis using tissue plasminogen activator (tPA) is not the leading strategy in the development of pharmacological treatments for acute ischaemic stroke.** The prospect of tPA becoming routine treatment in ischaemic stroke raises several issues the magnitude of the treatment load, the requisite neurological and neuroradiological diagnostic qualifications, identification of local reperfusion effects in the brain, and the pre-hospital and hospital management of acute stroke patients. The results of large randomised trials of intravenous tPA treatment are reviewed in the article, and the current state of our knowledge about interventional thrombolysis is reported. Recruitment for the second European intravenous tPA trail, ECASS II, has recently been completed, and the study findings will be available during the latter half of 1988. In the USA, tPA is already recommended treatment for acute ischaemic stroke within three hours after the onset of symptoms. In Europe, the formulation of guidelines awaits the results of ECASS II.

(5) Grond M, Rudolf J, Schmulling S, Stenzel C, Neveling M, Heiss WD

**EARLY INTRAVENOUS THROMBOLYSIS WITH RECOMBINANT TISSUE-TYPE PLASMINOGEN ACTIVATOR IN VERTEBROBASILAR ISCHEMIC STROKE.**

*Arch Neurol* 1998 Apr;55(4):466-9

Department of Neurology, University Hospital of Cologne, Germany.

**BACKGROUND:** The optimal therapy of vertebrobasilar ischemic stroke is under debate. In the case of underlying basilar artery occlusion, intra-arterial thrombolysis is recommended. Because this pathologic condition is rarely found and the procedure is time consuming and restricted to specialized centers, the question arises whether early intravenous thrombolysis could also effectively be applied in vertebrobasilar ischemic stroke. **OBJECTIVE:** To determine if early intravenous thrombolysis could be used effectively in vertebrobasilar ischemic stroke. **DESIGN:** A case series of 12 consecutive patients with acute vertebrobasilar ischemia were followed up 3 months after thrombolytic treatment at the Department of Neurology of the University Hospital of Cologne, Cologne, Germany, a primary care and
referral center. METHODS: Patients with clinically diagnosed moderate to severe vertebrobasilar ischemic stroke with clearly determined symptom onset were treated with intravenous recombinant tissue-type plasminogen activator within 3 hours after symptom onset following a protocol similar to that of the National Institute of Neurological Disorders and Stroke study. RESULTS: On admission, 7 patients exhibited moderate to severe brainstem symptoms without impairment of consciousness and 5 patients had impairment of consciousness, of whom 2 were comatose. Of 12 patients, 10 had a favorable outcome after 3 months defined as full independence (Barthel index score of 100) or return to premorbid condition. One patient had a poor outcome with complete dependency due to reocclusion after primarily successful thrombolysis, and 1 patient died of severe brainstem infarction and additional space occupying parietal hemorrhage. CONCLUSION: Favorable outcome could be achieved in the majority of 12 consecutive patients with moderate to severe vertebrobasilar ischemic stroke treated with intravenous recombinant tissue-type plasminogen activator within 3 hours after symptom onset.


(6) Wardlaw JM, Warlow CP, Counsell C
SYSTEMATIC REVIEW OF EVIDENCE ON THROMBOLYTIC THERAPY FOR ACUTE ISCHAEMIC STROKE.

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BACKGROUND: Recent trials of thrombolytic therapy in acute ischaemic stroke have given apparently conflicting results. Only one trial, the National Institute of Neurological Disorders and Stroke trial of tissue plasminogen activator (tPA), suggested that thrombolysis was definitely beneficial. To make sense of these results, we have done a systematic review of all available randomised trials of thrombolysis in acute ischaemic stroke. METHODS: From all available completed randomised trials of thrombolytic therapy compared with control in acute ischaemic stroke (with prerandomisation CT), we checked tabular data on deaths during roughly the first 2 weeks, deaths from all causes and functional outcome (disability) at the end of the trial follow-up period, and early symptomatic and fatal intracranial haemorrhages. FINDINGS: 12 trials included 3435 patients, of whom 694 (20%) were dead and 1001 (39%) of 2567 were functionally dependent at the end of follow-up (duration of follow-up varied between trials, but the longest was 6 months). 214 (6%) of the 3435 patients had early symptomatic or fatal intracranial haemorrhages. Thrombolytic therapy was associated with a significant excess of early deaths (91 per 1000 patients treated [95% CI 54-134]), and total deaths (37 per 1000 [20-83]), but there was nevertheless a significant reduction in the number of patients in the combined outcome of dead or dependent (65 fewer per 1000 patients treated [28-107]). There was a substantial and significant excess of symptomatic and fatal intracranial haemorrhages with thrombolysis—which was similar in all recent trials-of about 70 extra symptomatic intracranial haemorrhages per 1000 patients treated (of which 51 per 1000 were fatal). In the cohort of patients randomised within 3 h of stroke, there was a significant reduction in the number of patients who were dead or dependent at the end of follow-up (141 fewer dead or dependent per 1000 patients treated [75-206] and a non-significant increase in the number dead (nine per 1000 treated [-39 to 70]). There was significant heterogeneity between the trials for total deaths at the end of follow-up, which may be partly explained by differences in the use of antithrombotic drugs within the first 24 h of thrombolysis; the variation in severity of strokes included: the time window to thrombolytic treatment; and the dose of thrombolytic drug used. There were no direct comparisons of tPA with streptokinase or urokinase: much of the poor outcome in the streptokinase-treated patients might be explained by differences in the use of antithrombotic drugs, higher doses, and the longer time to treatment compared with the trials that used tPA.

INTERPRETATION: Thrombolysis requires further testing in large randomised trials because the risks seem substantial, and the benefit uncertain. The time window for effective treatment remains unclear. There is no objective evidence to suggest that tPA is safer than streptokinase; the apparent hazards and benefits may be similar when differences in trial design and baseline variables are accounted for.

d) NIDS trial
(1) Luisi A, Hume AL

**THROMBOLYSIS IN ACUTE ISCHEMIC STROKE.**


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The administration of rt-PA to patients with acute ischemic stroke can result in improved functional outcomes. The safe and effective use of rt-PA in routine medical practice requires that patients seek help early, have a well-defined onset of their symptoms, be carefully examined for contraindications to rt-PA, receive a CT scan and interpretation to exclude hemorrhage, and receive the drug within a 3-hour period (Table 5). Intravenous rt-PA is given in a dosage of 0.9 mg/kg (up to a maximum of 90 mg) with 10 percent of the dose administered as a bolus followed by a 60-minute infusion within 3 hours of the onset of symptoms. If these conditions cannot be achieved, the drug should not be administered. Although most patients will not meet the criteria of the NINDS trial, rt-PA is an important advance in the treatment of acute ischemic stroke.


**CODE STROKE: RAPID TRANSPORT, TRIAGE AND TREATMENT USING RT-PA THERAPY. THE NINDS RT-PA STROKE STUDY GROUP.**

*J Neurosci Nurs* 1997 Dec;29(6):361-6

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With the approval of rt-PA therapy for ischemic stroke, stroke care has acutely transitioned from focusing on rehabilitative services to emergency services. This treatment, which must be initiated within the first three hours after the onset of stroke symptoms, requires reorganization of current management approaches. Developing a Code Stroke Team facilitates this process and helps to identify potential thrombolysis candidates. A pathway to deliver rapid care begins with 911 notification and transport, emergency department triage and procedures, and moves through the initiation of thrombolytic therapy. We call this pathway "Code Stroke".


**NURSING MANAGEMENT OF ACUTE COMPLICATIONS FOLLOWING RT-PA IN ACUTE ISCHEMIC STROKE. THE NINDS RT-PA STROKE STUDY GROUP.**

*J Neurosci Nurs* 1997 Dec;29(6):367-72

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In the National Institutes of Neurologic Disorders and Stroke (NINDS) recombinant tissue plasminogen activator (rt-PA) stroke trial, the primary adverse events monitored were intracranial hemorrhage (ICH), systemic bleeding, death and new stroke. Nurses caring for the study patients noted these adverse events and other complications. In addition to what is known about acute ischemic stroke (AIS), the NINDS trial provides further information for optimal care of this specific group of patients. The complications found in this trial require expert nursing care to monitor, prevent and intervene, making clinical decisions relevant to the patients needs. The critical decision-making process must be grounded in knowledge of acute stroke physiology and thrombolysis.

(4) NINDS t PA Study investigators

**GENERALIZED EFFICACY OF T-PA FOR ACUTE STROKE. SUBGROUP ANALYSIS OF THE NINDS T-PA STROKE TRIAL.**

*Stroke* 1997 Nov;28(11):2119-25

BACKGROUND AND PURPOSE: We sought to identify subgroups of stroke patients in whom thrombolytic therapy is particularly hazardous or efficacious. METHODS: We conducted a post hoc subgroup analysis of a randomized, double-blind, placebo-controlled clinical trial of intravenous tissue plasminogen activator (t-PA) for stroke patients presenting within 3 hours after symptom onset. Before treatment, historical, physical, and laboratory findings were summarized. We identified variables that might predict outcome and/or differential response to t-PA therapy. Outcome was measured with four stroke rating scales administered 3 months after treatment. Statistical significance was assessed
with a global outcome procedure that considers the results of all four scales simultaneously. Using regression analysis, we compared the information collected before treatment with the global outcome. Multivariable procedures were used to find information that could guide selection of patients for t-PA therapy.

**RESULTS:** No pretreatment information significantly affected patients response to t-PA. The power of the model to detect a treatment interaction was greater than 90%, and therefore the probability of a type II error is very low. Apart from t-PA therapy, outcome was related to age-by-deficit severity interaction, diabetes, age-by-blood pressure interaction, and early CT findings. These variables and interactions altered long-term patient outcome irrespective of t-PA treatment but did not alter the likelihood of responding favorably to t-PA therapy. **CONCLUSIONS:** Patients should be selected for t-PA thrombolysis according to the guidelines published in the report of the NINDS t-PA Stroke Trial. Further subselection of patients, such as by age or stroke severity, is not supported by our post hoc analysis.

(5) Alberts MJ

**HYPERACUTE STROKE THERAPY WITH TISSUE PLASMINOGEN ACTIVATOR.**

*Am J Cardiol* 1997 Aug 28;80(4C):29D-34D; discussion 35D-39D

Division of Neurology, Duke University Medical Center, Durham, North Carolina 27710, USA.

The past year has seen tremendous progress in developing new therapies aimed at reversing the effects of acute stroke. Thrombolytic therapy with various agents has been extensively studied in stroke patients for the past 7 years. Tissue plasminogen activator (t-PA) received formal US Food and Drug Administration approval in June 1996 for use in patients within 3 hours of onset of an ischemic stroke. Treatment with t-PA improves neurologic outcome and functional disability to such a degree that, for every 100 stroke patients treated with t-PA, an additional 11-13 will be normal or nearly normal 3 months after their stroke. The downside of t-PA therapy is a 6% rate of symptomatic intracerebral hemorrhage (ICH) and a 3% rate of fatal ICH. Studies are under way to determine whether t-PA can be administered with an acceptable margin of safety within 5 hours of stroke, to evaluate the therapeutic benefits of intraarterial pro-urokinase, and to assess the use of magnetic resonance spectroscopy to identify which patients are most likely to benefit from thrombolysis. Combination thrombolytic-neuroprotectant therapy is also being studied. In theory, patients could be given an initial dose of a neuroprotectant by paramedics and receive thrombolytic therapy in the hospital. We are now entering an era of proactive, not reactive, stroke therapies. These treatments may reverse some or all acute stroke symptoms and improve functional outcomes.

(6) Tong DC, Yenari MA, Albers GW

**INTRAVENOUS THROMBOLYTIC THERAPY IN ACUTE STROKE.**

*Vasc Med* 1997;2(1):51-60

Department of Neurology, Stanford University Medical Center, California, USA.

The article reviews the experimental basis of thrombolytic therapy, and summarizes the results of the recent trials of thrombolysis. Five large clinical trials have evaluated intravenous thrombolytic therapy for the treatment of hyperacute (< 6 h) stroke. Three of these studies were negative, one was equivocal, and one was strongly positive. The failure of demonstrate efficacy definitively in four of these trials may be related to a number of methodological factors, including the type and dose of drug administered, the timing of drug administered, and the method of patient selection for treatment. The NINDS recombinant tissue plasminogen activator (rt-PA) study showed that thrombolytic therapy can be of substantial benefit when administered within 3 h of stroke onset using strict patient selection criteria and rt-PA is now FDA approved for treatment of acute stroke. However, the risk of clinically significant bleeding is elevated. To achieve the favorable risk/benefit ratio demonstrated in the NINDS trial, patients must be screened by experienced clinicians for contraindications to thrombolysis and the acute computerized tomography (CT) brain scan must be carefully evaluated for radiographic features that increase the risk of cerebral hemorrhage. Guidelines for the use of rt-PA are provided, as well as insights into future thrombolytic treatment strategies.

10. tPA intraarterial Leg Thrombolysis
(1) Sandison AJ, Edmondson RA, Panayiotopoulos Y, Reidy JF, McColl I, Taylor PR
SUCCESSFUL INTRAARTERIAL THROMBOLYSIS OF AN ISCHEMIC LIMB FOUR
DAYS AFTER LAPAROSCOPIC CHOLECYSTECTOMY.


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Intraarterial thrombolysis is usually contraindicated after abdominal surgery because of the risk of bleeding. However, it is a highly effective treatment for embolic acute limb ischemia, particularly for clearing the distal vessels. We report a case in which intraarterial thrombolysis was safely used 4 days after laparoscopic cholecystectomy in a patient with an acutely ischemic leg due to embolus.

(2) Braithwaite BD, Davies B, Birch PA, Heather BP, Earnshaw JJ
MANAGEMENT OF ACUTE LEG ISCHAEMIA IN THE ELDERLY.


Department of Surgery, Gloucestershire Royal Hospital, UK.

**BACKGROUND:** Peripheral thrombolysis is advocated by some as the best initial treatment for acute leg ischaemia; but this may not be true for elderly patients. This study reviewed the management of acute leg ischaemia in patients aged over 75 years. **METHODS:** Over a 5-year interval, 91 events of acute leg ischaemia in 84 patients were managed in a single district general hospital according to a local protocol. There were 60 women and 24 men of median age 81 (range 75-100) years. Fifteen patients were too elderly and infirm for active treatment and received anticoagulation alone. Some 76 events (84 per cent) occurred in patients suitable for active therapy; 33 were managed by initial surgery and 43 by peripheral thrombolysis with tissue plasminogen activator. **RESULTS:** Overall outcome after 30 days was limb salvage in 48 (53 per cent), amputation in five (5 per cent) and death in 38 (42 per cent). In actively treated patients the corresponding values were 43 (57 per cent), four (5 per cent) and 29 (38 per cent). Initial successful revascularization was more likely following surgery (29 of 33 versus 25 of 43 events with thrombolysis, P < 0.01), but the 30-day outcome was similar in the actively treated groups owing to subsequent morbidity and mortality. **CONCLUSION:** A group of patients (mostly women) with emboli could be identified, using clinical criteria, who had a high chance of successful revascularization following embolectomy. Late outcome remained poor due to associated co-morbid conditions. Thrombolysis is associated with substantial risk in the elderly, and with high complication rates.

11. tPA in Deep Vein Thrombosis (DVT)

(1) Verhaeghe R, Stockx L, Lacroix H, Vermyleen J, Baert AL
CATHETER-DIRECTED LYSIS OF IlioFEMORAL VEIN THROMBOSIS WITH USE OF RT-PA.

*Eur Radiol* 1997;7(7):996-1001

Department of Radiology, Centre of Vascular Pathology, University Hospital Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium.

The aim of our study was to evaluate the results of catheter-directed thrombolysis and complementary procedures to treat acute iliofemoral deep vein thrombosis (DVT). A total of 24 consecutive patients with acute iliofemoral DVT underwent intrathrombus drip infusion of alteplase (3 mg/h; mean dosage 86 mg, range 45-174 mg), while intravenous heparin (1000 U/h) was continued. Complementary procedures were hydrodynamic thrombectomy in 3 and primary insertion of a Wallstent in 9 patients. Patency of 19 thrombosed veins (79 %) was restored with prompt symptomatic relief. An underlying anatomical anomaly or lesion was present in 13 patients: iliac vein compression syndrome (n = 8), absent (n = 2) or obstructed (n = 1) vena cava or venous stenosis (n = 2). Ten of the abnormalities were known before lysis and eight were relieved by stent deployment. Puncture site bleeding was the only complication but led to transfusion in 6 patients (25 %). Symptomatic recocclusion occurred in 4 patients. Catheter thrombolysis of iliofemoral vein thrombosis revealed many anatomical abnormalities which may predispose to thrombosis and are often amenable to stenting.
12. tPA for Ophthalmologic Thrombolysis in Submacular Hemorrhage

(1) Humayun M, Lewis H, Flynn HW Jr, Sternberg P Jr, Blumenkranz MS

**MANAGEMENT OF SUBMACULAR HEMORRHAGE ASSOCIATED WITH RETINAL ARTERIAL MACROANEURYSMS.**

_Am J Ophthalmol_ 1998 Sep;126(3):358-61

Division of Ophthalmology, The Cleveland Clinic Foundation, Ohio 44195, USA.

PURPOSE: Experience is reported with intraoperative pharmacologic lysis of recent submacular hemorrhage with tissue plasminogen activator followed by surgical drainage of the unclotted blood in patients with retinal arterial macroaneurysms. METHODS: Nine eyes (nine patients) with a recent (< or = 7 days old) submacular hemorrhage involving the center of the fovea secondary to retinal arterial macroaneurysms that were managed with recombinant tissue plasminogen activator-assisted subretinal hemorrhage evacuation, including subretinal injection of tissue plasminogen activator and removal of the liquefied blood. Patients were followed for a mean 18 +/- 7 months (range, 7 to 30 months), RESULTS: All nine eyes had improved final corrected visual acuity after surgery, and eight eyes (89%) attained a corrected visual acuity of 20/60 or better (mean, 20/40; range, 20/20 to 20/200). Final corrected visual acuity was limited to 20/200 in one eye. Two eyes developed a cataract that required surgery. CONCLUSIONS: Submacular surgery with tissue plasminogen activator-assisted thrombolysis achieved improved best-corrected visual acuity in eyes with recent submacular hemorrhage involving the center of the fovea associated with retinal arterial macroaneurysm.

13. tPA in Kawasaki disease

(1) Horigome H, Sekijima T, Miyamoto T

**SUCCESSFUL THROMBOLYSIS WITH INTRACORONARY ADMINISTRATION OF TISSUE PLASMINOGEN ACTIVATOR IN AN INFANT WITH KAWASAKI DISEASE.**

_Heart_ 1997 Nov;78(5):517-8

Department of Pediatrics, University of Tsukuba, Japan.

B. tPA Complications

1. tPA induced Intracranial Hemorrhage

(1) Gurwitz JH, Gore JM, Goldberg RJ, Barron HV, Breen T, Rundle AC, Sloan MA, French W, Rogers WJ

**RISK FOR INTRACRANIAL HEMORRHAGE AFTER TISSUE PLASMINOGEN ACTIVATOR TREATMENT FOR ACUTE MYOCARDIAL INFARCTION. PARTICIPANTS IN THE NATIONAL REGISTRY OF MYOCARDIAL INFARCTION 2.**


University of Massachusetts Medical School and the Fallon Healthcare System, Worcester 01608, USA.

BACKGROUND: The efficacy of thrombolytic therapy in reducing mortality from acute myocardial infarction has been unequivocally shown. However, thrombolysis is related to bleeding complications, including intracranial hemorrhage. OBJECTIVE: To determine the frequency of and risk factors for intracranial hemorrhage after recombinant tissue-type plasminogen activator (tPA) given for acute myocardial infarction in patients receiving usual care. DESIGN: Large national registry of patients who have had acute myocardial infarction. SETTING: 1484 U.S. hospitals. PATIENTS: 71073 patients who had had acute myocardial infarction from 1 June 1994 to 30 September 1996, received tPA as the initial reperfusion strategy, and did not receive a second dose of any thrombolytic agent. MEASUREMENT: Intracranial hemorrhage confirmed by computed tomography or magnetic resonance imaging. RESULTS: 673 patients (0.95%) were reported to have had intracranial hemorrhage during hospitalization for acute myocardial infarction; 625 patients (0.88%) had the event confirmed by computed tomography or magnetic resonance imaging. Of the 625 patients with confirmed intracranial hemorrhage, 331 (53%) died during hospitalization. An additional 158
patients (25.3%) who survived to hospital discharge had residual neurologic deficit. In multivariable models for the main effects of candidate risk factors, older age, female sex, black ethnicity, systolic blood pressure of 140 mm Hg or more, diastolic blood pressure of 100 mm Hg or more, history of stroke, tPA dose more than 1.5 mg/kg, and lower body weight were significantly associated with intracranial hemorrhage. CONCLUSIONS: Intracranial hemorrhage is a rare but serious complication of tPA in patients with acute myocardial infarction. Appropriate drug dosing may reduce the risk for this complication. Other therapies, such as primary coronary angioplasty, may be preferable in patients with acute myocardial infarction who have a history of stroke.

(2) Gebel JM, Sila CA, Sloan MA, Granger CB, Mahaffey KW, Weisenberger J, Green CL, White HD, Gore JM, Weaver WD, Califf RM, Topol EJ

THROMBOLYSIS-RELATED INTRACRANIAL HEMORRHAGE: A RADIOGRAPHIC ANALYSIS OF 244 CASES FROM THE GUSTO-1 TRIAL WITH CLINICAL CORRELATION. GLOBAL UTILIZATION OF STREPTOKINASE AND TISSUE PLASMINOGEN ACTIVATOR FOR OCCLUDED CORONARY ARTERIES.


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BACKGROUND AND PURPOSE: Intracranial hemorrhage (ICH) is a serious complication of thrombolytic therapy. We systematically reviewed the radiographic features of 244 cases of symptomatic ICH complicating thrombolysis for acute myocardial infarction in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-1) trial, correlated these observations with clinical data, and speculated on hemorrhage pathogenesis. METHODS: CT scans from 244 patients suffering symptomatic ICH were systematically reviewed for selected radiographic features, including ICH type, location, hematoma characteristics, mass effect features, hydrocephalus, and preexisting lesions. Hematoma volume was estimated by computer-assisted volumetric analysis. Data from this analysis were correlated with clinical data including hypertension, anticoagulation, age, thrombolytic regimen, and ICH timing. RESULTS: Most hemorrhages were large (median [25th, 75th percentile] volume, 72 mL [39, 118]), solitary (66%), lobar (77%), confluent (80%), and intraparenchymal (82%) with a blood/fluid level (82%) and little edema (median [25th, 75th percentile] volume, 9 mL [5, 16]). Hydrocephalus (P<.001), any one mass effect feature (P<.001), intraventricular hemorrhage (P=.022), mottled hematoma appearance (P=.050), and hematoma blood/fluid level (P<.001) were associated with higher hemorrhage volume in the radiographic analysis, as were older age (P=.005), treatment with combined streptokinase and tissue plasminogen activator (P=.034), and hemorrhage onset 8 to 13 hours after treatment (P=.008) in the clinical analysis. Subdural hemorrhage was a high-volume subgroup whose risk increased with antecedent trauma (P=.026) or syncope (P=.006). Deep intraparenchymal hemorrhage was associated with hypertension (P=.016), and multifocal ICH occurred significantly earlier after treatment (P=.002). CONCLUSIONS: Although the majority of postthrombolytic ICH are large, solitary, and supratentorial, the spectrum is diverse. Features of mass effect reflected the large volumes, and hematoma characteristics of mottling and blood/fluid levels were frequent. Thrombolysis-related coagulopathy and age appear to be the most important identifiable factors in the genesis of postthrombolytic ICH, but the hemorrhage subtype seen may reflect an interaction with other factors such as hypertension, ICH timing, antecedent head trauma, and syncope.

(3) Serebruany VL, Gurbel PA, Shustov AR, Dalesandro MR, Gumbs CI, Grabletz LB, Bahr RD, Ohman EM, Topol EJ

DEPRESSED PLATELET STATUS IN AN ELDERLY PATIENT WITH HEMORRHAGIC STROKE AFTER THROMBOLYSIS FOR ACUTE MYOCARDIAL INFARCTION. GUSTO-III INVESTIGATORS.

Stroke 1998 Jan;29(1):235-8

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BACKGROUND: Impaired platelet function has been reported in acute myocardial infarction (AMI) and stroke. However, prospective data on the changes of platelet status in patients before the occurrence of hemorrhagic stroke after thrombolytic therapy are unavailable. CASE DESCRIPTION: An 86-year-old male patient was among the 23 AMI patients enrolled in the platelet study for the GUSTO-III trial. He received 325 mg of aspirin daily for at least 6 years, suffered an AMI, and was
successfully reperfused with alteplase, but after 44 hours developed a large hemorrhagic stroke resulting in paraplegia. Platelet aggregation and receptor expression were measured by flow cytometry and ELISA before thrombolysis and at 3, 6, 12, and 24 hours thereafter. The percentage of platelet aggregation was lower in the stroke patient at every time point when induced by 5 micromol/L of ADP, by 10 micromol/L of ADP, and by thrombin than in the rest of the AMI group. Ristocetin and collagen-induced aggregability were within the group range. Decreased platelet glycoprotein Ib, IIb, IIIa, and IIb/IIIa and vitronectin receptor expression were observed in the stroke patient. No other differences in p24 (CD9), very late antigen-2, P-selectin, and platelet/endothelial cell adhesion molecule-1 expression were determined. CONCLUSIONS: Profound depression of platelet status preceded the occurrence of hemorrhagic stroke in an elderly long-term aspirin user treated with thrombolytic therapy. Initial "exhausted" platelets may be responsible for the increased risk for hemorrhagic stroke after coronary thrombolysis. Comment in: Stroke 1998 Sep;29(9):2002-3

2. tPA induced Hemorrhagic Ocular Complications

(1) Chorich LJ, Derick RJ, Chambers RB, Cahill KV, Quartetti EJ, Fry JA, Bush CA
HEMORRHAGIC OCULAR COMPLICATIONS ASSOCIATED WITH THE USE OF SYSTEMIC THROMBOLYTIC AGENTS.

Department of Ophthalmology, Ohio State University College of Medicine, Columbus, USA. OBJECTIVE: This study aimed to report three patients with hemorrhagic ocular and orbital complications associated with the use of systemic thrombolytic agents. DESIGN: The study design was a retrospective small case series. PARTICIPANTS: Three eyes of three patients were studied. INTERVENTION: Surgical procedures to reduce intraocular pressure or relieve optic nerve compression were performed. MAIN OUTCOME MEASURES: Visual acuity and intraocular pressure were measured. RESULTS: Three patients received an intravenous thrombolytic agent on diagnosis of an acute myocardial infarction. One patient had a spontaneous suprachoroidal hemorrhage develop with secondary acute angle closure glaucoma shortly after receiving tissue plasminogen activator. Another patient had an orbital hemorrhage develop on receiving tissue plasminogen activator 4 days after an uncomplicated cataract extraction. The third patient experienced an orbital hemorrhage while receiving streptokinase 1 day after undergoing an external levator resection. Two patients suffered significant visual loss due to glaucoma or compressive optic neuropathy. CONCLUSIONS: The onset of eye pain or visual loss after the administration of a systemic thrombolytic agent should alert the physician to the possibility of an ocular or adnexal hemorrhage. Prompt diagnosis and treatment can improve the likelihood of a favorable visual outcome.

3. tPA induced Hemopericardium, Cardiac Tamponade

(1) Kasner SE, Villar-Cordova CE, Tong D, Grotta JC
HEMOPERICARDIUM AND CARDIAC TAMPOANDE AFTER THROMBOLYSIS FOR ACUTE ISCHEMIC STROKE.

University of Pennsylvania Medical Center, Philadelphia, USA. Hemorrhage is the major complication of IV recombinant tissue plasminogen activator (rt-PA) treatment for stroke. We report three patients with mild or indistinct cardiac symptoms prior to thrombolysis in whom hemodynamically significant cardiac tamponade occurred after treatment with rt-PA. Acute ischemic stroke patients may have undetected myocardial or pericardial disease that may pose a risk for hemopericardium and life-threatening tamponade after treatment with rt-PA.

C. Urokinase (UK)

A. Function and Fields of Use
1. UK in Acute Arterial Thrombosis

MECHANICAL THROMBOLYSIS OF ACUTE OCCLUSION OF BOTH THE SUPERFICIAL AND THE DEEP FEMORAL ARTERIES USING A THROMBECTOMY DEVICE.
AJR Am J Roentgenol 1998 May;170(5):1177-80

Department of Radiology, University of Ulm, Germany.
OBJECTIVE: Our objective was to evaluate the efficacy of the Amplatz thrombectomy device for recanalization of acute occlusions of both the superficial and the deep femoral arteries. MATERIALS AND METHODS: Eighteen patients with acute occlusions of the femoral arteries (eight male, 10 female; 10-87 years old) were treated using the Amplatz thrombectomy clot macerator. The duration of occlusion was 16 +/- 8 hr. Eighteen patients underwent treatment of the deep femoral artery, and 16 patients had additional involvement of the superficial femoral artery. After primary recanalization of the deep femoral artery, the superficial femoral artery was also recanalized using the Amplatz thrombectomy device. Nine patients required additional aspiration thrombectomy of the tibial arteries, five patients required additional aspiration thrombectomy of side branches of the deep femoral artery, and 12 patients required additional local thrombolysis with urokinase. RESULTS: In 14 (78%) of 18 patients, recanalization of the deep femoral artery was complete without demonstrable residual thrombi. Arterial spasms were observed in five patients (28%). The rate of limb salvage was 94% at a mean follow-up interval of 8.9 +/- 4.1 months. In the 18 patients, the ankle-brachial pressure index went from a median value of 0.56 before therapy to a median value of 0.91 after therapy. No severe complications occurred. CONCLUSION: Mechanical thrombolysis in the deep femoral artery with the Amplatz thrombectomy device is an effective, rapid method of treatment and is rarely associated with complications. In cases of concomitant occlusion of the tibial arteries, recanalization should always be attempted because the deep femoral artery may provide a functionally decisive collateral artery between the iliac and tibial vasculature.

(2) Neudeck BL, Blumenschein K, Endean ED, Loh FK, Rapp RP
INTRA-ARTERIAL UROKINASE VERSUS SURGERY FOR ACUTE PERIPHERAL ARTERIAL OCCLUSION.
Am J Health Syst Pharm 1997 Sep 1;54(17):1963-8

College of Pharmacy, University of Michigan, Ann Arbor, USA.
The outcomes of intra-arterial urokinase versus surgery for acute peripheral arterial occlusion (PAO) were compared. Patients at a university hospital who had received intraarterial urokinase for PAO were identified by computer and pair-matched on the basis of comorbidities, age, sex, and site of occlusion to computer-selected patients who had undergone surgery. Only patients with category I or II ischemia were considered. The study period for the urokinase group was February 1995 through January 1996, and the period for the surgery group was June 1993 through January 1996. Twenty-eight patients in each group met the selection criteria. Patients who had received urokinase had a significantly shorter median length of stay (8.5 days) than patients in the surgery group (13 days) and significantly fewer infectious complications (2 versus 10). No differences in amputation rates, total hospital costs, or mortality rates were detected. Patients who received intra-arterial urokinase for PAO had a shorter length of stay in the hospital and fewer infectious complications than those who underwent surgery.

2. UK in Deep Vein Thrombosis

(1) Schweizer J, Elix H, Altmann E, Hellner G, Forkmann L
COMPARATIVE RESULTS OF THROMBOLYSIS TREATMENT WITH RT-PA AND UROKINASE: A PILOT STUDY.

Clinic of Internal Medicine I, Chemnitz Hospital, Dresden, Germany.
BACKGROUND: The aim of the following prospective study was to investigate whether patients benefited from locoregional lysis treatment of recent deep leg vein thrombosis after 1 year. PATIENTS AND METHODS: The prospective study included 69 patients aged between 22 and 58 years, in whom recent lower leg vein and popliteal vein thromboses were diagnosed by phlebography. Patients were randomized to one of three treatment groups: (1) one group was treated for a maximum of 7 days with full heparinization and daily dose of 20 mg rt-PA administered locoregionally over a period of 4 hours; (2) a second group received 100,000 IU/h urokinase locoregionally for a maximum of 7 days, in addition to full heparinization; and (3) in the third group (control group), intravenous heparin infusions after PTT constituted the only form of treatment. All patients were given phenprocoumon from day 7 and received compression treatment. Before treatment began and before the course of phenprocoumon started, phlebography and colour duplex sonography examinations were carried out. After 12 months, follow-up duplex sonography was conducted to evaluate the reflux times over the popliteal vein and the degree of patency of the deep leg veins. RESULTS: Complete lysis was achieved in 6 of 22 patients in the recombinant tissue plasminogen activator (rt-PA) group and in 11 of 22 patients in the urokinase group. At follow-up examination after 12 months, there were serious post-thrombotic changes in 14 of 22 patients in the rt-PA group, in 9 of 22 patients in the urokinase group and in 15 of 22 patients in the group of patients who received no lysis treatment. CONCLUSION: Patients with recently formed thromboses in the lower leg and popliteal veins who underwent 7 days of locoregional lysis treatment with urokinase demonstrated significantly fewer clinical symptoms of post-thrombotic syndrome after 1 year than those who received locoregional treatment with rt-PA over a similar period or a control group treated with anticoagulants only.

(2) Ouriel K, Veith FJ, Sasahara AA

A COMPARISON OF RECOMBINANT UROKINASE WITH VASCULAR SURGERY AS INITIAL TREATMENT FOR ACUTE ARTERIAL OCCLUSION OF THE LEGS. THROMBOLYSIS OR PERIPHERAL ARTERIAL SURGERY (TOPAS) INVESTIGATORS.


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BACKGROUND: Recent controlled trials suggest that thrombolytic therapy may be an effective initial treatment for acute arterial occlusion of the legs. A major potential benefit of initial thrombolytic therapy is that limb ischemia can be managed with less invasive interventions. METHODS: In this randomized, multicenter trial conducted at 113 North American and European sites, we compared vascular surgery (e.g., thrombectomy or bypass surgery) with thrombolysis by catheter-directed intraarterial recombinant urokinase; all patients (272 per group) had had acute arterial obstruction of the legs for 14 days or less. Infusions were limited to a period of 48 hours (mean [+/−SE], 24.4+/−0.86), after which lesions were corrected by surgery or angioplasty if needed. The primary end point was the amputation-free survival rate at six months. RESULTS: Final angiograms, which were available for 246 patients treated with urokinase, revealed recanalization in 196 (79.7 percent) and complete dissolution of thrombus in 167 (67.9 percent). Both treatment groups had similar significant improvements in mean ankle-brachial blood-pressure index. Amputation-free survival rates in the urokinase group were 71.8 percent at six months and 65.0 percent at one year, as compared with respective rates of 74.8 percent and 69.9 percent in the surgery group; the 95 percent confidence intervals for the differences were −10.5 to 4.5 percentage points at six months (P=0.43) and −12.9 to 3.1 percentage points at one year (P=0.23). At six months the surgery group had undergone 551 open operative procedures (excluding amputations), as compared with 315 in the thrombolysis group. Major hemorrhage occurred in 32 patients in the urokinase group (12.5 percent) as compared with 14 patients in the surgery group (5.5 percent) (P= 0.005). There were four episodes of intracranial hemorrhage in the urokinase group (1.6 percent), one of which was fatal. By contrast, there were no episodes of intracranial hemorrhage in the surgery group. CONCLUSIONS: Despite its association with a higher frequency of hemorrhagic complications, intraarterial infusion of urokinase reduced the need for open surgical procedures, with no significantly increased risk of amputation or death.

3. UK in Mesenterial Vein Thrombosis
(1) Sanabria JR, Hiruki T, Szalay DA, Tandan V, Gallinger S

**SUPERIOR MESENTERIC VEIN THROMBOSIS AFTER THE WHIPPLE PROCEDURE: AN AGGRESSIVE, COMBINED TREATMENT APPROACH.**

*Can J Surg* 1997 Dec;40(6):467-70

Department of Surgery, Mount Sinai Hospital, University of Toronto, Ont.

It is now recognized that occlusion of the mesenteric veins not only may complicate a number of disease processes but may occur as a life-threatening complication after abdominal surgery. A 32-year-old woman had mesenteric venous thrombosis after resection of a duodenal inflammatory pseudotumour by pancreatoduodenectomy. She recovered fully after treatment, which consisted of thrombectomy, flushing with urokinase and intravenous administration of heparin. Papaverine infused for 4 days substantially improved bowel viability. Current concepts in mesenteric vein occlusion and the principles of clinical management are reviewed.


**SUPERIOR MESENTERIC ARTERIAL EMBOLISM: LOCAL FIBRINOLYTIC TREATMENT WITH UROKINASE.**

*Radiology* 1997 Sep;204(3):775-9

Department of Radiology, Hospital General Universitario Gregorio Maranon, Madrid, Spain.

PURPOSE: To evaluate the efficacy of intraarterial urokinase in the treatment of superior mesenteric arterial (SMA) embolism. MATERIALS AND METHODS: Within 3 years, 10 patients (six men, four women; aged 62-82 years) with angiographically proved SMA emboli were selected on the basis of absence of peritoneal signs of intestinal necrosis at physical examination and normal abdominal plain radiographs to undergo local lysis with urokinase. RESULTS: The procedure was performed without complications in all 10 patients. The embolus was successfully lysed in nine patients (90%). Clinical success was achieved in seven patients (70%); however, in one patient laparotomy was required to confirm the clinical finding. None of these patients had recurrent embolism or postischemic intestinal stenosis during follow-up (mean, 11.2 months). The three remaining patients (30%) underwent laparotomy subsequent to failure of intraarterial treatment with urokinase. CONCLUSION: Fibrinolytic treatment with urokinase may be an effective alternative to surgical embolectomy in patients with SMA embolism without clinical or radiologic signs of intestinal infarction. In this small series, abatement of abdominal pain in the 1st hour of fibrinolytic treatment was the best indicator of clinical success. Pain persisted in patients with intestinal infarction.

4. UK in Pulmonary Thromboembolism

(1) Satoh A, Daimaru O, Magaki K, Morishita M, Katoh H, Kawajiri T, Miyara H, Sakurai E, Tutui S, Oguri T

**[PULMONARY THROMBOEMBOLISM THAT DEVELOPED DURING AN AIRPLANE FLIGHT "ECONOMY-CLASS SYNDROME"].***[ARTICLE IN JAPANESE]*


2nd Department of Internal Medicine, Aichi Medical University, Japan.

The occurrence of thromboembolic phenomena during long-duration airplane flights is called "economy-class syndrome". Recently it has become more popular for Japanese to go abroad by airplane, and an increase in the prevalence of pulmonary thromboembolism should be expected. However, there are few reports of the economy-class syndrome in Japan. A 52-year-old woman was admitted to our hospital because of chest discomfort and dyspnea that developed during an airplane flight. We suspected pulmonary thromboembolism, on the basis of a chest X-ray film and on electrocardiogram. A ventilation-perfusion lung scan disclosed mismatching between ventilation and perfusion in the right upper lung field. Pulmonary thromboembolism was confirmed by pulmonary arteriography. The patient was treated with heparin and urokinase. A phlebogram of the legs showed no significant findings. There was no history of thromboembolic disease or of consumption of oral contraceptives. We conclude that the pulmonary thromboembolism might have been caused by stasis of blood in the lower limb veins during the airplane flight. We emphasize the importance of including pulmonary
thromboembolism in the differential diagnosis of patients with chest discomfort and dyspnea that develop during airplane flights. No noninvasive test can lead to a definitive diagnosis of pulmonary thromboembolism. Early pulmonary angiography should be recommended when pulmonary thromboembolism is suspected.

(2) Soltesz S, Berg K, Molter G
[SUCCESSFUL THROMBOLYSIS OF A FULMINANT LUNG EMBOLISM DURING CARDIOPULMONARY RESUSCITATION]. [ARTICLE IN GERMAN]
Anaesthesist 1997 Oct;46(10):890-4
Klinik fur Anaesthesiologie und Intensivmedizin, Universitätskliniken des Saarlandes, Homburg.
A healthy 38-year-old woman suffered a sudden cardiac arrest 2 days after a vaginal hysterectomy. Although standard cardiac life support (CPR) was instituted immediately after the event, it was not possible to re-establish a spontaneous circulation for about 40 min. Systemic intravenous thrombolytic therapy with slow injection of 1.5 million IU urokinase was performed as a final life-maintaining measure because of the high probability that the underlying cause was a pulmonary embolus; 10 min later (after 60 min of ongoing CPR) the patient regained a stable circulation. She survived without neurological deficit in spite of the long duration of CPR.

(3) Bousamra M 2nd, Mewissen MW, Batter J, Presberg KW, Schlüeter DP, Haasler GB
PULMONARY ARTERY THROMBOLYSIS AND STENTING AFTER A BILATERAL SEQUENTIAL LUNG TRANSPLANTATION.
J Heart Lung Transplant 1997 Jun;16(6):678-80
Department of Cardiothoracic Surgery, Medical College of Wisconsin, Milwaukee, USA.
Bilateral sequential lung transplantation was complicated by pulmonary artery anastomotic stenosis and bilateral pulmonary thromboemboli. Pulmonary artery thrombus was eliminated by intrathrombotic but not by systemic administration of urokinase. The pulmonary emboli resulted in localized pulmonary infarctions, supporting the need for thrombolytic intervention to restore pulmonary perfusion in the absence of collateral bronchial blood flow after lung transplantation. Pulmonary artery stenosis was relieved by endovascular stenting, avoiding an early reoperative procedure. This case suggests that direct administration of thrombolytic agent may be superior to intravenous administration in the treatment of pulmonary thromboemboli. Pulmonary arterial anastomotic stenoses after lung transplantation can be relieved by endovascular procedures.

5. UK in IntraVentricular Cerebral Hemorrhage

(1) Coplin WM, Vinas FC, Agris JM, Buciuc R, Michael DB, Diaz FG, Muizelaar JP
A COHORT STUDY OF THE SAFETY AND FEASIBILITY OF INTRAVENTRICULAR UROKINASE FOR NONANEURYSMAL SPONTANEOUS INTRAVENTRICULAR HEMORRHAGE.
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BACKGROUND AND PURPOSE: Small case series have reported potential benefit from thrombolysis after spontaneous intraventricular hemorrhage (IVH). Our objective was to review our experience using intraventricular urokinase (UK) in treating selected patients with IVH. METHODS: Using medical records, we identified all patients who received ventriculostomies for CT-confirmed nonaneurysmal nontraumatic spontaneous IVH from December 1992 through November 1996. We reviewed charts and CT images and examined the data for associations with specific outcomes. RESULTS: We identified 40 patients, 18 treated with ventriculostomy alone and 22 receiving adjunctive intraventricular UK. The initial Glasgow Coma Scale (GCS) scores of the two groups were similar (P = 0.5). While there was a trend for patients with any intraparenchymal hemorrhage (IPH) to receive UK (P = 0.07), the mean size of IPH in those who received ventriculostomy alone was larger than in those who received adjunctive UK (P = 0.002). There was lower mortality in the group treated with
UK (31.8 versus 66.7%; P = 0.03), but there was only a trend toward an increase in favorable outcome (22.2% versus 36.4%; P = 0.3). Overall, the most significant association with outcome was neurological condition at presentation (GCS >5 versus ≤ 5; P = 0.003). Receiving UK did not increase the occurrence of complications or hospital length of stay for survivors (P = 0.5).

CONCLUSIONS: Intraventricular UK remains a safe and potentially beneficial intervention. While it appeared to lower mortality, a randomized, placebo-controlled trial is needed to explore whether the therapy can increase the incidence of favorable outcomes.

(2) Hansen AR, Volpe JJ, Goumnerova LC, Madsen JR

INTRAVENTRICULAR UROKINASE FOR THE TREATMENT OF POSTHEMORRHAGIC HYDROCEPHALUS.


Joint Program in Neonatology, Harvard Medical School, Boston, Massachusetts, USA.

This case series pilot study assessed the safety of intraventricular urokinase administration, alternating with cerebrospinal fluid (CSF) drainage. A secondary objective was to comment on whether this therapy achieves fibrinolysis, and whether this fibrinolysis is sufficient to prevent progression of hydrocephalus to requirement for ventriculoperitoneal shunt. Six preterm infants with progressive posthemorrhagic hydrocephalus requiring treatment with a ventricular drain received an infusion of intraventricular urokinase alternating with CSF drainage for 3 days. Of the 6 treated patients, the median gestation at birth was 26.5 weeks and the median age at treatment was 30 days. One patient had an elevation in CSF erythrocyte count most likely due to successful clot lysis. One patient had an elevated CSF leukocyte count consistent with transient meningeal irritation. No other side effects were noted. Fibrinolysis was achieved in the CSF, as documented by markedly elevated D-dimer levels. Clot size diminished ultrasonographically. However, all 6 patients eventually required a ventriculoperitoneal shunt. We conclude that intermittent infusion of intraventricular urokinase alternating with periods of CSF drainage is probably a safe way to achieve a fibrinolytic state. However, when administered at the relatively late point in the neonatal course when a ventricular drain is required, this fibrinolytic state is not sufficient to decrease the requirement for ventriculoperitoneal shunt.

(3) Hudgins RJ, Boydston WR, Hudgins PA, Morris R, Adler SM, Gilreath CL

INTRATHECAL UROKINASE AS A TREATMENT FOR INTRAVENTRICULAR HEMORRHAGE IN THE PRETERM INFANT.


Department of Pediatric Neurosurgery, Scottish Rite Children's Medical Center, Atlanta, Ga, USA.

Despite improvements in the care of preterm infants, intraventricular hemorrhage (IVH) and posthemorrhagic hydrocephalus (PHH) continue to be frequent occurrences in this patient population. Shunt procedures in these children are frequently complicated by obstruction and/or infection. As the hydrocephalus is usually caused by an obliterate arachnoiditis due to contact of the blood with the basilar meninges, it was postulated that infusion of urokinase into the ventricles of infants who have sustained an IVH would clear the blood, mitigate the arachnoiditis, and prevent the progression of PHH. Accordingly, 18 preterm infants who had sustained IVH and subsequently developed PHH were treated with intraventricular urokinase instilled via a surgically implanted subcutaneous reservoir. There were no complications associated with the urokinase. Infants were divided into two dosage groups: low dose (110,000-140,000 IU total) and high dose (280,000 IU total). One infant in the low-dose group died at 1 month of life due to respiratory complications. In the low-dose group, 3 of 8 (37%) infants required shunt placement; in the high-dose group, all 9 required shunt placement. For the total group, the shunt rate was 71%. This compares to a historical control group shunt rate of 92%. While the difference between the treatment group as a whole and control group approaches, but does not reach, statistical significance (p = 0.068), there was a significant reduction in the shunt rate when the low-dose group was considered separately (p < 0.002). For those infants that required shunt placement, there were fewer shunt revisions performed in the treatment group than in the control group during the first 24 months following shunt placement: 0.67 versus 1.5 shunt revisions/shunted child. Initial experience with intraventricular urokinase following IVH and PHH in preterm infants suggests a beneficial effect in reducing the shunt revision rate in both high- and low-dose groups. Reduction in shunt placement rate is seen only in the low-dose group.
6. UK in Dural Sinus Thrombosis

(1) Kuether TA, O'Neill O, Nesbit GM, Barnwell SL

**ENDOVASCULAR TREATMENT OF TRAUMATIC DURAL SINUS THROMBOSIS: CASE REPORT.**

*Neurosurgery* 1998 May;42(5):1163-6; discussion 1166-7

Department of Neurosurgery, Oregon Health Sciences University, Portland 97201-3098, USA.

**OBJECTIVE:** Dural sinus thrombosis has rarely been associated with closed head injury. We present a unique case involving the use of endovascular thrombolysis in the treatment of traumatic dural sinus thrombosis, which has not been reported. **CLINICAL PRESENTATION:** A 20-year-old male patient suffered a severe closed head injury while skiing. He developed refractory elevated intracranial pressure requiring barbiturate coma. Angiography demonstrated thrombosis of the dominant right transverse and sigmoid sinuses, with partial thrombosis of the superior sagittal sinus. Urokinase was administered via a microcatheter within the thrombus as a bolus of 250,000 units and then as a continuous infusion of 60,000 to 100,000 units per hour for 48 hours. The patient was maintained in a barbiturate coma and heparinized. Serial angiography was performed to assess the sinus patency and efficacy of thrombolysis. **RESULTS:** After 48 hours of thrombolysis, angiography demonstrated normal patency of the superior sagittal, right transverse, and right sigmoid sinuses. The intracranial pressure decreased after thrombolysis and was manageable with conventional techniques. Within 48 hours of the completed thrombolysis, the barbiturates were withdrawn and the patient's neurological status rapidly improved until the time of discharge 2 weeks later. **DISCUSSION AND CONCLUSION:** This case documents a rare instance of traumatic dural sinus thrombosis resulting from a closed head injury. In addition, endovascular thrombolysis resulted in subsequent opening of the dural sinuses and effective intracranial pressure management, despite the presence of a hemorrhagic contusion. Heparin was effective in maintaining sinus patency and was used safely in conjunction with urokinase in this setting of head injury.

(2) D’Alise MD, Fichtel F, Horowitz M

**SAGITTAL SINUS THROMBOSIS FOLLOWING MINOR HEAD INJURY TREATED WITH CONTINUOUS UROKINASE INFUSION.**


Department of Neurosurgery, University of Texas Southwestern Medical Center at Dallas, 75235-8855, USA.

**BACKGROUND:** Cerebral dural sinus thrombosis is a rare clinical entity. Symptoms may be vague, and left untreated thrombus progression may be fatal because of venous congestion and infarction. **METHODS:** We report a case of post-traumatic dural sinus thrombosis treated with selective transfemoral, transvenous catheterization and infusion of urokinase. **RESULTS:** Urokinase infusion into the dural venous sinuses using a microcatheter introduced from the femoral vein was successfully carried out, and patency of the venous sinuses was reestablished. **CONCLUSION:** Venous sinus thrombosis can be an overlooked sequel to head injury. If the diagnosis is entertained, prompt performance of appropriate imaging studies should be instituted so that therapy can be initiated. The use of selective sinus catheterization using microcatheter techniques with instillation of urokinase is an excellent mode of therapy that should be considered in any patient with symptomatic occlusion.

7. UK in Stroke


**LOCAL INTRA-ARTERIAL THROMBOLYSIS IN ACUTE ISCHEMIC STROKE.**

*Stroke* 1998 Sep;29(9):1894-900

Department of Neuroradiology, Inselspital, University of Berne, Switzerland.

**BACKGROUND AND PURPOSE:** We performed a retrospective analysis of the prognostic factors in patients treated with local intra-arterial thrombolysis (LIT). The purpose of this study was to evaluate...
the safety and efficacy of LIT using urokinase in patients with acute ischemic stroke of the anterior or posterior circulation and to determine the influence of clinical and radiological parameters on outcome. **METHODS:** Forty-three patients were treated with LIT using urokinase (median dose, 0.75x10^6 IU). The median National Institutes of Health Stroke Scale (NIHSS) score at hospital admission was 18 (range, 9 to 36). Nine patients had occlusions of the internal carotid artery (ICA), 23 of the middle cerebral artery (MCA), 1 of the anterior cerebral artery, and 10 of the basilar artery (BA). Outcome was assessed after 3 months and classified as good for Rankin Scale (RS) scores of 0 to 3 and poor for RS scores of 4 or 5 and death. **RESULTS:** Nine patients (21%) recovered to RS scores 0 or 1, 17 (40%) to scores of 2 or 3, and 7 (16%) to scores of 4 or 5. Ten patients (23%) died. Outcome was good in 17 patients (80%) with MCA occlusions, in 3 patients (33%) with ICA, and in 5 patients (50%) with BA occlusions. Good outcome was associated with an initial NIHSS score of <20 (P<0.001), improvement by 4 or more points on NIHSS score within 24 hours (P=0.001), and vessel recanalization (P=0.02). Recanalization was more likely if LIT was started within 4 hours (P=0.01). Symptomatic cerebral hemorrhage occurred in 2 patients (4.7%). **CONCLUSIONS:** LIT was most efficacious in patients with MCA and BA occlusions when the initial NIHSS score was less than 20 and when treated within 4 hours. It is of limited value in patients with distal ICA occlusions.

8. UK in Myocardial Infarction

(1) Park SJ  
**COMPARISON OF DOUBLE BOLUS UROKINASE VERSUS FRONT-LOADED ALTEPLASE REGIMEN FOR ACUTE MYOCARDIAL INFARCTION. THROMBOLYSIS IN MYOCARDIAL INFARCTION IN KOREA (TIMIKO) STUDY GROUP.**  
*Am J Cardiol* 1998 Sep 15;82(6):811-3, A10  
Department of Medicine, University of Ulsan, Asan Medical Center, Seoul, Korea.  
This study was performed to compare the double bolus urokinase regimen with the front-loaded alteplase regimen for acute myocardial infarction. Double bolus urokinase is an easy, safe, and effective thrombolytic regimen with comparable results to standard front-loaded alteplase in acute myocardial infarction.

9. UK for Dialysis Catheter Thrombolysis

(1) Seddon PA, Hriinya MK, Gaynord MA, Lion CM, Mangold BM, Bruns FJ  
**EFFECTIVENESS OF LOW DOSE UROKINASE ON DIALYSIS CATHETER THROMBOLYSIS.**  
Renal Electrolyte Division, University of Pittsburgh Medical Center, Pennsylvania 15213, USA.  
Thrombosis, a major cause of hemodialysis catheter dysfunction, can be treated with urokinase. We compared protocols using full strength urokinase to the volume of the catheter with low dose therapy. Clotting episodes and successful declottings (blood flow > 200 ml/min) were tracked for 6 months. One hundred four clotting episodes were treated with 5,000 U/ml urokinase to the volume of the catheter lumen for a 1 hr dwell. If unsuccessful, a second dose of 5,000 U/ml was administered and, if needed, a third dose of 125,000 U/lumen. Post treatment, catheters were locked with 5,000 U/ml heparin to the volume of the lumen. Using new protocols, clotting episodes were treated with 2,500 U/lumen urokinase, followed by saline to the volume of the lumen for a 1 hr dwell. A mid dwell injection of 0.2 ml/lumen saline was added to advance the front of active urokinase. If unsuccessful, a second 2,500 U/lumen dose was administered. Heparin lock was 10,000 U/ml heparin to the volume of the lumen. Revised protocols decreased clotting episodes 60% and urokinase charges 81%, while maintaining successful declottings at 74%. Low dose urokinase was as effective as full strength when the active front was advanced mid dwell.

10. UK for Inferior and Superior Vena Cava Thrombosis
(1) Angle JF, Matsumoto AH, Al Shammari M, Hagspiel KD, Spinosa DJ, Humphries JE

**TRANSCATHETER REGIONAL UROKINASE THERAPY IN THE MANAGEMENT OF INFERIOR VENA CAVA THROMBOSIS.**


University of Virginia, Health Sciences Center, Charlottesville 22908, USA.

PURPOSE: To study the efficacy of local infusion of urokinase (UK) in the treatment of symptomatic inferior vena cava (IVC) thrombosis. MATERIALS AND METHODS: Eight patients (five men and three women) who ranged in age from 19 years to 75 years (mean, 56 years) with symptomatic IVC thrombosis underwent local catheter-directed infusion of UK with use of up to three access sites. Infrarenal IVC thrombus and iliac vein thrombus was identified in all patients. Four patients had extension of thrombus proximal to the renal veins. Seven of eight patients had at least one risk factor for IVC thrombosis: hypercoagulable state (n = 3), IVC filter (n = 3), malignancy (n = 2), recent surgery (n = 2), and oral contraceptive use (n = 1). No serious procedure-related complications were encountered, although one patient died 5 days after UK therapy of pulmonary failure due to advanced lung cancer. UK was infused for an average of 79 hours (range, 24-140 hours) and a mean total dose of 7.4 million U of UK (range, 2.9-14.4 million U). Adjunctive balloon angioplasty was performed in three patients. No vascular stents were placed. Clinical and/or radiographic follow-up was obtained in all eight patients. RESULTS: Thrombolysis was successful in seven of eight (88%) IVCs with no or minimal residual thrombus. The remaining seven patients had no lower extremity swelling 2-24 months (mean, 11 months) after the procedure. Three of seven patients had computed tomographic or venographic follow-up (mean, 9 months; range, 1.5-15 months), demonstrating unchanged or improved IVC patency. CONCLUSIONS: Transcatheter regional infusion of UK for re-establishing venous patency in acute IVC thrombosis appears to be effective with good short-term and mid-term clinical benefit.

(2) Sze DY, Robbins RC, Semba CP, Razavi MK, Dake MD

**SUPERIOR VENA CAVA SYNDROME AFTER HEART TRANSPLANTATION: PERCUTANEOUS TREATMENT OF A COMPLICATION OF BICAVAL ANASTOMOSES.**


Division of Cardiovascular and Interventional Radiology, Stanford University Medical Center, Calif 94305-5450, USA.

OBJECTIVES: Our objectives were (1) to investigate the incidence and cause of symptomatic superior vena caval anastomotic stenosis and central venous thrombosis in patients receiving heart or heart-lung transplantation and (2) to explore percutaneous methods of thrombolysis and endoluminal intervention to treat these complications. METHODS: Review of 1016 cases revealed three cases of superior vena cava syndrome. Anatomy, surgical technique, and medical risk factors were examined. Percutaneous treatments, including urokinase thrombolysis, mechanical thrombolysis, balloon angioplasty, and stent placement, were attempted. RESULTS: All three of these patients underwent transplantation by means of the bicaudal anastomotic technique. In addition, the diameters of the donor and recipient cavae were grossly mismatched in all three. Stenoses in all patients were successfully treated percutaneously with balloon angioplasty and stent placement. Treatment of the accompanying large-volume thrombus was problematic in these patients, and two had hemorrhagic complications of urokinase thrombolysis. A mechanical thrombolysis device was used successfully in the third patient. CONCLUSIONS: Anastomotic stricture and central venous thrombosis is an uncommon complication of the bicaudal anastomotic technique of heart and heart-lung transplantation. Discrepancy between donor and recipient caval diameters appears to be the major risk factor. Endoluminal thrombolysis and stenting provides rapid and enduring relief of symptoms and precludes repeat sternotomy, cardiopulmonary bypass, and general anesthesia.

(3) Pisco JM, Nobre I, Fernandes O, Garcia V, Martins JM, Duarte AC, Freitas MG

**[THE USE OF ENDOPROSTHESIS IN SUPERIOR VENA CAVA SYNDROME CAUSED BY LUNG NEOPLASMS]. [ARTICLE IN PORTUGESE]**


Servicio de Radiologia, Hospital de Santa Marta, Lisboa.
We present six cases of superior vena cava syndrome caused by a malignant tumor that were treated by percutaneous endoprostheses. The technique is described and the results evaluated. In one case there was acute thrombosis of the endoprosthesis that was treated by urokinase. No other complications were observed. A patient died one month later due to progression of the tumor. The remaining cases were asymptomatic for longer than 6 months. It was concluded that endoprostheses for superior vena cava syndrome are efficient, with quick improvement of the symptomatology.

11. UK in Paget Schroetter Syndrome and Thoracic Outlet Syndrome (TOS)

(1) Urschel HC Jr, Razzuk MA

NEUROVASCULAR COMPRESSION IN THE THORACIC OUTLET: CHANGING MANAGEMENT OVER 50 YEARS.


University of Texas Southwestern Medical School, Baylor University Medical Center, Dallas, USA.

SUMMARY BACKGROUND DATA: During the past five decades, significant improvements have been made in the diagnosis and treatment of thoracic outlet syndrome (TOS) secondary to sports activities, breast implants, or median sternotomy. METHODS, RESULTS, AND CONCLUSIONS: Of more than 15,000 patients evaluated for TOS, 3914 underwent primary neurovascular decompression procedures and 1221 underwent second surgical procedures for recurrent symptoms. Of 2210 consecutive patients, 250 had symptoms of upper plexus compression only (median nerve), 1508 had symptoms of lower plexus compression only (ulnar nerve), and 452 patients had symptoms of both. Ulnar and median nerve conduction velocities confirmed the clinical diagnosis. Transaxillary first rib removal alone for neurovascular decompression relieved both upper and lower plexus symptoms (without a combined transaxillary and supraclavicular approach). There are two reasons for this: most upper compression mechanisms attach to the first rib, and the median nerve is also supplied by C8 and T1 as well as C5, C6, and C7 nerve roots. Axillary subclavian artery aneurysm or occlusion was treated successfully in 240 patients. Dorsal sympathectomy was performed concomitantly in 71 patients for occlusion or embolectomy. It was combined with first rib resection in 1974 patients for sympathetic maintained pain syndrome and causalgia that did not improve with conservative therapy. Of 264 patients with effort thrombosis (Paget-Schroetter syndrome), 211 were treated by urokinase thrombolysis and prompt first rib resection with excellent long-term results. Recurrent TOS symptoms required a second procedure using the posterior approach in 1221 patients with brachial plexus neurolysis and dorsal sympathectomy. The use of hyaluronic acid significantly reduced recurrent scarring.

12. UK in Plastic Reconstructive Surgery

(1) Serletti JM, Moran SL, Orlando GS, O'Connor T, Herrera HR

UROKINASE PROTOCOL FOR FREE-FLAP SALVAGE FOLLOWING PROLONGED VENOUS THROMBOSIS.


Division of Plastic Surgery at the University of Rochester Medical Center, NY 14642, USA.

The incidence of free-flap failure is reported at 4 to 5 percent. Often, these failures are attributed to postoperative venous thrombosis with salvage rates reported at 42 per cent. The use of thrombolytics has been effective in laboratory protocols; however, there have been only case reports to substantiate their use in humans. In this study, we establish a protocol for the administration of urokinase for postoperative venous thrombosis. Upon clinical evidence of venous thrombosis, all patients were urgently returned to the operating room, where the venous anastomosis was resected and a new venous anastomosis was performed. A solution of 250,000 units of urokinase was then infused over 30 minutes through a 25-gauge butterfly inserted into the recipient artery just proximal to the arterial anastomosis. Patients were continued on a daily aspirin (325 mg). More than 600 free flaps have been performed by our group since 1990. In that group of patients, five were diagnosed with postoperative venous thrombosis. Flaps consisted of four radial forearm flaps and one free transverse rectus abdominis muscle flap. All patients were diagnosed late based upon significant changes within the flap. Thromboses were clinically apparent on postoperative days 1 through 6, with an average of 3.6 days. All five patients
received urokinase as described. The average age of the patients treated was 43. There were no
postoperative hematomas, blood transfusions, or bleeding complications. There were no allergic or
anaphylactic reactions to the urokinase. All flaps survived (100 percent) with a mean follow-up of 27
months. The use of urokinase as described in our protocol has been an effective thrombolytic,
capable of reversing clinically advanced venous thrombosis when combined with repeated venous
anastomosis. We believe this protocol provides a viable option for the treatment of postoperative
venous thrombosis.

(2) Wheatley MJ, Swift R
SUCCESSFUL HAND REVASCULARIZATION WITH UROKINASE FOLLOWING A
CRUSH INJURY.

Department of Surgery, Oregon Health Sciences University, Portland Veterans
Administration Medical Center 97201-3098, USA.

Acute hand ischemia is a medical emergency requiring immediate treatment. We report a case of
acute hand ischemia due to a crush injury of the wrist. Management with urokinase was successful in
reestablishing flow to the ulnar artery and the digital vessels. In the setting of acute trauma with
extensive thrombosis of the vessels of the hand, thrombolytic therapy may offer a better treatment
option than surgical exploration with bypass grafting.

13. UK for Heparin induced Thrombocytopenia (HIT)

(1) Weinmann EE, Carpenter JP
INTRAOPERATIVE UROKINASE AS AN ALTERNATIVE TO HEPARIN FOR
PATIENTS WITH SUSPECTED HEPARIN-INDUCED THROMBOCYTOPENIA
REQUIRING ARTERIAL RECONSTRUCTION: REPORT OF A CASE AND REVIEW
OF THE LITERATURE.

Department of Surgery, University of Pennsylvania, School of Medicine, Philadelphia, USA.

Patients with heparin-induced thrombocytopenia (HIT) require an alternative antithrombotic
treatment to heparin during arterial reconstruction. Ancrod and Illoprost have been employed but
are not readily available and carry the risks of systemic side effects (depletion of fibrinogen,
hypotension). A patient with HIT in whom intraoperative intraarterial urokinase (UK) was
successfully utilized to enable safe arterial reconstruction is described. An 80 year old white female
with diffuse arteriosclerotic cardiovascular disease and multiple vascular reconstructions had
thrombotic complications following use for heparin during two of her prior operations associated
with documented thrombocytopenia and anti-platelet antibodies. She presented with limb-threatening
ischemia which was evaluated with angiography revealing severe stenosis of the proximal left
superficial femoral artery, occlusion of both anterior tibial and peroneal arteries and several digital
vessels, with intact posterior tibial runoff. A common femoral to mid-superficial femoral artery
bypass was performed, utilizing contralateral reversed greater saphenous vein, while being treated with
aspirin and a continuous intravenous infusion of low molecular weight dextran. During the procedure the
clamped arteries were locally perfused with a high volume of dilute UK solution to prevent blood stasis,
and enable local delivery of a thrombolytic agent. Although clot formation was observed in the
operative field, none occurred within the clamped arteries. A total of 191,200 units of UK were
employed with no bleeding complications. Following surgery the patient had a palpable pedal pulse
and markedly improved perfusion of her toes. She was discharged on aspirin and coumadin on
postoperative day five. It is concluded that for patients with HIT, systemic aspirin and dextran
combined with local intraarterial UK are a simple and effective substitute for systemic
anticoagulation with heparin during arterial reconstruction.
14. UK in DIC (Experimental)

(1) Vasquez Y, Williams CH, Hardaway RM

**EFFECT OF UROKINASE ON DISSEMINATED INTRAVASCULAR COAGULATION.**


Departments of Anesthesiology, Biochemistry, and Surgery, Texas Tech University Health Science Center, El Paso, Texas 79905, USA.

Our study evaluated the possible therapeutic effect of urokinase in treating the microthrombotic effects of disseminated intravascular coagulation by assisting the activation of endogenous plasminogen. Twenty-six pigs were anesthetized, intubated, mechanically ventilated, and surgically catheterized. Septic shock was induced in all 26 pigs by an intravenous infusion of heat-killed Escherichia coli. The pigs were divided into two sets of experiments: in experiment 2 (n = 14), one-half received an intravenous dose of urokinase 1 h after heat-killed E. coli infusion and in experiment 3 (n = 12) one-half received an intravenous bolus dose and a continuous drip of urokinase 2 h after heat-killed E. coli infusion. The untreated pigs served as controls. Hemodynamic parameters, blood chemistries, and blood gases were analyzed. Urokinase given 1 h after bacterial toxin infusion significantly restored blood flow, resulting in an increase in cardiovascular and pulmonary function and improved survival rate (43% control vs. 100% treated, 24-h experimental period). Treatment given after 2 h showed some significant effect on pulmonary function; however, within 10 h of E. coli infusion, mortality rates in control and treated groups were 100 and 83%, respectively. Early administration of urokinase after onset of disseminated intravascular coagulation restored blood flow and helped resolve organ damage.

15. UK in Antiphospholipid Syndrome

(1) Takeuchi S, Obayashi T, Toyama J

**PRIMARY ANTIPHOSPHOLIPID SYNDROME WITH ACUTE MYOCARDIAL INFARCTION RECANALISED BY PTCA.**

*Heart* 1998 Jan;79(1):96-8

Department of Cardiology, Kariya General Hospital, Japan.

A 20 year old man with severe chest pain was hospitalised for acute myocardial infarction. Coronary angiography revealed total obstruction of his right coronary artery, which was successfully recanalised.
by direct percutaneous transluminal coronary angioplasty (PTCA). There was also diffuse thrombi in the left coronary artery that was not recanalised by perfusion with 3000 U pro-urokinase. Anticoagulant therapy was performed after PTCA. Creatine kinase peaked one day after hospitalisation (4805 U/l). The activated partial thromboplastin time was 62.6 seconds (45%). Plasma anticardiolipin IgG antibodies were high (3.8 and 2.7) in repeated examinations. The PTCA site was patent after three months. Primary antiphospholipid syndrome should be considered as a cause of acute myocardial infarction in young adults, and PTCA with anticoagulant treatment is effective for initial treatment of the syndrome.

16. UK in Kawasaki Disease

(1) Katayama F, Hiraishi S, Takeda N, Misawa H
INTRACORONARY UROKINASE AND POST-THROMBOLYTIC REGIMEN IN AN INFANT WITH KAWASAKI DISEASE AND ACUTE MYOCARDIAL INFARCTION.
*Heart* 1997 Dec;78(6):621-2
Department of Pediatrics, Kitasato University School of Medicine, Kanagawa, Japan.

(2) Morita H, Kinoshita I, Fukita H, Fukumoto H, Nishimoto T, Itoh M
ACUTE MYOCARDIAL INFARCTION IN A YOUNG ADULT AS POSSIBLE SEQUELA OF KAWASAKI DISEASE--A CASE REPORT OF SUCCESSFUL INTRACORONARY THROMBOLYTIC THERAPY AND HISTOLOGICAL STUDY OF AN ANEURYSM.
*Jpn Circ J* 1992 Jul;56(7):681-6
Department of Internal Medicine, Osaka-fu Mishima Critical Care Medical Center, Japan.

Emergency coronary angiography in a 28-year-old male suffering an acute anteroseptal myocardial infarction revealed complete obstruction of the left anterior descending artery in association with multiple aneurysms of the 3 major coronary arteries. Successful intracoronary thrombolytic treatment with urokinase infusion directly into the infarct-related artery was performed 2 h after the onset. Follow-up left ventriculogram showed preservation of left ventricular wall motion. Fifty days after the infarction, he underwent aorto-coronary bypass surgery. Histological examination of the biopsy specimen obtained from the aneurysm of the distal portion of the right coronary artery revealed that the 3-layer architecture of the arterial wall had been completely lost. The wall was replaced by fibrotic tissue, with slight mononuclear cell infiltration around the small vessels, but no acute inflammatory reaction or atheromatous change was seen. In spite of the presence of the coronary risk factors of hypertension and hyperlipidemia, angiography revealed no evidence of atherosclerosis of systemic arteries. It is suggested that the coronary aneurysms in this case are possible sequela of Kawasaki disease in childhood.

(3) Myler RK, Schechtmann NS, Rosenblum J, Collinsworth KA, Bashour TT, Ward K, Murphy MC, Stertzer SH
MULTIPLE CORONARY ARTERY ANEURYSMS IN AN ADULT ASSOCIATED WITH EXTENSIVE THROMBUS FORMATION RESULTING IN ACUTE MYOCARDIAL INFARCTION: SUCCESSFUL TREATMENT WITH INTRACORONARY UROKINASE, INTRAVENOUS HEPARIN, AND ORAL ANTICOAGULATION.
*Cathet Cardiovase Diagn* 1991 Sep;24(1):51-4
San Francisco Heart Institute, Seton Medical Center, Daly City, California 94015.

A 37-yr-old white female was admitted to hospital with an evolving anterior myocardial infarction. Coronary arteriography revealed multiple aneurysms in the left anterior descending (and right) coronary arteries. In the left anterior descending artery, there was evidence of extensive thrombus formation. The patient was successfully treated with intracoronary urokinase, intravenous heparin, and oral warfarin. There was partial thrombolysis in 16 hr and complete thrombolysis noted 6 wk later. This case of multiple coronary aneurysms, secondary to presumed Kawasaki disease, is the first documentation of antemortem intra-aneurysmal coronary thrombosis treated successfully by thrombolytic and anticoagulant therapy.
B. Urokinase induced Complications "Bleedings"

II. DEFIBRINOGENATING ENZYMES

A. ANCROD Fibrinogenolytic Protease (ANC)

A. Function and Fields of Use

1. ANC in General Effects

a) ANC effect on Fibrin uptake by injured vessel wall

(1) Hatton MW, Ross B, Southward SM, DeReske M, Richardson M

PRETREATMENT OF RABBITS WITH EITHER HIRUDIN, ANCROD, OR WARFARIN SIGNIFICANTLY REDUCES THE IMMEDIATE UPTAKE OF FIBRINOGEN AND PLATELETS BY THE DEENDOTHELIALIZED AORTA WALL AFTER BALLOON-CATHETER INJURY IN VIVO.


Department of Pathology, McMaster University Health Sciences Centre, Hamilton, Ontario, Canada. hattonm@mcmaster.ca

Fibrinogen and platelets rapidly saturate the exposed subendothelium of a freshly deendothelialized aorta in vivo. As thrombin generated within the site of injury is largely responsible for fibrin(ogen) deposition, we questioned whether various anticoagulant treatments would inhibit uptake of both fibrinogen and platelets in vivo. Rabbits were anticoagulated by pretreatment with either Warfarin, Ancrod, or recombinant hirudin. Each anesthetized, anticoagulated (or saline-injected control) rabbit was injected i.v. with rabbit 51Cr-platelets and 125I-fibrinogen before a balloon-catheter deendothelializing (or sham) injury of the thoracic aorta. At 10 minutes after injury, the rabbit was exsanguinated and the aorta excised. Platelet adsorption by the deendothelialized aorta surface was substantially reduced in anticoagulated rabbits (controls, 2.2x10(5)/mm2; Warfarin-treated, 1.2x10(5)/mm2; Ancrod-treated, 5.3x10(4)/mm2; r-hirudin-treated [5 mg/kg], 5.3x10(4)/mm2), and a significant reduction of fibrinogen associated with the platelet layer (from 5.3 to 1 to 2 pmol/cm2) and within the underlying intima-media layer (from 16.9 to 5 to 6 pmol/cm2) was observed in the r-hirudin-and Warfarin-treated rabbits. The pattern of aorta-deposited 51Cr-platelets and 125I-fibrin in the anticoagulated rabbits corresponded well with an assessment by transmission electron microscopy of aortic tissue samples. We conclude that approximately 70% of fibrinogen uptake is thrombin dependent and that approximately 80% of platelet adsorption depends on codeposited fibrin(ogen) during the 10-minute interval after balloon injury. Pretreatment with an agent that interferes with either thrombin or fibrin production will inhibit the immediate interaction of fibrinogen and platelets with the freshly exposed subendothelium.

b) ANC for Hyperfibrinogenemia

(1) Cole CW

CONTROLLING ACUTE ELEVATION OF PLASMA FIBRINOGEN WITH ANCROD.

Cerebrovasc Dis 1998 Jan;8 Suppl 1:29-34

cole@infonet.ca

2. ANC in Myocardial Infarction and Coronary Arterial Disease
(1) Pothoulakis AJ, Neerukonda SK, Ansel G, Jantz RD

**ANCROD FOR CORONARY ANGIOPLASTY.**

*Tex Heart Inst J* 1995;22(4):342-6

Department of Internal Medicine, Medical College of Ohio, Toledo 43699, USA.

Anticoagulation in the form of intravenous heparin is used after coronary angioplasty to prevent thrombosis. Ancrod, a rapid-acting defibrinogenating agent, has been used in various clinical settings that require anticoagulation. We present the use of ancrod after percutaneous transluminal coronary angioplasty in a patient with heparin-induced thrombopathy.

(2) Zhang SY, Jin L, Yan XW

**[THE EVALUATION OF THROMBOLYTIC EFFECT OF SNAKE VENOM ANTITHROMBUS ENZYME IN TREATMENT OF ACUTE MYOCARDIAL INFARCTION.][ARTICLE IN CHINESE]**

*Chung Hua Nei Ko Tsa Chih* 1994 Apr;33(4):244-7

Department of Medicine, Peking Union Medical College Hospital, Beijing.

To evaluate the thrombolytic effect of Snake Venom Antithrombus Enzyme (SVATE) in the treatment of early acute myocardial infarction (AMI), 52 cases with AMI were randomly allocated to three groups, control (22 cases), SVATE (15 cases), and Urokinase (15 cases). The results show that SVATE can inhibit platelet aggregation, activate slightly fibrinolytic system and decrease markedly plasma fibrinogen level. However, the thrombolytic effect of SVATE in early treatment of AMI is not ideal, it can be used in combination with effective thrombolytic drugs to prevent reocclusion and reinfarction in AMI.

3. ANC in Cardiac Surgery (CPB)


**CARDIOPULMONARY BYPASS WITH DANAPAROID SODIUM AND ANCROD IN HEPARIN-INDUCED THROMBOCYTOPENIA.**


Department of Cardiothoracic Surgery, St George's Hospital, London, England.

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Heparin is the standard anticoagulant for patients undergoing cardiopulmonary bypass. There are some patients for whom heparin is unsuitable and ancrod (a defibrinogenating enzyme) has been used as an alternative. We present a patient with heparin-induced thrombocytopenia in whom treatment ancrod was ineffective. The addition of danaparoid sodium (a heparinoid) allowed safe cardiopulmonary bypass. We discuss the reasons for this and suggest that the combination of ancrod and danaparoid sodium is a logical one in such cases.

(2) Smith RE, Townsend GE, Berry BR, Bowen T

**ENOXAPARIN FOR UNSTABLE ANGINA AND ANCROD FOR CARDIAC SURGERY FOLLOWING HEPARIN ALLERGY.**

*Ann Pharmacother* 1996 May;30(5):476-80

Royal Jubilee Hospital, Victoria, British Columbia, Canada. resmith@loki.govhs.gov.bc.ca

OBJECTIVE: To describe a patient who presented with heparin allergy and required alternate anticoagulation for unstable angina and coronary artery bypass surgery. To review therapeutic alternatives to porcine heparin for patients with hypersensitivity or intolerance to standard heparin anticoagulation. CASE SUMMARY: A 74-year-old man with a 15-year-old coronary artery bypass graft presented to the emergency room with unstable angina and was scheduled for urgent coronary artery revascularization. A bolus dose of porcine heparin was administered followed by a continuous infusion. Shortly afterward the patient developed a type I allergic reaction to the porcine heparin that was confirmed by rechallenge. Three alternatives to porcine heparin were tried, including bovine lung
heparin, low-molecular-weight heparin (enoxaparin), and ancrod. The patient was found to be cross-sensitive to bovine lung heparin, but tolerated enoxaparin for unstable angina without cross-sensitivity. Anticoagulation for cardiopulmonary bypass was achieved with an infusion of ancrod that was later reversed with cryoprecipitate. The patient was discharged postoperatively on day 5 without the complication of excessive bleeding. DISCUSSION: Type I allergic reaction to unfractionated heparin is a rare occurrence and could be the result of a variety of factors. Possible causes for the reaction include a porcine protein, a preservative contained in the heparin solution, or a hapten formed between heparin and a plasma protein. We considered four alternatives to heparin anticoagulation: rush desensitization, bovine lung heparin, low-molecular-weight heparin, and ancrod. The patient was cross-sensitive to bovine lung heparin, but was able to tolerate low-molecular-weight heparin (enoxaparin). This was unexpected because enoxaparin is derived from unfractionated porcine heparin. Testing for cross-sensitivity had no value in this case, as two negative subcutaneous test doses were followed by dramatic reactions when the drugs were given intravenously. Although enoxaparin has been used for anticoagulation during bypass surgery, there is more experience with ancrod as an alternative to heparin. Repeat bypass surgery, which normally results in above-average blood loss, was successfully performed with a very low fibrinogen concentration (< 0.15 g/L) during ancrod anticoagulation. CONCLUSIONS: We conclude that ancrod was a safe and effective alternative to heparin for coronary artery bypass surgery in this patient in whom a heparin product had caused a hypersensitivity reaction. We discovered on two occasions that a negative subcutaneous test dose for heparin allergy did not predict a severe type I allergic reaction when the heparin was later administered intravenously. Furthermore, we found that a low-molecular-weight heparin administered subcutaneously for a short period of time did not cause cross-sensitivity in a patient with a type I allergy to unfractionated heparin.


Department of Anesthesia, University of Washington, Seattle 98195, USA.


Department of Surgery, Deborah Heart and Lung Center, Browns Mills, New Jersey 08015-1799.

A case is reported of a 22-year-old man with heparin-induced thrombocytopenia and thrombosis syndrome and a right atrial foreign body (Greenfield filter). Heparinless cardiopulmonary bypass for removal of the foreign body was conducted by pretreatment with ancrod, a rapid-acting fibrinogenolytic of pit viper venom origin. Treatment protocol and a literature review are included in this article.

4. ANC in Stroke


Mercy General Hospital Sacramento, Calif. 95819, USA.

(2) Atkinson RP ANCROD IN THE TREATMENT OF ACUTE ISCHAEMIC STROKE. Drugs 1997;54 Suppl 3:100-8
Mercy General Hospital, Sacramento, California, USA.

Ancrod converts fibrinogen into soluble fibrin products, resulting in a decrease in plasma fibrinogen and blood viscosity, and also induces the release of endogenous tissue-type plasminogen activator from the vessel wall. These activities suggest that treating patients with acute ischaemic stroke with ancrod might result in improved cerebral blood flow and patient outcome. Two large randomised placebo-controlled studies have evaluated treatment with ancrod in patients with acute ischaemic stroke. In the first, patients were treated within 6 hours of symptom onset: this was not successful in quickly lowering fibrinogen levels to the target range (0.7 to 1.0 g/L) and the results were inconclusive. However, a post hoc analysis suggested that treatment with ancrod was effective in patients whose fibrinogen level was reduced to less than 1.3 g/L within 6 hours of starting treatment. A second larger study is still in progress, but preliminary results in patients treated within 3 hours of onset of ischaemic stroke are available and indicate that the target fibrinogen level of less than 1 g/L within 6 hours of instituting treatment is being achieved in most patients.

(3) The Ancrod Stroke Study Investigators.

ANCROD FOR THE TREATMENT OF ACUTE ISCHEMIC BRAIN INFARCTION. THE ANCROD STROKE STUDY INVESTIGATORS.

*Stroke* 1994 Sep;25(9):1755-9

BACKGROUND AND PURPOSE: There is no acute therapy proven to be of benefit for ischemic stroke. Ancrod is a potentially effective therapy because of the advantageous consequences of fibrinogen lowering. METHODS: We studied the safety and efficacy of ancrod in patients with acute ischemic stroke administered within 6 hours of stroke onset. In a double-blind, randomized, placebo-controlled trial 64 patients received intravenous ancrod and 68 received placebo for 7 days. Neurological outcome, disability, and brain infarct volume were measured. RESULTS: There was no significant difference in overall mean scores on the Scandinavian Stroke Scale. No increase in bleeding occurred in the ancrod-treated patients. The target reduction of plasma fibrinogen levels of less than 100 mg/dL was achieved in only 15 (23%) of 64 ancrod-treated patients. Those patients with ancrod-induced 6-hour fibrinogen levels 130 mg/dL or less had a marginally significantly better neurological outcome on the Scandinavian Stroke Scale, mortality, and Barthel Index than ancrod-treated patients with higher fibrinogen levels. CONCLUSIONS: Ancrod appears safe and potentially effective when administered to patients within 6 hours of onset of ischemic stroke.

(4) Elger B, Laux V, Schwarz M

MAGNETIC RESONANCE IMAGING STUDIES ON THE EFFECT OF THE FIBRINOGEN-LOWERING AGENT ANCROD ON CEREBRAL LESIONS IN TWO RAT MODELS OF ACUTE STROKE.


Knoll AG, Ludwigshafen, Germany.

In vivo magnetic resonance imaging was used to study the effect of ancrod (CAS 9046-56-4, Arwin), a plasma fibrinogen level lowering agent, on brain lesion in two rat models of acute focal cerebral ischaemia. Total lesion volume was determined by multislice T2-weighted magnetic resonance imaging 24 h after permanent middle cerebral artery occlusion. Intravenous infusion of ancrod starting 30 min after middle cerebral artery occlusion at dosages of 10, 30, 50 or 70 IU/kg (n = 9/group) significantly diminished cerebral lesion volume by 20 to 33% as compared to vehicle-infused controls (n = 12). None of the ancrod-treated rats showed evidence of intracerebral bleeding on T2-weighted magnetic resonance images taken after 24 h. In photochemically induced (rose bengal) unilateral thrombotic cortical infarction brain damage was displayed by multislice diffusion-weighted magnetic resonance imaging after 24 h. Again, post treatment with ancrod reduced total volume of cerebral lesion dose-dependently from 142 +/- 28 mm3 in the controls (n = 10) to 121 +/- 28 mm3 (n = 10) and 111 +/- 20 mm3 (n = 11, p < 0.05) in rats treated with 10 and 30 IU/kg ancrod, respectively (means +/- S.D.). These results suggest cerebroprotection in focal cerebral ischaemia by improvements in the cerebral microcirculation which may offer a potential and safe approach for therapy of acute stroke.

5. ANC in Trauma
(1) Hatton MW, Ross B, Southward SM, DeReske M, Richardson M

PRETREATMENT OF RABBITS WITH EITHER HIRUDIN, ANCROD, OR WARFARIN SIGNIFICANTLY REDUCES THE IMMEDIATE UPTAKE OF FIBRINOGEN AND PLATELETS BY THE DEENDOTHELIALIZED AORTA WALL AFTER BALLOON-CATHETER INJURY IN VIVO.


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Fibrinogen and platelets rapidly saturate the exposed subendothelium of a freshly deendothelialized aorta in vivo. As thrombin generated within the site of injury is largely responsible for fibrin(ogen) deposition, we questioned whether various anticoagulant treatments would inhibit uptake of both fibrinogen and platelets in vivo. Rabbits were anticoagulated by pretreatment with either Warfarin, Ancrod, or recombinant hirudin. Each anesthetized, anticoagulated (or saline-injected control) rabbit was injected i.v. with rabbit 51Cr-platelets and 125I-fibrinogen before a balloon-catheter deendothelializing (or sham) injury of the thoracic aorta. At 10 minutes after injury, the rabbit was exsanguinated and the aorta excised. Platelet adsorption by the deendothelialized aorta surface was substantially reduced in anticoagulated rabbits (controls, 2.2×10⁵/mm²; Warfarin-treated, 1.2×10⁵/mm²; Ancrod-treated, 5.3×10⁴/mm²; r-hirudin-treated [5 mg/kg], 5.3×10⁴/mm²), and a significant reduction of fibrinogen associated with the platelet layer (from 5.3 to 1 to 2 pmol/cm²) and within the underlying intima-media layer (from 16.9 to 5 to 6 pmol/cm²) was observed in the r-hirudin-and Warfarin-treated rabbits. The pattern of aorta-deposited 51Cr-platelets and 125I-fibrin in the anticoagulated rabbits corresponded well with an assessment by transmission electron microscopy of aortic tissue samples. We conclude that approximately 70% of fibrinogen uptake is thrombin dependent and that approximately 80% of platelet adsorption depends on codeposited fibrin(ogen) during the 10-minute interval after balloon injury. Pretreatment with an agent that interferes with either thrombin or fibrin production will inhibit the immediate interaction of fibrinogen and platelets with the freshly exposed subendothelium.

(2) Cole CW, Shea B, Bormanis J

ANCROD AS PROPHYLAXIS OR TREATMENT FOR THROMBOEMBOLISM IN PATIENTS WITH MULTIPLE TRAUMA.


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OBJECTIVE: To report the initial clinical experience with fibrinogen depletion using ancrod as prophylaxis and treatment for deep vein thrombosis and pulmonary embolism (DVT/PE) in patients with multiple trauma. DESIGN: A series of cases, selected because of their extreme risk of DVT/PE or because of the appearance of thromboembolic complications despite prophylaxis using conventional methods. SETTING: University teaching hospital. PATIENTS: A referred sample comprising 30 patients with multiple blunt trauma. The mean injury severity score was 30. Most cases involved a combination of lower extremity, pelvic and chest injuries. INTERVENTIONS: Fibrinogen was slowly depleted over 24 to 36 hours and the concentration maintained at 0.2 to 0.5 g/L thereafter. Ancrod was continued prophylactically (22 patients) or for established DVT/PE (8 patients) until the patients were mobilized or until there was no longer a contraindication to heparin, or until treatment with warfarin became practical. MAIN OUTCOME MEASURE: Monitoring for DVT by duplex ultrasonography or iodine-125-labelled-fibrinogen scanning, whichever could be applied. RESULTS: Twenty patients were treated with ancrod for prophylaxis from the outset because it offered theoretic and practical benefits over other methods. No patient treated with ancrod for prophylaxis suffered a clinically significant DVT/PE. Patients in whom heparin prophylaxis failed and who experienced thromboembolic complications were effectively managed with ancrod. There were no deaths and no bleeding complications specifically due to the therapy. CONCLUSIONS: Slow depletion of fibrinogen with ancrod may provide a safe and effective means to prevent DVT/PE in multiple trauma patients or to treat DVT/PE when the risk of bleeding from heparin is great. This initial experience should be evaluated by a randomized controlled trial.

6. ANC for Venous Thrombosis
Sensitivity of Experimental Venous and Arterial Thrombosis and Bleeding to Ancrod-Induced Defibrinogenation.


The effect of ancrod-induced defibrinogenation on thrombosis and bleeding time was determined in anesthetized rats. Functional plasma fibrinogen levels were reduced 42, 71, 94 and 93% by ancrod doses of 5, 10, 20 and 30 U/kg, respectively, while a 2.5 U/kg dose was without significant effect. Ancrod inhibited vena cava thrombosis induced by partial stasis of blood flow combined with mild vascular injury. Thrombus weight was decreased 85 and 93% by the 10 and 20 U/kg doses, but was unaffected at lower doses. In contrast, ancrod doses of up to 30 U/kg did not significantly decrease carotid artery thrombi formed in response to oxidative transmural vessel injury. Ancrod caused a dose-dependent increase in bleeding time measured by puncturing small mesenteric arteries with a hypodermic needle. The bleeding time increase was approximately 38% in response to the 2.5 and 5 U/kg doses, and 182% in response to the 10 U/kg dose. These studies demonstrate that ancrod-induced reductions in plasma fibrinogen more effectively inhibit venous compared to arterial thrombosis, although these activities require doses that also increase bleeding time in small arteries.

Adhesion Prevention with Ancrod Released Via a Tissue-Adherent Hydrogel.


The objective of this investigation was to evaluate the effect of ancrod, a fibrinogenolytic protease from Malayan pit viper venom, locally delivered through a photopolymerized biodegradable hydrogel in preventing postoperative adhesions. The experimental model involved ischemic and serosal injury to the uterine horns of rats with measurement of adhesions 7 days after injury. Ancrod was delivered intravenously for 5 days preoperatively through 3 days postoperatively, intraperitoneally for 5 days preoperatively, intraperitoneally for 3 days postoperatively, and locally via the hydrogel formed upon the uterine horns by photopolymerization of an aqueous precursor solution. Systemic defibrinogenation by intravenous administration pre-through postoperatively reduced the extent of adhesions by 63% without dose sensitivity from 5 to 20 units/kg/day. Preoperative defibrinogenation by intraperitoneal administration reduced adhesion extent by up to 57%, while postoperative administration was more effective, reducing adhesions by up to 84% with a dose-dependent response from 5 to 20 units/kg/day. Administration of ancrod by local release from a tissue- adherent hydrogel was more effective than either the hydrogel alone or the same amount of ancrod administered by postoperative intraperitoneal injection. Adhesions were reduced by 82% at a local dose of 10 units/kg, compared to a reduction of 68% due to the barrier properties of the gel alone (P < 0.01) and of 19% due to the same amount of drug given at the time of surgery (P < 0.001). Local delivery of ancrod from a tissue-adherent hydrogel barrier thus provided an efficacious prevention to postoperative adhesions while permitting administration of a low total dose of the protease.

ANC in Heparin Induced Thrombocytopenia (HIT)

J Thromb Thrombolysis 1999 Jun;7(3):259-64

Heparin induced thrombocytopenia: diagnosis and contemporary antithrombin management.

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Heparin-induced thrombocytopenia (HIT) may be complicated by severe thrombotic complications and death. Currently no specific laboratory test is available to make the diagnosis. When HIT is clinically suspected, heparin should be discontinued immediately. While no specific therapy for HIT exists, there is increasing evidence that acute antithrombin therapy may significantly reduce morbidity and mortality. Among several agents, the direct antithrombins, such as r-hirudin and argatroban, look the most promising for acute treatment.

(2) Warkentin TE
LIMITATIONS OF CONVENTIONAL TREATMENT OPTIONS FOR HEPARIN-INDUCED THROMBOCYTOPENIA.

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Thrombosis is a common and potentially serious complication of immune-mediated heparin-induced thrombocytopenia (HIT). Discontinuation of heparin is a simple and important maneuver in patients with suspected HIT. Unfortunately, thrombosis often occurs even in those patients in whom heparin was discontinued because of thrombocytopenia alone ("isolated" HIT). It therefore is reasonable to consider prophylactic anticoagulation with an alternate anticoagulant in patients with suspected HIT, especially if their initial indication for anticoagulation persists. For patients with thrombosis complicating HIT, conventional treatment options often have important limitations. Warfarin has a slow onset of action, and its use in patients with acute HIT and deep venous thrombosis has been associated with the devastating syndrome of venous limb gangrene. Ancrod, a defibrinogenating snake venom with thrombin-like activity, has also been used to treat HIT. However, this agent does not inhibit thrombin generation in HIT, which could explain why some patients who have been treated with this agent have developed certain adverse clinical events, such as warfarin-associated venous limb gangrene. The use of low-molecular-weight heparin (LMWH) to treat patients with HIT is limited by their high rate (up to 100%) of in vitro cross-reactivity with HIT sera, and the relatively frequent occurrence of new or recurrent thrombocytopenia or thrombosis during treatment of HIT with this class of agents. In contrast, the mixture of anticoagulant glycosaminoglycans known as danaparoid sodium has a much lower frequency of in vitro cross-reactivity with HIT sera (10% to 40%, depending upon the sensitivity of the assay). Moreover, clinically significant cross-reactivity during treatment with danaparoid appears to be uncommon, even in patients in whom in vitro cross-reactivity is demonstrable.

CARDIOPULMONARY BYPASS WITH DANAPAROID SODIUM AND ANCROD IN HEPARIN-INDUCED THROMBOCYTOPENIA.

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Heparin is the standard anticoagulant for patients undergoing cardiopulmonary bypass. There are some patients for whom heparin is unsuitable and ancrod (a defibrinogenating enzyme) has been used as an alternative. We present a patient with heparin-induced thrombocytopenia in whom treatment ancrod was ineffective. The addition of danaparoid sodium (a heparinoid) allowed safe cardiopulmonary bypass. We discuss the reasons for this and suggest that the combination of ancrod and danaparoid sodium is a logical one in such cases.

HEMATOLOGIC CHANGES IN A PATIENT WITH HEPARIN-INDUCED THROMBOCYTOPENIA WHO UNDERWENT CARDIOPULMONARY BYPASS AFTER ANCROD DEFIBRINOGENATION.
J Cardiothorac Vasc Anesth 1996 Dec;10(7):918-21

Department of Anesthesia, University of Washington, Seattle 98195, USA.
(5) Lathan LO, Staggers SL
ANCROD: THE USE OF SNAKE VENOM IN THE TREATMENT OF PATIENTS WITH HEPARIN-INDUCED THROMBOCYTOPENIA AND THROMBOSIS UNDERGOING CORONARY ARTERY BYPASS GRAFTING: NURSING MANAGEMENT.
*Heart Lung* 1996 Nov-Dec;25(6):451-60; quiz 461-2

University of Virginia Health Sciences Center, Charlottesville, USA.

Heparin-induced thrombocytopenia and thrombosis, also known as heparin-associated thrombocytopenia and thrombosis, was diagnosed in a 73-year-old man who had sustained a pelvic fracture, which was complicated by a left, deep-vein thrombosis. Heparin was administered and thrombocytopenia and arterial thrombosis of his left foot developed, which required amputation of three lateral toes. Four years later, the patient experienced a heart attack, and subsequently postinfarction angina developed, which was refractory to treatment with aspirin, nitrates, and beta-blockers. He was referred to a large, 750-bed teaching hospital for cardiac catheterization and possible coronary artery bypass grafting. An alternative treatment was needed for rapid anticoagulation. Ancrod, snake venom from the Malayan pit viper, was used to lower plasma fibrinogen levels, which allowed successful cardiac catheterization and coronary artery bypass grafting. We present a case study of the successful treatment of this patient with use of ancrod, and the nursing management for patients with heparin-induced or heparin-associated thrombocytopenia and thrombosis receiving this drug.

(6) Fondu P
HEPARIN-ASSOCIATED THROMBOCYTOPENIA: AN UPDATE.

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The use of heparin may be complicated by two types of thrombocytopenia (HAT): type I occurs early, is transient, and has no clinical relevance, while type II may lead to very severe manifestations (arterial or venous thromboses and more rarely bleedings), that are still underestimated by some clinicians. HAT-type II most frequently develops after use of therapeutic doses of unfractionated heparin (UH) but has also been described less frequently after use of very low doses of UH, of low molecular weight heparins (LMWH), and even of polysulfated glycosaminoglycosans devoid of anticoagulant action. The estimation of the incidence of HAT-type II and of related thromboses is a very difficult matter. Recent observations suggest that thromboses (notably venous) may be more frequent than previously estimated. HAT-type II pathophysiology includes the formation of immune complexes at the surface of platelets; the antigen has been shown to be most often platelet factor 4 bound to heparin while the antibody is recognized by platelet Fc gamma RI receptors. Thromboses result most probably from activation of both platelets (leading to the formation of microparticles) and endothelial cells. Several biological tests are presently available for diagnosing HAT-type II but none of them has been shown to be ideal. The prevention of HAT-type II requires history taking preference of LMWH to UH, early start of oral anticoagulation, and platelet monitoring from the fifth day of heparin therapy. The therapy of HAT-type II implies immediate discontinuation of heparin and avoidance of platelet transfusions, unless severe bleeding occurs. If further antithrombotic treatment is deemed necessary (probably in all cases), several options are possible but presently, the most recommended ones are Org 10172 or Ancrod; embolectomy or thrombolysis may also be required if a new thrombotic event has developed. A very difficult dilemma concerns patients previously sensitized to heparin and who present a clinical situation that theoretically mandates re-exposure to UH, such as by-pass surgery; prostacyclin analogues may be successfully used in such cases. Recent developments in the therapy of HAT-type II include recombinant hirudin or synthetic analogs, or use of some intravenous immunoglobulin preparations. Possible candidates are the heparin synthetic pentasaccharide and recombinant tissue factor pathway inhibitor.

(7) Munver R, Schulman IC, Wolf DJ, Rosengart TK
HEPARIN-INDUCED THROMBOCYTOPENIA AND THROMBOSIS: PRESENTATION AFTER CARDIOPULMONARY BYPASS.

New York Hospital-Cornell University Medical College, New York 10021.
Heparin-induced thrombocytopenia and thrombosis syndrome was diagnosed in a 63-year-old woman 11 days after coronary artery bypass grafting. Her only presenting complaints were incisional leg pain and vague chest discomfort. The syndrome was suspected when her platelet count was found to be 37,000/μL. A subsequent ventilation-perfusion lung scan showed findings highly probable for pulmonary embolism. An inferior venacavogram obtained before a pulmonary angiogram revealed a large retrohepatic thrombus at the right atrial junction. The patient was successfully treated with the defibrinogenating agent ancrod (Arvin). A diagnosis of heparin-induced thrombocytopenia and thrombosis syndrome should be considered and heparin therapy should be avoided in patients with low platelet counts who have been previously treated with heparin.

ANCROD INFUSION FOR ANTICOAGULATION DURING AND AFTER PTCA IN A PATIENT WITH HEPARIN-INDUCED THROMBOCYTOPENIA.
*Cathet Cardiovasc Diagn* 1994 Jul;32(3):286-7

Department of Internal Medicine, Medical College of Ohio, Toledo.

Ancrod is a rapid-acting defibrinogenating agent derived from the venom of the Malayan pit viper which has been used successfully as an alternative to heparin sulfate for anticoagulation during peripheral vascular procedures and coronary artery bypass surgery. We describe the first use of ancrod for anticoagulation before and during percutaneous transluminal coronary angioplasty (PTCA) in a patient with heparin-associated thrombocytopenia.

(9) Lewis BE, Leya FS, Wallis D, Grassman E
FAILURE OF ANCROD IN THE TREATMENT OF HEPARIN-INDUCED ARTERIAL THROMBOSIS.
*Can J Cardiol* 1994 Jun;10(5):559-61

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The morbidity and mortality associated with heparin-induced thrombosis remain high despite numerous empirical therapies. Ancrod has been used successfully for prophylaxis against development of thrombosis in patients with heparin-induced platelet aggregation who require brief reexposure to heparin, but its success in patients who have developed the thrombosis syndrome is not well defined. The authors present a case of failure of ancrod treatment in a patient with heparin-associated thrombocytopenia.

(10) Brennan MB, MacKean GL
HEPARIN-INDUCED THROMBOSIS TREATED WITH ANCROD.
*Can J Surg* 1994 Apr;37(2):161-4

Department of Surgery, Camp Hill Hospital, Halifax, NS.

Heparin used in the treatment of thromboembolic disease may produce an immune response in the patient, leading to thrombocytopenia and even thrombosis. These complications may arise at any time after the institution of heparin therapy. The authors report a case of heparin-induced thrombocytopenia with thrombosis in a 70-year-old woman. The complication was treated successfully with thrombectomy and the administration of warfarin and ancrod, which is a natural fibrinolytic agent. The nature of heparin-induced thrombosis and the mechanism of action of ancrod are discussed. The authors emphasize that all patients receiving heparin therapy should be closely monitored to detect hematologic disorders and to prevent their sequelae. Ancrod provides a reasonable therapeutic option if thrombosis does occur.

B. Ancrod induced Complications

1. Snake envenomation

STUDIES ON BLOOD COAGULATION AND FIBRINOLYSIS IN PATIENTS BITTEN BY BOTHROPS JARARACA (JARARACA).


Department of Physiology, Miyazaki Medical College, Japan.

The blood coagulation and the fibrinolytic systems of nine patients envenomed by Bothrops jararaca in Sao Paulo (Brazil) were studied. Five of the accidents were caused by young snakes (less than 50 cm). On admission, four patients had non-clotting and three partially-clotting blood. Fibrinogen levels were decreased due to the thrombin-like activity of the venom as expected. Consequent secondary activation of the fibrinolytic system was evident from the low levels of alpha-2-antiplasmin and the high titres of fibrinogen degradation products. High titres of cross-linked fibrin fragment D (D-dimer) in seven patients together with decreased platelet counts and/or factor V, and/or factor VIII in some, suggests intrinsic thrombin formation as these factors are not consumed in the defibrinogenation induced by venom thrombin-like fractions such as Ancrod and Batroxobin. However, normal or increased levels of antithrombin III in all and normal levels of factor II in eight patients do not support this interpretation. The existence of variable concentrations of other proteins in the venom of B. jararaca such as botrocetin and thrombocytin isolated from B. jararaca and B. atrox or crotalocytin from Crotalus horridus venom should be considered. Such proteins are known to activate factors V, VIII, XIII, and platelets without affecting prothrombin (factor II) and antithrombin III. Slower recovery of the haemostatic disturbances after antivenom administration to patients bitten by young snakes suggests a more severe coagulopathy in such accidents. This is supported by clinical observations.

CONSIDERATIONS ON HAEMOSTASIS

If there is a considerable DANGER OF THROMBOSIS, it may be possible to change to another anticoagulant treatment which is easier to direct. Turn, for example, from DICUMAROL to HEPARIN, with PROTAMIN or APROTININ as an antidote.

1. General Aspects of Decision Making

(1) Liptay MJ, Fry WA

COMPLICATIONS FROM INDUCTION REGIMENS FOR THORACIC MALIGNANCIES. PERIOPERATIVE CONSIDERATIONS.


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The treatment of locoregionally advanced non-small cell lung cancer is evolving rapidly, and we as surgeons should continue to take a prominent role, from the pretreatment evaluation phase, through reassessment after induction therapy and intraoperative decision making, to vigilant postoperative care. These are by far the most challenging thoracic oncologic patients to care for. The multidisciplinary team formula required for optimal results and mandates the leadership that we, as surgeons familiar with all facets of patient care, can provide.

2. Perioperative Oxygen Delivery

(1) Marley RA

POSTOPERATIVE OXYGEN THERAPY.


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Much has been published in the medical literature concerning adverse events relating to the surgical patient. Among the notable disorders requiring the expertise of the postanesthesia care unit nurse are the diagnosis and management of respiratory dysfunction acutely attributable to the effects of surgery and anesthesia. Inhalational and/or intravenous anesthetic agents contribute to pathophysiological alterations that lead to the development of hypoxemia in the postoperative period. When patients present with preexisting respiratory disease, their care is frequently more complex and challenging. This review session will address the oxygenation component of respiration and the perioperative influences that alter it as well as treatment considerations for normalizing oxygenation.

(2) Wolff M, Fandrey J, Hirner A, Jelkmann W
PERIOPERATIVE USE OF RECOMBINANT HUMAN ERYTHROPOIETIN IN PATIENTS REFUSING BLOOD TRANSFUSIONS. PATHOPHYSIOLOGICAL CONSIDERATIONS BASED ON 5 CASES.

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The efficacy of the administration of recombinant human erythropoietin (rHuEPO) in the treatment of anaemia in critically ill surgical patients refusing red cell transfusions requires further documentation. Herein, we report the outcome of 5 consecutive severely anaemic Jehovah's Witness patients (lowest haemoglobin concentration 27 g/l), who were discharged from the hospital in good condition after treatment. RHuEPO (50-280 U/kg body weight) was daily administered to 4 of the patients, who either exhibited preoperative anaemia or developed postoperative anaemia refractory to endogenous EPO probably due to inflammation. RHuEPO treatment was followed by a steep rise in reticulocytes and haemoglobin concentration. The fifth patient, who exhibited no signs of systemic inflammation following emergency hemicolectomy, was also treated with intravenous iron, but not with rHuEPO. His blood haemoglobin concentration rose from 27 g/l to 92 g/l in 3 wk. These observations indicate that the administration of rHuEPO is justified in the management of life-threatening anaemia, although only on a humanitarian basis, because there is no predictor for the possible spontaneous recovery.

(3) Cooper JR Jr
PERIOPERATIVE CONSIDERATIONS IN JEHOVAH’S WITNESSES.

Division of Cardiovascular Anesthesiology, Texas Heart Institute, Houston 77225-0345.

3. Infection Risk Considerations

(1) Platt R
ANTIBIOTIC PROPHYLAXIS IN CLEAN SURGERY: DOES IT WORK? SHOULD IT BE USED IF IT DOES?
_New Horiz_ 1998 May;6(2 Suppl):S53-7

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Perioperative antibiotic prophylaxis has been demonstrated to prevent postoperative wound infection after clean surgery in a majority of clinical trials with sufficient power to identify a 50% reduction in risk. The low risk of infection after many clean procedures requires studies of more than 1,000 procedures (sometimes many more) to detect such reductions reliably. This is a serious obstacle to performing conclusive tests of efficacy, and it all but precludes use of conventional clinical trials to identify optimal regimens. Regimens that have been shown to be effective have usually been those with efficacy against _Staphylococcus aureus_ and other pathogens that may be carried in the nares or on the skin. In addition, relatively long half-life in the serum and low cost are important considerations. Cefazolin is a good prophylaxis agent for many clean surgical procedures, although special characteristics of the procedure, increased likelihood of antimicrobial resistance, or antibiotic utilization concerns may make other agents more suitable in specific situations. The decision to use perioperative antibiotic prophylaxis for clean surgical procedures depends not only on its efficacy, but also on the cost of preventing infection. Few cost-benefit analyses have been performed, especially for procedures in which prophylaxis
has been least used. To perform such analyses, it will be necessary to acquire information that is currently lacking for many procedures. This includes the risk and cost of postoperative infection, adverse reactions to the prophylaxis agent, and increased antimicrobial resistance; in addition, detailed information is needed on infection-associated costs of medical care, lost productivity, and the value that the infected person places on avoiding infection. For many procedures, timely use of an appropriate antibiotic is the single most effective infection prevention method that can be implemented and monitored on a broad scale. These features make it amenable to adoption as a subject of continuous quality improvement activities. To accomplish this, it is necessary to articulate standards of care clearly so that systems to support the intended goal can be developed. Both the standards and the support systems can be tailored to specific surgical situations and to the values of providers and patients.

4. Perioperative Anesthetic Considerations

(1) Bach A, Schmidt H, Bottiger BW, Motsch J

[ECONOMIC ASPECTS OF ANESTHESIA. II. COST CONTROL IN CLINICAL ANESTHESIA]. [ARTICLE IN GERMAN]

Anesthesiol Intensivmed Notfallmed Schmerzther 1998 Apr;33(4):210-31

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The primary scope of economic analyses is the quantification of the costs (input) in relation to the results (outcome, output). According to whether a similar or different dimension of outcome parameters is chosen, it is possible to differentiate between cost minimisation, cost effectiveness, cost benefit and cost utility analyses. Decision trees and sensitivity analyses serve to develop or examine cost outcome studies. The principal perspective of economic analysis is of crucial significance. In the present overview of cost control programmes in clinical anaesthesia, the perspective chosen throughout is that of budget responsibility in a department of anaesthesiology. With regard to economic factors in clinical anaesthesiology, the cost of medical and nursing staff represents the largest cost block. It is, therefore, essential that personnel is efficiently employed, i.e. how the perioperative procedure is organised. In the area of material costs, blood products—including coagulation factors and plasma substitutes—are particularly cost intensive, followed by medical products and drugs, especially muscle relaxants and inhalational anaesthetics. In the perioperative context, the costs of anaesthesia personnel account for 5-15% of the total costs of patient care, while material costs account for 2-10%. In view of this small portion of the total costs, cost control programmes in anaesthesia can only make a relatively small contribution to reducing overall cost. However, it must be realised that anaesthesia care is vitally important for the perioperative process which means that in this context cost-effectiveness interventions have consequences that also affect other fields, e.g. postoperative pain service besides anaesthesia. In conducting economic analyses, cost considerations or reductions cannot be targeted alone, but must always also integrate outcome aspects so that costs and quality are regarded in relation to one another.

(2) Waegerle JD

PRACTICAL CONSIDERATIONS OF INTRAVENOUS SEDATION FOR THE PERIOPERATIVE NURSE.

Semin Perioper Nurs 1998 Jan;7(1):21-8

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There has been a recent increase in the number and types of cases performed with conscious sedation in the operating room and in minor operative suites (endoscopy, plastics, etc.), with nurse administering conscious sedation to healthy, uncomplicated patients under the direction of a physician. The literature is replete with articles which proffer guidelines, discuss the basics of conscious sedation, the role of the nurse, training and competency issues, and policy development. This article provides perioperative nurses with some practical, hands-on information to aid them in providing safe, quality care to their patients. There are detailed sections which address required equipment, perioperative patient assessment and monitoring, and information on commonly used medications and their side effects. The author offers this information based on literature review, education, and experience, and does not reflect the official position of any one organization.
(3) Conran AM, Kahana M
ANESTHETIC CONSIDERATIONS IN NEONATAL NEUROSURGICAL PATIENTS.

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Neonatal neurosurgery patients have specific considerations throughout the perioperative course in addition to the usual care of neonates undergoing other surgical procedures. Prematurity, with its associated comorbidity, temperature, and glucose control are important topics to consider in this age group. This article addresses practical aspects of preoperative assessment, intraoperative management, and postoperative care. Because CSF shunting and myelomeningocele repair are common neonatal procedures, these specific procedures are the focus of this article.

(4) Littlewood K
ANESTHETIC CONSIDERATIONS FOR HEPATIC CRYOTHERAPY.

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The evolution of hepatic cryotherapy as an accepted treatment for patients with non-resectable hepatic malignancy has required concurrent evaluation and development of perioperative anesthetic management of these cases. Review of published and institutional experience demonstrates that hepatic cryotherapy presents the anesthesiologist with an array of challenges, all of which are not intuitively apparent. Specifically, such issues as management of coexisting physiologic perturbations of the oncology patient, heat conservation during the procedure, and readiness for a more extensive procedure would be readily anticipated by most clinicians. Description and reasonable management of problems ranging from mild or moderate postoperative thrombocytopenia to the so-called cryoshock syndrome with the possibility of severe postoperative coagulopathy, renal dysfunction, and pulmonary complications, however, could emerge only with the education of experience. The goal of this article is to address the key issues faced by anesthesiologists consulted in the perioperative care of patients undergoing hepatic cryotherapy.

(5) Barkmeier LD, Hood DB, Sumner DS, Mansour MA, Hodgson KJ, Mattos MA, Ramsey D
LOCAL ANESTHESIA FOR INFRAGINGUINAL ARTERIAL RECONSTRUCTION.

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PURPOSE: Perioperative cardiac complications occur in 4% to 6% of patients undergoing infrainguinal revascularization under general, spinal, or epidural anesthesia. The risk may be even greater in patients whose cardiac disease cannot be fully evaluated or treated before urgent limb salvage operations. Prompted by these considerations, we investigated the feasibility and results of using local anesthesia in these high-risk patients. METHODS: From January 1, 1994, through August 30, 1996, 86 infrainguinal reconstructions were performed under local infiltration anesthesia (0.5% or 1.0% lidocaine). Supplementary intravenous sedation with propofol or other agents was given as needed for patients comfort. Most patients had arterial lines but Swan Ganz catheters were used infrequently. Postoperatively, continuous electrocardiographic monitoring was continued in the intermediate or intensive care units. Patients ranged in age from 37 to 86 years (mean 68 +/- 12); 47% were diabetic, 69% had severe coronary artery disease, and 14% had end-stage renal disease. RESULTS: Operations included 7 femoral-femoral, 21 femoral-popliteal, 16 femoral-tibial and 13 popliteal-tibial bypass grafts, 9 pseudoaneurysms, and 20 distal graft revisions (+/- thrombectomy). Autogenous vein was used in eight of the femoral-popliteal and all of the femoral-tibial and popliteal-tibial bypass grafts. There were two postoperative deaths. One patient died of a stroke (1.2%) on postoperative day (POD) 2 and one died on POD 27 of unknown cause. Two other (2%) patients had nonfatal subendocardial myocardial infarctions. Conversion to general anesthesia was required in four (5%) operations, three because patients became agitated and one because a long segment of vein had to be harvested from the opposite leg. Otherwise, patients tolerated the procedures well and postanesthetic recovery problems were minimized. CONCLUSIONS: Limb salvage operations can be done under local
anesthesia with acceptable complication rates. In selected patients with high-risk coronary artery disease, local anesthesia has theoretic and practical advantages and should be considered an alternative to general or regional anesthesia.

(6) Singh H, Bossard RF

PERIOPERATIVE ANAESTHETIC CONSIDERATIONS FOR PATIENTS UNDERGOING LUNG TRANSPLANTATION.


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PURPOSE: Five thousand, two hundred and eight lung transplants were performed worldwide before April, 1996. This review will discuss lung transplantation from an historical perspective, its indications, donor and recipient selection criteria, donor lung preparation, surgical considerations, perioperative anaesthetic management, and associated morbidity and mortality. SOURCE: Recent literature on perioperative anaesthetic management of lung transplantation and experience from international centres including the Toronto Lung Transplant Group and the St. Louis Lung Transplant Group. PRINCIPAL FINDINGS: Lung transplantation comprises of a family of operations, including single lung transplant, bilateral single lung transplant, lobar transplant and block heart-lung transplant. Improved donor lung preservation techniques have increased the duration of cold ischaemic time. The advent of bilateral single lung transplant has decreased the requirement for cardiopulmonary bypass, and airway complications have been reduced by adoption of the telescoping bronchial anastomoses. Advances in perioperative monitoring (including transoesophageal echocardiography), pulmonary vasodilators (e.g., nitric oxide and prostaglandin E1), cardiopulmonary bypass and ventilatory management, and a better understanding of the pathophysiological processes during the procedure have improved perioperative anaesthetic management. Also, advances in broad spectrum antibiotics and immunosuppressant drugs have improved the outcome by better management of the complications of infection and rejection.

CONCLUSION: Lung transplantation improves the quality of life with marginal improvement in life expectancy of the recipients. It is an expensive procedure requiring continued resources for long term management of these patients.

5. Considerations in a Rheumatoid Arthritis Patient

(1) Shaw M, Mandell BF

PERIOPERATIVE MANAGEMENT OF SELECTED PROBLEMS IN PATIENTS WITH RHEUMATIC DISEASES.


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Patients undergoing surgery are subject to multiple perioperative problems. This article reviews several issues that occur in surgical patients with rheumatic diseases, including management of medications, diagnosis of fat embolism syndrome, prophylaxis against endocarditis, postoperative fever, and perioperative myocardial infarction.

(2) Palmer LM

MANAGEMENT OF THE PATIENT WITH A TOTAL JOINT REPLACEMENT: THE PRIMARY CARE PRACTITIONER'S ROLE.


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The primary care practitioner assumes chief responsibility for patients with arthritis. More than 40 million Americans experience some form of arthritis. Management of the patient with arthritis may include a referral to an orthopedic surgeon for surgical intervention. As estimated, up to 500,000 total joint replacement procedures are performed by orthopedic surgeons each year in the United States. Presurgical evaluation for a total joint replacement is imperative to ensure that the patient
can safely undergo this surgical procedure. Postsurgical care of a patient with total joint replacement involves coordinating care with the physical therapist and orthopedic surgeon to ensure adequate follow-through with the recommended rehabilitation program, prophylactic antibiotic coverage, and observation for any complications including infection, deep-vein thrombosis, or loosening of the total-joint prosthesis.

(3) Widman J, Isacson J

SURGICAL HEMOSTASIS AFTER TOURNIQUET RELEASE DOES NOT REDUCE BLOOD LOSS IN KNEE REPLACEMENT. A PROSPECTIVE RANDOMIZED STUDY OF 81 PATIENTS.


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We studied the effect of timing of tourniquet release on blood loss in 81 patients (85 knees) who were operated on for total knee replacement. The patients were randomly allocated to one of two groups. In one group, the tourniquet was released for hemostasis before wound closure and in the other group, the tourniquet was not released until the wound was closed and a compressive dressing applied. We found no difference in total blood loss between the two groups and conclude that intraoperative release of the tourniquet for hemostasis is not effective for reducing blood loss in total knee replacement.

(4) MacKenzie CR, Sharrock NE

PERIOPERATIVE MEDICAL CONSIDERATIONS IN PATIENTS WITH RHEUMATOID ARTHRITIS.


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Patients who suffer from chronic rheumatologic diseases, such as rheumatoid arthritis, frequently require orthopedic surgical intervention during the course of their illness. This article provides the reader with an overview of approaches to postoperative risk stratification. Reviewed are the basic concepts that underlie perioperative medical management, including such issues as the preoperative medical assessment, the currently employed anesthetic techniques, and approaches to postoperative analgesia. The impact of comorbid conditions on surgical outcome is discussed as are specific clinical problems that have particular relevance to the patient with rheumatoid arthritis.

(5) Bridges SL Jr, Moreland LW

PERIOPERATIVE USE OF METHOTREXATE IN PATIENTS WITH RHEUMATOID ARTHRITIS UNDERGOING ORTHOPEDIC SURGERY.


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Methotrexate (MTX) is commonly prescribed for the treatment of rheumatoid arthritis. Its use seems to be an independent risk factor for infection with common pathogens and opportunistic organisms. Some rheumatologists and orthopedic surgeons hold the opinion that MTX should be temporarily withheld to lessen the likelihood of postoperative infection or poor wound healing. Alternatively, some clinicians believe that MTX should be continued throughout the perioperative period to avoid flares in rheumatoid arthritis disease activity. There are no definitive studies on which to rely in this decision-making process, but the authors believe that withholding MTX for 2 weeks of the perioperative period is a reasonable and prudent approach.

(6) Steuer A, Keat AC

PERIOPERATIVE USE OF METHOTREXATE--A SURVEY OF CLINICAL PRACTICE IN THE UK.

Br J Rheumatol 1997 Sep;36(9):1009-1011.
Department of Rheumatology, Northwick Park and St Mark’s Hospital, Harrow.

We have surveyed the use of methotrexate in the perioperative period in patients with rheumatoid arthritis (RA) undergoing surgery. A total of 200 consultant rheumatologists and 200 consultant orthopaedic surgeons in the UK were sent a postal questionnaire. Thirty-five per cent of rheumatologists and 46% of orthopaedic surgeons were concerned that the drug may increase the risk of post-operative complications, although significantly less ‘always’ stopped the drug around the time of surgery. There was great variation in the timing of stopping the drug with most stopping treatment within 2 weeks before surgery and restarting within 2 weeks after surgery. The majority of clinicians surveyed (70%) felt that national guidelines for the perioperative use of methotrexate would be helpful.

(7) Schneller S
MEDICAL CONSIDERATIONS AND PERIOPERATIVE CARE FOR RHEUMATOID SURGERY.

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Surgery on patients with RA should be undertaken after careful consideration of a number of issues. These include an overall assessment of the status of the patient’s arthritis, general health and preparedness for the procedure and the rehabilitation which follows. Special attention must be given to organs that may be affected by the systemic involvement which occurs with rheumatoid disease. Sites requiring specific review include the cervical spine, lungs, airway, bone, and bone marrow. Intraoperatively and postoperatively rheumatoid patients may require supplementary corticosteroids and an adjustment of the dose of their antirheumatic medications. Various systemic rheumatic diseases can have predominantly hand signs and symptoms at their onset. It is valuable to be familiar with the clinical features of gout with tophaceous inflammation, psoriatic arthritis, Raynaud’s disease, and amyloidosis.

6. Nutritional Considerations

(1) Edelson GW
SYSTEMIC AND NUTRITIONAL CONSIDERATIONS IN DIABETIC WOUND HEALING.

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Metabolic and nutritional aspects of wound healing are discussed in this article, as well as the effects of both acute and chronic hyperglycemia, hyperinsulinemia, end-organ complications of diabetes, and impaired nutritional status of wound healing. Specific recommendations regarding the perioperative management of patients with diabetes mellitus are set forth, and the importance of achieving tight glucose control and overall improved metabolic control are emphasized.

(2) Kelly DG, Fleming CR
NUTRITIONAL CONSIDERATIONS IN INFLAMMATORY BOWEL DISEASES.
Gastroenterol Clin North Am 1995 Sep;24(3):597-611

Mayo Medical School, Rochester, Minnesota, USA.

Although many foods have been suggested to play a role in the cause of IBD, there are not yet definitive data to support diet as a cause of either CD or UC. Malnutrition is a common occurrence in IBD, and this must be considered in the treatment of these diseases. Nutritional support in IBD has limited use as primary therapy (Table 2). Even though parenteral and enteral nutrition have been associated with remission, relapse frequently occurs when normal food intake is resumed. Likewise, fistulae may resolve with aggressive, nutritional therapy, but they frequently recur with reinstitution of food. In short bowel syndrome caused by extensive intestinal resection performed in CD, parenteral nutrition provides an important mode of therapy. In addition, perioperative use of nutritional support may decrease the incidence of postoperative complications in patients who are
malnourished. Nutritional support in pediatric patients with CD who have growth failure has been effective in stimulating growth.

7. Considerations of Hemostasis

(1) Turitto VT, Hall CL  
MECHANICAL FACTORS AFFECTING HEMOSTASIS AND THROMBOSIS.  

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Both physical and chemical factors can influence the activity of platelets and coagulation factors responsible for the formation of thrombotic and hemostatic masses in the vicinity of an injured vessel wall. Studies performed in controlled shear devices (viscometers) have indicated that physical factors alone can induce platelet aggregation, even in the absence of exogenous chemical factors. The physical considerations which appear to be important for the local activation of hemostatic/thrombotic mechanisms appear to be related to the magnitude of the shear rate/stress, the duration of the applied physical force and the local geometry. Blood flow alone has multiple influences on platelet and coagulative mechanisms. It has been well established that at physiologically encountered shear conditions, increases in the local shear rate enhance the attachment of platelets to the vessel wall and the growth of platelet aggregates on adherent platelets. In contrast, increases in local shear conditions inhibit the production of fibrin formation on surfaces where tissue factor (TF) is exposed. At levels of shear rate/stress high as compared to normal physiological conditions, but comparable to those observed at the apex of severely stenosed vessels, platelet aggregate formation is dependent on the duration of the exposure time. Considerable advances in our understanding of flow-related mechanisms have evolved from the use of well-defined perfusion chambers employing parallel flow streamlines. However, processes leading to hemostasis and thrombosis generally occur in more complicated flow situations where flow streamlines are not parallel and in which abnormally high, as well as abnormally low, shear rates and shear stress levels may be encountered in close proximity to each other.

(2) Knofler R, Weissbach G, Kuhlisch E  
PLATELET FUNCTION TESTS IN CHILDHOOD. MEASURING AGGREGATION AND RELEASE REACTION IN WHOLE BLOOD.  
*Semin Thromb Hemost* 1998;24(6):513-21

Department of Pediatrics, Medical Faculty of Technical University, Dresden, Germany.  
Blood samples from 42 newborns, 78 infants and schoolchildren, and 81 healthy adults were tested for the parameters of primary hemostasis. Only whole blood techniques were used. Agonist-induced aggregation and release-reaction studies were performed in a whole blood lumi-aggregometer simultaneously. The release of adenosine triphosphate (ATP) was detected by the luciferin-luciferase method. The in vitro bleeding time was measured by the PFA 100 system. The results of these studies were ostensibly influenced by blood cells. Many aggregation phenomena were correlated with the platelet count. Aggregation and release reaction by collagen were inversely correlated with the hematocrit. In the PFA 100, hematocrit and leukocyte count were also inversely correlated with the closure time and the maximal blood flow velocity. Both parameters were diminished in newborns. The aggregation response to adenosine diphosphate (ADP) was similar in the three groups. The same was true for the aggregation and release reaction by arachidonic acid and for the agglutination by ristocetin. The aggregation and release reaction by collagen were diminished in the specimens from newborns. For the explanation of this transient hypofunction, only theoretical considerations exist. Beyond the postnatal period and during childhood, no remarkable differences from the adult norm were found.

(3) Mann KG  
THROMBOSIS: THEORETICAL CONSIDERATIONS.  
*Am J Clin Nutr* 1997 May;65(5 Suppl):1657S-1664S

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The blood coagulation process is initiated in response to vascular injury and results in either hemostasis or thrombosis. The process can be divided conceptually into separate steps including initiation, propagation, termination, elimination, and repair. Concise descriptions of each of these processes are provided in the present review together with an attempt to integrate these processes at a conceptual level so as to avoid the unfortunate tendency to apply linear logic to the complex temporal interplay among the various processes in the blood coagulation system.

(4) Sindet-Pedersen S

HAEMOSTASIS IN ORAL SURGERY--THE POSSIBLE PATHOGENETIC IMPLICATIONS OF ORAL FIBRINOLYSIS ON BLEEDING. EXPERIMENTAL AND CLINICAL STUDIES OF THE HAEMOSTATIC BALANCE IN THE ORAL CAVITY, WITH PARTICULAR REFERENCE TO PATIENTS WITH ACQUIRED AND CONGENITAL DEFECTS OF THE COAGULATION SYSTEM.


Department of Clinical Chemistry, Ribe County Hospital, Esbjerg.

Activation and inhibition of the haemostatic system was reviewed including the interaction between the four biological systems involved in haemostasis: the vessel wall, the platelets, the coagulation system and the fibrinolytic system. The haemostatic mechanism is initiated at the site of injury through local activation of surfaces and release of tissue thromboplastin, resulting in formation and deposition of fibrin. The coagulation process is regulated by physiological anticoagulants. Activation of fibrinolysis is triggered by the presence of fibrin, and the role of tissue-type plasminogen activators (t-PA) at the site of fibrin formation in particular is emphasized. The process is regulated by physiological inhibitors, of which alpha 2-antiplasmin, histidine-rich glycoprotein and plasminogen activator inhibitor are reported to be of major physiological significance. The role of fibrinolysis in the regulation of the dynamic haemostatic balance is discussed, elucidated through examples of congenital deficiencies of the coagulation and the fibrinolytic system. Pharmacological inhibitors of fibrinolysis (i.e. epsilon-aminocaproic acid and tranexamic acid) and their possible effect on the haemostatic system are described. The systemic effects on the fibrinolytic system of surgery and oral surgery is reviewed, and it is concluded, that oral surgery has insignificant effects on blood fibrinolysis. In contrast, oral surgery induces changes of fibrinolysis in the oral environment; initially the fibrinolytic activity of saliva is reduced, due to the presence of inhibitors of fibrinolysis originating from the blood and the wound exudate. When bleeding and exudation cease, the fibrinolytic activity of the saliva will increase. Plasminogen and plasminogen activator, identified as t-PA are present in the oral environment under physiological conditions. Plasminogen is secreted in the saliva and the sources of t-PA include oral epithelial cells and gingival crevicular fluid. The presence of plasminogen and t-PA in the oral environment implies that when fibrin is present (i.e. after surgery), fibrinolysis is triggered. Haemorrhagic complications to oral surgery in patients without known defects of the coagulation system is reviewed. It is concluded that the investigations conducted to the present day do not permit final conclusions with respect to the pathophysiological role of defects in the coagulation and the fibrinolytic systems for the development of bleeding after oral surgery. Further investigations are necessary in order to clarify these aspects, and should include extensive laboratory analyses to reveal rare congenital defects such as factor XIII- and alpha 2-antiplasmin deficiencies.

If on HEPARIN . . . can you stop that treatment? Or . . . neutralize with PROTAMIN?

If THROMBOCYTE-FUNCTION is already disturbed, counteract with DESMOPRESSIN (DDAVP) or APROTININ.