

HEPARIN KINETICS AND COAGULATION STUDIES AFTER SUBCUTANEOUS AND JET INJECTION OF LOW-DOSE HEPARIN. R.C. Briel, Department of Obstetrics and Gynecology, D-74 Tuebingen FRG

Administration of low-dose heparin by jet injection is regarded as most suitable for both patient and staff. The present study deals with the comparison of plasma heparin levels and various coagulation parameters after s.c. and jet injection (K3-pistol Sandoz) of 5000 IU calcium heparin in 0.2 ml and 5000 IU sodium heparin + 0.5 mg dihydroergotamin (DHE) in 0.7 ml. The injection sites were upper arm, abdomen or upper leg. Estimations were performed in 10 healthy volunteers each receiving 12 different injections. Heparin level profiles (chromogenic substrate S-2222), AT III activity (S-2238) and concentration (Mancini technique), antifactor Xa (S-2222), antiheparin activity (S-2222), antiplasmin (S-2251), TT, aPTT and TEG r+k were measured.

There was a positive and significant correlation between postinjection heparin levels and body weight, preinjection "endogenous heparin", AT III activity and concentration, and a negative correlation to the antiheparin activity found before injection. Heparin levels were slightly higher after heparin/DHE than after heparin alone, but the differences were not significant. 30 min after jet injection heparin levels were slightly higher than after s.c. injection, while after 1 hr they were similar. After 2 to 3 hrs the highest levels were found, being significantly higher after s.c. injection. After 4 and 6 hrs there were no differences between s.c. and jet injection. TT, aPTT and TEG showed similar behavior patterns. The values were independent of the injection site, upper arm or abdomen with both s.c. and jet injection. They were lower, however, if heparin jet injection was done in the upper leg. Thus, the pretreatment measurement of AT III, endogenous heparin and antiheparin activity with chromogenic substrates may be helpful in the management of an individualized heparin prophylaxis. After heparin jet injection, altered heparin kinetic has to be considered: a more rapid initial absorption is followed by lower peak heparin levels. The upper leg can not be recommended as injection site for heparin jet injection.

PROPHYLAXIS AGAINST DEEP VEIN THROMBOSIS FOLLOWING TOTAL HIP REPLACEMENT USING A COMBINATION OF HEPARIN AND DIHYDRO-ERGOTAMINE. V.V. Kakkar, J. Fok, B. Djazaeri, R. Ham, M. Fletcher. Thrombosis Research Unit, King's College Hospital Medical School, London, England.

Venous thromboembolism is a frequent and important complication of total hip replacement. Changes in blood coagulability and stasis in the deep veins of the lower limb are major factors in the pathogenesis of deep vein thrombosis (DVT). Prophylactic efforts aimed at changes in coagulability have met with little success in this group. Dihydroergotamine mesylate (DHE), a potent venoconstrictor acting mainly on the capacitance vessels of the limbs is capable of doubling the velocity of venous flow and should minimise stasis.

Four hundred and six patients undergoing total hip replacement were investigated for the efficacy of a combination of heparin (5000IU) and DHE (0.5mg) given 8 hourly subcutaneously in the prevention of postoperative venous thromboembolism. High risk patients were scanned using the  $^{125}$ I-labelled fibrinogen uptake test and all patients underwent bilateral ascending phlebography on the 14th postoperative day unless there was clinical or isotopic evidence necessitating earlier investigation.

There were 117 DVT (28.8%), 19 (16.4%) of which were bilateral. Three pulmonary emboli (0.7%) occurred, one of which was fatal. Prophylaxis was discontinued in 6 patients (1.5%) because of postoperative bleeding and wound haematoma developed in 23 patients (5.7%) - 6 of which required evacuation.

Heparin and DHE combination in prophylaxis represents a considerable improvement over the use of heparin alone (52% incidence DVT) and Aspirin (80%).

SEX DIFFERENCE IN HEPARIN INDUCED PLATELET AGGREGATION IN WHOLE BLOOD. F. Kohanna, B. Ransil, M.A. Smith, E.W. Salzman. Departments of Surgery and Medicine, Beth Israel Hospital and Harvard Medical School, Boston MA, U.S.A.

The Clay Adams Ultraflo-100 cell counter coupled with the Nuclear Data 60 pulse-height analyzer permits detection of platelet aggregates in whole blood. Its high resolution recognizes lesser degrees of aggregation than can be seen in PRP by conventional aggregometry. Platelet aggregates are manifested by a drop in number of single platelets. We used this device to study platelet aggregation induced by beef-lung heparin in whole blood.

Blood was drawn by venepuncture into a syringe containing either heparin (10 u/ml, n=15) or tri-sodium citrate (0.130 M, n=7). Samples were gently rocked at 37° for 0, 1, 2, 3, 5, 10 and 30 minutes and then fixed in buffered formaldehyde.

Platelet counts of both sexes in citrated whole blood decreased linearly over time (males: n=4; females: n=3; 12% decrease at 30 min. in both). Platelet counts in heparinized blood at time 0 for both males and females were bimodally distributed. Subsequent changes in platelet count also suggested bimodality, with high and low responders (HR and LR) in each sex, corresponding to the bimodal grouping of initial platelet counts. Males exhibited an exponential decay in concentration of single platelets within the first 5 minutes; counts at 30 minutes fell 31% (HR, n=3) and 23% (LR, n=4) respectively. Females (both HR and LR) demonstrated a biphasic early response with a deep minimum at 2 minutes (HR=45% decrease, n=4; LR= 26% decrease, n=4) followed by rapid partial disaggregation by 3-5 minutes and subsequent exponential-like decay.

Results suggest a profound effect of heparin on platelet aggregation in whole blood, which is markedly different in males and females. The explanation for the sex difference is not known.

ON THE EFFECTIVE HEPARIN THERAPY WITH NO COMPLICATIONS. Y. Oguma, H. Takei, T. Seiya, T. Murakoshi, M. Yamauchi, H. Nagata, H. Hasegawa. First Dept. of Internal Medicine, Hokkaido University School of Med., Sapporo, Hokkaido, Japan.

In order to establish the effective heparin (HP) therapy without any complicated episodes, we investigated the changes of plasma HP concentrations (COATEST HP, KABI), APTT, FPA, AT III activity (AT III F), AT III immunology (AT III I), and PF 4 in 40 patients receiving HP treatment (15 cases in DIC, 25 cases in the other disease). There was a correlation between HP concentrations and APTT. However, the regression lines varied significantly in each case, especially between DIC group\* and non-DIC group\* ( $p < 0.005$ ). So, it was suggested that single estimation of HP concentration or APTT might not give a correct information and both estimations were required for appropriate HP therapy. In the patients with complete remissions obtained by HP administration, FPA improved most initially and normalized continuously thereafter in the range of 0.2-1.2 IU/ml of HP concentration and 45-250 sec. of APTT and no hemorrhagic incidents occurred. Considering FPA is the most sensitive indicator of thrombin action on fibrinogen, we are convinced that this range is the effective therapeutic range with no complications. AT III F and AT III I showed a good correlation ( $r: 0.827$ ,  $p < 0.01$ ) but the ratio of AT III F/AT III I was prominently depressed in acute decompensated DIC. In most cases, both AT III levels were decreased reflecting the pathologic consumption. The HP treatment for these cases led further decrease of AT III for a couple of days and returned afterwards to normal levels in HP effective cases, while decreased more in HP ineffective cases. The minimum AT III levels indispensable for HP therapy were also considered 40% of normal values. In thrombotic diseases, PF 4 was elevated with a good correlation to BTG, except in patients with extremely low platelet counts. But the changes of PF 4 was not always coincident with FPA changes. When HP was administered to normal subjects, elevated PF 4 levels were found while BTG remained normal, suggesting the different release mechanism of PF 4 and BTG.