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A DOSE RANGING STUDY DESIGNED TO ASSESS THE SAFETY AND EFFICACY OF A LOW MOLECULAR WEIGHT HEPARIN FRAGMENT (FRAGMIN) AS PROPHYLAXIS AGAINST DEEP VEIN THROMBOSIS.

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A preliminary study has reported that a single daily injection of 2500 and 5000 U of Fragmin was equally effective in preventing deep vein thrombosis[1] (DVT). All the patients who developed DVT (4.9%) had undergone surgery for malignant disease. However, small numbers of patients were investigated and therefore detailed subject analysis was not possible. In the present study, 1000 patients scheduled to undergo elective major abdominal, urological or gynaecological surgery were investigated. They received one of three regimens; 5000 (Group I), 2500 (Group II) or 1500 (Group III) U of Fragmin daily as a single injection. The ^{125}I-fibrinogen uptake test was used to detect DVT. Operative and postoperative blood loss, transfusion requirements, fall in postoperative haemoglobin and frequency of haematoma formation were recorded to assess the safety of three regimens. An analysis of variance was carried out using a computerized statistical package. Isotopic DVT was detected in 60 patients (6.7%). 11.1% of patients with malignant disease and 5.8% with benign disease developed DVT (p 0.01). Data were also analyzed in respect of age and there was a highly significant increase in the frequency of thromboembolic disease in patients over sixty years (10.1%) compared to 2.6% in the under 60 group (p 0.001). Significant differences were observed in the frequency of bleeding complications in the three groups and these were related not only to underlying disease process but also the type of surgery being performed. The detailed results will be presented and a safe and effective regimen for different groups of patients will be defined.

1. Efficacy and Safety of Two Regimens of Low Molecular Weight Heparin Fragment (Fragmin) in Preventing Postoperative Venous Thrombolism. Kakkar VV, Kakkar S, Sanderson RM, Peers CE. Haemostasis 16(Suppl.2) 1986, pp 19-24.

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LOW MOLECULAR WEIGHT HEPARIN (FRAGMIN) PROPHYLAXIS IN GYNECOLOGIC SURGERY

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In a prospective, randomized study patients undergoing hysterectomy were treated either by the low molecular weight heparin Fragmin or by the combination of unfractionated sodium heparin + dihydroergotamin (HDHE). The dosage in the Fragmin group was 2x2500 anti Xa-U on day 1 = day of surgery, from day 2-8: 1x5000 anti Xa-U, in the HDHE-group from day 1-8: 2x5000 IU heparin + 0.5 mg DHE. 99 patients were randomly allocated to prophylaxis with Fragmin, 101 to HDHE prophylaxis. 95 and 96 respectively were evaluated, the others excluded for different reasons. The 2 groups were comparable for general data and risk factors. Duration of surgery, intraoperative blood loss, transfusion rates and postoperative hemoglobin levels were identical. Blood volumes in subcutaneous and subfascial drainages were slightly but not significantly higher in the Fragmin group. In patients with an additional Marshall-Marchetti-operation, blood volumes in the drainages of the spatium retzii were significantly higher in patients on Fragmin. No differences were observed in the incidence of minor and major wound hematoma. Painful injections and sugillations at the injection sites were more frequently observed in the HDHE-group. The thermographic DeVeTherm test, which was carried out daily for diagnosis of DVT, gave positiv results (= temperature difference 1°C) on one day only in 14 patients of each group. The test was positive on 2 or more consecutive days in 4 patients on Fragmin and 2 patients on HDHE. Phlebography, which was carried out in the latter patients, gave a positive result in 1 patient of each group. Localization of DVT was mainly the lower limb. Plasma anti-Xa activity (S-2222) 4 hrs. after injection of 5000 anti-Xa IU Fragmin was 0.45 IU/ml being 10 fold higher than after HDHE. aPTT was slightly prolonged in both groups, thrombin time and thrombelastogramm gave even more pronounced changes in the Fragmin group. The present data indicate that Fragmin dosage should be further decreased to avoid bleeding complications.

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THE SAFETY AND EFFICACY OF A LOW MOLECULAR WEIGHT HEPARIN (FRAGMIN) IN THE PREVENTION OF DEEP VEIN THROMBOSIS IN MEDICAL PATIENTS: A RANDOMIZED DOUBLE-BLIND TRIAL.

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The safety and efficacy of 2500 anti-Factor Xa U of a low molecular weight heparin (Kabi 2165,Fragmin) subcutaneously once a day, and 5000 IU of standard unfractionated Heparin (KabiVitrum, Stockholm) subcutaneously twice daily as thromboprophylaxis was compared in 200 medical patients in a randomized double blind trial. According to the risk of DVT the patients were stratified before randomization in a high and low risk group. The high risk group consisted of 100 patients mainly with malignant diseases and/or previous history of thromboembolism, the low risk group of 100 patients with mainly myocardial infarction and/or coronary heart disease. The prophylaxis was given for seven to ten days. In 192 consecutive patients the clinical status and thermographic screening for DVT (leg temperature profiles, DeVeTherm) were daily evaluated. In two cases of suspected DVT and one case of suspected PE, the following phlebography or pulmonary scintigraphy were found to be negative. In the high risk group, one patient treated with Fragmin having a central venous catheter developed on day 10 symptoms of an arm vein thrombosis. There were no bleeding complications observed in either of the two treatment groups. Two patients with trombocytopenia (25.000 and 22.000/µl) due to chemotherapy and underlying malignant disease were successfully treated with Fragmin without developing any bleeding complications. In eight patients during Fragmin prophylaxis invasive diagnostic methods as heart catheterization, gastroscopy, bronchoscopy or spinal puncture were performed without noticing any bleeding events. 2500 anti-Factor Xa U of Fragmin gave plasma levels by anti-Factor Xa assay (S-2222, Kabi) of mean 0,1 U/ml when blood was sampled three to four hours after the subcutaneus application. There was no accumulation during the treatment periode observed.
This study suggests that 2500 anti-Factor Xa U of Fragmin once daily is as safe and effective as 5000 IU of standard heparin twice daily in these medical patients. Especially in patients who need prophylaxis for a long time eg. with malignant disease, the once daily injection is welcomed.

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A STUDY OF THE ANTI-THROMBOTIC POTENTIAL OF LOW MOLECULAR WEIGHT HEPARIN LHN-1 (NOVO) IN NORMAL VOLUNTEERS.

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Studies of low molecular weight heparin have shown a molecular sized dependency of the anti-coagulant activity. We studied the effects of a low molecular weight heparin LHN-1 (Novo) with a mean molecular weight of 5-7000 daltons on the coagulation mechanism and platelet function of normal volunteers. The heparin was given for 5 days on a once daily dose of 2500, 5000 or 7500 anti-Xa units to 3 groups of volunteers and in a twice daily regime of 2500 and 5000 anti-Xa units in 2 further groups of volunteers. After subcutaneous injection LHN-1 produced a significant ($p<0.01$) increase in anti-Xa activity which peaked between 3-4 hours after subcutaneous injection on both once and twice daily regime. On once daily regime there was no significant measureable anti-Xa activity 24 hours after the last injection. There was a small but significant increase in both KCCT and thrombin time ($p<0.01$) following injection, which was also dose related. Bleeding time did not change and there was no effect on platelet function. There was a significant ($p<0.01$) increase in fibrinolysis as measured by the fibrin plate method. There were no bleeding problems. These findings would suggest that LHN-1 merits further clinical evaluation to confirm its anti-thrombotic and profibrinolytic potential.