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LONG TERM PROPHYLAXIS OF THROMBOEMBOLISM IN OUTPATIENTS WITH LOW MOLECULAR WEIGHT HEPARIN. J. Harenberg, G. Leber, R. Raedsch, R. Zimmermann, W. Kübler. Department of Internal Medicine III, Medical University Clinic, 6900 Heidelberg, FRG.

The prophylaxis of thromboembolism with oral anticoagulants and low dose heparin is established. However, bleeding episodes and other side effects may occur. Alternative compunds for further anticoagulation do not exist so far. We report, therefore, of the experiences of 66 outpatients who were treated with low molecular weight heparin up to nineteen months.

All patients had major bleeding on conventional anticoagulants. Further anticoagulation was strongly indicated because of recurrent thromboembolism, artificial heart valves, dilative cardiomyopathy or heart valve diseases with artrial fibrillation. The dose ranged from 2.500 to 15.000 aXa units once daily subcutaneously. The LMW heparin Tedelparin (Kabi 2165) was used. The dose was chosen according to the risk of bleeding or thromboembolism, and body weight of each patient. In patients with high bleeding risks (esophagial varices) the average dose was 100 units/kg bodyweight and in patients with high risk of thromboembolism (artificial heart valves) the average dose was 140 units/kg bodyweight. The dose was adjusted according to the aXa activity and aPTT inhibition: 2-4 hours after the s.c. administration 0,3 - 0,6 heparin units/ml or 0,6 - 1,0 units/ml in the above mentioned groups should be reached respectively, and the aPTT should be not more than 10 sec above the upper normal limit.

Four of 66 patients experienced rethrombosis, 2 of them were noncompliant. Six of 66 patients had minor haemorrhages, 0 major or fatal bleeding occured. Bleeding was more frequent when the aXa activity increased to more than 1 unit/ml. With a dose reduction of 20 % no recurrence of bleeding was seen and antithrombotic effect was still maintained.

The data demonstrate that LMW heparin can be safely and effectively used for long term anticoagulation in patients with major haemorrhage due to conventional anticoagulants.

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RANDOMIZED DOUBLE BLINDED STUDY OF NORMAL AND A LOW MOLECULAR WEIGHT HEPARIN IN GENERAL MEDICAL PATIENTS. J. Harenberg, B. Kallenbach, U. Martin, and R. Zimmermann. Department of Internal Medicine, Medical University Clinic, 6900 Heidelberg, FRG.

Low molecular weight (LMW) heparin has been proven effectively and safely at low doses with one injection per day in the postoperative medicine. This has not been confirmed so far in general medical patients requiring prophylaxis of thromboembolism. We report here of the results of a double blinded prospective randomized trial with normal and LMW heparin.

Two hundred patients were included into the study after having given informed consent. They received 3 x 5.000 units sodium pig intestinal mucosa heparin (MW 12.000) or 1 x 1.500 aPTT units (MW 3.800, Sandoz AG, Nürnberg, FRG) for 10 days. The development of thromboses was screened by clinical investigation, impedance plethysmography and Doppler sonography of the femoral vein at days 1,3,5,7 and 10. The incidence of haemorrhage was assessed by clinical examination, hemoglobin and hematuria at the same time intervals and factor Xa inhibition, aPTT, thrombin inhibition, antithrombin III and thrombocyte count were measured.

The following incidences occured in the heparin / LMW heparin treated groups: clinically evident thrombosis 4 / 3 (phlebography being indicated only in 1 patient of the LMW heparin group and documenting fresh thrombosis), pulmonary embolism 0 / 0, local allergy 1 / 0, fatal bleeding complication 2 / 0, mortality 2 / 3 (mortality was not due to thromboembolism or treatment related complications in the LMW heparin group, one patient being antopsied). Local hematomas were 3 times more frequent in the heparin group ($p < 0,05$).

It is concluded that one daily injection of low doses of LMW heparin is as effective as normal heparin in preventing thromboembolism in hospitalized patients in general medicine.

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PROPHYLAXIS AGAINST POSTOPERATIVE DEEP VEIN THROMBOSIS (DVT) - A DOUBLE-BLIND MULTICENTER TRIAL COMPARING A HEPARIN FRAGMENT GIVEN ON THE EVENING BEFORE SURGERY WITH CONVENTIONAL LOW DOSE HEPARIN. D. Bergqvist, J. Frisell, T. Hallböök, A. Horn, A. Lindhagen, H. Ljungnér, K.G. Ljungström, T. Mätzsch, H. Önarheim, B. Risberg, S. Törngren, P. Örtenwall, U.S. Burmark. Depts of Surgery, Malmö, Stockholm, Skövde, Bergen, Halmstad, Göteborg and KabiVitrum AB Stockholm, Sweden and Norway.

At the Xth Int. Congress on Thrombosis and Haemostasis in San Diego results from a multicenter trial on 432 patients were presented, comparing a low molecular weight heparin (LMWH) fragment (Fragmin, Kabi) once daily with low dose heparin twice daily. Prophylaxis started 2 hours preoperatively. The frequency of postoperative DVT did not differ (6.4 % v. 4.3 %) but the onset of thrombosis was delayed in the LMWH group. Haemorrhagic complications occurred significantly more often in the LMWH group (11.6 % v. 4.6 %). The results were similar independent whether the analysis was made according to the intention to treat principle or based on patients with correct prophylaxis. On the basis of these data and newer knowledge regarding the pharmacokinetics of LMWH a second prospective randomized double-blind multicenter trial on patients older than 40 years undergoing elective abdominal surgery was started. The only difference was that the first dose of 5000 anti-factor Xa units of LMWH was given on the evening before surgery. Only conventional low dose heparin was given 2 h before surgery. The study is designed to include 1000 patients, a number which will be obtained during the spring 1987. At the time of abstract deadline 799 patients have been included. The over-all frequency of DVT (fibrinogen uptake test) is 6.8 %, the frequency of haemorrhagic complications 3.6 % and mortality 1.8 % (one fatal pulmonary embolism). These frequencies remained unaltered after inclusion of 336, 576, 655 and 799 patients. Although the code has not been broken yet, it can be concluded that the new regimen with start of prophylaxis the evening before surgery has not altered the frequency of DVT or mortality whereas the frequency of haemorrhagic side effects has decreased considerably.

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LOW DOSE HEPARIN PROPHYLAXIS IN HIP FRACTURE SURGEY -HEPARIN EFFECT; INHIBITORS; FIBRINOLYSIS AND INCIDENCE OF DVT.

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In a prospective studie 129 patients with hip fracture surgery under LDH-prophylaxis (3x5000 U Na-heparinat) were examined in order to find an answer to the question, if there is a correlation between inhibitor activity, parameters of fibrinolysis, plasma heparin activity and the incidence of DVT.
100 patients with ascending phlebography on day 7 to 9 post op. were taken into final consideration (blood collection on admission and on day 1, 2, 4, 7 after surgery):

1) Incidence of DVT: 17 %.
2) Inhibitors: No difference between patients with and without DVT with respect to AT III activity and prot. C concentration (prot. C activity in progress).
3) Fibrinolysis: Elevated levels of DD-fragment ($\bar{x}$ = 1 780 mg/ml), t-PA Inhibitor ($\bar{x}$ = 31 AU) and fibrinogen (417 mg/dl) before operation due to preceding trauma. No significant difference between t-PA, t-PA inhibitor and antiplasmin with respect to DVT. While plasminogen concent was significantly increased in patients with DVT on day 4 and 7, DD-fragments had lower values on day 7 ($\bar{x}$ = 1395 / $\bar{x}$ = 2140 ng/ml).
4) Heparin effect: Plasma heparin activity was assesed by an amidolytic anti II_a assay. Although plasmatic heparin action only represents one aspect of thromboprophylactic heparin-activity, there is an obvious difference between patients with and without DVT with respect to plasmatic heparin activity ($p < 0.005$).