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LONGTERM TREATMENT WITH SUBCUTANEOUS HEPARIN DURING PREGNANCY. M. Hellgren and E-B Nygårds, Dept. of blood coagulation disorders and gynecology and obstetrics, Karolinska Hospital, Stockholm, Sweden.

Twenty women were treated with i.v./s.c. heparin during pregnancy because of acute thromboembolic complications (T-E) and 15 were given s.c. heparin as prophylaxis because of earlier T-E. All women injected themselves without problems. Minor allergic reactions disappeared when preservative was avoided. The therapeutic treatment was adjusted to 1.5-2 times prolongation of APTT and the prophylaxis was decided sufficient if 5-10 secs. prolongation of APTT was registered 3-4 hours postinjection. Twentyfive pregnancies were uncomplicated. Six pregnancies were connected with various obstetric complications and 5 with minor bleeding complications such as wound and vaginal hematomas. Eight pregnancies were complicated by incipient prematur labour. No rethrombosis occurred in the prophylactic group but 5 of the 20 women in the therapeutic group had rethrombosis before prophylaxis had started. All children were in good health but one had low birth weight for gestational age.

The level of antithrombin (AT) and platelet count were studied in 16 women and liver function was registered in 13 of them. The level of AT decreased to a mean of 55%, measured by chromogenic substrate S-2238, after 2-4 weeks s.c. therapy in the prophylactic group. In the therapeutic group an expected mean decrease to maximum 56% was noted initially during i.v./s.c. heparin treatment. In both groups the level of AT normalized during continued heparin treatment. After finished treatment all women had normal level of AT. Platelet count and liverfunction were mainly unchanged.

These regimes seem adequate during pregnancy but AT ought to be analysed in order to avoid increased risk for T-E if heparin must be withdrawn or decreased. Examination for incipient prematur labour should probably be more intensive in these groups of pregnant women.

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ANALYSIS OF SUBCUTANEOUS SODIUM AND CALCIUM HEPARIN. J.A. Caprini, J.P. Vagher, L. Zuckerman, J. Mitchell. Department of Surgery, Evanston Hospital, Evanston, IL.

Thirteen normal adults were randomized to receive a 15,000 unit subcutaneous injection of sodium (Na-hep) or calcium (Ca-hep) heparin and seven days later the experiment was repeated with the other heparin. The APTT, Thrombin-Calcium clot time (TCCT), Lee-White clot time (LWCT) and Heparin 10-A (10-A) assays were determined prior to the injection and 1,2,6, and 10 hours post-injection. With the Na-hep injection, the APTT, TCCT, and LWCT showed a more rapid onset and persistently greater anticoagulant activity during the 10 hour period with statistically significant prolongations for 1 and 2 hour samples. The 10-A activity was higher in the Ca-hep group with significance at 10 hours. All the test values showed anticoagulant activity 1.5 to 2.0 times the control at 10 hours for both heparin preparations.

An additional 13 normal adults were randomized to receive 5000 units of Na-hep or Ca-hep subcutaneously every 12 hours for 4 time intervals and after seven days the other heparin preparation was given. The APTT, TCCT, LWCT, and 10-A assays were determined prior to the initial injection and at 2,6,and 10 hours post injections. All APTT values varied between 1 and 1.4 times control with significant elevation at 6 hours in the Ca-hep group. The 10-A assay showed significant differences throughout the study with greater activity in the Na-hep group.

We conclude that subcutaneous injections of 5000 units sodium or calcium heparin are bioequivalent despite minor test differences which are magnified by increasing the subcutaneous dose. Therapeutic levels of heparin are maintained for greater than 10 hours following a single 15,000 unit injection and less than 6 hours for 5000 units of either heparin in normal adults. The lack of correlation of either 10-A with other results and the large standard deviation may indicate lack of sensitivity of this assay, rather than differences between heparin salts.

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INCREASED ANTI-Xa BIOAVAILABILITY OF HEPARIN BY JET INJECTION. D. Arleth, J. Harenberg, K. Mattes and R. Zimmermann. Internal Medicine, University of Heidelberg, GFR.

To improve the standardisation and to diminish the time requirement of the subcutaneous (s.c.) application of low dose heparin a semiautomatic injection pistol was compared to the commonly used one way syringe.

The precision of the injected amount of heparin was significantly higher by jet injection (VK 1% vs 4%). The time required for one injection was 110 sec by jet injection and 215 sec by the one way syringe including all preparation times.

7500 USP heparin were injected into 10 volunteers by both techniques at weekly intervals randomly. The pharmacodynamic effects were controlled on the factor IIa activity (thrombin clotting time), aPTT and factor Xa activity (chromogenic substrate S2222) for 10 hrs by 12 blood samples. No differences were observed on the factor IIa activity and aPTT between the two injection techniques. The anti-Xa-activity of the heparin applicated by jet injection was significantly higher (maximal effect after 3 hrs: 0.24 vs 0.20 USP heparin/ml plasma, $p < 0.01$, area under the time related curve $p < 0.01$).

The data indicate, that the bioavailability of heparin for factor Xa is even higher after the s.c. application by the jet injection method than after the one way syringe technique. These differences should be considered, when an improvement of the prophylaxis of thromboembolic diseases is discussed.

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THE CLINICAL IMPORTANCE OF HEPARIN ASSAYS IN PLASMA.CRITICAL ASPECTS IN ANTIXa TECHNIQUES. R Giuliani E.Szwarcer, E. Martinez Aquino. Thrombosis Section, Ramos Mejia Hospital Buenos Aires, Argentina

Different clotting assays for heparin measurement in plasma, based on AntiXa potentiating effect were studied, to determine the causes of variability in results in the currently used techniques. A modified 2 steps technique was also used (step I:o.1ml test plasma (PPP)+0.3ml buffer+0.1 mlXa.2' incubation at 37°C;step II: 0.1ml of step I mixture+0.2ml of substrate plasma+CaCl 0.1ml. (Xa and VII-X defficitary bo vine plasma+cefalin: Thame, Oxon.Triz-Mal buffer,ionic strength 0.15,PH7.5 and CaCl 0.025M). Three modifications of the technique were used, varying test plasma treatment: a) using oxalated PPP, adsorbed with BaS04 b) like in a) plus heating it at 56°C 15'; c)using untreated plasma.

Using a) assay (K dependant factors absent), straight regression lines and low variability of results was obtained, relating heparin concentrations to clotting times;using b) it was seen that heat diminishes AntiXa reactivity to heparin; using c)high variability in results was obtained. To show the difficulties in monitoring heparin in cases where lox AntiXa concentrations, variable amounts of clotting factors and differents amounts of heparin might be present, a pool of normal plasmas, a normal plasma, and a cirrhotic one were compared, using the modified AntiXa assay in its 3 variations. Wide differences in results may be obtained while studying the cirrhotic plasma, using techniques that can vary AntiXa reactivity, or mask the real heparin in plasma, because of its variable content in K dependant factors.

We did not find a way of clearing test plasma of K dependant factors when heparin is in it without altering heparin concentration or AntiXa reactivity.

Thus, it is suggested, for clinical monitoring of the drug to use heated or untreated plasma, and to compare results with the same individuals plasma, studied under equal conditions, and not with a pool of normal plasmas, as commonly suggested.