

CONTINUOUS SUBCUTANEOUS HEPARIN INFUSION DURING PREGNANCY IN A PATIENT WITH A PROSTHETIC MITRAL VALVE. CLINICAL AND LABORATORY CONSIDERATION. Harry L. Messmore, Jawed Fareed, Barbara Hixon, Judith Kniffin and Grace Squillaci, Loyola University Medical Center, Maywood, IL 60153 USA.

Administration of heparin for prolonged periods during pregnancy has usually been by the intravenous route when full anticoagulant dosages are required. Bolus subcutaneous injection of heparin has also been used, however this requires medical supervision and proper laboratory control. We have administered heparin (Elkins - Sinn) to a pregnant patient by the subcutaneous route utilizing an infusion pump (Auto-Syringe Model AS3A) for 15 weeks, maintaining an activated partial thromboplastin time (APTT) of approximately 50 sec (N=22-35) using "ACTIN" (Dade) brand ellagic acid cephaloplastin reagent. The average heparin dose has been 26,000 units/24 hours during the 4th to 19th week of her pregnancy. In order to establish the presence of circulating heparin we also performed Xa and thrombin-based amidolytic assays for the absolute levels of heparin in patient's plasma. A poor correlation was seen between the heparin levels and the APTT values. These data indicate that absolute levels of heparin may not be taken as an index of heparinization in certain clinical conditions. Lack of serious complications and ease of administration has prompted us to continue heparin by this route during the remainder of her pregnancy.

## 1192

IN VITRO CHARACTERIZATION OF LOW MOLECULAR WEIGHT FRACTIONS OF HEPARIN. Jawed Fareed, Harry L. Messmore, Daniel A. Walz, Jean Choay and J. C. Lormeau. Loyola University Medical Center, Maywood, IL 60153 USA, Wayne State University, Detroit, MI and Choay Institute, Paris, France.

Numerous extraction, chromatographic (ion exchange, gel, and affinity), chemical and enzymatic degradation methods have been employed to obtain heparin fractions. The present assays to evaluate potency (e.g. pharmacopeial and coagulant) do not truly reflect the antithrombotic properties of these fractions. In addition, the synthetic peptide substrate based assays to measure the anti Xa activity do not correlate with the coagulant anti Xa assays. We have developed an in vitro test battery to evaluate low molecular weight heparin fractions. Porcine mucosal heparin fractions are assayed for anti Xa activity in coagulant and amidolytic assays and the results are expressed as a ratio. The effect of these fractions on coagulant assays such as prothrombin time (PT), partial thromboplastin time (PTT), thrombin time (TT), Stypven time (ST) on freshly prepared normal human plasma (NHP) is determined. The retention characteristics of these fractions on platelet factor 4 and AT-III bound sepharose columns were also determined. We have compared the extracted and chemically depolymerized heparin fractions and found that the anti Xa activity doesn't always correlate with the other parameters studied. The extracted fractions were slightly stronger in the USP assays and showed a biphasic retention on the PF-4 column whereas the chemically depolymerized product showed only one peak. On the other hand, on the AT-III column both fractions showed similar elution patterns. Our studies suggest that heparin and its fractions exhibit differential behavior on various assays and a specific test may not be used as an index of the potency of their antithrombotic effects. Furthermore, the potency of these fractions should be stated on a weight basis when evaluated in the in vivo animal models rather than in terms of a specific test (e.g. anti Xa activity and US Pharmacopeial assays).

## 1191

LOW-DOSE HEPARIN OR ASPIRIN-DIPYRIDIMOLE IN PREVENTION OF POSTOPERATIVE DEEP VENOUS THROMBOSIS? J.H.Kennedy. Middlesex Hospital Medical School, Central Middlesex Hospital, London, England.

Venous thrombosis and pulmonary embolism remain a serious threat to postoperative patients. Kakker et al have reported favorable effects of low-dose heparin in a prospective study in 4,121 patients in 23 hospitals.

In a prospective randomized study, between May 1978 and August 1980, 375 patients were collated into 7 groups 146 were excluded because of a contraindication to Heparin or lack of general anesthesia; those over 45 who received a general anesthesia were given either 2,500 u Heparin with premedication and daily until discharge (Group V) or 1 Gram Aspirin-100 mgm Dipyridimole on the same schedule (Group VI); the remainder served as controls.

The results supported protective treatment of over 45 who receive a general anaesthetic and surgery; in untreated patients there were 6 nonfatal thrombotic episodes in 1397 patient-days at risk, but none in either treatment group, together totalling 756 patient-days at risk for the Heparin group and 238 patient-days at risk for the Aspirin-Dipyridimole group.

## 1193

COMPARISON OF PROGRESSIVE ANTI-THROMBIN ACTIVITY AND THE CONCENTRATION OF THREE THROMBIN INHIBITORS IN NEPHROTIC SYNDROME. B. Boneu, F. Bouissou, P. Sié, C. Caranobe, M. Abbal, P. Barthe. Laboratoire d'Hémostase et Service de Pédiatrie, Hôpital Purpan, 31059 Toulouse cedex, France.

A study was planned in 28 children affected with a nephrotic syndrome (group 1) in order to compare the total plasma progressive antithrombin activity (Howie method) to the concentrations of three thrombin inhibitors, assayed by immunological methods: antithrombin III (AT III),  $\alpha_2$  macroglobulin ( $\alpha_2$  M), and  $\alpha_1$  antitrypsin ( $\alpha_1$  AT). The results were compared to those obtained in 21 normal children of the same age (group 2) and in 10 normal adults (age range: 25 - 50 yrs). The calibration curves were made with a pool of plasma from normal blood donors. The results (mean  $\pm$  SD) and the comparison between groups 1 - 3 to group 2 are summarized in the following table:

| GROUP | HOWIE %                   | AT III %                  | $\alpha_2$ M(g/l)           | $\alpha_1$ AT(g/l)        |
|-------|---------------------------|---------------------------|-----------------------------|---------------------------|
| 1     | 132 $\pm$ 28 <sup>o</sup> | 74 $\pm$ 29 <sup>oo</sup> | 5.6 $\pm$ 2.2 <sup>oo</sup> | 1.7 $\pm$ 12 <sup>o</sup> |
| 2     | 117 $\pm$ 19              | 101 $\pm$ 12              | 3.9 $\pm$ 0.4               | 2.3 $\pm$ 0.6             |
| 3     | 96 $\pm$ 13 <sup>oo</sup> | 102 $\pm$ 10              | 1.9 $\pm$ 0.6 <sup>oo</sup> | 2.6 $\pm$ 0.6             |

<sup>o</sup> P < 0.05

<sup>oo</sup> P < 0.01

A subgroup of 15 affected children which a low AT III level (less than 80%) was isolated (mean AT III = 51%  $\pm$  18); the mean of the total progressive antithrombin activity was 124%  $\pm$  16. A significant negative relationship was found between AT III and  $\alpha_2$  M level in the group 1 (r = -0.71, P < 0.01).

The high plasmatic level of  $\alpha_2$  M (1) accounts for the increased progressive antithrombin activity in all the affected children in spite of very low levels of AT III; (2) could explain the absence of thrombotic events in this series; (3) suggests that the benefit of heparin therapy might be doubtful since it has been recently reported that heparin inhibit the binding of  $\alpha_2$  M to thrombin.