446

DERMATAN SULPHATE PREVENTS VENOUS THROMBOSIS IN RATS WITHOUT INCREASING BLEEDING. A. Maggi (1), M. Abbadini (1), R. Salemi (1), J. Pangrazzi (1), P.G. Pagella (2) and M.B. Donati (1). Istituto Mario Negri (1) and Mediolanum Farmaceutici S.p.A. (2), Milano, Italy.

Studies have suggested that endogenous proteoglycans, structurally similar to heparin, contribute to the "non-thrombogenicity" of the vascular wall. Our studies concentrated on Dermatan Sulphate (DS-MF 701) Heparin Sulphate (HS) and Standard Heparin (SH), all from Mediolanum Farmaceutici. The antithrombotic potential of these GAGs was evaluated in a well established model of venous thrombosis consisting in the ligature of the vena cava, 15 min after i.v. administration of the drug. A dose response-curve was obtained for DS (0.25-4 mg/kg), HS (1-5 mg/kg) and SH (0.5-2 mg/kg).

At the dose of 2 mg/kg DS was able to inhibit thrombotic occurrence by 80%, as compared to heparin 100% and HS 40%. The haemorrhagic potential of these GAGs was then evaluated using two in vivo tests, the "template" method, which detects any alterations in primary haemostasis, and the tail "transection" method which is not only sensitive to changes in primary haemostasis but also to coagulation and fibrinolytic abnormalities; the tests were carried out 15 min after drug administration. Unlike SH, DS did not induce bleeding at equipotent antithrombotic doses whereas HS induced bleeding even if not to the same extent as SH. DS did not modify the coagulation tests (APTT, TT and anti-Xa), again unlike SH. In conclusion, DS in the venous thrombosis model used, showed the peculiarity to prevent thrombus formation without inducing bleeding complications.

447

CLINICAL PHARMACOLOGY OF DERMATAN SULFATE: EFFECT ON HAEMOSTATIC PARAMETERS. F. Piovella (1), E.M. Pogliani (2), P. Custodi (1), R. Antonioli (2) and F. Gianese (3). Istituto di Clinica Medica IIa, University of Pavia (1), Istituto di Patologia Medica IIa, University of Milan, Ospedale S. Gerardo, Monza (2) and Medical Department, Mediolanum Farmaceutici, Milan (3), Italy.

In experimental studies dermatan sulfate (DS) has been characterized as an effective antithrombotic agent. This property is not associated with modifications of standard coagulation tests or increased blood loss "in vivo".(*)

In view of a possible clinical use of DS, we performed a preliminary study on 10 consenting hospitalized patients without evidence of haemostatic abnormalities.

Each subject was given i.m. single increasing doses (50, 100, 200 mg) of DS (MF 701, Mediolanum Farmaceutici), separated by 3 days wash-out intervals. Prothrombin Time (PT), Partial Thromboplastin Time (PTT), Antithrombin III (ATIII), Heparin Cofactor II activity (HCII, measured by amidolytic method) were determined before each administration and after 30, 60, 120 and 240 minutes. Bleeding time (BT) and platelet count (PlC) were determined before and after 120 or 240 minutes respectively.

No systemic or local adverse reactions were observed. Analysis of variance showed no significant modifications of PT, PTT, ATIII, BT and PlC following DS administrations nor significant differences between the three doses. A trend towards reduction was registered for HCII activity at 100 and 200 mg doses.

Our results suggest that DS can be safely considered for further clinical investigation.

(*) F. Fernandez et al, Br J. Hematol, 64, 309, 1986.

448

MODIFICATION OF COAGULATION AND FIBRINOLYSIS DURING TRANSLUMINAL ANGIOPLASTY IN PATIENTS RECEIVING HEPARIN OR PENTOSAN POLYSULFATE (HEMOCLAR). N. Bel Lakhal, J.M. Pernes, D. Lichtenstein, M. Roncato, J.C. Gaux, W. Nieuwenhuizen, M. Aiach. Hôpital Broussais, Paris, France and Gaubius Institute, Leiden, The Netherlands.

Twenty patients with high stenosis of iliac or femoral artery were randomely allocated to receive by intra arterial route (IA) either 5,000 IU heparin or 50 mg Hemoclar immediately before starting the angioplasty. Those receiving Hemoclar were given a second IA 50 mg bolus at the end of the dilatation.

Two blood samples were obtained by venous punction 1) after an initial 30 min resting (V_1), 2) at the end of the procedure (V_2). Arterial punction by the dilatation catheter was also performed immediately before and after the dilatation leading to two other samples A_1 and A_2.

The coagulation studies include activated partial thromboplastin time (APTT), thrombin time (TT), hep test (Hemachem, St-Louis, USA), anti Xa activity (Stachrom heparin, Diagnostica-Stago Asnières, France). There was a significant increase in APTT, TT, and hep test between A_1 and A_2 as well as V_1 and V_2 in both groups of patients. However, the prolongation was significantly higher for heparin. Anti Xa activity significantly increased only in heparin group.

Fibrinolysis was studied by measuring tPA by the SOFIA assay described by Angles-Cano (Anal. Biochem. 1985, 153, 201), euglobulin lysis time (ELT) and a new plasma ELISA assay specific for fibrinogen degradation products (FDPs) using monoclonal antibody described at the Gaubius Institute (Blood 1985, 66, 503). A significant increase in tPA was observed during the dilatation (A_2/A_1) and V_2/V_1) only in the patients receiving Hemoclar. The slight increase of the fibrinolytic activity was further corroborated by a significant increase in FDPs (A_2/A_1). In both groups, but only in the venous samples (V_2/V_1), ELT was shortened ($p < 0.05$) and fibrinogen was decreased ($p < 0.05$).

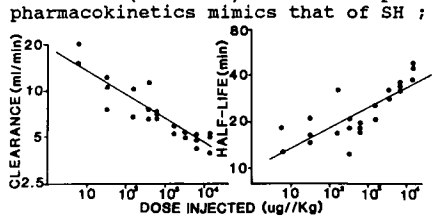
No thrombotic complications were observed during the procedure in both groups.

Conclusion: This study confirms that Hemoclar has an inhibiting effect on coagulation by inhibiting thrombin and thrombin generation, but no anti Xa activity. However, the anticoagulant potency is much reduced when compared to heparin. The profibrinolytic effect seems to be related to the release of free tPA.

449

THE PHARMACOKINETICS OF ^{125}I PENTOSAN POLYSULFATE IN THE RABBIT : EVIDENCE FOR A SATURABLE MECHANISM OF CLEARANCE. **C. Caranobe (1), G. Houin (2), C. Picard (3), J.M. Pereillo (3), B. Boneu (1). Laboratoire d'Hémostase, Centre de Transfusion Sanguine (1), Unité de Pharmacocinétique, Hôpital Purpan, 31052 Toulouse (2) and Sanofi Recherche, 31035 Toulouse (3) FRANCE.**

Pentosan polysulfate (PPS) is an antithrombotic sulfated polysaccharide with a MW distribution comparable to commercial low molecular weight heparins (LMWH). Unlike LMWH, but as standard heparin, the half life of the drug after bolus injection is dose-dependent. We demonstrate that PPS disappearance results from a saturable mechanism of clearance. Tyrosine was incorporated onto the xylose chains of the molecule and iodinated with the chloramine T method. The labelled derivative had the same MW distribution than the parent compound and unchanged biological activities. Five ucies of ^{125}I-PPS were injected with increasing doses (6-12000 ug/kg) of unlabelled PPS to groups of 2-3 animals each. The CPM curves were broken into 3 exponentials (alpha, beta, gamma) ; the beta exponential was close from the curve of biological activity disappearance, assessed by IIa-^{125}I-HC II complexes quantitation. The main pharmacokinetic parameters were calculated using conventional methods. The distribution volume (246 ± 81 ml) was independent of the dose delivered while there were significant correlations between the dose, the clearance (r=0.91) and the half life (r = 0.81). Thus in spite of its LMWH, PPS pharmacokinetics mimics that of SH ; this may be the consequence of the over sulfation of the molecule, and of its strong affinity to endothelial cells.



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