POSTER SYMPOSIUM VIII

Thrombosis: Heparin Pharmacokinetics.

HEPARIN PHARMACOKINETICS. C.A.M.de Swart, J.W.N.Akkerman, A.Nijmeijer and J.J.Sixma.
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In heparin therapy different schedules for safe and effective treatment have been advocated, but they are not based on firm knowledge of the pharmacokinetics of heparin. We report on the application of two tests (diluted APTT test according to Marder and anti-Xa assay according to Yin) to the study of the pharmacokinetics of the anticoagulant effect of four commercially available brands of heparin. The drug was administered as a single large bolus or by continuous infusion. In contrary to reported pharmacokinetics a non exponential disappearance was observed after single dose administration. Continuous infusion allowed a mathematical description of elimination of heparin activity, in which two mechanisms could be demonstrated. Firstly, a mechanism which is saturable and eliminates heparin activity at low levels at a high rate. Secondly, a mechanism which is linearly related to heparin activity. Studies carried out on the elimination of ^{35}S heparin showed that the disappearance of the radioactivity differed from that of the anticoagulant effect. Binding studies with an antibody directed against antithrombin III which was insolubilized on Sepharose 4B showed a close relationship between the disappearance of that part of the radiolabel that bound to the Sepharose-antibody complex and the disappearance of the anticoagulant effect.

STUDIES WITH HIGH AND LOW MOLECULAR WEIGHT TRITIUM-LABELLED HEPARIN IN VIVO AND IN VITRO.
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When defibrinated platelet-poor plasma is chromatographed on Sephadex G-200, fractions with antithrombin-heparin cofactor activity are found in only one area. When platelet-poor plasma treated with a tritium-labelled heparin is chromatographed on Sephadex G-200, radioactivity, signifying the presence of heparin, is spread across all of the protein fractions, whereas immediate antithrombin activity is located in two main areas. Tritiated heparin produced from porcine intestinal mucosa was fractionated on a Sephadex G-200 column with separation of the higher and lower molecular weight fractions. These fractions were added to platelet-poor plasma which was then rechromatographed on Sephadex G-200. With the higher molecular weight, heparin radioactivity appeared in fractions which usually have immediate antithrombin activity, whereas, with the lower molecular weight heparin, it did not. A comparison of the activities of the higher and lower molecular weight material was made after intravenous injection into rats. The higher molecular weight heparin gave higher concentrations of radioactivity in the liver and blood. In addition, the anticoagulant activity as measured by a whole blood recalcification clotting time was maintained for a much longer period. The lower molecular weight heparin was excreted more rapidly in the urine. It is concluded that only the higher molecular weight heparins have anticoagulant activity in combining with antithrombin whereas lower molecular weight heparins do not combine with antithrombin but are eliminated in the urine.