

THE CONTROL OF ANTITHROMBOTIC PROPHYLAXIS AND THERAPY: A PRO-COAGULANT EFFECT OF HEPARIN. E. Swarcer, R. Giuliani, E. Martinez Aquino. Thrombosis Section, Ramos Mejia Hospital, Buenos Aires, Argentina.

For studying heparin effect on blood coagulation and on inhibitors, the drug was added at increasing amounts to a normal platelet poor plasma (PPP), and to plasmas of patients with variable amounts of clotting factors (cirrhotic, pregnant, etc) -IN VITRO STUDIES-, and infused to the same individuals -IN VIVO STUDIES-. Modifications on two clotting assays (KCCT-TT) were compared to heparin potentiating effect on AntiXa (Denson & Bonnar tech).

When studied IN VITRO, the sensibility of KCCT, TT, and AntiXa techniques for heparin measurement was similar. IN VIVO, an apparently greater sensibility using AntiXa technique was observed.

For determining if this phenomena was related to a specific enhanced potentiating effect of the inhibitor against Xa, exerted by heparin IN VIVO, experiences were repeated IN VITRO and IN VIVO, measuring heparin effect on KCCT, TT, and on the inhibitor, studied against Xa and thrombin. A personal technique was used for the measurement of Antithrombin III heparin potentiating effect, using diluted platelet poor test plasma, heated (56°C 15') and incubated with thrombin during a fixed time, and reading residual thrombin on citrated human PPP. IN VITRO, all techniques were similar in their ability to show heparin presence.

IN VIVO, the potentiating effect of heparin on the inhibitor, measured against Xa or thrombin, was greater than the changes obtained on KCCT or TT.

So, AntiXa-Antithrombin III techniques seem to be more sensitive for heparin measurement IN VIVO.

This "dissociation" of results in between the potentiating effect on the inhibitor, that is not simultaneously exerted on global coagulation, is interpreted as a heparin pro-coagulant effect, exerted by the drug IN VIVO.

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EFFECT OF HEPARIN IN HEREDITARY ANTITHROMBIN III DEFICIENCY. H. Losonczy, I. Nagy, 1st Department of Medicine, University of Pécs Medical School, Pécs, Hungary

Hereditary antithrombin III (AT III) deficiency was divided into three types: In type I, both quantity and function of AT III were diminished, in type II, AT III was normal in quantity but abnormal in function, and in type III, quantity and function were normal but activation of AT III by heparin was diminished. In the present study, the response to heparin of the different types of AT III deficiency was examined. Tests were carried out on 10 healthy volunteers and on 14 patients with known AT III deficiencies who had suffered from recurring thrombotic episodes. In addition, 7 relatives of these patients without a history of thromboembolism were examined. Three patients belonged to type I, 7 to type II, and 4 to type III. All patients and controls received an intravenous infusion of 10,000 I.U. heparin within 1 hour. On a second occasion, 20,000 I.U. heparin was given in the same way. Activities of AT III and plasma heparin levels were assayed by amidolytic methods (Coatest AT III and Coatest Heparin, KABI). AT III activity of the controls was between 80% and 130% of the normal average. This activity was not influenced by the two doses of heparin. In type I, average AT III activity was 57.5% (minimum 25%, maximum 80%). After heparin, a further 20% decrease of AT III activity was observed. In type II, the heparin-induced decrease of AT III activity averaged 15.4% whilst in type III AT III activity was not influenced by heparin. Though the difference of plasma heparin levels after the two different doses of heparin was comparatively small, there was a significant difference of the AT III decreasing effect.

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MONITORING RESPONSE OF DISEASE TO HEPARIN THERAPY WITH THE ACTIVATED COAGULATION TIME (ACT). P. G. Hattersley, J.C. Mitsuoka and J. H. King. Departments of Internal Medicine, Pathology and Pharmacy, University of California, Davis, California.

Believing that treatment of thromboembolic disease with heparin is treatment of a dangerous group of disorders with a potentially dangerous drug, and that sensitivity to heparin varies greatly, one patient to the next, we attempted to model heparin infusion rates to the specific needs of the patient. We gave initial doses proportionate to body weight, and monitored responses by the ACT. We chose this test because it is a precise bedside procedure which reliably reflects the variable responses of patients.

Our protocol: (1) Screen for conditions causing a high risk of bleeding on heparin; (2) Infuse an initial i.v. heparin bolus of about 50 units per kilogram of body weight; (3) Follow with pump-controlled i.v. infusion of 15 to 25 units/kilo/hr.; (4) Subsequently alter the infusion rate as needed to maintain an ACT of 150 to 190 seconds; (5) When the ACT has been established within this range, start appropriate oral doses of warfarin; (6) After 3 days or more, when the prothrombin time is 2 to 2-1/2 times the control, discontinue heparin and maintain patient on oral warfarin.

Of 100 patients with proven thromboembolic disease treated at close to this protocol, there were none with progressive thromboembolic disease; 95 patients responded, and were converted to oral warfarin; 5 developed major bleeding necessitating discontinuing heparin. Of these 5, 2 were unrecognized high risk patients who should not have received full dose heparin. The other 3 all had ACT's well above 190 seconds.

Our conclusion: For treatment of patients with deep venous thrombosis and/or pulmonary embolism, this protocol of heparin therapy, if followed carefully is effective and reasonably safe.

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HEPARIN-INDUCED THROMBOCYTOPENIA. J.A. Caprini, A.J. Sholder, J.P. Vagher, J. Mitchell. Department of Surgery, Evanston Hospital and Northwestern University, Evanston, IL.

Review of 6,000 patient records from our laboratory showed 609 individuals who received continuous intravenous infusion heparin therapy for thromboembolic disease. 40/609 (6.5%) of these patients were found to have a platelet count of less than 150,000 cell/mm³. Of this group, 34/40 (85%) exhibited thrombocytopenia prior to heparin therapy that was attributable to consumptive coagulopathy in 21/40 (52.5%), sepsis or malignancy in 11/40 (27.5%), and cimetidine or sulfisoxazole in 2/40 (5%). Heparin therapy had no adverse effect on the platelet count in these individuals, and the count returned to normal in surviving individuals if the underlying cause was successfully treated or the offending drug removed.

Only 6/40 (15%) of the patients developed low platelet counts during the course of heparin therapy; this represents 6/609 (0.98%) of the population receiving heparin. The etiology of thrombocytopenia in 5/6 (83%) of the cases was traced to metastatic cancer (3), burn wound sepsis (1), and septic shock (1). Only 1/609 (0.16%) of these patients developed low platelet count that could be attributed to heparin. Thus, the incidence of heparin-induced thrombocytopenia is extremely rare in our hospital population.