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PROTECTIVE EFFECT OF VITAMIN K AGAINST ACETAMINOPHEN (PARACETAMOL) TOXICITY IN THE HAMSTER

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We have previously reported that paracetamol may interfere with the metabolism of vitamin K via the vitamin K 2, 3-epoxide cycle. (Thrombosis and Haemostasis, 54,205,1985). In this study we have examined the effects of large doses of vitamin K on experimentally induced paracetamol hepatic necrosis in a hamster model. Paracetamol (1.2g/Kg) when given by gavage to 24 hamsters (Group I) resulted in 10 deaths (42%) at 24 hours. Simultaneous administration of 1mg vitamin K intraperitoneally (Group II) reduced mortality to 3/24 (12%); mortality was 2/24 (8%) if vitamin K was given 4 hours after the paracetamol (Group III). In a further series of experiments (N=18) the prothrombin time in Group I was prolonged by 28 seconds compared with 14 seconds in Group II and 10 seconds in Group III. In samples taken for biochemical and histological analysis there was evidence of severe hepatic necrosis in all groups. When the dose of paracetamol was reduced to 1.0g/Kg (N=18) there was substantially less histological damage in Group II compared with other groups and the prothrombin times were only prolonged by 2 seconds (Group I); 1.5 seconds (Group II) and 3.5 seconds (Group III) respectively. In the final experiment (N=18) when Group II animals were divided into 3 sub-groups and the dose of vitamin K given was altered to 1.0, 0.5 and 0.1mg following the paracetamol (1.2g/Kg) the prothrombin times were prolonged by 8 seconds, (1.0mg vitamin K), 21 seconds (0.5mg vitamin K) and 35 seconds (0.1mg vitamin K) respectively, indicating a dose dependant effect. The hypothesis that paracetamol induced hepatic necrosis occurs solely as a consequence of failure of glutathione to conjugate the reactive metabolites of paracetamol is not consistent with the protective effects of vitamin K observed here and the known mode of action of the vitamin. Other mechanisms such as free radical scavenging deserve to be studied.

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A HEPARINE-LIKE ANTICOAGULANT IN A PATIENT WITH WEGENER'S GRANULOMATOSIS.

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In a 23-year-old man with Wegener's granulomatosis and mild bleeding coagulation studies revealed a significant prolongation of the coagulation time (CT) prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin time (TT), failure of TT and aPTT to correct in a 1:1 mixture with pooled normal plasma (PNP), correction of the prolonged TT with toluidine blue and correction of TT and aPTT both in vitro and in vivo protamine sulphate (P.S.).

	Patient	Mixture with PNP 1:1	Control
CT (min)	>30	-	<10
PT (s)	33,6	20,8	15,6
aPTT (s)	45,6	37,3	30,3
TT (s)	>120,0	82,5	18,5

Addition of Protamine Sulphate (10µg/ml)

	Patient	P.S.	Control
TT (s)	>120	26,6	25,4
aPTT (s)	53,6	24,0	20,8

All other coagulation tests, i.e., bleeding time, platelet count, fibrinogen level, euglobuline lysis time were within normal limits. The patient did not receive heparine. TT after administration of 5ml of protamine sulphate i.v. to the patient became normal - 18,2 s (19,7 s).

In summary a patient with Wegener's granulomatosis associated with an endogenous heparine-like anticoagulant is reported. The anticoagulant could be corrected both in vitro and in vivo by protamine sulphate.

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EFFECTS OF GABEXATE MESILATE (FOY), A NEW SYNTHETIC SERINE PROTEASE INHIBITOR, ON BLOOD COAGULATION IN PATIENTS WITH DIC.

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A pilot open controlled study of FOY was performed in 20 intensive care patients (pts, age 18-63) with DIC diagnosed with standard laboratory criteria (at least 3 of the following: Normotest 70%, fibrinogen 150 mg%, AT III 80%, FDP 20 ug/ml, platelets 150000). Besides the usual treatments, FOY was given to 10 pts (FOY G.) by continuous i.v. infusion (1mg/kg/h) for up to 7 days, while in 10 control pts (Hep.G.) the treatment included low dose s.c. heparin. Blood clotting tests were performed at admission to the study and daily for 7 days; we consider here results obtained at baseline and at the 4th (7 survivors in FOY G. and 10 in Hep.G.) and the 7th day (6 surv. in FOY G. and 9 in Hep. G.). Statistical evaluation was made by means of the two-tailed Wilcoxon test for non parametric paired data. In the FOY G. depressed baseline AT III and plasminogen (Plgn) activities (61.8+/-5.3% and 57+/-5.5% respectively) significantly increased at 4th day (92+/-11.2% and 83+/-3.1%, $p<0.05$), Plgn furtherly significantly increased at 7th d. ($p<0.05$). In the Hep.G. Normotest, Plgn and Platelets significantly ($p<0.05$) increased at 4th day, but no changes in AT III were found. Fibrinogen increased in both groups during the observation period ($p<0.05$). Serum and especially "plasma" FDP (specific monoclonal Ab to fgn and fibrin degradation products), as well as D-Dimer and HMW fgn complexes measured by exclusion chromatography, decreased especially in the FOY G. These results show that FOY modifies the clotting laboratory pattern in DIC pts, likely by an antithrombin effect. The clinical significance of these effects remains, however, to be explored.

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ANTI-THROMBIN$_{neo}$ IgG IN AN ASYMPTOMATIC PATIENT WITH A BENIGN MONOCLONAL GAMMOPATHY.

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A 68 year old male hospitalized for cardiac disease was found to have an elevated prothrombin time (18.5/12.4 s) and aPTT (59.6/25.9 s). He had no history of excessive bleeding or bruising. Subsequent evaluation revealed: thrombin time >500/34.1 s; fibrinogen 260 mg/dl functional and 522 mg/dl immunologic; reptilase 25.6/18.1 s; thrombin-induced platelet release of ATP (patient=0 and control=14.6 nmoles/10^9 platelets at 0.5 U/ml); AT-III 89% functional and 36.5 mg/dl immunologic; and prothrombin 167%. Mixing experiments showed the presence of an inhibitor of the thrombin time, and purification of IgG by protein A affinity chromatography showed the inhibitor of fibrin formation to reside in the IgG fraction. When coupled to Affi-gel 10, patient IgG (but not control IgG) removed purified thrombin from solution; the same gel did not remove prothrombin. The patient's IgG did not inhibit thrombin's cleavage of a chromogenic substrate (Chromozym TH). Studies on the patient's serum revealed: IgG 2,360 mg/dl, IgA 371 mg/dl, and IgM 107 mg/dl. Serum protein electrophoresis and immunoelectrophoresis showed a monoclonal IgG lambda protein with probably normal amounts of normal IgG. Other parameters (hematocrit, albumin, calcium, bone marrow histology, bone X-rays) indicated that the patient has a benign monoclonal gammopathy, not multiple myeloma. We conclude that our patient is producing an IgG inhibitor that reacts with a neo-antigen produced by the cleavage of prothrombin to thrombin; the IgG can prevent the interaction of thrombin with fibrinogen and the thrombin receptor on platelets, but not small synthetic substrates. We suspect that his monoclonal IgG is the inhibitor and find it remarkable that he has no increase in bleeding.