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MODERATE DECREASE OF FACTOR VII AND PROTEIN C WITHOUT OCCURRENCE OF HEPATIC VENO-OCCLUSIVE DISEASE AFTER ALLOGENEIC BONE MARROW TRANSPLANTATION IN 18 PATIENTS TREATED WITH LOW DOSE HEPARIN. C. CARON*, J.P. JOUET**, J. HIMPENS**, P. HIVES*, H. GRUSON*, J. COUDEMAND*. *Laboratoire d'Hématologie et **Service des Maladies du Sang du C.H.R. - LILLE - FRANCE

Decrease of factor VII (F VII) and protein C (PC) has been said to allow an early detection of hepatic veno-occlusive disease (VOD) (VILMER, Path. Biol. 1986, 34 : 79), that represents a serious complication of bone marrow transplantation (BMT). In this purpose, F VII (activity) and PC (antigen) have been measured in 18 patients (aged 9 to 45 yr- $\bar{m}$ : 26 yr) who underwent allogeneic bone marrow graft for chronic myelogenous leukemia (9 cases), acute lymphocytic leukemia (7 cases) acute myelogenous leukemia (2 cases). All patients received as preparation for BMT total body irradiation (mean dose = 10 Gy) along with cyclophosphamide (120 mg/Kg). All were given low dose heparin (100 UI/Kg/24 hr) from days -7 to +30. None of the patients developed VOD but graft-versus-host disease occurred in 13 out of them between days 18 and 52. Moreover, coagulation studies performed from days 1 to 28 detected a moderate decrease of F VII and PC (maximum on day 11). These parameters were normalized on day 28. The level of the other vitamin K-dependent factors was not significantly changed.

| | | Day 1 | Day 6 | Day 11 | Day 18 | Day 25 | Day 28 |
|---|---|---|---|---|---|---|---|
| F VII (%) | $\bar{m}$ | 109 | 105 | 77 | 77 | 98 | 105 |
| | SD | 26 | 27,5 | 23 | 28 | 31 | 32 |
| PC (%) | $\bar{m}$ | 95 | 88 | 76 | 82 | 95 | 96,5 |
| | SD | 24 | 35 | 27 | 27 | 44 | 29 |

So the moderate decrease of F VII and PC found in the post-graft period was not associated with hepatic VOD. However, as none of the patients developed this complication, these results do not exclude that a major decrease of these parameters could serve as an early diagnosis of VOD. On the other hand, a prophylactic effect of low dose heparin cannot be ruled out.

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THE EFFECT OF THE VENOM OF THE ORIENTAL HORNET ON COAGULATION FACTORS. A. Kornberg (1), S. Kaufman (1), L. Silber (1), J. Ishay (2). Depts. of Hematology, Assaf Harofeh Medical Center (1) and of Physiology and Pharmacology, Tel Aviv University (2), Israel.

The extract from the venom sac of Vespa orientalis (VSE) inactivates exogenous and endogenous thromboplastin (Joshua and Ishay, Toxicon, 13:11-20,1975). The prolongation of both prothrombin time (PT) and recalcification time suggests inactivation of other factors. The aim of the present study is to investigate the effect of VSE on clotting factors. A lyophilized VSE with protein concentration of 5 mg/ml was used. Studies were performed in vitro with human plasma and in vivo in cats. Routine methods were employed for the assay of PT, activated tissue thromboplastin (APTT), thrombin time (TT), fibrinogen degradation products (FDP), fibrinogen and factors V,VII,VIII,IX,X. Human plasma was incubated with various concentrations of VSE (0,1,5,10,50,100 µg/ml) for 60 min and for various incubation times (0,5,15,30,+60,90,120 min) with 50 µg/ml VSE (n=8). 1 µg/ml VSE prolonged PT from 13.5 to 16 sec ($p<0.05$) and APTT from 62 to 180 sec. PT was maximal (17.7 sec) with 10 µg/ml and APTT (442 sec) with 50 µg/ml VSE. Factors V,VII,X decreased gradually from 94-105% to 11%,11% and 29% with 100 µg/ml VSE and VIII and IX to 1% even with 1 µg/ml VSE. After 5 min with constant concentration of VSE (50 µg/ml) PT was 14.9 sec (normal 13 sec) and APTT 165 sec (normal 54 sec). Both were maximal (17.5 and 298 sec) after 60 min. Factors VII and X decreased to 13% and 32% and VIII and IX to >1% after 60 min of incubation. Injection of 5 mg/kg VSE to cats (n=6-8) resulted in prolongation of PT from 9.4 to 11.2 sec and of APTT from 19.5 to 63 sec after 5 min. Both were maximal after 90 min (12.3 and 127 sec). Factors V,VII and X decreased from 100% to 7.6%, 13% and 37% and VIII and IX to 1% after 10 min. In all experiments TT and plasma fibrinogen were not affected and FDP were normal. Heating of VSE for 5 min at 80°C abolished completely the anticoagulant activity but dialysis for 24 hr at 4°C had no effect on it. The activity was eluted on Sephadex-25 both in void and post void volumes. The results show that VSE has a potent anticoagulant activity against various factors. Factors VIII and IX are markedly decreased. The effect on V, VII and X is moderate. Plasma fibrinogen is not affected. The nature and clinical significance of the anticoagulant activity merit further investigation.

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A STUDY OF THE EARLY HAEMOSTATIC CHANGES FOLLOWING RUSSELL'S VIPER BITE IN HUMANS. Than Than, Khin Ei Han, Hutton RA,* Myint Lwin,** Tin Nu Swe,** Warrell DA.*** Pathology Research Division and Clinical Research Unit,** Dept of Medical Research, Rangoon, Burma, Haemophilia Centre,* Dept of Haematology, Royal Free Hospital, London and Nuffield Dept of Medicine,*** Oxford University, Oxford, England.

Amongst its many actions, Russell's viper (RV) venom activates factors X and V and enhances fibrinolysis, leading to defibrination which contributes to the clinical sequelae of RV bite. Early administration of antivenom may be life-saving, but not all of those bitten become sufficiently envenomed to require treatment. In an attempt to predict at an early stage those subjects who will progress to defibrination, we have serially monitored the haemostatic changes in 20 bite victims using the PT, APTT, thrombin time, platelet count, assays for factors X and V and fibrinogen and fibrin(ogen) degradation products (FDP).
In five patients, no evidence of defibrination was seen at any time and none of these developed obvious clinical symptoms. In a further six subjects, slight prolongation of the PT (16-21/14s), APTT (39-51/38s) and thrombin time (16-25/14s) occurred concomitantly with a moderate fall in factor X (20-80%), factor V (30-66%) and fibrinogen (0.6-2.0g/l), but FDP never exceeded 40ug/ml. In the remaining nine subjects who all eventually defibrinated completely, moderate coagulation factor deficiency and thrombocytopenia developed as early as 1-2h after bite. The most pronounced and consistent changes were a rise in FDP to above 80ug/ml (80-640ug/ml) and a fall in factor V (2-50%), these results being obtained on admission, 1-12h after bite. We conclude that an FDP level of 80ug/ml or more is highly suggestive of impending defibrination and could be regarded as a criterion for commencing antivenom therapy.

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SERUM VITAMIN $K_1$ LEVELS AS AN EARLY INDICATOR OF HYPOPROTHROMBINAEMIA ASSOCIATED WITH ANTIBIOTIC THERAPY. S.J. Machin, H. Cohen, I.J. Mackie, *M. Shearer, **S.D. Scott. Haematology Department, Middlesex Hospital, *Guy's Hospital, London, & **Dept of Surgery, Southampton.

The prothrombin time is an insensitive indicator of early vitamin K deficiency and serum vitamin $K_1$ levels may correlate with liver stores. A random non-fasting range of serum vitamin $K_1$ was established in 45 healthy adults of 150-1,530 pg/ml (mean 412 pg/ml). Nine well nourished patients, with normal serum vitamin $K_1$ levels, (mean 546, range 310-1,350 pg/ml), maintained normal prothrombin times and factor VII clotting activity throughout 7 days therapy with cefotetan disodium, an NMTT-containing cephalosporin antibiotic. However, 11 of 20 patients with acute intra-abdominal sepsis and an initially normal prothrombin time who underwent emergency surgery, developed a raised prothrombin time (INR 1.4-3.1) associated with reduction in factor VII activity (0.74 to 0.38 iu/ml) after 3-7 days of antibiotic therapy and the presence of PIVKA II by crossed-immunoelectrophoresis. Nine of these 11 patients had clinical evidence of malnutrition by anthropometric assessment and subnormal serum vitamin $K_1$ (mean 119, range 43-354 pg/ml) levels on admission. Seven received cefotetan but 4 were treated with other non-NMTT containing antibiotics. The 9 patients who maintained normal prothrombin times and factor VII levels had normal nutritional status and normal serum vitamin $K_1$ levels (mean 279, range 103-915 pg/ml) at presentation. A low serum vitamin $K_1$ level was associated with a high incidence of hypoprothrombinaemia developing following antibiotic therapy and would appear a more sensitive indicator of reduced vitamin K stores than the prothrombin time.