

SYNDROME OF ACQUIRED PROTHROMBIN DEFICIENCY AND THE "LUPUS ANTICOAGULANT": DEMONSTRATION OF A PROTHROMBIN ANTIBODY THAT DOES NOT NEUTRALIZE PROTHROMBIN CLOTTING ACTIVITY IN VITRO. S.P.Bajaj, K.D.Herbst, D.B.Schwartz, D.Fierer and S.I.Rapaport. University of California & Children's Hospital, San Diego, California.

A child was seen after an acute illness with bruising, the "lupus anticoagulant", and the virtual absence of plasma prothrombin clotting activity. Screening test results were: patient's plasma, PTT 117", prothrombin time 36"; 1/1 mixture of patient's and normal plasma, PTT 162" (cofactor phenomenon), prothrombin time 18". F. XII, XI, IX, and VIII assays were typical for the "lupus anticoagulant", yielding higher values with increasing dilution of the patient's plasma. The patient's plasma contained 0.05 U/ml of prothrombin activity in a one-stage assay and no demonstrable prothrombin antigen by double immunodiffusion or electroimmunassay with a goat anti-prothrombin antiserum. Prothrombin clotting activity was not inhibited when the patient's plasma was incubated with varying concentrations of normal plasma or purified human prothrombin. Nevertheless, when the patient's plasma was used as a source of antibody in agar immunodiffusion plates precipitin lines of identity were observed against normal plasma and purified prothrombin. Presence of an antibody against human prothrombin was further demonstrated by incubating varying concentrations of 125I-prothrombin with the patient's plasma followed by ammonium sulfate precipitation of the antigen-antibody complex (estimated affinity, 2.5×10^9). Over a 3-week period prothrombin activity and antigen increased, prothrombin antibody decreased, and the bruising subsided. This study demonstrates: (1) that the acquired deficiency of prothrombin clotting activity in this rare syndrome stems from the disappearance of the prothrombin molecule from the plasma, and (2) that a prothrombin antibody is present in the plasma despite its inability to neutralize prothrombin in vitro. Rapid clearance of prothrombin antigen-antibody complexes could be a mechanism for the acquired hypoprothrombinemia of this unusual syndrome.

PROLONGATION OF THE BLEEDING TIME AND INCREASED INTRAOPERATIVE BLEEDING IN NEUROSURGICAL PATIENTS TREATED WITH HIGH DOSE ϵ -AMINOCAPROIC ACID. D. Green, R. Glick, and C. Ts'ao. Departments of Medicine, Neurosurgery, and Pathology, Northwestern University-McGaw Medical Center, Chicago, Illinois.

ϵ -Aminocaproic acid (EACA) is an inhibitor of fibrinolysis which crosses the blood brain barrier. Several studies have shown that in doses of 24 G/day, EACA reduces the incidence of rebleeding in patients with intracranial aneurysms. Recently, however, intravenous doses of up to 48 G/day have been recommended. At this dose level, we observed rebleeding and increased intraoperative blood loss (> 1000 ml) in 5 of 8 patients, and in two of 5 patients on 36 G/day, whereas no such bleeding occurred in 4 patients on lesser doses. Laboratory investigation revealed that the template bleeding time was prolonged in all patients receiving EACA in daily intravenous doses of 36 or 48 G. Values of greater than 20 min were recorded in 4/8 patients on the 48 G dose and 3/5 on the 36 G dose, whereas no prolongation was observed with 24 G/day. Bleeding times returned to normal in all but one patient when the drug was stopped. Platelet aggregation studies showed impaired responses to ADP, collagen, and epinephrine during drug administration which returned to normal when the drug was discontinued. We conclude that EACA exerts a dose-dependent inhibitory effect on platelet function, and that patients receiving doses in excess of 24 G/day are at risk for serious bleeding. Patients receiving EACA should be monitored with serial bleeding time tests.

CAPILLARY FRAGILITY INDUCED BY PSYCHOTROPIC SEROTONERGIC DRUGS. D. Shepro and H.B. Hechtman*. Biological Science Center, Boston University and Department of Surgery, Harvard Medical School*, Boston, MA.

In defining a mechanism for the putative platelet support of microvascular structural integrity, we have shown that serotonin (5-HT) injected into thrombocytopenic animals prevents petechial formation for as long as 6 h, and that psychomotor drugs inhibit this palliative action. Our data suggest that a platelet's role is to deliver-release 5-HT into the cutaneous microcirculation in amounts physiologically above plasma levels, which acts as a signal to maintain "endothelial tone". In this study psychotropic drugs known to inhibit 5-HT uptake, such as imipramine, amitriptyline, fluoxetine, were studied for their effect on endothelial structural integrity in normal adult hamsters. Adrenergic receptors, inhibitors and catecholamines were also used in conjunction with psychotropic drugs. Bleeding times and plasma levels of 5-HT were quantitated. Following a single injection or daily injection for 21 days of all substances tested, petechial sensitivity increased significantly in normal hamsters. Norepinephrine decreased and propranolol enhanced petechial formation. Microhemorrhages were observed within 5 min post-injection with fluoxetine (4.5×10^{-3} mg/100 g⁻¹) and with amitriptyline (0.04 mg/100 g⁻¹). Petechiae occurred for one week following a single injection of fluoxetine, which indicates that the stable metabolite of this antidepressant is biologically active. All other parameters measured were normal except bleeding times, which increased three-fold compared to controls. In published reports, 5-HT has been shown to alter microfilament orientation, especially at junctions. Based upon this observation and the present data, we theorize that the blockade of a 5-HT signal by the uptake antagonist effects endothelial cytoskeletal support of junctions.

FIBRINOPEPTIDE A AND BETA-THROMBOGLOBULIN LEVELS IN PRE-ECLAMPSIA AND HYPERTENSIVE PREGNANCY. Jessie T. Douglas, M. Shah, G.D.O. Lowe and C.R.M. Prentice. Departments of Medicine and Obstetrics and Gynaecology, Royal Infirmary, Glasgow, Scotland.

To evaluate thrombin generation and platelet activation in pre-eclampsia we have measured fibrinopeptide A (FPA) and beta-thromboglobulin (BTG) by radioimmunoassay in patients with this disorder and have compared them to patients with essential hypertension of pregnancy and normal controls. In 10 patients with pre-eclampsia significantly elevated levels were found of FPA (8.3 ± 4.3 ng/ul; mean normal 1.6 ± 0.8 ng/ul, $p < 0.01$) and of BTG (51.9 ± 16 ng/ul; mean normal 31 ± 16 ng/ul, $p < 0.01$). In 5 patients with pregnancy and essential hypertension the levels of FPA (5.65 ± 2.2 ng/ul, $p < 0.01$) were lower than in pre-eclampsia but were still significantly elevated. BTG (37 ± 2.5 ng/ul) was not significantly increased in these patients. These results are consistent with increased thrombin generation and platelet release in pre-eclampsia. In pre-eclampsia there is evidence of intravascular coagulation which occurs to a greater degree than in pregnant patients with comparable raised blood pressure due to essential hypertension. Serial FPA measurements may prove useful in monitoring the development and treatment of pre-eclampsia.