0863

THERAPEUTIC TRIAL OF PROSTACYCLIN IN THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP). G. Thomas Budd, M.D., Ronald M. Bukowski, M.D., Fred V. Lucas, M.D., Linda F. Cook*, and David M. Cocchetto*, B.S. Cleveland Clinic Foundation, Cleveland, Ohio and *Burroughs Wellcome Co., Research Triangle Park, N.C.

Deficiency of a plasma factor stimulating vascular prostacyclin (PGI_2) generation has been implicated in the pathogenesis of TTP, raising the possibility that PGI_2 replacement therapy might be useful in the treatment of TTP. A diagnosis of TTP was made in a 47-year old woman presenting with weakness, fever, and fluctuating neurologic signs. Initial hematologic values were: hemoglobin 7.3 gm/dl, platelets 8000/mm^3, reticulocytes 23%. Peripheral smear demonstrated marked microangiopathic changes. Initial therapy was with 8 plasmaphereses, each consisting of a 3 liter exchange. Fresh frozen plasma was the replacement solution in all but the last 2, where 5% plasma protein fraction was substituted due to a suspected plasma hypersensitivity reaction. Additionally, prednisone, aspirin, and dipyridamole were administered during the last 3 plasma exchanges. Transient increase in platelet count occurred but returned to 9000/mm^3. Neurologic symptoms remained unchanged. A continuous I.V. infusion of PGI_2 was then initiated, and used alone for days 1-5. Aspirin and dipyridamole were added during days 6-8. Prior to use, each PGI_2 preparation was assayed for in vitro ability to inhibit ADP-induced platelet aggregation. The average PGI_2 infusion rate was 1.9 ng/kg/min for days 1-5 and 3.8 ng/ml/min during the final 3 days. Toxicity included nausea, vomiting, and headache and prevented further dose escalation of PGI_2. Platelet count during the 8 days of PGI_2 ranged from 5,000-30000/mm^3. The patient expired on day 8 due to intracerebral hemorrhage. Postmortem examination demonstrated widespread microthrombi in multiple organ sites. PGI_2 infusion in the dosage range employed was a therapeutic failure in this case of TTP refractory to conventional therapy; further trials are in progress.

0864

PROSTACYCLIN IN THE TREATMENT OF RAYNAUD'S SYNDROME. J.J.F. Belch, P. Newman, J. Drury, P. Leiberman, C.D. Forbes and C.R.M. Prentice. University Dept. of Medicine, Royal Infirmary, Glasgow, Scotland and Department of Clinical Physics and Bioengineering, West of Scotland Health Board.

There is evidence to suggest that platelet activation occurs in Raynaud's syndrome in the form of raised β-thromboglobulin and enhanced ADP induced aggregation. We evaluated the effect of prostacyclin (PGI_2) in 5 female patients with Raynaud's syndrome. Out-patient visits were made at weekly intervals for 4 weeks. At the first visit buffer solution (Wellcome Laboratories) was infused intravenously for 5 hours, thereafter three five hour infusions of PGI_2 at a peak dose of 10 ng/Kg/min were given. Six weeks after the infusions patients were reviewed. Symptomatic improvement including healing of ischaemic ulcers occurred in 4 out of 5 patients. Thermography of the hands confirmed an increase in hand temperature in 3 patients. No increase in temperature was observed in the one patient who did not improve symptomatically, nor in another patient who improved clinically but who had initially inflammation of the hand. Nausea and headache were experienced by all patients but only one patient required a decrease in PGI_2 dose to 7.5 ng/Kg/min. We conclude that further evaluation of PGI_2 in the treatment of Raynaud's syndrome is warranted, especially as the duration of improvement far exceeded the duration of treatment.

0865

PROSTAGLANDINS AND UTERINE BLEEDING. C.F. Goodfellow, R.C. Paton, S. Moncada, J.A. Salmon, J.A. Davies and G.P. McNicol. University Departments of Medicine and Obstetrics, Leeds, and Wellcome Research Laboratories, Beckenham, U.K.

There is little information about haemostatic function in the uterus in relation to menstrual bleeding. We measured platelet count and platelet retention in glass-bead columns, and plasma levels of FPA, TxB_2 and 6-oxo-$PGF_{1\alpha}$ in samples taken simultaneously from uterine vein (UV) and peripheral vein (PV) in 18 women (2 post-menopausal) undergoing hysterectomy. Platelet counts and FPA concentrations were similar in both sets of samples. Plasma levels of 6-oxo-$PGF_{1\alpha}$ were significantly ($p<0.01$) higher in UV (1.34 ± 1.27 ng/ml, mean ± SD) than in PV (0.18 ± 0.39 ng/ml) as were levels of TxB_2 (0.46 ± 0.54 and 0.1 ± 0.13 ng/ml). Platelet retention in UV blood was about half that observed in PV blood and the degree of platelet retention correlated inversely with plasma concentration of 6-oxo-$PGF_{1\alpha}$ ($r = -0.48$, $p<0.01$). There was a highly significant ($p<0.01$) rank order between the time since menstruation and plasma 6-oxo-$PGF_{1\alpha}$ concentration in UV blood. TxB_2 levels were highest on day 4 and then fell suddenly with time since menstruation. The results indicate that prostaglandins may modulate uterine bleeding at menstruation. Release of PGI_2 from uterine vessels could contribute to the lack of platelet deposition in the menstruating uterus and by this mechanism to the persistence of menstrual bleeding.

0866

DECREASED PROSTACYCLIN OR PGI_2 PRODUCTION IN THE INFANT OF THE DIABETIC MOTHER (IDM). CORRELATION WITH MATERNAL HbA_{1c}. M.J.Stuart, S.G.Sunderji, J.B.Allen SUNY, Upst. Med. Ctr., Depts. of Peds and Perinatology, Syracuse, N.Y., U.S.A.

Platelet and vascular prostaglandins are important regulators of normal hemostasis. Platelets produce endoperoxides and thromboxanes which are proaggregatory and prothrombotic, whereas vessels produce PGI_2 which is antiaggregatory and antithrombotic. Since the IDM has an increased predisposition to thrombosis, we evaluated arachidonic acid (AA) metabolism and PGI_2 production in the umbilical vessels of 12 control infants and 9 IDM of similar gestational age. Mean uptake of ^{14}CAA into vascular tissue of controls and IDM were similar at 9157 ± 1096 (1SE) and 12036 ± 1691 cpm per 30 mgm vascular tissue resp. Thrombin stimulated release of ^{14}CAA was similar in the controls (5.0 ± 0.7) when compared to IDM (5.5 ± 1.3). However in the IDM, the production of vascular 6-Keto-$PGF_{1\alpha}$ (the stable end product of PGI_2) was decreased ($p<0.02$). Controls incorporated 5003 ± 533 cpm (5.2 ± 0.4%) into 6-Keto-$PGF_{1\alpha}$ when compared to 3033 ± 490 cpm (3.2 ± 0.6%) in the IDM. No correlation was observed between maternal blood glucose levels and fetal PGI_2 production. However, a significant inverse correlation ($r=0.87$; $p<0.02$) was observed between maternal HbA_{1c} levels and the conversion of AA to 6-Keto-$PGF_{1\alpha}$ in the IDM. Rigorous control of maternal diabetes appears to be the best prophylaxis against the decrease in PGI_2 in the IDM. We have previously shown that platelet endoperoxides are increased in the IDM. Thus, the normal balance between proaggregatory (platelet) and antiaggregatory (vascular) prostaglandins is disrupted in the IDM, a factor which favors thrombosis.