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IN VIVO SELECTIVITY BETWEEN HYPOTENSIVE AND PLATELET ANTIAGGREGATING ACTIONS OF ILOPROST AND PGI_2 IN BEAGLE DOGS. F.Hermán, P.Hadházy and K.Magyar. Semmelweis University of Medicine, Department of Pharmacodynamics 1089.Budapest, Nagyvárad tér 4. HUNGARY

Iloprost (Schering A.G.) is a chemically stable derivative of prostacyclin. We compared the hypotensive and antiaggregatory effects of PGI_2 and Iloprost. The concentration producing 50% inhibition (IC_{50}) of ADP-induced platelet aggregation in vitro was 0.35±0.15 nmol/l for PGI_2 and 0.56±0.2 nmol/l for Iloprost (n=5). The in vivo antiaggregatory activity was measured with a modified filtration pressure technique (F.Hermán et al.Thromb. Res.44 /1986/, 575) in anaesthetized beagle dogs; the change in arterial blood pressure was recorded simultaneously. Using this technique, the dose-response relationship and the duration of action of prostacyclin and Iloprost following bolus administration have been determined. PGI_2 was equipotent with Iloprost in inhibiting platelet aggregation in vivo (ED_{25}: 0.25±0.04 nmol/kg; 0.28±0.05 respectively). At the same time PGI_2 was two times as potent as Iloprost in decreasing the mean arterial blood pressure (ED_{25}: 0.41±0.12 nmol/kg; 0.87±0.14 nmol/kg respectively). The antiaggregatory and hypotensive effects of Iloprost last longer in each experiment than that of PGI_2, but did not reach the level of significance probably due to the considerable interindividual differences. The in vivo selectivity ratios (hypotensive potency/anti-aggregatory potency) of Iloprost and PGI_2 were 0.32 and 0.6 respectively. These results show that in anesthetized beagles Iloprost is somewhat more selective than PGI_2 in inhibiting platelet aggregation.

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EFFECT OF A SYNTHETIC ANTICOAGULANT (MD 805) ON PLATELETS IN HUMAN VOLUNTEERS AND HEMODIALYSIS PATIENTS.

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Twelve normal subjects were injected with 5000 U of commercial mucous heparin with or without preloading of 1.0 g aspirin, and 0.2 mg/kg MD 805, an arginine derivative, which is a new synthetic compound with an extremely strong affinity for thrombin, at an interval of 4 weeks after each injection. Heparin injection with or without aspirin significantly increased platelet factor 4 release. In contrast, the preloading of aspirin significantly inhibited the decrease of platelet count and the elevation of β thromboglobulin induced by heparin. However, MD 805 had no effect on platelet release proteins, and adequate anticoagulation by APTT was still present 60 min after the injection. MD 805 shows no stimulative effects on platelets such as with heparin.

In the case of the patient's study, three patients complicated with heparin induced thrombocytopenia plus thrombus formation in the extracorporeal circulation during hemodialysis, and were treated with MD 805 instead of heparin. The platelet counts in those patients quickly returned to within the normal range, and adequate anticoagulation was obtained in the following hemodialysis sessions and no further bleeding or clot formation was noted.

In conclusion, MD 805 may represent a useful alternative anticoagulant in patients with heparin induced thrombocytopenia.

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PULMONARY MICROEMBOLISATION IN SURGICAL SHOCK: THE EFFECT OF CYCLO-OXYGENASE INHIBITION. CM Backhouse, AC Meek, KR Poskitt, CN McCollum. Department of Surgery, Charing Cross & Westminster Medical School, London, UK.

Thromboxane release from platelet microemboli during major arterial surgery may mediate depression of cardio-pulmonary function. The effect of cyclo-oxygenase inhibition by aspirin has been studied in a porcine model of aortic surgery.

Following autologous platelet labelling with 111-Indium, 24 pigs (20-25kg) were randomised to low dose (LD) aspirin (0.5mg/kg), high dose (HD) aspirin (10mg/kg) or placebo. Arterial and Swann Ganz catheters were inserted prior to surgery consisting of midline laparotomy, small bowel exteriorisation, 1.5 hours of aortic clamping and 1 hour shock before resuscitation. On induction, during shock and at 3 days, platelet and leucocyte counts, lung platelet uptake (LPU), venous aggregates by screen filtration (SFP), mean arterial pressure (BP), cardiac output (CO), pulmonary shunt (PS) and alveolar-arterial pO_2 difference ($A\text{-}adO_2$) were measured.

	Fall in BP (mmHg)	LPU	PS (%CO)	$A\text{-}adO_2$ (mmHg)
Placebo	35.5±9.7	9.0±0.7	8.7±2.8	21.9±3.8
LD aspirin	9.0±7.1*	7.2±0.4*	4.9±1.3	11.9±3.7*
HD aspirin	11.2±6.9*	7.5±0.3	4.0±1.7*	7.7±2.2*

Results as mean ± sem *p<0.05 Mann Whitney U-test compared to placebo.

During shock following aortic declamping aspirin preserved blood pressure by increasing vascular resistance rather than CO. Venous aggregates by SFP tended to be lower on aspirin with significantly reduced LPU, subsequent pulmonary shunting and $A\text{-}adO_2$. The improvement in PS but not $A\text{-}adO_2$ remained significant at 3 days (p<0.05).

Cyclo-oxygenase inhibition improved pulmonary function during surgical shock either by inhibiting platelet microemboli or by a direct effect on pulmonary arteriovenous shunts.

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BLOOD PLATELET FUNCTION OF HYPERLIPIDEMIC PATIENTS TREATED WITH BEZAFIBRATE. A.Borowska.Department of Cardiology, Medical Academy,Białystok,Poland.

Platelets from patients with hyperlipoproteinemia (HLP) are more sensitive to some aggregating agents than platelets from normal persons.On the other hand, it is known that from 15% to 20% of patients with coronary heart disease have primary or secondary HLP.The progress of the knowledge in this field has been expressed in production of the new drugs diminishing HLP.Bezafibrate is a new derivative of clofibric acid,which has been used in the treatment of HLP.The purpose of our study was and assessment of the effect of bezafibrate on platelet aggregation and thromboxane (TXB_2) generation.The experiments were carried out in 18 patients (7 women and 11 men),aged 32-60 (mean 46 years) with type IIa HLP.The control group of consisted of 10 healthy volunteers.For 6 weeks the patients with HLP were given bezafibrate (Bezalip-Boehringer Mannheim) 600mg daily in divided doses and were taking the same diet as before the treatment.Blood platelet aggregation and ^{14}C arachidonic acid (AA) conversion to thromboxane in washed platelets (using thin-layer-chromatography) were determined before and after bezafibrate administration.The obtained results are presented in the table (mean±S.E.).

	Control	before treatment	after treatment
blood platelet aggregation to ADP (in %)	46.8±9.7	84.9±8.8 $p < 0.001$	49.6±10.2
% conversion of ^{14}C AA to TXB_2	11.5±1.1	19.7±2.7 $p < 0.001$	12.4±1.6

It is concluded that the main arteriosclerosis-protecting bezafibrate action lies not only in decreasing of lipid levels in serum, but also in normalization of platelet function.