0859

STIMULATION OF PROSTACYCLIN RELEASE BY A NEW VASODILATORY COUMARIN DERIVATIVE (AD6). Elisabetta Dejana, Conxita de Castellarnau, Domenico Rotilio and Giovanni de Gaetano. Istituto di Ricerche Farmacologiche " Mario Negri ", Milan, Italy.

AD6 (8-monochloro-3-β-diethylamino-ethyl-4-methyl-7-ethoxy-carbonyl-methoxy-coumarin) reportedly exerts specific coronary vasodilatory activity and reduces platelet aggregation in laboratory animals. We investigated whether AD6 stimulates prostacyclin (PGI_2) synthesis by the vessel wall. Segments of thoracic aorta were obtained from rats 30 min after i.v. injection of AD6 (4 mg/kg). PGI_2 production measured by bioassay and confirmed by RIA of 6-Keto-$PGF_{1\alpha}$ was significantly higher in the vessels of treated (3.27±0.3 ng/mg wet tissue) than of control animals (2.09±0.2 ng/mg wet tissue). ^{14}C-arachidonic acid (^{14}C-AA) was incubated with vascular specimens for 4 hours, the free excess removed and the metabolites produced during the following 5 hours were studied by thin layer radiochromatography. The vessels from AD6-treated animals converted significantly more ^{14}C-AA to 6-Keto-$PGF_{1\alpha}$ (3.7% total radioactivity) and PGE_2 (2.1% total radioactivity) than controls (1.1% and 0.6%, respectively). In vitro incubation of the drug with the vessels had no demonstrable effect on PGI_2 production at any concentrations used (0.01 - 1 mM).
This data shows that in vivo treatment with AD6 resulted in stimulation of the metabolism of AA in rat thoracic aorta. It is proposed that the previously described vasodilatory activity of the drug might be mediated through the stimulation of PGI_2 release.

0860

PLATELET ANTIAGGREGATION AND HEMODYNAMIC EFFECTS OF ADENOSINE AND PROSTAGLANDIN E_1. T.N. Masters, G.V.R. Born and F. Robicsek. Heineman Medical Research Center, Charlotte Memorial Hospital & Medical Center, Charlotte, N.C. 28232 and Department of Pharmacology, Kings College, London, England.

The efficacy of using adenosine (ADEN) or prostaglandin E_1 to prevent platelet loss during cardiopulmonary bypass (CPB) was tested in experiments conducted with a simulated CPB circuit with cardiotomy suction. The hemodynamic effects of the compounds were tested in a canine model to ascertain hemodynamic tolerance of platelet-salvaging concentrations. Platelet concentrations were determined with a Coulter Counter Model S-Plus in 3 separate groups each composed of 10 experiments in which ADEN (1 mM) and PGE_1 (0.5 and 1.0 μM) were added to the bypass circuit to determine platelet protection. It was found that PGE_1 at both concentrations was effective in salvaging platelets (0.5 μM-70% and 1.0 μM-95%) and ADEN at 1 mM salvaged approximately 45%. Hemodynamic effects of PGE_1 and ADEN were studied in heparinized (3 mg/Kg) mongrel dogs weighing between 20-27 Kg which were artificially ventilated and catheters placed to measure LV and arterial pressures and dP/dT. Via a left thoracotomy a 15 mm Statham Blood Flowmeter Probe placed around the ascending aorta measured Cardiac Output (CO). ADEN, in seven increasing doses (range: 0.45-3.40 mg/Kg/min), was infused for 2 min with 5 min between doses. In two groups of 10 dogs each, PGE_1 was infused with two dose ranges: 0.40-3.00 and 2.0-15.0 μg/Kg/min. PGE_1 was infused in seven increasing doses in each range and hemodynamic changes recorded during 3 min of infusion. Hemodynamically, ADEN reduced heart rate and systemic resistance progressively as dose increased. The unchanging CO accompanied by reduced dP/dT and LV pressure suggests the myocardium is not directly affected. PGE_1 on the other hand, continually reduced CO and dP/dT with increasing doses, but with the smallest dose reduced arterial pressure 20% which remained unchanged with increasing doses. PGE_1 therefore appears to directly depress the myocardium with maximal resistance changes occurring with the smallest doses. Platelet salvaging concentrations for ADEN were within acceptable limits, whereas PGE_1 was not.

0861

THE EFFECT ON SERUM-THROMBOXAN B_2 PRODUCTION, PLATELET AGGREGATION, SEROTONIN RELEASE, PF-4 AND 6-KETO-$PGF_{1\alpha}$ OF A NOVEL SPECIFIC THROMBOXAN A_2 SYNTHETASE-INHIBITOR IN PATIENTS WITH HYPERACTIVE PLATELETS. J.B.Knudsen, A.Juhl, J. Gormsen. Coagulation Laboratory, 3rd Medical Department, Kommunehospitalet, Copenhagen, Denmark.

A novel, specific Thromboxan A_2-synthetase inhibitor 4-1-2-(1 H-imidazol-1-yl)ethoxy-benzoic acid hydrochloride was given to nine patients with hyperactive platelets (defined by an aggregation threshold ≤ o.o5 ug/ml epinepherine) and nine controls. The effects on serum Thromboxan B_2, platelet aggregation, serotonin release, PF-4, and 6-keto-PGF_1 were evaluated in sequential blood samples from ½ to 24 h after single dose of loo mg. The serum-thromboxan production measured by RIA was reduced 96% ± 4.3 sd ½ h to 2 h after dosing. Platelet aggregation was reduced 89 ± lo.2% with epinephrine, 92 ± 11.4% with collagen and 56 ± 14.3% with ADP. Serotonin release induced by ADP was reduced 65 ± 9.8%, while PF-4 showed no consistant changes. When crushed rat aorta or microsome preparations from human umbilical cord arteries were incubated with PRP from patients before and after dosing, and aggregation induced by 16 uM ADP, a 6 fold increase in 6-keto $PGF_{1\alpha}$ production measured by RIA was observed. The Ivy-bleeding time was prolonged by 65 ± 14 sd %.
Conclusion: Specific inhibition of the platelet thromboxane synthetase in patients induces a highly effective inhibition of thromboxane production, and inhibition of platelet aggregability and serotonin release and an increase in Endoperoxide availability which by rat and human endothelial cell prostacycline synthetase can be utilized for increase prostacyclin production.

0862

REDUCED PRODUCTION OF 6-KETO-$PGF_{1\alpha}$ BY UMBILICAL ARTERY IN PRE-ECLAMPSIA. L.O. Carreras, A. Van Assche, G. Defreyn, E. Van Houtte, J. Vermylen. Center for Thrombosis and Vascular Research, Department of Medical Research, University of Leuven, Belgium.

Decreased production of PGI_2 activity by fetal and maternal vessels and low values of PGI_2 activity in amniotic fluid have recently been observed in patients with severe pre-eclampsia. In this study we measured the production of 6-keto-$PGF_{1\alpha}$ by the umbilical artery and placental veins in 5 cases of severe pre-eclampsia (diastolic blood pressure > 100 mmHg) and 5 normal pregnancies. No mother had ingested aspirin for at least a week before delivery. Vascular specimens were obtained immediately after expulsion of the placenta, immersed in tris buffer 0.05 M, pH 7.4 and cut into fine rings. The production of 6 keto-$PGF_{1\alpha}$ was studied within 2 hours. Vascular fragments were incubated on a gentle rocker platform at 22°C in 2.5 ml of the following media : a) tris buffer ; b) tris buffer containing sodium arachidonate (AA) 5 μM. 100 μl subsamples were removed from the incubation dishes at 0, 4, 8, 12, 16 and 24 minutes. The 6-keto-$PGF_{1\alpha}$ level in each of the subsamples was measured by radioimmunoassay. The mean values obtained, expressed as $pg.mg^{-1}min^{-1}$ ± SEM are shown in the table :

	Normal Pregnancies		Pre-eclampsia	
	Tris	Tris+AA	Tris	Tris+AA
Umbilical artery	23.7±8.29	22.7±4.99	0.42±0.15	7.72±2.40
Placental vein	6.04±1.55	6.71±0.73	5.07±2.80	7.74±2.2?

A significant reduction in the production of 6-keto-$PGF_{1\alpha}$ by umbilical artery incubated in tris buffer ($p < 0.01$) and tris buffer containing sodium arachidonate 5 μM ($p < 0.025$) was observed in the cases of severe pre-eclampsia. In contrast, no significant decrease in the production of 6-keto-$PGF_{1\alpha}$ by placental veins was obtained. Considering that fetal umbilical arteries generate much greater PGI_2 activity than vessels from normal adults, a central role for this substance in the regulation of fetal circulation has been postulated. The marked reduction in the production of PGI_2 could seriously affect fetal outcome in severe pre-eclampsia.