oster
oard
5-026

0462 EFFECT OF SULPHINPYRAZONE (SP) ASPIRIN (ASA) AND DIPYRIDAMOLE (DP) ON PLATELET-VESSEL WALL INTERACTION AFTER ORAL ADMINISTRATION TO RABBITS.

J.A. Davies* & V.C. Menys, University Department of Medicine, Leeds, U.K.

Clinical trials of anti-platelet drugs have suggested that they may be useful in the prevention of thrombotic disease. While such drugs inhibit platelet function, those which act on cyclo-oxygenase also reduce $PGI_2$ synthesis and may interfere with tne natural antithrombotic properties of the vessel wall. We studied the effects of SP, ASA and DP *ex vivo* on the platelet-vessel wall interaction. Rabbits were dosed by mouth with drug (at about twice the weight-adjusted human dose) or placebo for 5 days, then exsanguinated and aortas removed. Washed platelets prepared from the blood were labelled with $^{51}Cr$. and their adhesion to everted aorta prepared from treated or control rabbits was measured in a perfusion device. $PGI_2$-like activity in aortic rings was assayed by its inhibitory effect on platelet aggregation to ADP. Adhesion of platelets to aortas from SP-treated rabbits was increased ($p < 0.025$), $PGI_2$-like activity was partially inhibited, but overall adhesion of SP-treated platelets to aortas from SP-treated animals reduced by 30% ($p < 0.02$). Adhesion to aortas of ASA-treated rabbits was slightly increased ($p > 0.1$), $PGI_2$-like activity abolished, and no overall reduction in platelet adhesion seen. DP had no effect on adhesion or $PGI_2$-like activity. These results support the evidence that cyclo-oxygenase inhibitors reduce the inherent resistance of the vessel wall to platelet adhesion. However with SP, inhibitory effects on platelets appear to be more important.

5-027 0463 MODULATION BY DIPYRIDAMOLE OF THE ARACHIDONIC ACID METABOLIC PATHWAY IN PLATELETS. AN IN VIVO AND IN VITRO STUDY

G.G. Neri Serneri, G.F.Gensini[x], R.Abbate, S.Favilla and R.Laureano,
Istituto di Patologia Medica II, University of Florence, Florence, Italy

Dipyridamole is a useful antiplatelet agent in specific clinical conditions, but its effects on $TxB_2$ production by platelets are now being debated. Resting platelets from patients with 1.5-2 µg/ml serum dipyridamole (spectrofluorimetric assay), administered by venous infusion or by oral route, showed an increased concentration (m.v. +58%, $P<0.001$) of cAMP (radiometric assay). After stimulation with thrombin (5U/ml) platelets produced a significantly decreased amount of $TxB_2$ (m.v. -60%, $P<0.001$) (radioimmunoassay with antibody kindly supplied by Doctor J.B.Smith, Philadelphia). However also after stimulation with arachidonic acid (A.A.) 1 mM $TxB_2$ production was decreased (m.v. -50%, $P<0.001$). The incubation of control platelets with different concentrations of dipyridamole (0.5,1 and 2 µg/ml) for 20 min at 37°C resulted in an increase of cAMP and in a decrease of $TxB_2$ production after stimulation with thrombin and with A.A.. These results indicate that dipyridamole is endowed with direct antiaggregating activity caused by a decreased production of $TxB_2$. This in turn seems due to an inhibitory modulating effect of cAMP on arachidonic acid cyclo-oxygenation. However our findings do not rule out an inhibitory effect also on phospholipase $A_2$.

P5-028 0464 INCREASE OF CIRCULATING $PGI_2$ AND $PGI_2$ RELEASED BY VESSEL WALL AFTER DIPYRIDAMOLE

G. Masotti*, L.Poggesi, G.Galanti, G.G. Neri Serneri
Istituto di Patologia Medica II, University of Florence, Florence, Italy

$PGI_2$ present in circulating blood is produced by the lungs (Gryglewski et al.1978) and in humans can be also produced by vessel wall after 3 min. ischemia (Neri Serneri et al. 1978). We studied the effects of Dipyridamole (Dp) on circulating $PGI_2$ and on its release by vessel wall induced by ischemia. $PGI_2$ was assayed by Vane superfusion technique. Dp in acute infusion such to deliver a 1.5-2 ug/ml serum concentration (spectrofluorimetric determination) provoked in 4 patients an increase in circulating $PGI_2$ (between 30% and 500%); in 2 patients the appearance of $PGI_2$ previously undetectable; and no changes in the last 2 patients. Also $PGI_2$ production by vessel wall after ischemia was increased by Dp in 6 out of 8 patients but at a lesser extent (increase of $PGI_2$ output between 12% and 40%). The effects of Dp were prevented by pretreatment with indomethacin. Our results indicate that antiaggregating activity of Dp in vivo is connected not only with its effects on platelets, but also to enhanced production of $PGI_2$ not necessarily due to an increased level of intracellular cAMP.