

THE BIPHASIC EFFECT OF SULFINPYRAZONE ON PLATELET FUNCTION. M.R. Buchanan, J. Rosenfeld and J. Hirsh. McMaster University Medical Centre, Hamilton, Ontario, Canada.

Experiments performed in vitro have shown that the effect of sulfinpyrazone (SUL) on platelet function is associated with inhibition of platelet prostaglandin synthesis. We have studied platelet aggregation in vivo, plasma-drug levels and platelet MDA production in rabbits after treatment with SUL. At a dose of 100mg/kg, collagen-induced platelet aggregation in vivo was inhibited by 44% at  $\frac{1}{2}$  hr, 20% at 4 hr and then increased to a maximum inhibition of 57% at 18hr. This latter effect was achieved when there was no detectable SUL in the plasma ( $<0.5\mu\text{g/ml}$ ). Platelets prepared from rabbits given 100mg/kg SUL either 2 or 8 hr beforehand were washed, labelled with  $^{51}\text{Cr}$  and injected into normal rabbits and platelet aggregation in vivo was measured. The response to collagen of platelets exposed for 2 hr to SUL was normal, whereas the response of platelets exposed for 18 hr to SUL was inhibited by 32%. MDA production by platelets incubated for 60 min in PPP prepared from rabbits which had been treated with either 10mg/kg 1 hr beforehand or 100mg/kg 18 hr beforehand, was measured. (The SUL levels of the former and the latter plasmas were 4.4 and  $<0.5\mu\text{g/ml}$  respectively.) Platelet MDA production was inhibited 15% after incubation in the 10mg/kg-1 hr PPP and 32% after incubation in the 100mg/kg-18 hr PPP ( $p<0.0001$ ).

It is concluded that SUL has a biphasic effect on collagen-induced platelet aggregation in vivo. Both effects are associated with inhibition of MDA production but the initial effect is reversible with washing and less marked than the secondary effect which is irreversible and could be due to a metabolite still present in the plasma at 18 hr.

INHIBITION OF PLATELET THROMBOSIS BY N-ACETYL NEURAMINIC ACID (NANA). Iren B. Kovács and G.V.R. Born, Department of Pharmacology, University of Cambridge, Cambridge, England.

In normal venules of hamster cheek pouch, platelet thrombogenesis is inhibited by intravenous neuraminidase or by NANA at concentrations (up to  $50\mu\text{g/ml}$ ) produced by neuraminidase from endogenous sources (A. Atherton & G.V.R. Born, 1973; J. Physiol., 234, 66P). To find out whether this inhibition also occurs in damaged vessels, venules in hamster cheek pouch or rat mesoappendix were irradiated from a HeNe laser for 5 sec. every min., after an intravenous injection of Evan's blue (T1824) to absorb the laser energy (I.B. Kovács, A. Tigyí-sebes, K. Trombitas & P. Görög, 1975; Microvasc. Res., 10, 107). In hamsters, intravenous NANA ( $10\mu\text{g/g}$  body weight) decreased thrombus growth rate after 3 to 9 min. by about 72%. In rats the same dose inhibited thrombogenesis completely for up to 30 min.;  $5\mu\text{g/g}$  decreased the growth rate. NANA inhibited whether injected at pH 2.3 or 6.0. Under these conditions NANA did not alter blood pH, platelet concentration, or blood flow. Thrombus growth was not inhibited by D-glucuronic acid or by the  $\beta$ -methyl glycoside of NANA at the same molar concentrations as NANA. Therefore, inhibition by NANA of platelet thrombogenesis occurs in damaged as in undamaged vessels.

PREVENTION OF ARTERIAL THROMBOEMBOLISM WITH ACETYLSALICYLIC ACID IN PATIENTS WITH PROSTHETIC HEART VALVES. J. Dale, Institute for Thrombosis Research, Oslo, Norway.

A double-blind study has been performed in patients with aortic ball valves in order to study the antithrombotic effects of one gm of acetylsalicylic acid (ASA) daily combined with anticoagulants, as compared with that of anticoagulants alone. The combined treatment offered a significantly better protection, the incidence in the two groups being 1.8 and 9.3 arterial thromboembolic complications per 100 patients per year, respectively. Encouraged by these results, a pilot study on the effects of ASA alone was started in 77 patients from both groups of the first study. They all received one gm of ASA daily, then the dose of anticoagulants was reduced gradually and the drug discontinued on average five weeks later. Six arterial thromboembolic episodes occurred in five patients during the following five months, the incidence being 14.5 complications per 100 patients per year. The study was therefore ended, and anticoagulant therapy re-instituted in addition to ASA. The results indicate that combined treatment with ASA and anticoagulants more effectively inhibits arterial thrombus formation than does each of the drugs alone.