PLATELET INHIBITORS

SURPRISING EFFECTS OF THE CONSECUTIVE ADMINISTRATION OF PENTOXIFILLine AND LOW DOSE ACETYLSALICYLIC ACID ON THROMBUS FORMATION. D. Skripec, U. Kuhlmann. Department of Pharmacology, Hoechst AG Wopf Albert, 6200 Wiesbaden 12, FRG

The effect of the combined oral administration of pentoxifylline (pof) and low dose acetylsalicylic acid (ASA) was evaluated with the help of the laser-induced thrombus model in rat mesenteric arterioles. Laser-induced thrombus formation is inhibited in a dose-dependent way by both drugs. The administration of ASA, either simultaneously with or 1 hour prior to pof, does not show any effects in the laser model. On the contrary, the administration of pof followed 1 hour later by ASA not only exhibited a significant effect but also produced a supraadditive inhibition of the laser-induced thrombus formation. Specific investigations concerning the time interval between the administration of both drugs determined that a significant effect can be achieved only after an interval of 30 to 90 minutes (principle of HWA 5112).

The striking results could also be shown in diseased animals after consecutive chronic administration of pof 1 hour prior to ASA. HWA 5112 exhibits significant effects on laser-induced thrombus formation in the following chronic animal models: 1. adjuvant arthritic rats. 2. supraadditive antithrombotic effect.

The effect of the combined oral administration of pof and ASA on bleeding time (BT), fibrin formation, as measured with standard coagulation tests.

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<th>2.15-7.30</th>
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<td>Median (range)</td>
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EFFECTS OF INHIBITORS ON COLLAGEN INDUCED PLATELET AGGREGATION IN SIX DIFFERENT SPECIES. I.W.C.M. Janzen-Duphar b.v., Dept. of Pharmacology, P.O. Box 2, 1380 AA Wemp, The Netherlands.

One approach to the development of antithrombotics is inhibition of platelet aggregation. The pharmacological approach often used is to test compounds on collagen induced platelet aggregation measured in platelet rich plasma. Therefore we have compared inhibitors with different mechanism of action on aggregation of platelets from six different species commonly used in pharmacological studies. Aggregation was induced with submaximal amounts of collagen (Hormone Chemie).

Inhibitors of the cyclooxygenase system, aspirin and indomethacin, were very potent in inhibiting aggregation of platelets from human guinea pig and dog (IC50 20-60 and 1-3 μM resp.). Aggregation of pig and rat platelets was poorly inhibited by both of these compounds (IC50 700-900 μM), whereas platelets from mice showed intermediate sensitivity (IC50 ca.100 μM).

The combined lipooxygenase/cyclooxygenase inhibitor BW755C, was extremely active on platelets of guinea pig (IC50 1 μM) and poorly active in mice platelets (IC50 300 μM). In the other species the inhibitory activity ranged from 20-80 μM.

The phosphodiesterase inhibitors, papaverine and BL3459 inhibited aggregation in all species in all but with lower activity (IC50 >100 μM).

Conclusion: remarkable species differences are present with respect to inhibition of collagen induced platelet aggregation by the various compounds e.g. rat and rabbit platelet aggregation was hardly inhibited by cyclooxygenase inhibitors. The effects of the compounds on human platelets are comparable to the effects on canine platelets.

ORALLY ADMINISTERED VITAMIN B6 PROLONGS THE BLEEDING TIME AND INHIBITS PLATELET AGGREGATION IN HUMAN VOLUNTEERS. A. M. Randi, K. Secchi and N. Cattaneo. A.Bianchi Bonomi Haemophilia and Thrombosis Ctr. Maggiore Hosp. and Univ. of Milano, Italy.

It is known that mM concentrations of vitamin B6 inhibit human platelet aggregation and fibrin formation in vitro. There are very few and controversial data on the ex vivo effects of vitamin B6 on hemostatic parameters. We evaluated the effects of oral administration of vitamin B6 on bleeding time (BT), fibrin formation, platelet aggregation (PA) and the release reaction (RR). Vitamin B6 500 mg/day p.o., was given to 16 healthy volunteers (8 M, 10 F, aged 23-35) for 8 days. BT was measured before the first dose (Baseline), 2 hr after the first (Day 1) and the last dose (Day 8). In 7 subjects BT was measured also 7 days after the suspension of the drug (Day 15). Before and 2 hr after the first dose, protrombin time (PT), partial thromboplastin time (PTT), thrombin time (TT), PA and the RR induced by different concentrations of ADP, PAF-α, collagen (coll), epinephrine (epi), arachidonate (AA) were studied. BT was significantly prolonged after vitamin B6 administration, and returned to baseline values 7 days after discontinuation of the drug. PA and the RR induced by 1 μM ADP, 1 μg/ml colloidal gold or 5 μM epi were significantly inhibited 2 hours after vitamin B6 administration. Vitamin B6, however, did not affect PA or the RR induced by 0.2-2 μM PAF-α, 2 μM ADP, 1 μg/ml AA, 2 μg/ml coll, nor did it affect PT, PTT or TT. These data show that orally administered vitamin B6 impairs primary hemostasis, but does not affect fibrin formation, as measured with standard coagulation tests.

**N° of subjects** Baseline Day 1 Day 8 Day 15

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EFFECTS OF FUROSEMIDE ON PLATELET AGGREGATION AND ON ALPHA-ADRENOCEPTOR-DENSITY IN MAN. A. Kribben, F. Fritscha, M. Sibold, M. Faehnle, L. Valles, R. Tenner, Dept. of Internal Medicine, Klinikum Steglitz, FU Berlin, F.R.G.

Furosemide (FUR) reduces the α2-adrenoceptor- (α2-R) mediated pressor effect of norepinephrine. Since it has been shown that FUR reduces platelet aggregation (FUR-AGG) we studied the effect of FUR on α2-R as well as that on the α2-R-mediated epinephrine (EPI)-induced AGG (EPI-AGG) α2-vivo and b) in-vitro. For comparison the effect of FUR on ADP-induced AGG was also studied.

Methods: a) 8 normotensive men received FUR (30 mg b.i.d.) for 3 weeks. EPI- (1 μmol/l) and ADP- (1 μmol/l) induced platelet AGG were measured before as well as after 3 weeks of FUR application with a semi-automatic device (APACT). Platelet α2-R-density was measured by [H]-yohimbine-binding and the fraction of high-affinity binding-sites was measured by competition of [H]-yohimbine with EPI. b) Platelet-rich plasma was incubated with FUR (1 mmol/l) for 10 min at 37°C and AGG was measured (n=7) as described.

Results: a) FUR decreased α2-R-density from 29±28 to 25±21 (2 mol/g protein (p<0.01) and high affinity binding-sites from 64±3 to 55±5 % (p<0.01). FUR inhibited ADP-induced AGG α2-vivo while EPI-induced AGG did not change (table). b) In-vitro FUR inhibited ADP-induced AGG α2-vivo while EPI-induced AGG did not change (table).