0070

08:45 h

SALICYLATE ACCUMULATING DURING REPEATED ASPIRIN ADMINISTRATION PREVENTS THE INHIBITORY EFFECT OF ASPIRIN ON VASCULAR PROSTACYCLIN. E. Dejana, C. Cerletti, C. de Castellarnau, F. Galletti, and G. de Gaetano. Istituto di Ricerche Farmacologiche "Mario Negri", Milan, Italy.

In vitro studies have shown that salicylate(SA)effectively protects cyclooxygenase from aspirin(ASA)inhibition. The purpose of this study was to investigate in vivo this pharmacological interaction and to evaluate the possibility that SA accumulating during repeated ASA treatment interferes with the inhibitory effect of the unchanged drug on vascular prostacyclin(PGI_2). Male CD-COBS rats were given i.v. saline or SA (25-100 mg/kg) followed after 15 min by ASA (2.5-10 mg/kg). The animals were killed 30 min after the last treatment. PGI_2 activity was bioassayed on thoracic aorta rings and confirmed by RIA of 6-Keto-$PGF_{1\alpha}$. Blood SA levels were measured by fluorimetric assay. SA pretreatment showed dose-related competitive prevention of the inhibitory effect of ASA on vascular PGI_2 which was almost complete at a dose ratio of 5:1. Further experiments were performed with single or repeated doses of ASA (200 mg/kg). This resulted in different blood SA levels after 24 hours when in all conditions vascular PGI_2 recovered by more than 50% of basal value. At that moment further inhibition (60-90%) of PGI_2 by a test dose of ASA (10 mg/kg) could only be obtained if blood SA levels were lower than 100 µg/ml. Above this level an inverse linear correlation ($r = 0.87$, $p<0.01$) was found between blood SA levels and the inhibitory activity of ASA. In particular, almost no ASA activity could be detected at blood SA levels around 250 µg/ml. These results show that SA and ASA interact in vivo at vascular levels. This interaction could have clinical implications in view of the rapid hydrolysis of ASA to SA and slow elimination of SA from blood. These observations add a new piece of information to the current debate on the optimal ASA treatment schedule for thrombosis prevention.

0071

09:00 h

SINGLE ORAL DOSE ADMINISTRATION OF A SPECIFIC THROMBOXANE SYNTHETASE INHIBITOR TO NORMAL VOLUNTEERS - A DOUBLE BLIND PLACEBO CONTROLLED STUDY. V.V. Kakkar, J. Westwick, J. Zahavi, H. Tyler. Thrombosis Research Unit, King's College Hospital Medical School, London, England, and Pfizer Central Research, Sandwich, Kent, England.

A specific thromboxane synthetase inhibitor (UK-37248-01) is a new imidazole derivative synthesised by Pfizer Central Research. In vitro and animal experiments showed the compound to be a potent, selective and orally active one.

Six healthy male volunteers received a single dose of 100mg of a specific thromboxane synthetase inhibitor or a matching placebo in a double blind cross-over study, there being a 2 week interval between treatments. Production of thromboxane B_2 in serum was markedly reduced 1 hour after the drug administration, with about 50% inhibition still evident at 6 hours. The drug had no effect no circulating β-thromboglobulin and platelet factor 4 antigen levels, or on platelet aggregation to ADP or collagen, though release of 5HT was reduced. Increase in bleeding time (2-3 minutes) was recorded in 3 volunteers 1 hour after the drug administration.

Chemical assay of the compound showed that up to 45% of the oral dose was excreted in the urine within 24 hours; 90% of this was excreted within the first 4 hours. Routine haematology and clinical chemistry tests repeated 24 hours and 4 days after dosing gave no indication of drug related toxicity.

0072

09:15 h

DIPYRIDAMOLE REVERSES THE INHIBITORY EFFECT OF ASPIRIN ON PROSTACYCLIN SYNTHESIS. C.A. Jackson, F.E. Preston, M. Greaves. University Department of Haematology, Royal Hallamshire Hospital, Sheffield, U.K.

The value of aspirin (ASA) as an antithrombotic agent is limited by the fact that it inhibits the production of prostacyclin (PGI_2) by the vessel wall. However, there is evidence that the combination of ASA and dipyridamole (DP) has antithrombotic potential for patients with certain types of thrombovascular disease and there appears to be some synergism between the two drugs. To study the relationship between ASA and DP we have examined the effect of the two drugs, singly and in combination on thromboxane (TX) production and PGI_2 synthesis by platelets and vessel walls respectively. Rings of venous tissue prepared from veins obtained during surgery were incubated in Ringers solution with ASA, DP or a combination of both. PGI_2 synthesis was assessed by radioimmunoassay for 6-keto PGF1α, its stable metabolite on aliquots of supernatant from the incubation mixture during a thirty minute period. All control samples synthesized PGI_2. 0.1mM ASA caused 42-99 per cent inhibition of PGI_2. DP at a concentration of 0.05mg/ml had no significant effect on PGI_2 production compared with values obtained in controls. The combination of DP and ASA caused significantly less inhibition of PGI_2 synthesis compared with almost complete inhibition observed with ASA alone.

In similar studies on platelet rich plasma, TXA_2 synthesis, determined by radioimmunoassay for TXB_2, was abolished by ASA 0.15mM, whereas DP 0.05mg/ml had minimal inhibitory action. However, at lower concentrations of ASA the inhibition of both aggregation and TXA_2 synthesis was markedly potentiated by DP 0.05mg/ml.

These results provide an explanation for the reported synergism between ASA and DP.

0073

09:45 h

AN ANALOG OF THIAZOLE WHICH HAS POTENTIAL ANTITHROMBOTIC ACTIVITY WITH LOW TOXICITY. E.E. Nishizawa, R. H. Rynbrandt A.R. Mendoza, D.P. Balgoyen, K.A. Annis. Diabetes and Atherosclerosis Research, The Upjohn Company, Kalamazoo, Michigan 49001. U.S.A.

Chemical modification of a compound found active in preventing death in mice following intravenous administration of collagen led to the development of an inhibitor of collagen-induced platelet aggregation which was active at 1 ng/ml in human PRP, namely 4,5-bis(p-methoxyphenyl)-2-(trifluoromethyl)-thiazole (TFT). It did not inhibit ADP, thrombin or PGH_2-induced aggregation but inhibited the collagen-induced release of radioactivity from platelets labelled with radioactive serotonin. It was active in many animal species and in the rabbit it had a duration of activity of about 8 hours at 1 mg/kg (p.o.).

TFT has cyclooxygenase inhibitory activity, but unlike aspirin (A) or flurbiprofen (F), it showed no incidence of ulcers at 500 mg/kg p.o. in rats. However, again unlike A or F, it had very little anti-inflammatory activity as measured by the carrageenan-induced hind paw edema assay in rats. Its LD_{50} in mice (i.p.) was greater than 1 gm/kg.

Thus TFT appears to be a potential antithrombotic agent with high antiplatelet specificity and a wide therapeutic margin as compared with A or F. The antiplatelet action of TFT may be due to its inhibition of cyclooxygenase.