Monday, July 13, 1981

Oral Presentations

Platelets, Drugs – I

08:00–09:30 h

Platelets, Drugs – II

09:45–11:00 h

Grand Ballroom East

0067

08:00 h

SALICYLATE, SULPHINPYRAZONE, INDOMETHACIN AND ASPIRIN MAY INTERACT WITH PLATELET CYCLOOXYGENASE AT A SITE DIFFERENT FROM THE SUBSTRATE BINDING SITE. C. Cerletti, M. Livio, G. Rajtar, and G. de Gaetano. Istituto di Ricerche Farmacologiche "Mario Negri", Milan, Italy.

In vitro studies have shown that salicylate(SA), inactive by itself, prevents the inhibitory effect of aspirin (ASA)on platelet prostaglandin production. The purpose of this study was to verify this interaction in vivo and the ability of other non-steroidal anti-inflammatory drugs to counter ASA effect on platelet cyclooxygenase. Groups of male CD-COBS rats received one of the following drugs : SA (25-200 mg/kg i.p.), sulphinpyrazone(200 mg/kg p.o.), indomethacin(0.5 mg/kg i.p.) or the corresponding vehicles, followed after 30 min by ASA(1-50 mg/kg i.p.)as its soluble lysine salt. One or 24 hours later platelet-rich plasma was prepared and MDA (spectrophotometric assay) or TxB_2 (RIA) generated on stimulation with 0.4-1 mM Na arachidonate were measured.All 3 compounds blunted ASA inhibitory action. In particular: 1. The preventing effect of SA was dose-dependent and could be overcome by increasing the dose of ASA. At a dose ratio (SA:ASA) of 20 the effect of ASA was reduced by about 50%, but no interaction was apparent at a ratio below 5. 2. Sulphinpyrazone had a greater preventing effect when it was administered 6 h (100%) than 3 h or 30 min (60%) before ASA (5 mg). 3. Indomethacin reduced by 50% the effect of 5 mg of ASA but not of 10 mg. Tests were made 24 h after ASA administration, when the inhibitory effect of indomethacin was no longer detectable. 4. 200 mg/kg SA reduced by 50% the inhibitory effect of indomethacin.
This data suggests that the 4 drugs interact with the same enzyme and that competition does not necessarily involve the substrate arachidonic acid. This supports the existence of a supplementary binding site which regulates cyclooxygenase activity, but is not directly involved with the substrate site. The clinical implications of these results include the interference of ASA with its hydrolysis product SA and a reappraisal of the pharmacological basis for the association of sulphinpyrazone and ASA in thrombosis prevention trials.

0068

08:15 h

INHIBITION AND RECOVERY OF PROSTACYCLIN AND THROMBOXANE A_2 AFTER LOW-DOSE ASPIRIN. F.E. Preston, C.A. Jackson, M. Greaves, C.J. Stoddard. University Department of Haematology, Royal Hallamshire Hospital, Sheffield.

We have compared the inhibitory effects of low-dose aspirin (ASA) on prostaglandin synthesis by vessel walls and platelets. Two groups of volunteers have been studied. Vein biopsies were obtained from five subjects before and at various intervals after 300 or 150 mg ASA. A further group of volunteers received aspirin 40 mg daily. In this group the second vein biopsy was taken three days after commencement of the drug. Prostacyclin synthesis was assessed by a radioimmunoassay (RIA) for 6-keto $PGF1\alpha$. Platelet thromboxane A_2 production was examined by RIA for thromboxane B_2 (TXB_2) 81-100 per cent inhibition of PgI_2 synthesis was apparent 2 hours after 300 or 150 mg ASA. 86 per cent inhibition was still evident at 8 hrs. Simultaneously complete inhibition of platelet TXA_2 production persisted more than 24 hrs. At this dose of ASA there is no difference in the initial inhibitory effect of aspirin on platelet and vessel wall cyclooxygenase. Also, in males the prolongation of the bleeding times following ASA does not appear to be the consequence of selective inhibition of TXA_2. ASA 40 mg daily produced a cumulative inhibitory effect on TXA_2 synthesis. Its effect on PgI_2 synthesis will be compared with that obtained after a single 300 mg dose ASA.

0069

08:30 h

THE DIFFERENT EFFECTS OF ASPIRIN ON EXPERIMENTAL ARTERIAL AND VENOUS THROMBUS FORMATION. M.Thiessen, R.Zimmermann, G.Weckesser, J.Harenberg. Medizinische Universitätsklinik, Heidelberg, GFR.

The influence of aspirin on platelet aggregation has given rise to frequent use as an antithrombotic agent.The knowledge of an unfavorable alteration of the thromboxane/prostacyclin ratio in the vessel wall at high dosage may favor therapy with low dosages of aspirin.

In order to obtain further information on the most effective dosage of aspirin the antithrombotic effect of repeated and different doses of aspirin was investigated in a standardized experimental model in 120 rabbits.In a 1. group aspirin 100 mg/kg were given 30 min before producing thrombosis.In two further groups aspirin was administered 12 hours and additionally 30 min before beginning the experiment.These rabbits received repeatedly either 10 mg (2.group) or 100 mg/kg (3. group) two times.In a 4.series aspirin was given at 50 mg/kg per day during three days.
A paradoxical thrombogenic effect with an increase of venous and arterial thrombus growth could be seen after a single high dose of 100 mg/kg aspirin, but not after an additional one.If applicated two times a thrombus size minor than under repeated low doses of 10 mg/kg aspirin has been observed in the arterial and venous system ($p < 0.05$).Additionally after repeated treatment with 50 mg/kg an antithrombotic effect could be seen.

According to our data the paradoxical effect of only a single or first high dose of aspirin has to be taken into account but cannot be observed after repeated doses.At a low dosage aspirin a paradoxical effect was seen later,after a second dose.Animal thrombosis experiments does not provide sufficient evidence to support antithrombotic therapy with low doses of aspirin.