

SUPPRESSION OF PLATELET AGGREGATION BY A NEW BETA-ADRENERGIC BLOCKER. M. Small, J.T. Douglas, Morna Orr, G.D.O. Lowe, C.D. Forbes and C.R.M. Prentice. University Department of Medicine, Royal Infirmary, Glasgow, Scotland.

Beta-blockers have been reported to have a variable effect on a number of haemostatic parameters. In view of their possible protective action in coronary artery disease, we studied the effect of the new long-acting beta-blocker, carteolol, on platelet function, coagulation and blood viscosity in 10 healthy male volunteers. Following carteolol (5 mg. orally) blood was taken at 2, 5 and 24 hours and we were able to demonstrate a significant inhibition of platelet aggregation to ADP, adrenaline and collagen ($p < 0.05$) at 5 hours post ingestion, but not at 2 or 24 hours. Platelet release as measured by plasma levels of beta-thromboglobulin, platelet count, fibrinopeptide A, whole blood viscosity and plasma viscosity was also unaltered.

0454

BIOLOGICAL NATURE OF PLATELET INHIBITORS FROM ALLIUM CEPA, ALLIUM SATIVUM AND AURICULARIA POLYTRICA. Amar N. Makheja, Chow Eng Low, J. Martyn Bailey. Department of Biochemistry, George Washington Univ., School of Medicine, Washington D.C.

Several lines of evidence indicate that extracts of onion (*Allium cepa*), garlic (*Allium sativum*) or Chinese black tree fungus (*Auricularia polytrica*) inhibit platelet aggregation both in-vitro and in-vivo.

A systematic study showed that aqueous extracts of these vegetables produced a dose-dependent inhibition of ADP, arachidonic acid (AA) or collagen-induced platelet aggregation. Onion and garlic juices were extracted sequentially into petroleum ether and diethyl ether. The anti-platelet activity in the aqueous phases was completely inactivated by purified adenosine deaminase. The activity in the petroleum ether layer was further characterised by its effects on the metabolism of ^{14}C -AA by platelets. This oily fraction of onion and garlic suppressed thromboxane synthesis completely and induced a redistribution in the products of the lipoxigenase pathway. Adenosine and allicin (found in the ether layer) inhibited aggregation without affecting AA metabolism. Preparative GC and GC/MS studies showed that the activity of the oily fraction was due principally to paraffinic polysulfides (PPS) of which dimethyl trisulfide was one of the most active. Authentic samples of dimethyl trisulfide duplicated the effects of onion and garlic oils on both aggregation and AA metabolism. Based on the analyses performed, the contribution of the identified compounds to the anti-platelet activities is summarized in the following table:

Vegetable	*Units of anti-platelet activity per 100g ^o			
	Total	Adenosine	Allicin	PPS
Onion	3,350	1,200	750	1,400
Garlic	17,250	8,000	5,000	4,250
Black Fungus	40,000	40,000	0	0

*One unit produces 50% inhibition of aggregation in 1ml of PRP. ^oFresh weight for onion and garlic, dry weight for black tree fungus.

0453

POSSIBLE DIFFERENCES IN THE MODE OF ACTION OF DITAZOLE AND NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AS POTENTIAL ANTI-THROMBOTIC AGENTS. A.K. Sim, A.P. McCraw, L. Caprino, F. Antonetti and L. Morelli. Division of Biochemical Pharmacology, Inveresk Research International, Musselburgh, Scotland and Department of Pharmacology, Istituto Farmacologico Sersono, Rome, Italy.

Ditazole (4,5-diphenyl-2-diethanolamino-oxazole), a weak anti-inflammatory drug, has been shown to be a potent inhibitor of platelet aggregation, adhesiveness and bleeding time. Acetylsalicylic acid (ASA), dipyridamole and a combination of these two drugs induced a platelet shape change which was much shorter lasting than their effect on platelet aggregation. Conversely, similar doses of ditazole induced a potent shape change but no effect on aggregation. Ditazole has now been shown to reversibly antagonise thromboxane A₂ (TXA₂)-induced contraction of rabbit aortic strips at an optimal concentration of 25 μ M in the perfusate. Separately, over a dose range of 50-400 mg/kg/p.o., TXA₂ production was inhibited between 39% and 85% in spontaneously clotted rabbit blood. In addition, we have shown that TXA₂ formation following arachidonic acid-induced aggregation of platelet-rich plasma (PRP) is similarly inhibited. Ditazole however did not inhibit prostacyclin (PGI₂) production in rabbit aortic rings following oral drug administration over a dose range of 50-400 mg/kg. At 1000 and 2000 mg/kg PGI₂ production was inhibited by 23% and 41% respectively. TXA₂ and PGI₂ levels were measured by radioimmunoassay of their stable derivatives TXB₂ and 6-keto-PGF_{1 α} . It is suggested that the mode of action of ditazole may be more specific than the cyclo-oxygenase/PG-synthetase blocking activity of most other non-steroidal anti-inflammatory drugs.

0455

INHIBITION OF PLATELET RELEASE REACTION BY CYTIDINE MONOPHOSPHATE (CMP): CORRELATION WITH INHIBITION OF MEMBRANE SIALYLTRANSFERASE ACTIVITY. K.K. Wu and C.S.L. Ku. Departments of Medicine and Immunology, Rush University, Chicago, IL, U.S.A.

To provide further evidence for the contention that platelet surface sialyltransferase plays a major role in platelet release reaction, we evaluated the effect of CMP, a sialyltransferase inhibitor, on platelet aggregation and release. CMP exerted a dose-related inhibitory effect (IC₅₀=1.5mM) on the basal enzyme activity of intact washed platelets or membrane preparation. It blocks the enzyme stimulation by collagen, thrombin, ADP and U46619, a thromboxane A₂ agonist. Serial experiments were then carried out in a lumiaggregometer to determine its effect on platelet release and aggregation. Pretreatment of platelet rich plasma or washed platelet suspension with CMP resulted in a significant reduction of ATP release induced by thrombin, collagen, ADP, U46619 and arachidonate. The dose-response curve of release inhibition was parallel to the enzyme inhibition. Platelet aggregation induced by ADP, collagen and sodium arachidonate was significantly inhibited by CMP but the dose-response curve shifted to the right. Platelet aggregation induced by thrombin or U46619 was unaffected. To determine whether the inhibitory effect of CMP might be mediated through stimulation of adenylate cyclase, platelet cyclic AMP content was determined by radioimmunoassay. There was no significant difference in the cyclic AMP content between CMP-treated and control platelets. CMP did not cause liberation of lactic dehydrogenase from platelets. These findings clearly indicate that inhibition of release reaction by CMP is linked to the inhibition of surface sialyltransferase and is independent of cyclic AMP. This study confirms the notion that platelet membrane sialyltransferase is involved in the initiation of platelet release reaction.