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SEX DIFFERENCE IN THE INHIBITORY EFFECT OF ASPIRIN UPON THE DEVELOPMENT OF OCCLUSIVE ARTERIAL THROMBOSIS IN RATS. A. Uzunova. Department of Pathophysiology, Pleven Medical Institute, Pleven, Bulgaria.

The aim of the study was to investigate the effect of aspirin upon the development of occlusive arterial thrombosis in rats of either sex. For this purpose 3 months old male and female Wistar rats were pretreated with three different doses of aspirin: 10, 30 and 60 mg/kg b.w., orally by stomach tube, 3 hours before the thrombosis procedure. Occlusive arterial thrombosis was induced by the method of Hornstra and Vendelmans-Starrenburg (1973). The dry thrombus weight (TW) and the obstruction time (OT) of the bypass-cannula served as criteria for the degree of the development of thrombosis.

The results showed a dose-dependent statistically significant inhibition of arterial thrombosis in male rats by all doses of aspirin studied. TW was decreased 2, 2.5 and 9 times by 10, 30 and 60 mg/kg aspirin respectively. OT was significantly prolonged in male rats by all doses of aspirin studied. Inhibition of arterial thrombosis in female rats was achieved only by the largest dose of aspirin tested - 60 mg/kg: TW was decreased and OT was prolonged. Paradoxically, female rats treated with 10 mg/kg aspirin showed a tendency for augmentation of arterial thrombosis which contrasted to the significantly decreased TW and prolonged OT of male rats given 10 mg/kg aspirin. Female rats treated with 30 mg/kg aspirin showed only a tendency for inhibition of arterial thrombosis without any significant difference for both, TW and OT. The results were interpreted as suggestive the existance of sex differences in cyclooxygenase inhibition by aspirin and/or the prostaglandin system in rats. The data obtained were in agreement with epidemiological observation of uneffectiveness of aspirin treatment of female patients with stroke. They also showed the need for the most appropriate dose of aspirin for clinical purposes which might be effective in females too.

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EFFECTS OF ORAL ASPIRIN ON PLATELET AND VASCULAR CYCLOOXYGENASE ACTIVITY IN RATS WITH PORTACAVAL SHUNT. C. Cerletti, M.C. Gambino, S. Passaghe, F. Bucchi, Z.M. Chen and G. de Gaetano. Istituto "Mario Negri", Milano, Italy

Oral aspirin can be extensively hydrolysed to salicylate in stomach and liver before entering the systemic circulation. "Pre-systemic" acetylation of the platelets may thus occur during aspirin absorption. This may result in concomitant sparing of peripheral vascular cyclooxygenase mainly exposed to salicylate. We tested whether the "biochemical selectivity" of oral aspirin as an inhibitor of platelet vs. vascular cyclooxygenase would be reduced by elimination of the "first-pass" hepatic metabolism. A portacaval shunt was inserted in anaesthetized rats by connecting the portal vein to the inferior vena cava through a "Y" heparinized polyethylene PE 60-160 cannula. Sham operated rats acted as controls. 90 min after recovery from anaesthesia rats were given aspirin orally (10 mg/kg) and 45 min later serum TxB2 and 6-keto-PGF1α formation by vascular rings were evaluated by radioimmunoassay. Serum TxB2 was completely suppressed in all animals; in contrast, vascular 6-keto-PGF1α was significantly reduced (by 40-60% in aorta and vena cava) in rats with portacaval shunt but not in controls. The results in rats with portacaval shunt were similar to those previously obtained after i.v. aspirin. 15 min after aspirin administration, plasma levels of unmetabolized drug measured by HPLC were significantly higher in rats with portacaval shunt (0.56±0.16 μg/ml; n= 5) than in sham operated controls (0.16±0.22 μg/ml; n= 5). This study directly supports the role of " first-pass" hepatic metabolism in determining the "biochemical selectivity" of oral aspirin.

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TICLOPIDINE AND INDOBUFEN: EFFECTS ON HAEMOSTATIC FUNCTIONS. G.P. Montecchio, P. Custodi, S. Carbone, C. Bendotti, F. Piovella. Istituto di Clinica Medica II°, I.R.C.C.S. Policlinico S. Matteo, University of Pavia, 27100 Pavia, Italy.

Many different mechanisms are involved in thrombus formation. We compared the effects on haemostatic function of two drugs having different mechanism of action, the one interfering with arachidonic acid metabolic cascade (Indobufen) and the other (Ticlopidine) independent from it. 18 adult patients of both sexes suffering from cerebral Transient Ischaemic Attack (T.I.A.) or Reversible Ischaemic Neurologic Disability (R.I.N.D.) have been treated with Indobufen (400 mg daily) or Ticlopidine (500 mg daily) for three weeks. The effects on various haemostatic parameters including bleeding time, platelet adhesion to glass beads, platelet aggregation induced by ADP, collagen, platelet activating factor (PAF), have been evaluated at the beginning and at the end of treatment. Both drugs prolonged the bleeding time, Ticlopidine being more effective than Indobufen. ADP-induced platelet aggregation was more effectively inhibited by Ticlopidine, while Indobufen was more effective on collagen-induced aggregation. PAF-induced platelet aggregation was inhibited by Ticlopidine, while Indobufen was ineffective. Platelet adhesion to glass beads was not influenced by treatment with either drugs. In conclusion, both drugs confirmed to be effective in inhibiting haemostatic function although with different mechanisms. Ticlopidine seems to be involved in more mechanisms, interfering with platelet aggregation induced by ADP, collagen, PAF and prolonging the bleeding time. Indobufen interferes with platelet aggregation induced by ADP and collagen, is less effective in prolonging the bleeding time, and does not affect PAF-induced platelet aggregation.

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TICLOPIDINE AND PREVENTION OF PLATELET ACCUMULATION IN CAROTID ENDARTERECTOMY. EVALUATION WITH INDIUM-111 LABELED PLATELETS. L. Catani (1), G. Vitacchiano (2), M. Scatigna (1), N. Monetti (3), L. Pedrini (2), L. Gugliotta (1). Institute of Haematology (1) and Chair of Vascular Surgery (2) University of Bologna, Dept. of Nuclear Medicine (3) Ospedale S. Orsola, Bologna - Italy

In endoarterectomy (EA) the vascular endothelium is removed, thus promoting platelet adhesion and aggregation. This situation may cause microembolic phenomena that manifest at the carotid level with the appearance of TIA in the postoperative period.
An interesting method of evaluating platelet behavior "in vivo" consists of the use of indium-111 labeled autologous platelets and the subsequent evaluation of scintigraphic images.
We used this method to perform a pilot study on the efficacy of ticlopidine, an antithrombotic drug with platelet antiaggregant activity, in the prevention of platelet accumulation after carotid EA.
A total of 20 patients undergoing carotid EA were randomly allocated to receive ticlopidine 500 mg/day (10 patients, T group) or placebo (10 patients, P group) in double-blind conditions. Drug administration was started 5 days before the operation and continued during the postoperative period; infusion of the labeled platelets was performed on the first and scintigraphic evaluation on the second postoperative day.
Analysis of the two groups, which were comparable for age, sex, risk factors and associated patologies, showed 3 scintigraphic-positive cases in the T group and 6 in the P group. The fixation index was 1.12 ± 0.18 in the T group and 1.20 ± 0.16 in the P group. One patient in the P group presented an episode of amaurosis fugax in the first postoperative day.
The results of this pilot study suggest that ticlopidine is effective in preventing platelet accumulation after carotid EA.

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