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EFFECTS OF SULFINPYRAZONE AND ITS METABOLITE G25671 ON PLATELET ACTIVATION AND DESENSITIZATION AND ON BRONCHOCONSTRICTION INDUCED BY THE PROSTAGLANDIN ENDOPEROXIDE ANALOGUE U46619.

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In previous studies we have found (Br. J. Pharmac. 85, 849, 1985) that a) human platelets pre-exposed to arachidonic acid or to the endoperoxide analogue, U46619 and then washed and resuspended, fail to respond to a second challenge by both arachidonic acid and U46619; b) desensitization by arachidonic acid and U46619 occurs at a site sensitive to endoperoxides / thromboxane (Tx) receptor antagonists; c) the desensitizing effects of U46619 are direct, whereas those of arachidonic acid are mediated by a cyclooxygenase-dependent metabolite. Sulfinpyrazone (100 µM) and its thioether metabolite G25671 (50 µM) are known to suppress arachidonic acid-induced platelet aggregation and Tx₂ formation (Eur. J. Pharmac, 101, 209, 1984). We now demonstrate that the presence of sulfinpyrazone or G25671 during platelet exposure to arachidonic acid or U46619 prevents desensitization. Platelet activation by the endoperoxide analogue U46619 is also prevented by sulfinpyrazone or G25671 (0.3-1 mM). The threshold aggregating concentrations of arachidonic acid and U46619 in healthy subjects before and after oral treatment with sulfinpyrazone were elevated by 2-3 fold and a good correlation between *ex vivo* and *in vitro* findings was established. We finally examined the actions of sulfinpyrazone and G25671 on the bronchoconstriction *in vivo* and parenchymal lung strip contraction *in vitro* induced by U46619. Neither drug had any preventive effect. Our results demonstrate that sulfinpyrazone and its metabolite G25671 are not only cyclooxygenase inhibitors but can also act as endoperoxide/Tx antagonists and indicate clearly that antagonism of U46619 by both drugs is selective for platelets.

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PRESYSTEMIC DEACETYLATION OF LOW DOSES OF ENTERIC COATED ASPIRIN IN A PIC MODEL. J.V. Lloyd (1), S.E. Rodgers (1), D.M. Siebert (2), F. Bochner (2), G.H. McIntosh (3), M. James (4). Division of Haematology, Institute of Medical and Veterinary Science, Adelaide, South Australia, Australia (1), Department of Clinical and Experimental Pharmacology, University of Adelaide, South Australia, Australia (2), Division of Human Nutrition, C.S.I.R.O., South Australia, Australia (3) and Department of Surgery, Flinders Medical Centre, South Australia, Australia (4).

The antithrombotic effect of aspirin might be enhanced if platelet cyclooxygenase could be inhibited in the portal circulation while sparing cyclooxygenase in the systemic vascular endothelium. This might be achieved by modifying the dose and formulation to maximise presystemic aspirin clearance by the liver. To test this hypothesis low dose enteric coated aspirin (Astrix, 50mg single dose, 100mg single dose and 100mg daily for 1 week) was orally administered to pigs with permanent indwelling arterial and portal vein catheters. Plasma aspirin concentrations were measured by high performance liquid chromatography in blood obtained simultaneously from the artery and portal vein for 6 hours after dosage. Platelet aggregation and thromboxane generation were measured in 4 pigs before and after the 100mg chronic dosage regimen. Aortic prostacyclin production was measured in aspirin treated (100mg daily for 1 week) and untreated pigs after sacrifice. After the 50mg single dose the arterial:portal areas under the plasma concentration versus time curve (AUC) ratio was 0.63±0.09 (n=6). In 3 pigs which received all 3 dosage regimens the arterial:portal AUC ratios were 0.48±0.05 after 50mg single dose, 0.52±0.02 after 100mg single dose and 0.47±0.03 after 100mg daily for 1 week. Platelet aggregation in response to sodium arachidonate (1.65mM) was completely abolished after chronic aspirin administration. Thromboxane production (pg/10⁶ platelets) by this stimulus decreased from 536±117 before aspirin to 57±14 after aspirin (n=4; p=0.017). Aortic prostacyclin synthesis (ng/disc after 10 min incubation) was 1.66±0.28 (n=4) in untreated pigs and 0.97±0.25 (n=4) in treated pigs (p=0.06).

With this slow release aspirin formulation there was substantial but incomplete clearance of aspirin by the liver. This may not be sufficient to spare cyclooxygenase in the systemic vessels from the effect of aspirin.

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EFFECT OF ASPIRIN AND ASPIRIN COMBINED WITH DIPYRIDAMOLE IN EARLY DIABETIC RETINOPATHY. M. Samama (1), C.E. Baudoin (2) for the DAMAD Study Group. Laboratoire Central d'Hématologie, Hôtel-Dieu, Paris (1) and INSERM, Villejuif (2), France.

In a double blind randomised controlled clinical trial the effect of antiplatelet agents (aspirin 330 mg x 3 x day) or in combination with dipyridamole (75 mg 3 x day) versus placebo, was tested in 475 patients with early diabetic retinopathy. Patients were followed fourmonthly for 3 years. Ophthalmological examinations were carried out initially and at yearly intervals. The assessment of retinopathy was based on changes in the number of microaneurysms (MA) present in the macular field as seen on fluorescein angiograms over a period of three years. Forty one patients did not complete the study. Among the others at least three readable initial and yearly angiograms were available on 420 patients who had a 3 year follow up (266 insulin treated and 154 non insulin treated). The results are based on these patients.

Comparison of the progression of microaneurysms between treatment groups (mean ± SD (n))

	NIT	IT	TOTAL
P	1.41 ± 3.74 (48)	1.46 ± 4.88 (85)	1.44 ± 4.49 (133)
A	0.75 ± 5.85 (54)	0.65 ± 4.63 (91)	0.69 ± 5.09 (145)
A/D	0.37 ± 1.90 (52)	0.33 ± 3.52 (90)	0.34 ± 3.01 (142)
TOTAL	0.83 ± 4.19 (154)	0.80 ± 4.38 (266)	0.81 ± 4.30 (420)

Aspirin versus Aspirin/dipyridamole : F¹₄₁₆ = 0.46 NS
 Aspirin plus Aspirin/dipyridamole versus placebo : F¹₄₁₆ = 4.21
 p=0.04

It is concluded that either Aspirin alone or in conjunction with dipyridamole significantly slows down the progression of MA evolution in early diabetic retinopathy. Because of the very small, although significant changes, the clinical relevance of these drugs has not been established.

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Effects of intermittent dosage of ASA on the increased in vivo formation of thromboxane during acute myocardial infarction. Vesterqvist, O(1), Rasmanis, G(2), Henriksson, P(2), Edhag, O(2) and Green, K(1). Department of Clinical Chemistry, Karolinska Hospital, Stockholm(1) and Department of Medicine, Huddinge Hospital, Huddinge(2), SWEDEN.

We have earlier demonstrated considerable increase of the in vivo formation of thromboxane (Tx) in connection with myocardial infarction (AMI). The in vivo formation of prostacyclin (PGI) was also increased, in some cases very much so, with a maximum after the CK peak. In normals ASA reduces the in vivo Tx synthesis to about 15% for several days while the PGI synthesis is only inhibited for 2-3 hrs. The in vivo synthesis of these prostanoids was measured by gas chromatographic mass spectrometric quantitation of the major urinary metabolites. In a serie of twenty patients with AMI we measured the in vivo synthesis of Tx and PGI during seven consecutive days. Ten patients received 0.5 g ASA every third day. In the nontreated group the Tx synthesis slowly decreased to about 70%, in the treated group to about 25% on day 3 as compared to the synthesis at admission. There was no difference in the in vivo synthesis of PGI between the two groups.

	admission	day1	day3
In vivo Tx synthesis	100%	42%	27%
ASA	100%	64%	73%
In vivo PGI synthesis	100%	94%	32%
ASA	100%	99%	29%

These data demonstrate that in most individuals with AMI it is possible to inhibit Tx synthesis considerably with intermittent dosages of 0.5g ASA while the PGI synthesis is essentially maintained intact. Therefore this regimen should be more beneficial to the patient than daily doses of any magnitude.