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THE EFFECT OF PROLONGED TREATMENT WITH SULPHINPYRAZONE ON THROMBOXANE A_2 AND PROSTACYCLIN IN MAN

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We studied the effect of 3 weeks' treatment with 4 × 200 mg of sulphinpyrazone daily (six healthy volunteers) on proaggregatory thromboxane A_2 (TxA_2) and antiaggregatory prostacyclin (PGI_2). Platelet TxA_2 production was evaluated by measuring its stable metabolite, immunoreactive thromboxane B_2, from serum, and vessel wall PGI_2 production by measuring its stable metabolite, immunoreactive 6-keto-prostaglandin $F_{1\alpha}$ in plasma. The TxA_2 production (initially 209.0 ± 27.1 ng/ml, mean ± s.e. mean) decreased to about 30% from the second day of the treatment onwards, and it recovered in three days after the discontinuation of the treatment. PGI_2 (initially 33.6 ± 3.6 pg/ml) did not change. The shift of the balance between TxA_2 and PGI_2 to the dominance of antiaggregatory PGI_2 during sulphinpyrazone treatment may be involved with the efficacy of the drug in the secondary prevention of myocardial infarction.

Introduction

Sulphinpyrazone, which originally was developed for the treatment of gout, has proved to be an effective drug also in the secondary prevention of myocardial infarction, although the mechanism of this action is not known (The Anturane Reinfarction Trial Research Group, 1978, 1980; The Anturan Reinfarction Italian Study Group, 1982). Because platelet activation takes place during cardiac ischaemia (Haerem, 1971; Kumpuris *et al.*, 1980; Green *et al.*, 1980), the known effects of sulphinpyrazone on platelets (Smythe *et al.*, 1965; Mustard *et al.*, 1967) may, however, be involved. We studied the effects of sulphinpyrazone on proaggregatory thromboxane A_2 (TxA_2) (Hamberg *et al.*, 1975) and antiaggregatory prostacyclin (PGI_2) (Moncada *et al.*, 1976; Johnson *et al.*, 1976), the balance of which potently regulates platelet function (Moncada & Vane, 1979).

Methods

We performed this study with six healthy non-smoking volunteers (three females, three males) aged 21–23 years. They were asked to refrain from all medications, other than the study treatments, 2 weeks before and during the trial. On the first 2 days of the experiment the volunteers ingested four placebo tablets, on days 3–22 four times 200 mg of sulphinpyrazone and on days 23–26 again placebo. Blood samples were drawn at 08.00 h on days 1 and 2 (basal samples), 3 (the first day of sulphinpyrazone, 1 h after ingesting the first 200 mg dose), 4, 5, 8, 12, 17, 22 (the last day of sulphinpyrazone), 23, 24, 25 and 26.

Platelet TxA_2 production was evaluated by measuring its stable metabolite, immunoreactive thromboxane B_2 (i TxB_2) (Hamberg *et al.*, 1975) in serum from blood having clotted at 37°C for 60 min (Viinikka & Ylikorkala, 1980). The amount of i TxB_2 formed in these circumstances correlates well with i TxB_2 generated during induced aggregation in platelet rich plasma (Viinikka & Ylikorkala, 1980). PGI_2 production was determined by assaying its stable metabolite, immunoreactive 6-keto-prostaglandin $F_{1\alpha}$ (i 6-keto-$PGF_{1\alpha}$) (Johnson *et al.*, 1976) in plasma obtained from blood, which was collected into ice-cold heparinized tubes containing indomethacin (10 μmol/l, final concentration) (Ylikorkala *et al.*, 1981).

Student's *t*-test for paired observations was used for the statistical analysis of the results.

Results

The generation of i TxB_2 by platelets during spontaneous clotting was decreased to about 60% of the initial value in the sample taken 1 h after the first dose

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of sulphinpyrazone. From the second day of the treatment onwards, i TxB_2 production remained on about 30% level of the initial and it recovered in 3 days after the discontinuation of sulphinpyrazone treatment. Plasma i 6-keto-$PGF_{1\alpha}$ did not change (Figure 1).

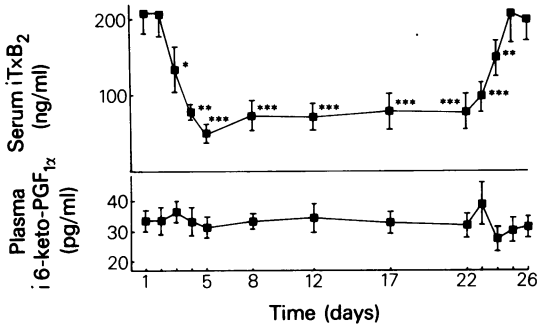

Figure 1 Serum i TxB_2 (mean ± s.e. mean) and plasma i 6-keto-$PGF_{1\alpha}$ before, during and after treatment with sulphinpyrazone. Six volunteers ingested 4 × 200 mg of the drug on days 3–22 and four placebo tablets daily on days 1–2 and 23–26. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$ in comparison with the initial level.

Discussion

Increased amounts of TxA_2 are released from activated platelets during cardiac ischaemia (Lewy *et al.*, 1980; Hirsh *et al.*, 1981; Neri Serneri *et al.*, 1981). The increased TxA_2 may further reduce the oxygen delivery of hypoxic myocardium by coronary vasoconstriction and mechanical obstruction of coronary vessels by platelet aggregates. The correlation between the concentration of i TxB_2 in coronary sinus and ventricular ectopic activity (Coker *et al.*, 1981) and the beneficial effects of the inhibition of TxA_2 synthesis in experimental infarction (Smith *et al.*, 1980; Coker & Parratt, 1981; Moschos *et al.*, 1981) further suggest the significance of TxA_2 in myocardial ischaemia. Thus, it is justified to presume that treatments, which decrease TxA_2 synthesis, might also have beneficial effects in myocardial ischaemia.

The data about the effect of sulphinpyrazone on the production of TxA_2 are scanty. Lorenz *et al.* (1981) showed that the generation of i TxA_2 was decreased after four day treatment with sulphinpyrazone. We present here the first data on the effects of long-term sulphinpyrazone treatment and they show that sulphinpyrazone, as applied in the secondary prevention of myocardial infarction (The Anturane Reinfarction Trial Research Group, 1978, 1980), inhibited more than half of the capacity of platelets to produce TxA_2 in response to thrombin induced aggregation during spontaneous clotting. The inhibition of TxA_2 generation was seen as late as 36 h after the ingestion of the last dose. This supports the hypothesis that sulphinpyrazone is metabolized into a long-acting active metabolite (McDonald *et al.*, 1980).

The data about the effect of sulphinpyrazone on PGI_2 production are scanty, too. Gordon & Pearson (1978) showed that 1 mmol/l of sulphinpyrazone had no effect on porcine endothelial cell PGI_2 production, and Livio *et al.* (1980) found no inhibition of PGI_2-like activity after the administration of 200 mg/kg of sulphinpyrazone into rats. Our data suggests that like in other species, the PGI_2 production also in human is resistant to the action of sulphinpyrazone.

The inhibition of platelet TxA_2 production could theoretically be the result of inhibition of cyclo-oxygenase or of thromboxane synthetase (Moncada & Vane, 1979). The findings that sulphinpyrazone was able to inhibit also the synthesis of other prostaglandins, and that it antagonized the irreversible inhibition of platelet cyclo-oxygenase by acetylsalicylic acid (Ali *et al.*, 1977; McDonald *et al.*, 1980), however, show that cyclo-oxygenase is the target of the action of sulphinpyrazone in the arachidonate cascade. The decreased TxA_2 production together with unchanged PGI_2 generation during sulphinpyrazone treatment seen in this study suggest that human platelet cyclo-oxygenase is more sensitive to the action of the drug than is endothelial cell cyclo-oxygenase. The mechanism of this difference remains, however, to be studied.

In conclusion, our data suggest that during prolonged treatment with sulphinpyrazone the balance between TxA_2 and PGI_2 is shifted to the direction of antiaggregatory, vasodilatory PGI_2. Because this change is likely to be favourable in coronary artery disease, we presume that the reduction of cardiac mortality in the secondary prevention of myocardial infarction by sulphinpyrazone might have been mediated through inhibition of TxA_2 synthesis.

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