EVIDENCE FOR A DUAL ACTION OF SULPHINPYRAZONE ON DRUG METABOLISM IN MAN: THEOPHYLLINE-SULPHINPYRAZONE INTERACTION

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The effects of sulphinpyrazone administration on the metabolic and renal clearances of theophylline in man were investigated. Sulphinpyrazone increased total plasma theophylline clearance by 22%. This was the sum of increases in metabolic clearances by 3-demethylation (32%), 1-demethylation (30%) and 8-oxidation (22%) and of a decrease in renal clearance (27%). It is proposed that sulphinpyrazone has differential effects on at least two forms of cytochrome P-450 inhibiting one enzyme or group of enzymes which metabolises tolbutamide, phenytoin and S(-)warfarin and inducing a form (or forms) which metabolises theophylline, antipyrine and R(+)warfarin.

Introduction

Sulphinpyrazone is a structural analogue of phenylbutazone with uricosuric, antithrombotic and anti-platelet effects. Like phenylbutazone, sulphinpyrazone is a potent inhibitor of the oxidative metabolism of the S(-)enantiomer of warfarin (Bailey & Reddy, 1980; Gallus & Birkett, 1980; O'Reilly, 1982), tolbutamide (Miners *et al.*, 1982a) and phenytoin (Hansen *et al.*, 1980). In contrast to these effects, induction of antipyrine metabolism by sulphinpyrazone has been reported (Walter *et al.*, 1981).

In a series of studies (Birkett *et al.*, 1983; Grygiel & Birkett, 1980, 1981; Grygiel *et al.*, 1979) we have previously shown that theophylline (1,3-dimethylxanthine) is eliminated by demethylations in the 1- or 3-positions to 3-methylxanthine (3MX) and 1-methylxanthine (1MX) respectively, and by 8-oxidation to 1,3-dimethyluric acid (1,3DMU). 1MX is rapidly converted to 1-methyluric acid (1MU) by xanthine oxidase. We also suggested that the two demethylations may be under different regulatory control to the 8-oxidation (Birkett *et al.*, 1982; Grygiel & Birkett, 1980). In this study we have investigated the effects of sulphinpyrazone on the individual metabolic and renal clearances of theophylline to define further its metabolic effects in man.

Methods

Protocol

The subjects were six non-smoking male volunteers aged 20 to 33 years who were healthy as determined

by medical history, physical examination and standard biochemical and haematological parameters. No medications other than those supplied for the study were taken for 1 week before or during each study and subjects abstained from tea, coffee, cocoa, chocolate and cola drinks for 3 days prior to and during each study. The study was approved by the Clinical Investigation Committee of Flinders Medical Centre.

On two separate occasions the subjects took theophylline 125 mg 8 hourly for 4 days. On day 4 of each study, venous blood samples (5 ml) were collected through an indwelling intravenous cannula in a forearm vein prior to and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6 and 8 h after the morning dose. The cannula was maintained patent by injection of 0.5 ml isotonic sodium chloride solution containing heparin 5 units/ml after each sample. Total urine was collected over the 8 h dosage interval after the morning dose. Sulphinpyrazone, 200 mg, 6 hourly, was administered for 3 days prior to and during the second theophylline study (i.e. for a total of 7 days). The two theophylline studies were separated by a period of at least 2 weeks.

Analytical procedures

Plasma was separated and stored at -20°C until assayed. Urine was stored at -20°C until assayed for theophylline but theophylline metabolites (1MU, 1MX, 3MX and 1,3DMU) were measured on the day of urine collection. High performance liquid chromatographic (h.p.l.c.) procedures were used for the determination of plasma and urine theophylline concentrations (Foenander *et al.*, 1980) and for urine

concentrations of theophylline metabolites (Grygiel *et al.*, 1979). Plasma sulphinpyrazone concentrations were also measured by h.p.l.c. (Miners *et al.*, 1982b).

Analysis of results

Area under the plasma theophylline concentration-time curve (AUC) was calculated by the trapezoidal rule and plasma theophylline clearance (CL_p) was determined as:

$$CL_p = \text{dose/AUC} \times \text{body weight (kg)}$$

Recoveries of theophylline products in urine were $87 \pm 2\%$ in the control phase and $86.4 \pm 6.5\%$ in the sulphinpyrazone phase. Individual metabolic and renal clearances of theophylline were calculated as:

$$CL_i = fi \times CL_p$$

where CL_i is the metabolic clearance to 1MU (CL_{1MU}), 3MX (CL_{3MX}) or 1,3DMU (CL_{DMU}) or the renal clearance of unchanged theophylline (CL_R) and fi is the fractional recovery of each product compared to total recovery of theophylline plus metabolites. Results are expressed as means $\pm$ s.e. mean and Student's *t*-test for paired samples was used to assess the significance of differences between study phases.

Results

Table 1 shows the effects of sulphinpyrazone administration on total plasma theophylline clearance and on the individual metabolic and renal clearances of theophylline. Plasma theophylline clearance was increased by 22% ($P < 0.025$) by sulphinpyrazone. This was due to increases in CL_{3MX} (30%, $P < 0.01$), CL_{1MU} (32%, $P < 0.005$) and CL_{DMU} (22%, $P < 0.025$). The increases in metabolic clearance were partly offset by a decrease in renal clearance of 27%

($P < 0.005$). Sulphinpyrazone plasma concentrations were measured prior to the last theophylline dose (taken at the same time as a sulphinpyrazone dose) and at 2 h after the doses and were 9.7 ± 1.7 mg/l and 19.5 ± 2.2 mg/l respectively.

Discussion

In all subjects sulphinpyrazone caused an increase in plasma theophylline clearance which ranged from 8.5–42%. This was due to induction of each of the individual metabolic clearances offset to a small extent by a reduction in the renal clearance of unchanged theophylline.

It is now clear that sulphinpyrazone has two quite distinct effects on oxidative drug metabolism in man. The metabolic clearances of tolbutamide (Miners *et al.*, 1982a), S(-)-warfarin (Miners *et al.*, 1982b; O'Reilly, 1982), and phenytoin (Hansen *et al.*, 1980) are inhibited by sulphinpyrazone whereas the total plasma clearances of antipyrine (Walter *et al.*, 1981) and R(+)-warfarin (O'Reilly, 1982) and the individual metabolic clearances of theophylline (this study) are all induced.

Two further inhibitory agents show a similar pattern of effects to that described above for sulphinpyrazone. Phenylbutazone inhibits the oxidative metabolism of S(-)-warfarin (Lewis *et al.*, 1974; O'Reilly *et al.*, 1980) and tolbutamide (Pond *et al.*, 1977) but has been reported to increase the elimination rate of R(+)-warfarin (Lewis *et al.*, 1974; O'Reilly *et al.*, 1980) and aminopyrine (Chen *et al.*, 1962). Sulphaphenazole is inhibitory towards tolbutamide (Pond *et al.*, 1977) and phenytoin (Skovsted *et al.*, 1974) but has no effect on plasma theophylline clearance (unpublished observation).

The most likely explanation to account for these dual effects is the presence of at least two forms of

Table 1 Effects of sulphinpyrazone on the metabolic and renal clearances of theophylline

Subject	Weight (kg)	CL_p^1		CL_{1MU}		CL_{3MX}		CL_{DMU}		CL_R	
		T^2	TS^2	T	TS	T	TS	T	TS	T	TS
1	91.3	24.5	26.7	5.0	6.4	2.6	3.9	13.0	13.6	3.9	2.8
2	78.1	63.4	68.8	16.7	19.1	10.6	11.6	32.3	35.1	3.9	3.0
3	91.3	26.9	36.1	5.5	8.8	3.5	5.5	15.6	19.6	2.3	2.2
4	79.9	68.9	82.2	19.8	22.4	12.2	15.5	33.2	41.4	3.7	2.9
5	83.2	43.9	56.3	10.8	17.3	9.3	11.4	21.3	26.1	2.5	1.4
6	65.6	43.4	61.5	11.0	17.4	7.6	11.4	21.2	30.7	3.4	2.0
Mean	81.6	45.2	55.3	11.5	15.2	7.6	9.9	22.8	27.8	3.3	2.4
s.e. mean	3.9	8.2	9.2	2.6	2.8	1.7	1.9	3.7	4.6	0.3	0.3
<i>P</i>		0.025		0.01		0.005		0.025		0.005	

¹units of clearance are $\text{ml h}^{-1} \text{kg}^{-1}$

²T - theophylline alone; TS - theophylline plus sulphinpyrazone

cytochrome P-450. One is inhibited by sulphinpyrazone, phenylbutazone and sulphaphenazole and plays a major role in the metabolic clearance of tolbutamide, S(-)-warfarin and phenytoin. The other form or forms plays a major role in the metabolic clearance of theophylline, antipyrine and possibly aminopyrine, and is induced by sulphinpyrazone and phenylbutazone but not affected by sulphaphenazole. The relationship of the inhibitory and inductive effects of sulphinpyrazone to the form of cytochrome P-450 involved in debrisoquine and sparteine oxidation is currently being investigated in our laboratory.

The small but statistically significant reduction of

theophylline renal clearance by sulphinpyrazone is interesting as such an effect has not been previously reported. Although theophylline renal clearance is known to be dependent on urine flow rate there was no difference in urine output during the control (323 ± 24 ml/8 h) and sulphinpyrazone (353 ± 35 ml/8 h) phases. A possible mechanism for this effect is that theophylline, a weak acid, may undergo active tubular secretion which is inhibited by sulphinpyrazone.

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