PHARMACOKINETICS OF SINGLE DOSES OF SULPHINPYRAZONE AND ITS MAJOR METABOLITES IN PLASMA AND URINE

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- 1 High pressure liquid chromatographic assays for the estimation of sulphinpyrazone and its sulphide, sulphone and *p*-hydroxy metabolites in plasma and urine are described.
- 2 Five normal volunteers received 200 mg and 400 mg sulphinpyrazone orally. Sulphinpyrazone was rapidly absorbed and eliminated with a half-life of approximately 4 h irrespective of dose. Peak plasma concentrations and area under the plasma concentration-time curves (AUC) were consistent with linear pharmacokinetic behaviour.
- 3 Plasma concentrations of the sulphone were low and peaked before those of the sulphide; its mean half-life was 3.1 h. The sulphide, which may be the sulphinpyrazone metabolite with activity on platelets, was eliminated with a mean half-life of 13.4 h. The AUC increases with dose of both metabolites suggested non-linearity.
- 4 Approximately 45–50% of the administered dose was eliminated in the urine as unchanged drug or as sulphone or *p*-hydroxy-sulphinpyrazone. The sulphide metabolite was not detected in the urine. The renal clearance of sulphinpyrazone was approximately 18 ml min⁻¹ and that for the sulphone was similar. Sigma minus plots of the urinary excretion yielded half-lives of 3.5 h for the sulphone and 1 h for *p*-hydroxy-sulphinpyrazone.

Introduction

Sulphinpyrazone, a potent uricosuric, has been used in the treatment of gout since 1959. Recently interest has centred upon its anti-thrombotic properties since it prevents thrombosis in arterio-venous shunts in patients undergoing chronic haemodialysis (Kaegi *et al.*, 1974), reduces systemic embolism in patients with rheumatic heart disease (Steele & Rainwater, 1980) and possibly has some value in the secondary prevention of myocardial infarction (Anturane Reinfarction Trial Research Group, 1980). Its kinetics have been fairly well studied although the relationship between the plasma sulphinpyrazone concentration and its effects on platelet function *in vivo* are not well understood. Recently some active metabolites of sulphinpyrazone have been identified. Buchanan *et al.* (1978) found that in rabbits treated with high doses of sulphinpyrazone inhibition of platelet aggregation persisted for a much longer period than the presence of sulphinpyrazone in the plasma would suggest. It was thus predicted that the plasma contained substance(s), probably a sulphinpyrazone metabolite, with anti-thrombotic activity. Kirstein Pedersen & Jacobsen (1979) identified sulphone and sulphide and

hydroxy-sulphide metabolites in rabbit plasma following sulphinpyrazone administration and showed that the sulphide had a long plasma half-life. The sulphide also exhibited more potency in inhibiting collagen-induced aggregation of human platelets than the parent compound. It has therefore been suggested that this metabolite is responsible for much of the effect of sulphinpyrazone on platelets *in vivo*. Preliminary *in vivo* data in man suggested that the anti-platelet effect built up more slowly when multiple doses of 200 mg sulphinpyrazone were given four times daily as compared to the administration of 400 mg twice daily (Butler *et al.*, 1980). This observation would suggest that the formation of the active metabolite from sulphinpyrazone may not occur via first-order pharmacokinetic processes and that the rate and extent of metabolite formation and/or elimination may be dose-dependent.

The present study has investigated the plasma pharmacokinetics of sulphinpyrazone (1,2-diphenyl-3,5-dioxo-4-(2'-phenylsulphonyl)ethyl-pyrazolidine; G 28,315) and its sulphide (1,2-diphenyl-3,5-dioxo-4-(2'-phenylsulphethyl)pyrazolidine; G 25,671) and

sulphone (1,2-diphenyl-3,5-dioxo-4-(2'-phenylsulphonyl-ethyl)-pyrazolidine; G 31,442) metabolites following single oral doses of 200 mg and 400 mg sulphinpyrazone. The urinary elimination of unchanged drug, sulphone and parahydroxysulphinpyrazone (1-phenyl-2-(p-hydroxyphenyl)-3,5-dioxo-4-(2'-phenylsulphonyl-ethyl)-pyrazolidine; G 32, 642) were also investigated. High pressure liquid chromatographic techniques for the estimation of all of these compounds in biological fluids are also described.

Methods

1. Study protocol

Five normal volunteers (three males aged 26 years, weighing 64, 73 and 76 kg; two females aged 33 and 39 years, weighing 58 and 52 kg) gave informed consent to take part in the study, the protocol of which had been approved by the Guy's Hospital Ethical Committee. All were ascertained to have normal values on routine biochemical and haematological testing prior to enrolment. Females also had negative pregnancy tests. They received 200 mg and 400 mg doses of sulphinpyrazone as commercial Anturan (Geigy Pharmaceuticals Ltd) 200 mg tablets in random order at intervals separated by not less than one week. The subjects took no other drugs during the period of the investigation and kept alcohol intake to a minimum between studies and abstained completely during the sample collection periods.

The subjects fasted for at least 12 h overnight prior to each study day. The tablets were administered at 09.00 h and taken with 100 ml water. Light standardised meals were given at 4 and 10 h after dosing. For the first 12 h of the study volunteers were given 200 ml water every 2 h. Blood samples (20 ml) for drug and metabolite estimations were drawn by venepuncture immediately before dosing and at 1, 2, 3, 5, 7, 9, 12, 24, 30, 36, 48 and 56 h thereafter, and placed into heparinised tubes. Samples were centrifuged immediately and the plasma isolated and stored at -20°C . Total urine voided over 0-2, 2-4, 4-6, 6-8, 8-12, 12-24, 24-36, 36-48 and 48-56 h post dosing was collected and the volumes recorded. No attempt was made to control urine pH nor was the pH of individual samples measured. Aliquots (20 ml) were taken for drug and metabolite estimations and stored at -20°C until analysed.

2. Analytical

(a) *Reagents and materials* Sulphinpyrazone and its metabolites were a gift from Ciba-Geigy Pharmaceuticals (Horsham, England). The internal standard, fenbufen (3-(4-biphenyl carbonyl) propionic acid), was a gift from Cyanamid (GB) Ltd, (Gosport,

England). All solvents and reagents were of analytical grade. All glassware used during the sample preparation was silanised before use.

(b) Sample preparation

i. *Plasma* Plasma (0.5 ml) was placed in a 10 ml glass stoppered tube and 20 μl of the internal standard solution (100 $\mu\text{g}/\text{ml}$ methanolic solution of 3-(4-biphenyl carbonyl) propionic acid), 1 ml of 1N HCl and 1.5 ml of the extraction solvent (1-chlorobutane : dichloroethane, mixed in 4:1 proportions) was added. The samples were extracted by vortex mixing for 20 s then centrifuged at 1000 g for 10 min to separate the aqueous and organic phases. The organic phase was transferred to a conical glass centrifuge tube and 200 μl of 0.1N NaOH were added. The tube was vortex mixed for 20 s then centrifuged for 2 min after 500 g. The lower aqueous phase (50 μl) was injected into the chromatograph.

ii. *Urine: sulphinpyrazone, sulphone and p-hydroxysulphinpyrazone* To 100 μl urine in a 2 ml glass tube was added 400 μl of distilled water. 50 μl of the solution were injected into the chromatograph. Sulphide in urine was extracted as for plasma except that a 0.2 ml sample of urine was used.

(c) *Chromatography* The high performance liquid chromatograph consisted of a LDC Consta Metric II G delivery pump (Laboratory Data Control, Stone, England) equipped with a Rheodyne 7010 injection valve and fitted with a Magnus Magnosphere C_{18} reversed phase column (15 $\times$ 0.4 cm i.d., particle size 5 μm) (Magnus Scientific, Sandbach, England). The absorbance was measured at 260 nm using a Pye LC-UV variable wavelength detector (Pye Unicam, Cambridge, England). For the analysis of plasma samples the mobile phase consisted of a mixture of 0.05 M ammonium phosphate buffer (pH 5.2) and methanol (68:32). The flow rate was 1.8 ml min $^{-1}$. For the analysis of the sulphide metabolite in urine the same mobile phase was used. For the analysis of sulphinpyrazone, sulphone and p-hydroxysulphinpyrazone from urine the mobile phase used was a mixture of 0.05 M ammonium phosphate buffer (pH 5.2) and methanol (70:30). The flow rate was 1.5 ml min $^{-1}$.

(d) Calibration and reproducibility

i. *Plasma* Calibration curves were constructed by adding known amounts of sulphinpyrazone and its metabolites to plasma and plotting the ratio of the peak height of sulphinpyrazone or metabolite to internal standard against the amounts added. The reproducibility of the method was studied by subjecting six replicate plasma samples containing 1, 5, 10 and 20 $\mu\text{g}/\text{ml}$ sulphinpyrazone to the entire procedure. The same procedure was followed for the

sulphone and sulphide metabolites excepting that concentrations of 0.5, 1.0, 2.0 and 10.0 $\mu\text{g/ml}$ were examined.

ii Urine Calibration curves were constructed by adding known amounts of sulphinpyrazone, sulphone and *p*-hydroxysulphinpyrazone to blank urine and plotting the peak heights against the amounts added. Calibration curves for the sulphide were made separately by a similar procedure using the extraction procedures outlined above.

The reproducibility of the methods was examined using six replicate samples containing 20, 100, 200 and 500 $\mu\text{g/ml}$ of sulphinpyrazone and 5, 10, 20 and 50 $\mu\text{g/ml}$ of the metabolites.

To estimate the extraction recoveries, the peak heights of analysed samples containing known amounts of sulphinpyrazone and the metabolites were compared to the respective peak heights obtained by injecting the pure substances directly into the chromatograph.

3. Pharmacokinetic analysis

The plasma concentration-time data for sulphinpyrazone was resolved into its component exponential

phases by a curve stripping program (Brown & Manno, 1978). In all cases a three-exponential fit yielded the most favourable coefficient of determination. This corresponds to a two compartment open pharmacokinetic model with first order absorption as expressed by

$$C_p^t = Ae^{-\alpha(t-t')} + Be^{-\beta(t-t')} - (A + B)e^{-k_a(t-t')}$$

where C_p^t is the plasma concentration at time t ; A and B are coefficients with units of concentration; α is the apparent first order distribution rate constant; β is the apparent first order disposition rate constant; k_a is the apparent first order absorption rate constant; t' is the lag time before drug appears in the plasma. Addition of a further compartment in the analysis of our data decreased the coefficient of determination (in contrast to the analysis of data following intravenous injection of sulphinpyrazone by Lecaillon *et al.*, 1979). The plasma $T_{1/2}\beta$ was calculated from

$$T_{1/2} = \frac{0.693}{\beta}.$$

Areas under the plasma concentration, time curve (AUC) were calculated using the linear trapezoidal

Figure 1 Chromatograms from plasma (detector response 0.02 a.u.f.s.) **a** blank; **b** plasma containing 1, sulphone ($1 \mu\text{g ml}^{-1}$); 2, sulphinpyrazone ($5 \mu\text{g ml}^{-1}$); 3, internal standard; 4, sulphide ($2 \mu\text{g ml}^{-1}$), and urine (detector response 0.04 a.u.f.s.); **c** blank; **d** urine containing 1, *p*-hydroxysulphinpyrazone ($10 \mu\text{g ml}^{-1}$); 2, sulphone ($10 \mu\text{g ml}^{-1}$); 3, sulphinpyrazone ($100 \mu\text{g ml}^{-1}$). In each chromatogram the injection peak is at the right-hand side.

rule with the addition of the correction C_p^{last}/β for the infinite portion of the curve where C_p^{last} is the last estimated plasma concentration.

In the case of the metabolites detailed analysis of the plasma concentration data was not possible because of the low levels found. The first order elimination rate constants (k) were determined by linear regression of $\ln$ (plasma concentration) with time. The $T_{1/2}$ was found from

$$T_{1/2} = \frac{0.693}{k}.$$

AUCs were approximated as before by the linear trapezoidal rule.

A model independent estimate of the steady state apparent volume of distribution V_{dss} was made by the method of Benet & Galeazzi (1979) where

$$V_{dss} = \frac{\text{Dose (AUMC}_{0 \rightarrow \infty})}{(\text{AUC}_{0 \rightarrow \infty})^2}$$

where (AUMC) is the area under the first moment of the plasma curve, i.e.

$$\int_0^{t_{\text{last}}} t C_p dt + \frac{t_{\text{last}} C_p^{\text{last}}}{\beta} + \frac{C_p^{\text{last}}}{\beta^2}.$$

The renal clearance of sulphinpyrazone and its metabolites was assessed from

$$Cl = \frac{X_u^{\infty}}{(\text{AUC})}$$

where X_u^{∞} is the total amount of drug excreted in the urine. Urinary excretion rate data was analysed by the one compartment sigma minus method (Gibaldi & Perrier, 1975).

Results

Using the extraction technique, based upon that of Lecaillon & Souppart (1976) and described above, extraction efficiencies of 70–80% were obtained for sulphinpyrazone and its sulphone and sulphide metabolites. Parahydroxysulphinpyrazone is poorly extracted by this technique and was not estimated in the plasma in this study. The limits of sensitivity were $0.1 \mu\text{g ml}^{-1}$ for sulphinpyrazone and its metabolites in plasma and $0.3 \mu\text{g ml}^{-1}$ in the urine.

Figure 1 shows representative chromatograms for blank plasma and plasma containing added amounts of sulphinpyrazone, sulphone and sulphide. Figure 1 shows representative chromatograms for blank urine and urine containing sulphinpyrazone and the sulphone and *p*-hydroxysulphinpyrazone metabolites. No endogenous compounds were found to interfere with the assay in either plasma or urine.

Table 1 Reproducibility studies ($n = 6$) for estimation of the concentration of sulphinpyrazone and its metabolites in plasma and urine

Drug		Concentration ($\mu\text{g ml}^{-1}$)	Coefficient of variation (%)
1. Plasma	Sulphinpyrazone	1	5.1
		5	4.7
		10	4.5
		20	3.9
		50	6.6
	Sulphone	0.5	6.3
		1	5.8
		2	5.9
		10	5.7
		50	6.6
	Sulphide	0.5	6.0
		1	6.1
		2	5.5
		10	5.6
		50	6.6
2. Urine	Sulphinpyrazone	20	6.8
		100	6.4
		200	3.9
		500	6.6
		1000	6.6
	Sulphone	5	6.4
		10	9.1
		20	6.0
		50	5.2
		100	5.2
	<i>p</i> -hydroxysulphinpyrazone	5	3.9
		10	4.5
		20	3.8
		50	3.2
		100	3.2

Figure 2 Plasma concentration-time profiles for sulphinpyrazone (●), sulphide (○) and sulphone (■) in a 39 year old female weighing 52 kg after receiving 200 mg (a) and 400 mg (b) sulphinpyrazone orally.

Table 1 summarises the results of the reproducibility studies from plasma and urine.

Sulphinpyrazone was rapidly absorbed following oral administration. Mean maximum plasma concentrations of $19.5 \mu\text{g ml}^{-1}$ and $42.3 \mu\text{g ml}^{-1}$ were found for the 200 mg and 400 mg doses respectively. The mean ratio of these values was 2.2. Figure 2 shows representative plasma concentration, time profiles for sulphinpyrazone and its sulphide and sulphone in one of the subjects. Table 2 details some pharmacokinetic parameters for sulphinpyrazone. The estimates of β , $T_{1/2}\beta$ and V_{dss} were similar at the two dose levels.

Table 3 details some pharmacokinetic parameters derived from the plasma concentrations of the

sulphide and sulphone metabolite of sulphinpyrazone. As found by Dieterle *et al.* (1980) the levels of sulphone were low and peaked earlier than the sulphide at about 2–3 h. The peak plasma concentrations of sulphide developed at about 13–16 h. The AUCs of the sulphide (a metabolite with putative therapeutic action on platelets—Kirstein Pedersen & Jacobsen, 1979; Pay *et al.*, 1980) show marked inter-individual variation. The ratios of AUCs after 200 and 400 mg would suggest a disproportionate formation of sulphide in some individuals. The mean $T_{1/2}$ of the sulphide was 13.4 h with a coefficient of variation of 30%. The pharmacokinetics of the sulphone in plasma can be studied only with difficulty after a single dose of 200 mg because of the low concentra-

Table 2 Some pharmacokinetic parameters for unchanged sulphinyprazole in plasma

Subject	β (h^{-1})		$T_{1/2}\beta$ (h)		$(AUC)_o^\infty$ ($\mu g\ ml^{-1}\ h$)		AUC_{400}	V_{dss} ($l\ kg^{-1}$)	
	200 mg	400 mg	200 mg	400 mg	200 mg	400 mg	AUC_{200}	200 mg	400 mg
1	0.246	0.175	2.82	3.96	47.1	103.5	2.1	0.18	0.20
2	0.203	0.146	3.41	3.75	49.1	112.7	2.3	0.21	0.21
3	0.196	0.126	3.54	5.50	93.0	166.4	1.8	0.13	0.19
4	0.177	0.197	3.92	3.52	95.2	271.3	2.9	0.17	0.13
5	0.132	0.168	5.25	4.13	113.8	305.4	2.7	0.23	0.16
Mean	0.191	0.162	3.79	4.17	79.6	191.9	2.4	0.18	0.18

tions developed and the $T_{1/2}$ cannot be accurately determined from our data. Utilising the results after the administration of the 400 mg dose, the $T_{1/2}$ was estimated to be 3.1 h.

Table 4 shows the urinary elimination of unchanged sulphinyprazole and its sulphone and parahydroxysulphinyprazole. Approximately 45% of the administered dose was recovered from the urine in these forms. Recovery was similar at the two dose levels. In no subject was the sulphide metabolite detected in the urine.

Table 5 summarises the results of sigma minus plots of the urinary excretion of sulphinyprazole and its sulphone and parahydroxy metabolites (the minimum correlation coefficient for these plots was 0.979). The renal clearance of unchanged sulphinyprazole and the sulphone appear in Table 6. The renal clearance of parahydroxysulphinyprazole could not be calculated in the absence of plasma concentrations of this substance.

Discussion

The $T_{1/2}$ of sulphinyprazole found in our subjects may be compared with the $T_{1/2}$ values of 3.9 ± 0.7 (s.d.) h and 3.8 ± 0.6 h derived by Lecaillon *et al.* (1979) for single oral doses of 200 mg and 400 mg in normal volunteers. Other published estimates of the plasma $T_{1/2}$ of sulphinyprazole include 4.29 ± 0.28 h in 10 normal males (Kadar *et al.*, 1973) and 3.5 h for ten normal subjects (Senczuk & Jodynis-Liebert, 1979), both estimates being made from studies of urinary elimination kinetics. Shorter half-lives, 2.2 and 2.7 h, were found in two normal males given radiolabelled sulphinyprazole by Dieterle *et al.* (1975). The estimated AUCs were also comparable with the data of Lecaillon *et al.* (1979) who found $89.2 \pm 23.0\ \mu g\ ml^{-1}\ h$ for a 200 mg oral dose and $204.3 \pm 113\ \mu g\ ml^{-1}\ h$ for 400 mg. The ratio of the AUCs at the two doses was overall 2.4 (c.f. 2.07 derived by Lecaillon *et al.*, 1979). However, the wider inter-individual variation will be noted. Taken together

with the effect of dose on the maximum plasma concentration the data would suggest that over this dose range there is no marked deviation from first-order kinetics.

Dieterle *et al.* (1975) showed that sulphinyprazole was completely absorbed following oral administration of the radio-labelled crystalline solid in a gelatine capsule. No bioavailability studies of film-coated tablets (such as Anturan®) with reference to intravenous drug administration have been published. Nevertheless, it was felt justified to assume complete absorption from this formulation and to estimate the apparent volume of distribution. Our estimate is larger than that of Lecaillon *et al.* (1979) who found a V_d of $0.06\ l\ kg^{-1}$ but their estimate is dependent upon the assumption of a three-compartment model. We have used a model independent estimation of V_{dss} to find a mean apparent volume of distribution of 0.18 l/kg. Ritschel & Hammer (1980) predicted a V_d of 0.12 l/kg from the extent of protein binding and the octanol/water partition coefficient.

The mean $T_{1/2}$ of the sulphide metabolite was found to be 13.4 h with a coefficient of variation of approximately 30%. The study of Dieterle *et al.* (1980) did not extend long enough for this to be estimated. It is, however, considerably longer than the $T_{1/2}$ of 3 h reported by Brodie *et al.* (1954) for this compound. The longer $T_{1/2}$ would be consistent with the long-lived platelet effects of sulphinyprazole administration (Buchanan *et al.* 1978; Butler *et al.*, 1979). The sulphide has been found to be 16 times more potent than sulphinyprazole as a competitive inhibitor of collagen-induced platelet aggregation although neither compound had any effect on thrombin-induced aggregation of rabbit platelet-rich plasma nor on ADP-induced platelet aggregation in rabbit or man (Pay *et al.*, 1980).

Our estimate for the $T_{1/2}$ of the sulphone was 3.1 h but must be regarded with caution because of the low plasma concentrations of the sulphone developed following a single dose of sulphinyprazole. This estimate is, however, apparently similar to that depicted in Figure 1 of the paper by Dieterle *et al.*

Table 3 Pharmacokinetic parameters estimated from the plasma concentration-time data for the sulphide and sulphone metabolites of sulphinpyrazone

Subject	Sulphide				Sulphone			
	AUC ($\mu\text{g ml}^{-1}\text{h}$)		$T_{1/2}$ (h)		AUC ($\mu\text{g ml}^{-1}\text{h}$)		$T_{1/2}$ (h)	
	200 mg	400 mg	200 mg	400 mg	200 mg	400 mg	200 mg	400 mg
1	3.7	21.1	11.0	12	7.2	11.3	4.4	1
2	2.6	10.9	11.6	30	2.1	9.0	2.9	2
3	10.5	35.2	20.1	14	3.3	9.3	3.6	1
4	13.2	19.8	13.9	12	5.6	18.0	3.7	3
5	39.7	75.8	10.2	7	10.1	35.1	4.6	3
Mean	13.9	32.6	13.4	15	5.7	16.5	3.8	2.4

(1980). Because of the nature of precursor-metabolite relationships it is not possible to determine with certainty the true elimination $T_{1/2}$ of a metabolite following administration of the precursor. Dayton *et al.* (1961) administered the sulphone to two normal subjects intravenously and found a $T_{1/2}$ of 3 h. It would therefore appear that this represents the true elimination of $T_{1/2}$ of the compound. The sulphide and sulphone metabolites are equipotent inhibitors of malonaldehyde synthesis by human platelets *in vitro* whereas sulphinpyrazone itself is ten times less active in inhibiting platelet prostaglandin synthesis (Pay *et al.*, 1980).

Although the plasma concentrations of both sulphide and sulphone were low the calculated AUCs were sufficiently reliable to demonstrate that their pharmacokinetic behaviour may not be linear. Such non-linearity would become accentuated with multiple dosing and a further study under these conditions would be required to confirm this impression.

Approximately 45–50% of the administered sulphinpyrazone at both dose levels was eliminated in the urine as unchanged drug or as sulphone or parahydroxysulphinpyrazone. These results are similar to those from the studies of Senczuk & Jodynis-Liebert (1980) who estimated sulphinpyrazone spectrophotometrically and those of Dieterle *et al.* (1975, 1980) who utilised radiolabelled drug. In common with Dieterle *et al.* (1975, 1980), we were unable to detect significant quantities of the sulphide in the urine. There was a small but significant increase in the urinary elimination of the sulphone after the higher dose. This is consonant with the finding of a higher plasma AUC for this compound at this dose relative to the 200 mg dose.

The sigma minus plots for sulphinpyrazone showed no significant difference between the elimination rate constants at the two dose levels. Although the values for k found were similar to those for β determined by direct measurement of plasma sulphinpyrazone concentrations they are not identical and the $T_{1/2}$ from plasma estimations is longer. This may be because $k \neq \beta$ since β is a disposition rate constant and includes a component associated with drug distribution in addition to elimination. The more complex two-compartment model adopted for analysis of plasma data is likely to yield the more accurate assessment of sulphinpyrazone $T_{1/2}$.

Similar sigma minus plots were constructed for the urinary elimination of the sulphone and *p*-OH sulphinpyrazone metabolites and the mean $T_{1/2}$ of the sulphone was approximately 3.5 h at both dose levels and is comparable with the estimate of the $T_{1/2}$ made from plasma levels. The $T_{1/2}$ of *p*-OH sulphinpyrazone was approximately 3.5 h. These values differ from the plasma $T_{1/2}$ of 1 h published by Dayton *et al.* (1964) who administered this compound intravenously. This may be due to analytical differences. Alternatively

Table 4 Urinary elimination of free sulphinpyrazone and the sulphide and *p*-OH sulphinpyrazone metabolites

Subject	% of administered dose excreted as sulphinpyrazone, sulphone or <i>p</i> -OH sulphinpyrazone		% of administered dose excreted as					
	<i>p</i> -OH sulphinpyrazone		sulphinpyrazone		sulphone		<i>p</i> -OH sulphinpyrazone	
	200 mg	400 mg	200 mg	400 mg	200 mg	400 mg	200 mg	400 mg
1	45.4	42.7	39.5	36.0	2.8	3.3	3.1	3.4
2	50.0	48.5	42.3	42.0	2.2	2.7	5.6	3.8
3	62.4	54.2	57.7	49.0	1.9	1.9	2.8	3.2
4	51.1	45.4	40.2	36.5	2.2	2.8	8.7	6.1
5	33.2	36.7	25.7	28.3	2.3	3.2	5.2	4.8
Mean	48.4	45.5	41.1	38.4	2.3	2.8	5.1	4.3

Table 5 Medians (mean absolute deviate) of parameters derived from sigma-minus plots for urinary elimination of sulphinpyrazone, and its sulphone and *p*-hydroxy metabolites

	Sulphinpyrazone		Sulphone		<i>p</i> -OH sulphinpyrazone	
	200 mg	400 mg	200 mg	400 mg	200 mg	400 mg
k (h ⁻¹)	0.223 (0.066)	0.214 (0.033)	0.227 (0.058)	0.232 (0.075)	0.256 (0.029)	0.199 (0.011)
T _{1/2} (h)	3.1 (0.9)	3.2 (0.6)	3.1 (1.0)	3.0 (1.2)	2.7 (0.3)	3.5 (0.4)

because of the 'flip-flop' nature of the equation upon which the sigma minus plot is based

$$M_u^{\infty} - M_u = \frac{M_u^{\infty}}{k_m - k} (k_m e^{-kt} - k e^{-k_m t})$$

(where M_u^{∞} is the total amount of metabolite excreted in the urine,
 M_u is the cumulative amount of metabolite excreted to time t ,
 k_m is the first order formation rate constant for the metabolite)

when $k_m < k$, k_m determines the slope of the linear terminal phase of the plot. The terminal $T_{1/2}$ of 3.5 h in this case would suggest that k_m is approximately 0.2 h⁻¹.

The urinary clearance of sulphinpyrazone may be compared with the value of 21.3 ± 11.4 ml min⁻¹ recalculated from the data of Perel *et al.* (1969) who administered 400 mg sulphinpyrazone to four patients with gout and measured the urinary excretion rate and a corresponding plasma level. The pK_a of sulphinpyrazone is 2.8 and its urinary elimination would thus be expected to depend to a certain extent on urinary pH.

The urinary clearance of sulphone was also calculated. No previous data on the renal clearance of this metabolite is available for comparison. Dayton *et al.* (1961) were unable to detect it in the urine following administration of sulphinpyrazone to human volunteers but this was probably due to an inadequate analytical method since the compound was found to

Table 6 Renal clearance (ml min⁻¹) of unchanged sulphinpyrazone and its sulphone

Subject	Sulphinpyrazone		Sulphone	
	200 mg	400 mg	200 mg	400 mg
1	28.0	23.2	13.2	20.2
2	28.7	24.9	35.7	20.4
3	20.9	19.6	19.4	14.2
4	14.1	9.0	13.8	10.7
5	7.5	6.3	6.3	7.9
Mean	19.8	16.6	17.7	14.7

account for approximately 3% of the urinary radioactivity following administration of radio-labelled sulphinpyrazone (Dieterle *et al.*, 1980).

The present study shows that the sulphide and sulphone metabolites are detectable in the plasma after a single oral dose of sulphinpyrazone at concentrations which are capable of partially inhibiting malonaldehyde synthesis by human platelets *in vitro* (both metabolites cause 50% inhibition at 2 µg ml⁻¹, c.f. 20 µg ml⁻¹ for sulphinpyrazone itself—Pay *et al.*, 1980). These preliminary experiments further suggest that on multiple dosing with sulphinpyrazone it is possible that a disproportionate increase in these active metabolites could occur which, coupled with the accumulation associated with the longer $T_{1/2}$ of the sulphide, may explain the effects of sulphinpyrazone on platelet function *in vivo*.

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