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Report

Pharmacokinetics and Reversible Biotransformation of Sulfinpyrazone and Its Metabolites in Rabbits. I. Single-Dose Study

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In rabbits receiving sulfinpyrazone (SO) and the sulfide metabolite (S) in four separate experiments, the biotransformation of SO into S was found to be reversible, which resulted in approximately parallel terminal disposition profiles for the three major substances in plasma, i.e., SO, S, and the p-OH-sulfide (OH-S). However, differences in disposition kinetics were observed between the intravenous and the peroral administration. The formation of OH-S was independent of both the administered compound and the administration route. The results obtained in the present studies, the previously documented enterohepatic recirculation, and the formation of S by hindgut flora may have implications for studies on sulfinpyrazone, which has been used as an antithrombotic agent.

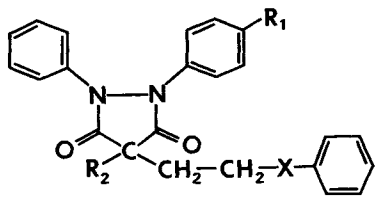
KEY WORDS: sulfinpyrazone; pharmacokinetics; reversible metabolism; single dose.

INTRODUCTION

Sulfinpyrazone (SO) is a sulfoxide metabolite of phenylbutazone with pronounced uricosuric properties (1,2). Since the 1965 report by Smythe *et al.* (3) of the prolongation of platelet survival and reduced platelet adhesiveness by the drug in humans, several clinical trials have shown probable beneficial effects of the drug in thromboembolic disorders (4–6). More recently, attention has focused on the metabolism of SO and the finding of a much more active sulfide metabolite (S) (7–10). The disposition of SO and its metabolites is further complicated by reversible metabolism (11,12), biliary recycling (11,12), and formation of S (11,13) by the microflora of the hindgut.

Six metabolites of SO have been proposed (7–10) in humans and in animals (Fig. 1). It has been shown that S is the most powerful inhibitor of platelet aggregation (14,15), indicating that SO is a prodrug in some sense. Althogh antiplatelet activity of SO was suggested to be related to S (7–10,16,17), the mechanism of action remains obscure. Large intersubject variations of drug disposition in humans have been reported, and direct administration of the preformed S may be desirable (18).

Interconversion between the sulfoxide and the sulfide has been reported earlier for dimethylsulfoxide (DMSO) (19) and sulindac (20–22,31). For SO, this reaction has been reported in rats (11) and rabbits (12). However, since the p-OH-sulfide metabolite (OH-S) reconstituted in alkaline solution after sample extraction decomposed slowly (11,12), the presence and importance of OH-S in plasma might be underestimated or obliterated. The purpose of the present study was to investigate the disposition kinetics in rabbits that received single doses of SO and S on separate occasions in *ex vivo* platelet aggregation studies.



	R_1	R_2	X
Sulfinpyrazone (SO)	H	H	SO
Sulfide (S)	H	H	S
Sulfone (SO_2)	H	H	SO_2
p-OH-Sulfinpyrazone (OH-SO)	OH	H	SO
p-OH-Sulfide (OH-S)	OH	H	S
p-OH-Sulfone (OH-SO_2)	OH	H	SO_2
4-OH-Sulfinpyrazone (4-OH-SO)	H	OH	SO

Fig. 1. Chemical structures of sulfinpyrazone and its metabolites.

MATERIALS AND METHODS

Experimental Design

Male, white New Zealand rabbits (Clerco Research Farm, Cincinnati, Ohio) weighing between 2.8 and 4.2 kg were included in the study. A crossover design with six animals for each of four studies was used. All animals received

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SO and S intravenously (iv) and perorally (po) on different occasions separated by 2 to 3 weeks. The compound administered to each rabbit was in the order of po S, po SO, iv S, and iv SO in separate experiments. All doses were 15 mg/kg body weight. SO and its derivatives (S and OH-S) were gifts from Ciba-Geigy, Basel, Switzerland.

Administration and Blood Sampling

For intravenous administration, stock solutions of SO and S were prepared by dissolving the substances in 1 *N* NaOH (2 g in 10 ml) and filtration through a disposable 0.22-μm filter (Millipore, Bedford, Mass.) into injection vials. Filtration did not cause loss of substance. These solutions were diluted with normal saline (final pH 12) before injection (10 ml) into a marginal ear vein. For peroral administration, SO and S, suspended in 2 ml of propylene glycol, were given by a stomach tube and flushed with 3 ml of distilled water. For all study events rabbits were fasted overnight with water available *ad libitum* prior to the administration of SO or S. Feeding was restored 4 hr after dosing. The rabbits were not anesthetized and blood samples (1.0 to 1.5 ml) were drawn by cardiac puncture at time zero and 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 30, 36, and 48 hr after dosing. Blood samples were citrated with 3.2% sodium citrate (9:1, v/v), and after measurement of platelet aggregation, an aliquot of plasma was pipetted into a glass tube and stored at −20°C until analyzed by a high-power liquid chromatographic (HPLC) method (23).

Pharmacokinetic Analysis of Plasma Data

The pharmacokinetic parameters were assessed using a model-independent AUC-RPP computer program (40) developed in our laboratory. The total area under the plasma concentration–time curve (AUC) from time zero to the last detectable plasma concentration was determined by the linear trapezoidal rule, and the AUC beyond the last detectable plasma concentration was calculated by dividing the last detectable plasma concentration by the terminal rate constant, β, which was calculated from the terminal slope by least-squares regression. All data are presented as means ± SD. The pharmacokinetic parameters were calculated as shown below.

The terminal half-life ($t_{1/2}$) was calculated as

$$t_{1/2} = 0.693/\beta \quad (1)$$

The mean residence time (MRT) was calculated as

$$\text{MRT} = \text{AUMC/AUC} \quad (2)$$

where AUMC denotes the total area under the first moment of the plasma concentration curve from time zero to infinity.

The apparent volume of distribution (V_{area}) corrected by the fraction of drug absorbed (F) was calculated as

$$V_{area}/F = \text{dose/AUC} \cdot \beta \quad (3)$$

The total clearance (CL) corrected by the fraction of drug absorbed (F) was calculated as

$$\text{CL}/F = D/\text{AUC} \cdot \beta \quad (4)$$

The volume of distribution at steady state (V_{ss}) after the intravenous dose was calculated as

$$V_{ss} = \text{dose} \cdot \text{MRT/AUC} \quad (5)$$

RESULTS

Intravenous and Peroral Sulfinpyrazone (SO)

After iv and po administration of sulfinpyrazone (SO), and sulfide (S) and the p-OH-sulfide (OH-S) were found to be the two major metabolites, while the sulfone (SO_2) was of minor quantitative significance (<2%), and the others were negligible (Figs. 2 and 3). SO was rapidly absorbed, reaching a mean peak time, t_{max}, of 1.5 hr (Table I). The mean t_{max} of the generated S was increased from 4.33 hr after intravenous to 9.67 hr after peroral administration. The AUCs of S and OH-S were increased by six times after peroral dosing of the drug. For example, the mean AUC of S was increased from 14.4 after intravenous to 96.0 (μg/ml)hr after peroral administration. A significant amount of OH-S was produced and

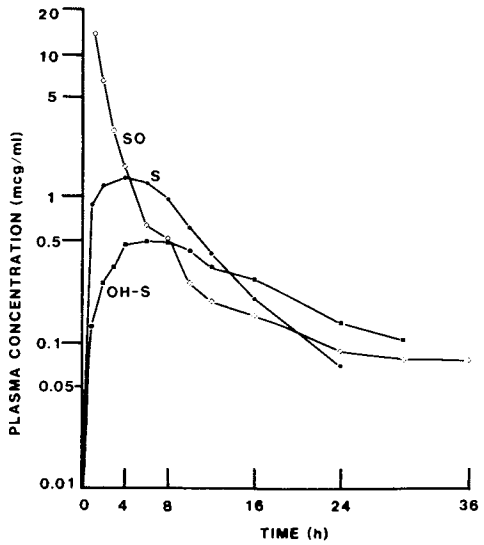

Fig. 2. Mean plasma concentration–time curves of sulfinpyrazone (SO), the sulfide (S), and the p-OH-sulfide (OH-S) after intravenous administration of 15 mg/kg sulfinpyrazone to six rabbits.

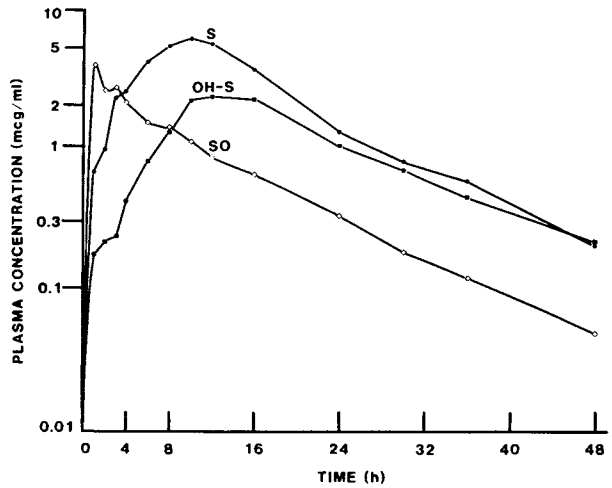

Fig. 3. Mean plasma concentration–time curves of sulfinpyrazone (SO), the sulfide (S), and the p-OH-sulfide (OH-S) after peroral administration of 15 mg/kg sulfinpyrazone to six rabbits.

Table I. Pharmacokinetic Parameters of Sulfinpyrazone (SO), the Sulfide (S), and the p-OH-Sulfide (OH-S) After Intravenous and Peroral Administration of 15 mg/kg Sulfinpyrazone (Mean ± SD)

Parameter (N = 6)	15 mg/mkg iv	15 mg/mkg po
BW (kg)	3.52 (0.37)	3.19 (0.41)
$t_{max,S}$ (hr)	4.33 (1.51)	9.67 (1.51)[a]
$t_{max,OH\text{-}S}$ (hr)	7.00 (2.45)	13.8 (2.66)[a]
$t_{max,SO}$ (hr)	—	1.50 (0.55)
AUC_S [(μg/ml)hr]	14.4 (5.80)	96.0 (40.3)[a]
$AUC_{OH\text{-}S}$ [(μg/ml)hr]	9.50 (5.80)	51.0 (11.2)[a]
AUC_{SO} [(μg/ml)hr]	47.2 (17.4)	29.7 (11.6)
AUC $ratio_{OH\text{-}S/S}$	0.68 (0.43)	0.61 (0.27)
AUC $ratio_{SO/S}$	3.38 (0.72)	0.37 (0.28)[a]
$t_{½,S}$ (hr)	4.44 (0.66)	10.1 (4.31)[a]
$t_{½,OH\text{-}S}$ (hr)	6.40 (2.11)	11.1 (6.62)
$t_{½,SO}$ (hr)	15.4 (7.75)	11.5 (3.43)
MRT_S (hr)	7.75 (1.08)	18.9 (6.99)[a]
$MRT_{OH\text{-}S}$ (hr)	13.9 (3.76)	24.7 (11.23)
MRT_{SO} (hr)	5.36 (2.44)	12.1 (3.13)[a]
CL/F_{SO} (ml/min)	20.1 (5.40)	30.4 (3.43)
V_{area}/F_{SO} (L/kg)	8.18 (4.64)	9.80 (5.50)
$V_{ss\ SO}$ (L/kg)	2.00 (1.18)	—

[a] Significant at $P < 0.05$.

its peroral AUC was about 1.5 times that of SO. The formation of OH-S was independent of the route of administration as demonstrated by the mean AUC ratio of OH-S to S, 0.61 for peroral and 0.68 for intravenous administration.

The mean peroral terminal disposition half-life, $t_{½}$, of the formed S (10.1 hr) was longer than that after intravenous dosing (Table I). The peroral $t_{½}$'s of the three substances were similar, resulting in approximately parallel terminal disposition profiles (Fig. 3). However, the parallelism of intravenous terminal decline was reduced (Fig. 2). Great intersubject variations in the intravenous $t_{½}$ of SO were observed, 15.4 ± 7.75 hr, which was much longer than that of S.

Compared to the intravenous data, the peroral mean residence times (MRT) of the three substances were increased by a factor of two (Table I). The intravenous V_{area} was 8.18 ± 4.64 liters/kg, which was similar to the peroral V_{area}/F (F, the fraction of drug absorbed). In either case, the volume of distribution for SO was extremely high. This could be an overestimated artifact, as the gallbladder is a part of the volume of distribution. The intravenous CL of the parent drug, 20.1 ± 5.40 ml/min, was not significantly different from the corrected CL (CL/F), 30.4 ± 3.43 ml/min, obtained after peroral administration. Comparison between these two routes of administration did not permit a reliable estimation of the fraction absorbed (F) for the drug due to the alteration of disposition profiles and the existence of reversible metabolism.

Intravenous and Peroral Sulfide (S)

After iv and po dosing with S, the generated SO and OH-S were found to be the two major metabolites, while the sulfone, SO_2 was of minor quantitative significance (<2%), and others were negligible (Figs. 4 and 5). The formation of SO documented the existence of interconversion with S. SO

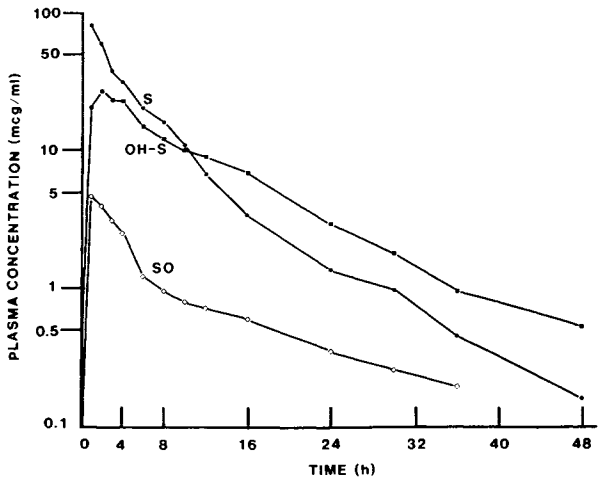

Fig. 4. Mean plasma concentration–time curves of sulfinpyrazone (SO), the sulfide (S), and the p-OH-sulfide (OH-S) after intravenous administration of 15 mg/kg sulfide to six rabbits.

was rapidly generated after intravenous administration, resulting in a t_{max} between 1 and 2 hr. A similar metabolic sequence was observed after peroral dosing. A sharp drop in plasma concentrations for the three substances were observed between 4 and 8 hr after peroral dosing, probably caused by biliary recycling, which created a delayed second t_{max} for each substance. There were great intersubject variations in intravenous AUCs of the three substances. The mean AUC ratio of OH-S to S for both routes of administration, 0.51 for peroral and 0.69 for intravenous administration, was not significantly different. These data (Table II) were not significantly different from their counterparts observed after intravenous or peroral administration of SO (Table I), supporting the contention that the p-hydroxylation of S was independent of both the administered compound and the administration route. However, the conversion of S back to SO after the intravenous dose was significantly smaller, as demonstrated by the mean AUC ratio of SO to S, which was about 0.07 (Table II).

Although not statistically significant, the peroral $t_{½}$'s of

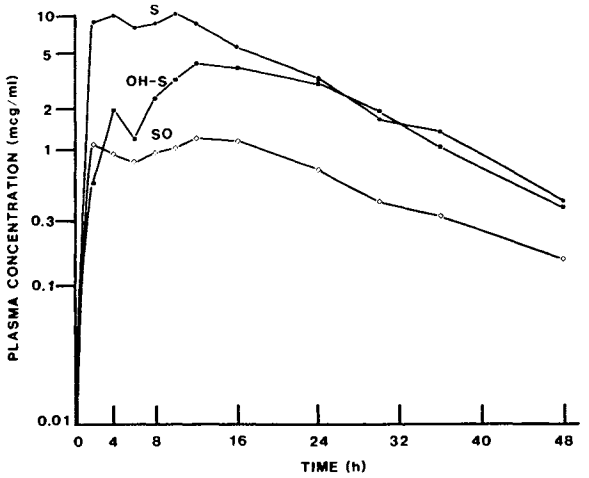

Fig. 5. Mean plasma concentration–time curves of sulfinpyrazone (SO), the sulfide (S), and the p-OH-sulfide (OH-S) after peroral administration of 15 mg/kg sulfide to six rabbits.

Table II. Pharmacokinetic Parameters of Sulfinpyrazone (SO), the Sulfide (S), and the p-OH-sulfide (OH-S) After Intravenous and Peroral Administration of 15 mg/kg Sulfide (Mean ± SD)

	15 mg/kg	
Parameter (N = 6)	iv	po
BW (kg)	3.50 (0.53)	3.00 (0.17)
$t_{max,S}$ (hr)	—	7.00 (4.86)
$t_{max,OH\text{-}S}$ (hr)	2.33 (0.89)	16.0 (6.57)[a]
$t_{max,SO}$ (hr)	1.77 (0.41)	6.33 (6.12)
AUC_S [(μg/ml)hr]	420 (132.3)	200 (50.8)
$AUC_{OH\text{-}S}$ [(μg/ml)hr]	282 (143.6)	101.5 (34.0)[a]
AUC_{SO} [(μg/ml)hr]	30.3 (20.8)	33.8 (14.1)
AUC $ratio_{OH\text{-}S/S}$	0.69 (0.32)	0.51 (0.11)
AUC $ratio_{SO/S}$	0.07 (0.06)	0.18 (0.07)[a]
$t_{½,S}$ (hr)	4.49 (1.72)	8.50 (4.32)
$t_{½,OH\text{-}S}$ (hr)	6.03 (1.73)	9.10 (3.80)
$t_{½,SO}$ (hr)	4.96 (3.61)	12.7 (5.88)
MRT_S (hr)	5.25 (1.57)	16.5 (4.44)[a]
$MRT_{OH\text{-}S}$ (hr)	9.74 (3.37)	23.2 (4.59)[a]
MRT_{SO} (hr)	6.54 (4.60)	21.7 (5.29)[a]
Cl/F_S (ml/min)	1.76 (0.45)	3.97 (1.11)[a]
V_{area}/F_S (L/kg)	0.25 (0.11)	1.05 (0.75)[a]
$V_{ss\ S}$ (L/kg)	0.20 (0.07)	—

[a] Significant at $P < 0.05$.

the three substances tended to be longer than their counterparts after intravenous administration (Table II). These tendencies were consistent with the longer peroral MRTs (about two times more) observed for the three substances. However, in both administrations, these three substances, to some extent, decayed in an approximately parallel fashion. It is noteworthy that after intravenous dosing with S the terminal $t_{½}$'s of S (4.49 ± 1.72 hr) and OH-S (6.03 ± 1.73 hr) (Table II) were virtually the same as their counterparts observed after an intravenous dose of SO was given, 4.44 ± 0.66 and 6.40 ± 2.11 hr, respectively (Table I). The CL, V_{area}, and V_{ss} of S (Table II) were much smaller than their counterparts of SO (Table I). On the other hand, relatively higher values of CL/F and V_{area}/F (F, fraction of the dose absorbed) were observed after peroral administration of S (Table II), indicating that the F might be less than 1. This might be due to incomplete absorption as reflected by the largely reduced peroral AUC of S [200 ± 50.8 (μg/ml)hr] compared to the intravenous AUC [420 ± 132.3 (μg/ml)hr].

DISCUSSION

The observation that six times more sulfide (S) (also p-OH-sulfide, OH-S) is generated in rabbits after peroral dosing with SO (Table I) is consistent with the previous report in rabbits receiving 10 mg/kg SO by Strong *et al.* (12), who have demonstrated that the contents of the cecum are the major site of reduction of the drug. The delayed peroral formation peak of S (also OH-S) (Fig. 3) is due to the time it takes for the drug to travel to the hindgut, where SO is reduced to S. S is then absorbed and subsequently *p*-hydroxylated. However, a minor portion of S may be produced in the liver as demonstrated in a previous report (12) that the capacity of reduction of SO in the liver is about one-sixth of that in the cecum contents. In humans S and SO_2 are the two major metabolites, while OH-S seems to be minor or negligible (13,15,18,27–30).

On the other hand, after intravenous dosing with SO the production of S may be due mainly to biliary secretion of the drug into the gut, where the drug is partly reabsorbed and partly reduced by the cecum contents and then absorbed. It has been reported that the secretion of the two formed metabolites (S and OH-S) into the bile is neglible (12), however, the synchronized drop in plasma concentrations was found after the preformed S was given perorally (Fig. 5). This suggests that, in addition to SO (12), the other two substances may be secreted into bile and recycled, which was accompanied by reversible biotransformation.

Since the recycling process may prolong elimination, therefore, if not overestimated, the longer elimination $t_{½}$ of SO could be expected. This is reflected by the estimated intravenous $t_{½}$ of 15.4 ± 7.75 hr for SO (Table I), which is very different from the previously reported value of 1.8 hr (12). It should be noted that reversible metabolism may also contribute to the longer SO $t_{½}$. In a broader sense biliary recycling can be viewed as one type of reversible metabolism (25), and drug entering the bile must be considered as drug administered perorally (26).

One of the impacts of interconversion on disposition may be featured in the parallel, postdistributive exponential curves of the parent compound and its convertible derivative, which can be examplified by dapsone (32), prednisolone (33,34), and sulindac (20). For SO, the parallelism among the plasma profiles of the three substances was observed after SO or S was given. However, the parallelism is reduced when SO is given intravenously.

The formation of OH-S is independent of the route of administration and substance administered as demonstrated by the AUC ratio of OH-S to S (Tables I and II). Dosing either with an intravenous or with a peroral dose of S, the reverse reaction of S to SO is very rapid and probably faster than the *p*-hydroxylation of S (Figs. 4 and 5). However, the extent of S oxidized to SO, as demonstrated by the AUC ratio of SO to S (Table II), is small, particularly when the intravenous dose was given. This suggests that presystemic metabolism is possible; and the forward reaction of SO to S appears to be predominant over the reverse reaction. Since we also dosed rabbits with a peroral dose of 7 mg/kg OH-S, in which SO was found to be a metabolite (data unpresented), the involvement (aromatic dehydroxylation) of OH-S in reversible metabolism is not impossible. Examples of aromatic dehydroxylation have been shown for caffeic acid (41) and protocatechuic acid (42). This reaction is caused by gut flora.

It is usually assumed that the metabolic process is unidirectional and kinetics is assessed accordingly based on the formation-rate limited (FRL) or elimination-rate limited (ERL) model (35). Although the graphical technique (36) and statistical moment (37) have been proposed to evaluate metabolite pharmacokinetics under certain conditions, the only way to elucidate accurately the disposition of a metabolite is to administer both metabolite and parent drug in separate experiments (38). However, for a drug associated with reversible metabolism and enterohepatic recirculation, a new technique or at least a revised classical pharmacokinetic procedure has to be applied because the contributions from

metabolic sources need to be accounted for (24,25). Furthermore, the extent of protein binding of SO and its metabolites is extremely high, greater than 98% (29,30,39), which may affect their disposition profiles by mutual displacement from binding sites (39) and, in turn, results in more complications in pharmacokinetics evaluation.

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