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Report

Pharmacokinetics and Reversible Biotransformation of Sulfinpyrazone and Its Metabolites in Rabbits. II. Multiple-Dose Study

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In crossover studies rabbits were given sulfinpyrazone (SO) and its sulfide metabolite (S) perorally once daily (10 mg/kg) for 5 days. Comparison of the pharmacokinetic parameters obtained after the first and the fifth dose indicates that repeated dosing does not alter disposition kinetics of both SO and S, except that in dosing with S the observed terminal half-life for S is significantly reduced, from 4.59 ± 0.55 to 2.86 ± 0.6 hr (SD). In other studies rabbits were given higher single doses (15, 25, and 50 mg/kg) perorally and comparison was made between these dose sizes and the first dose (10 mg/kg) of multiple administration with S. Some kinetic parameters tended to be altered in a nonlinear fashion, and greater intersubject variations were observed because of the dose increase, while oxidation to SO or *p*-hydroxylation to OH-S from S was not significantly altered.

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

INTRODUCTION

Sulfinpyrazone (SO), an antithrombotic agent, is metabolized to the sulfide metabolite (S), which was suggested to be the substance responsible for the pronounced and long-lasting effect on platelet activity (1–7). New interest in the pharmacokinetics of SO and its metabolites was generated after recognizing the role of the microflora in the hindgut in reduction of the drug (8–10), enterophepatic recirculation (4,8,9), and reversible metabolism (8,9). These events make pharmacokinetic evaluation complicated and may lead to false estimations of kinetic parameters if nonlinear disposition of the drug and/or its metabolites is involved.

Several reports in humans showed that S is much more slowly eliminated than its parent drug (9,11–14), which was suggested to be associated with the long-lasting effect on platelet function. In rabbits, however, the terminal half-life of S after the administration of SO was shown to be equal to or less than that of SO in our previous studies (21). It is possible that the long-lasting effect on rabbit platelet activity reported by Buchanan *et al.* (15) is due to nonlinear kinetics caused by the high dose of SO, in which the formed S persisted over a long period of time. In humans the onset of the antiplatelet effect after administration of the drug was more readily achieved when a daily dose of 2 × 400 mg, instead of 4 × 200 mg, was given (6), suggesting that the formation and/or elimination of S may not follow first-order kinetics (12). Chronic administration of SO (2 × 400 mg) resulted in autoinduction of the drug's metabolism and reduction of the terminal half-life of S (14). However, long-term treatment with daily doses of 4 × 200 mg did not cause a reduction of S's half-life (13). It is speculated that an increased dose or repeated dosing may alter the disposition profiles of SO and its metabolites.

The purpose of the present studies was to investigate the effects of increasing doses and repeated dosing on the disposition profiles in rabbits that received SO and S in *ex vivo* platelet aggregation studies.

MATERIALS AND METHODS

Experimental Design

Male, white New Zealand rabbits (Clerco Research Farm, Cincinnati, Ohio) weighing between 2.8 and 4.6 kg were included in the studies. Sulfinpyrazone (SO) and its metabolites were gifts from Ciba-Geigy, Basel, Switzerland. A crossover design was used for the multiple-dose studies with seven rabbits. SO and the sulfide metabolite (S) were administered perorally on different occasions. For each rabbit the S dose was given first and the SO dose was then given after a washout period of 2 to 3 weeks. A 10-mg/kg dose was given every 24 hr for 5 days. For single-dose studies, 25 and 50 mg/kg S were given on different occasions to other rabbits, which did not participate in the multiple-dose studies. The administration of 15 mg/kg SO or S was performed as described in the previous study (21).

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Administration and Blood Sampling

For peroral administration, the substances were suspended in 2 ml of propylene glycol, given by a stomach tube, and flushed with 3 ml of distilled water.

For all experiments, rabbits were fasted overnight with water available *ad libitum* prior to the administration of SO and S, and feeding was restored 4 hr after dosing, with an exception that in multiple-dose studies the rabbits were not fasted before the second, the third, and the fourth doses were given. Rabbits were kept in darkness between 7 PM and 7 AM and blood samples were collected under dim red light during this time period. All rabbits were not anesthetized. Blood samples (1.0 to 1.5 ml) were drawn by cardiac puncture at suitable time intervals. In multiple-dose studies eight or nine samples were drawn during the first and the fifth dosing interval (1, 3, 6, 9, 12, 15, 18, 21, and 24 hr after dosing), while only one blood sample was taken 9 hr after the second, the third, and the fourth doses were given. 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 (16).

Pharmacokinetic Analysis of Plasma Data.

Evaluation of pharmacokinetic parameters was performed using a model-independent (AUC-RPP) computer program (20) as described in the previous study (21). For multiple-dose studies, the estimation of AUC and other relevant parameters after administration of the first dose was based on the time period of 24 hr and the extrapolation to infinite time by least-squares regression, while the calculation of AUC after the fifth dose was given was based on the truncation between the 24-hr interval. Statistical analysis was carried out using the multiple comparison technique for unbalanced data. All data are presented as means ± SD.

RESULTS

Multiple Administration of Sulfinpyrazone (S)

Repeated dosing of 10 mg/kg SO per 24 hr for 5 days produced no significant changes in disposition kinetics of SO and its two major metabolites, i.e., the sulfide (S) and the p-OH-sulfide (OH-S). Plasma profiles for these substances are shown in Fig. 1. The pharmacokinetic parameters of 15 mg/kg SO given as a single dose and after repeated dosing with 10 mg/kg are compared in Table I. The AUCs of the three substances estimated after the first dosing were not significantly different from their counterparts after the fifth dose (Table I). More than 100% variation in AUC and AUC ratio of SO to S was observed. This is due to an extremely large AUC in one rabbit, which was 12 times higher than that of the other rabbits tested.

Compared to that after a single dose of 15 mg/kg SO, the estimated $t_{1/2}$'s for the three substances after multiple dosing (10 mg/kg) tended to be shorter (Table I). For all cases the AUC ratios of SO and OH-S to S were not significantly different from their counterparts. Similarly, all other parameters were not significantly changed; however, increasing the dose from 10 to 15 mg/kg tended to increase the values of the parameters and to increase the coefficient of variation. Under such a dosage regimen no significant accumulation was observed for SO and its metabolites.

Multiple Administration of Sulfide Metabolite (S)

Repeated dosing of 10 mg/kg S per 24 hr for 5 days produced little change in disposition kinetics of S and its two major metabolites, i.e., SO and OH-S, except that the $t_{1/2}$ of S was decreased. Plasma profiles for these substances are shown in Fig. 2. The pharmacokinetic parameters of 15 mg/kg S given as a single dose and after repeated dosing with 10 mg/kg are compared in Table II. The AUCs for the three substances estimated after the first dose were not significantly different from their counterparts after the fifth dose was given. There was a significant change in the $t_{1/2}$ of S, from 4.59 ± 0.55 to 2.86 ± 0.60 hr for the first and the fifth dosing, respectively.

Compared to that after a single dose of 15 mg/kg S, the estimated $t_{1/2}$'s for the three substances after multiple dosing with a lower dose tended to be shorter. The S plasma concentration decreased faster than that of the other two substances and parallelism of terminal disposition became less

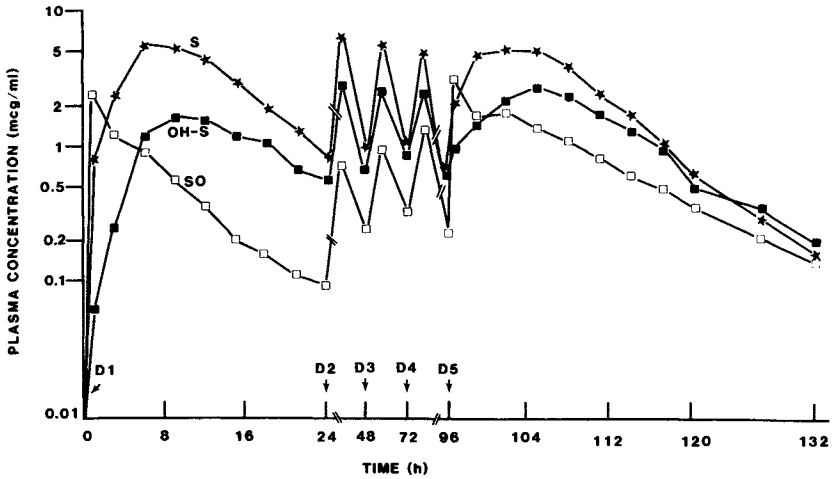

Fig. 1. Mean time courses of sulfinpyrazone (SO), the sulfide (S), and the p-OH-sulfide (OH-S) after multiple peroral administration of 10 mg/kg sulfinpyrazone (N = 7).

Table I. Pharmacokinetic Parameters for Sulfinpyrazone (SO), the Sulfide (S), and the p-OH-Sulfide (OH-S) After Multiple Peroral Doses of 10 mg/kg Sulfinpyrazone and a Single Peroral Dose of 15 mg/kg Sulfinpyrazone (Mean ± SD)[a]

Parameter	10 mg/kg (N = 7)		15 mg/kg (N = 6)
	1st dose	5th dose	
BW (kg)	4.02 (0.28)[a]	4.02 (0.28)[a]	3.19 (0.41)[b]
$t_{max,S}$ (hr)	8.57 (4.39)[a,b]	5.57 (2.01)[b]	9.67 (1.51)[a]
$t_{max,OH\text{-}S}$ (hr)	12.0 (4.58)[a,b]	8.57 (1.13)[b]	13.8 (2.66)[a]
$t_{max,SO}$ (hr)	1.00 (0.00)	1.00 (0.00)	1.50 (0.55)
AUC_S [(μg/ml)hr]	78.0 (18.1)	70.4 (23.8)	96.0 (40.3)
$AUC_{OH\text{-}S}$ [(μg/ml)hr]	30.9 (9.00)[a]	38.7 (13.0)[a]	51.0 (11.2)[b]
AUC_{SO} [(μg/ml)/hr]	15.2 (5.8)	30.2 (35.5)	29.7 (11.6)
AUC $ratio_{OH\text{-}S/S}$	0.43 (0.19)	0.55 (0.09)	0.61 (0.27)
AUC $ratio_{SO/S}$	0.25 (0.18)	0.67 (0.99)	0.37 (0.28)
$t_{½,S}$ (hr)	4.73 (1.51)	5.30 (1.95)	10.1 (4.31)
$t_{½,OH\text{-}S}$ (hr)	7.44 (5.69)	6.66 (1.63)	11.1 (6.62)
$t_{½,SO}$ (hr)	6.03 (2.50)[a]	6.28 (1.63)[a]	11.5 (3.43)[b]
MRT_S (hr)	12.6 (3.87)[a,b]	9.44 (0.78)[b]	18.9 (6.99)[a]
$MRT_{OH\text{-}S}$ (hr)	18.6 (10.7)	11.8 (1.79)	24.7 (11.2)
MRT_{SO} (hr)	8.36 (2.72)	7.72 (1.68)	12.1 (3.13)
CL/F_{SO} (ml/min)	47.4 (11.0)	43.0 (21.6)	30.4 (3.43)
V_{area}/F_{SO} (L/kg)	6.69 (3.30)	5.77 (4.14)	9.80 (5.50)

[a,b] Superscripts denote the dissimilarity between mean ± SD at $P < 0.05$.

pronounced after the fifth dose was given (Fig. 2). For multiple dosing the AUC ratios of SO and OH-S to S at the first dose were exactly the same as their counterparts at the fifth dose, suggesting that the oxidation backward to SO and *p*-hydroxylation forward to OH-S from S remained unchanged. Increasing the dose of S from 10 to 15 mg/kg resulted in an increase in the mean residence times (MRT) for all substances, e.g., from 8.73 ± 0.92 to 16.5 ± 4.44 hr for S after the first dose of 10 mg/kg and single dose of 15 mg/kg (Table II). For other parameters, no significant changes were found, however, the coefficients of variation increased with increasing doses.

Under such a dosage regimen no significant accumulation was observed for S and its metabolites. Instead, when comparing the trough concentrations at the end of each dosing, the S concentrations tended to progressively decrease as the time span was increased. The S concentrations at 48, 72, 96, and 120hr were 2.24 ± 1.70, 1.61 ± 1.24, 1.09 ± 0.52, and 0.77 ± 0.51 μg/ml, respectively, which further reflects a decreased $t_{½}$ after the fifth dose (Table II).

Dose Effect of the Sulfide (S) on Disposition

The pharmacokinetic parameters of 10 (the first dose of multiple administration), 15, 25, and 50 mg/kg S are compared in Table III. The comparative plasma profiles are presented in Figs. 3, 4, and 5 for S, OH-S, and SO, respectively. The most outstanding change is the absorption peak of S (Fig. 3) and the formation peaks of SO (Fig. 5) and OH-S (Fig. 4), which were significantly delayed. For example, the mean S peak time, t_{max}, was increased from 3.86 to 18.0 hr

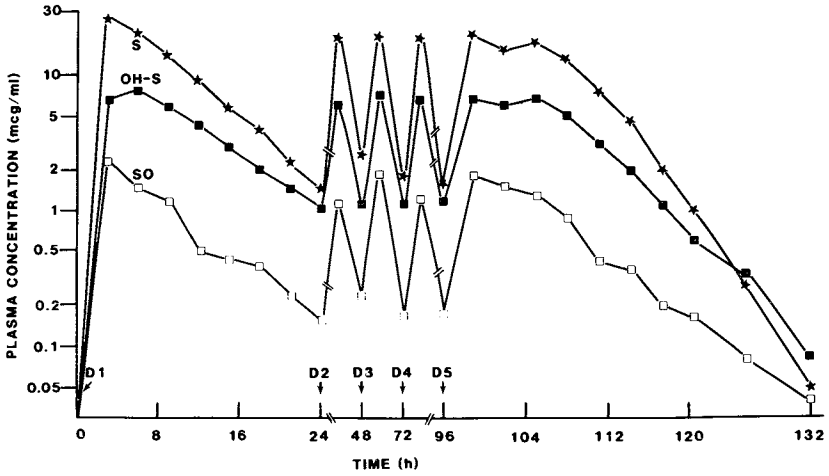

Fig. 2. Mean time courses of sulfinpyrazone (SO), the sulfide (S), and the p-OH-sulfide (OH-S) after multiple peroral administration of 10 mg/kg sulfide (N = 7).

Table II. Pharmacokinetic Parameters for Sulfinpyrazone (SO), the Sulfide (S), and the p-OH-Sulfide (OH-S) After Multiple Peroral Doses of 10 mg/kg Sulfide and a Single Peroral Dose of 15 mg/kg Sulfide (Mean ± SD)[a]

Parameter	10 mg/kg (N = 7) 1st dose	10 mg/kg (N = 7) 5th dose	15 mg/kg (N = 6)
BW (kg)	3.90 (0.33)[a]	3.90 (0.33)[a]	3.00 (0.17)[b]
$t_{max,S}$ (hr)	3.86 (1.46)[a,b]	4.71 (2.93)[b]	7.00 (4.86)
$t_{max,OH\text{-}S}$ (hr)	4.29 (1.60)[b]	8.14 (3.34)[a,b]	16.0 (6.57)[a]
$t_{max,SO}$ (hr)	3.43 (1.43)	7.71 (3.40)	6.33 (6.12)
AUC_S [(μg/ml)hr]	262 (101.0)	219 (108.6)	200 (50.8)
$AUC_{OH\text{-}S}$ [(μg/ml)hr]	104.4 (26.9)	86.1 (32.4)	101.5 (34.0)
AUC_{SO} [(μg/ml)hr]	22.4 (14.1)	17.8 (6.80)	33.8 (14.1)
AUC $ratio_{OH\text{-}S/S}$	0.41 (0.06)	0.41 (0.06)	0.51 (0.11)
AUC $ratio_{SO/S}$	0.09 (0.13)	0.09 (0.03)	0.18 (0.07)
$t_{½,S}$ (hr)	4.59 (0.55)[a]	2.86 (0.60)[b]	8.50 (4.32)[a]
$t_{½,OH\text{-}S}$ (hr)	5.75 (1.64)[a,b]	4.45 (1.29)[b]	9.10 (3.80)[a]
$t_{½,SO}$ (hr)	5.16 (0.88)[a]	5.85 (2.44)[a,b]	12.7 (5.88)[b]
MRT_S (hr)	8.73 (0.92)[a]	8.67 (1.55)[a]	16.5 (4.44)[b]
$MRT_{OH\text{-}S}$ (hr)	11.2 (2.63)[a]	9.2 (1.38)[a]	23.2 (4.59)[b]
MRT_{SO} (hr)	12.4 (9.10)[a]	9.15 (1.19)[a]	21.7 (5.29)[b]
CL/F_S (ml/min)	2.77 (1.00)	3.45 (1.23)	3.97 (1.11)
V_{area}/F_S (L/kg)	0.28 (0.13)	0.23 (0.12)	1.05 (0.75)

[a,b] Superscripts denote the dissimilarity between mean ± SD at $P < 0.05$.

for the 10- and the 50-mg/kg dose, respectively, suggesting that the absorption process might be nonlinear. The nonlinearity was also observed for the $t_{½}$, the MRT, and the AUC for the three substances. Although not statistically significant, there was a trend that the oxidation backward to SO or *p*-hydroxylation forward to OH-S from S was increased. For example, the mean AUC ratio of OH-S to S was increased from 0.41 to 0.72 for the 10- and the 50-mg/kg doses, respectively. Greater intersubject variations in pharmacokinetic parameters were observed with increasing dose size.

Table III. Pharmacokinetic Parameters for Sulfinpyrazone (SO), the Sulfide (S), and the p-OH-Sulfide (OH-S) After a Single Peroral Dose of 10, 15, 25, and 50 mg/kg Sulfide (Mean ± SD)[a]

Parameter	10 mg/kg (N = 7)	15 mg/kg (N = 6)	25 mg/kg (N = 5)	50 mg/kg (N = 6)
Sulfide (S)				
BW (kg)	3.90 (0.33)[a]	3.00 (0.17)[b]	3.55 (0.12)[a]	3.58 (0.18)[a]
t_{max} (hr)	3.86 (1.60)[a]	7.00 (4.86)[a,b]	7.20 (1.79)[b]	18.0 (10.4)[b]
C_{max} (μg/ml)	28.1 (11.9)[a]	13.8 (6.14)[a]	27.2 (11.8)[a]	68.3 (37.9)[b]
AUC [(μg/ml)hr]	262 (101.0)[a]	200 (50.8)[a]	471.3 (139)[a]	1826 (923.4)[b]
$t_{½}$ (hr)	4.59 (0.55)[a]	8.50 (4.32)[a]	9.11 (5.84)[a]	16.9 (9.03)[b]
MRT (hr)	8.73 (0.92)[a]	16.5 (4.44)[a,b]	17.9 (8.28)[a,b]	26.1 (9.66)[b]
V_{area}/F (L/kg)	0.28 (0.13)	1.05 (0.75)	0.83 (0.81)	0.64 (0.32)
CL/F (ml/min)	2.77 (1.00)[a,b]	3.97 (1.11)[a]	3.34 (0.93)[a,b]	2.07 (0.82)[b]
p-OH-Sulfide (OH-S)				
t_{max} (hr)	4.29 (1.60)[a]	16.0 (6.57)[b]	13.6 (9.63)[b]	25.2 (11.1)[b]
C_{max} (μg/ml)	8.17 (2.42)[a]	4.10 (1.81)[b]	13.0 (2.86)[c]	31.0 (12.4)[d]
AUC [(μg/ml)hr]	104.4 (26.9)[a]	101.5 (34.0)[a]	298.4 (174)[a]	1001 (247.3)[b]
AUC $ratio_{OH\text{-}S/S}$	0.41 (0.06)	0.51 (0.11)	0.62 (0.27)	0.72 (0.41)
$t_{½}$ (hr)	5.75 (1.64)	9.10 (3.80)	13.0 (10.7)	11.6 (8.36)
MRT (hr)	11.2 (2.63)[a]	23.2 (4.59)[b]	26.1 (16.5)[b]	30.9 (12.1)[b]
Sulfinpyrazone (SO)				
t_{max} (hr)	3.43 (1.43)[a]	6.33 (6.12)[a]	13.6 (9.63)[a]	23.1 (10.9)[b]
C_{max} (hr)	2.42 (1.97)[a]	1.69 (0.75)[a]	2.97 (1.67)[a]	8.93 (3.68)[b]
AUC [(μg/ml) hr]	22.4 (14.1)[a]	33.8 (14.1)[a]	54.8 (23.0)[a]	260.3 (98.1)[b]
AUC $ratio_{SO/S}$	0.09 (0.13)	0.18 (0.07)	0.12 (0.03)	0.18 (0.13)
$t_{½}$ (hr)	5.16 (0.88)	12.7 (5.88)	12.4 (7.77)	14.4 (13.7)
MRT (hr)	12.4 (9.10)[a]	21.7 (5.29)[a]	16.0 (3.32)[a]	32.9 (21.1)[b]

[a,b] Superscripts denote the dissimilarity between mean ± SD at $P < 0.05$.

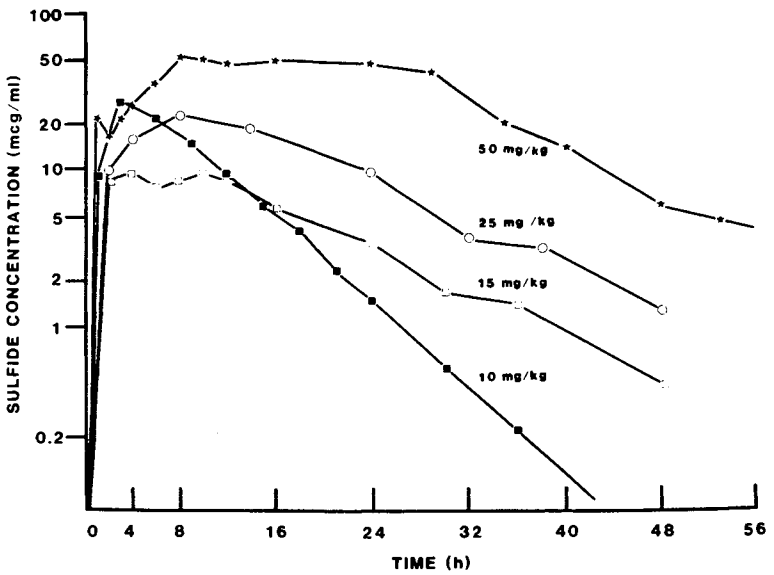

Fig. 3. Mean plasma profiles of the sulfide (S) after single peroral doses of 10 (N = 7), 15 (N = 6), 25 (N = 5), and 50 (N = 6) mg/kg sulfide.

DISCUSSION

After repeated dosing with SO (5 × 10 mg/kg/day), no significant changes in pharmacokinetic parameters were observed (Table I). However, this does not preclude the possibility of changes in disposition kinetics if more frequent dosing, larger dose sizes, or longer treatment is applied. It has been shown in humans that SO induces microsomal metabolic enzyme systems in the liver (17,18); chronic administration results in enzyme induction, increased formation of S by selection of gut bacteria, which in turn reduces the $t_{1/2}$ of S (14). In humans (9) and in rabbits (14) the production of S occurs mainly in the contents of the hindgut. Therefore, enzyme induction by SO and the subsequent decrease in S $t_{1/2}$ in rabbits are not impossible.

After repeated dosing with S (5 × 10 mg/kg/day) in the same rabbits receiving SO in separate experiments, some changes in disposition kinetics were observed in terms of $t_{1/2}$ and t_{max} (Table II). Due to the existence of reversible metabolism, as evidenced in earlier reports (8,9) and in part I of this study (21), the administration of SO or of S to the rabbits could be viewed as the same process, because in both cases the AUC of SO is always the lowest among the three substances and the terminal disappearance $t_{1/2}$ for each substance is similar (Tables I and II). We observed a significantly decreased S $t_{1/2}$ (Table II) after multiple dosing with S. This observation could partly support the hypothesis of enzyme induction by SO and/or S in rabbits. However, the AUC ratios of SO (0.09) and OH-S (0.4) to S remain unchanged. Since in repeated administrations of both SO and S the AUC of S is the highest of the three substances in plasma, it is possible that the previous reports of enzyme induction (9,17,18) and the drug–drug interactions (for review see Ref. 19) may be due to S, instead of SO.

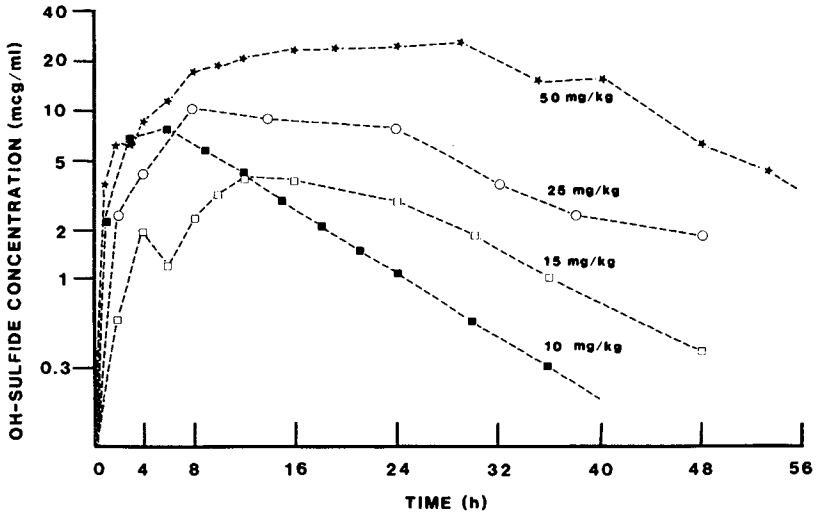

Fig. 4. Mean plasma profiles of the p-OH-sulfide (OH-S) after single peroral doses of 10 (N = 7), 15 (N = 6), 25 (N = 5), and 50 (N = 6) mg/kg sulfide (S).

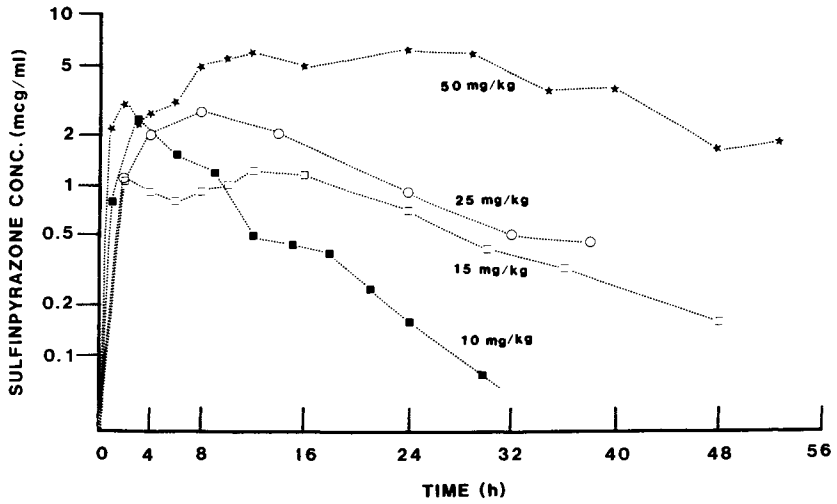

Fig. 5. Mean plasma profiles of sulfinpyrazone (SO) after single peroral doses of 10 (N = 7), 15 (N = 6), 25 (N = 5), and 50 (N = 6) mg/kg sulfide (S).

Contrary to the multiple administration of a lower S dose (Fig. 2), the single intake of a higher dose produces a somewhat different disposition picture (Figs. 3–5) and results in greater variations in pharmacokinetic parameters (Table III). The delayed peak concentrations may be caused by nonlinear absorption. However, enterohepatic recycling may also be responsible. It appears that higher single doses and lower chronic doses of S produce different disposition pictures.

Since three major events are associated with disposition kinetics, i.e., reversible metabolism, enterohepatic recirculation, and the role of hindgut bacteria, which complicate the explanations of kinetic changes, further investigations are required before the conclusion of dose-dependent disposition of SO and its metabolites can be verified.

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