CHIRALITY 10:747–753 (1998)

Stereoselective Chiral Inversion of Pantoprazole Enantiomers After Separate Doses to Rats

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ABSTRACT (±)-Pantoprazole ((±)-PAN), (±)-5-(difluoromethoxy)-2-[[(3.4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole) is a chiral sulfoxide that is used clinically as a racemic mixture. The disposition kinetics of (+)-PAN and (–)-PAN given separately has been studied in rats. Serum levels of (+)- and (–)-PAN and its metabolites, pantoprazole sulfone (PAN-SO_2), pantoprazole sulfide (PAN-S), 4′-O-demethyl pantoprazole sulfone (DMPAN-SO_2), and 4′-O-demethyl pantoprazole sulfide (DMPAN-S) were measured by HPLC. Following single intravenous or oral administration, both enantiomers were rapidly absorbed and metabolized, resulting in similar serum concentrations, suggesting that the two enantiomers have approximately the same disposition kinetics. The major metabolite of both (+)- and (–)-PAN was PAN-SO_2, while DMPAN-SO_2 was also detected as a minor metabolite. Serum levels of PAN-S and DMPAN-S could not be quantified after intravenous or oral administration of either enantiomer.

Significant chiral inversion occurred after intravenous and oral administration of (+)-PAN. The AUCs of (–)-PAN after intravenous and oral dosing of (+)-PAN were 36.3 and 28.1%, respectively of those of total [(+) + (–)] PAN. In contrast, the serum levels of (+)-PAN were below quantitation limits after intravenous or oral administration of (–)-PAN. Therefore, chiral inversion was observed only after administration of (+)-PAN, supporting the hypothesis that stereoselective inversion from (+)-PAN to (–)-PAN occurs in rats. *Chirality 10:747–753, 1998.*

KEY WORDS: pantoprazole; proton pump inhibitor; chiral inversion; stereoselective pharmacokinetics; rats

(±)-Pantoprazole ((±)-PAN), (±)-5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole is a substituted benzimidazole sulfoxide, which is a selective and long-acting proton pump inhibitor (PPI).[1] In healthy Caucasian subjects, PAN was well tolerated after single and multiple intravenous and oral administrations and resulted in a dose-dependent reduction in gastric acid output.[2–5] PAN has been approved for the treatment of acid-related gastrointestinal disorders such as reflux esophagitis and duodenal and gastric ulcers.[6] PAN is currently under Phase 2 clinical trials in Japan for use as an antiulcer drug.

Compounds that contain tricoordinated sulfur atoms in pyramidal structure exist in distinct optically active forms. This applies to the sulfoxide center of PAN, which is used clinically as the racemate (Fig. 1). Omeprazole,[7] the first substance of this class, and other PPIs like lansoprazole[8] and E3810[9] are all chiral benzimidazole sulfoxides and are administered as racemic mixtures.

The molecular chirality is of great concern in terms of drug metabolism and pharmacological mechanisms.[10–12] There are no significant differences in pharmacological activities between the enantiomers of PPIs in experimental animals,[13–16] as both enantiomers are converted by a sequence of chemical reactions to the same active, achiral form.[13] Recent advances in analytical methods for the separation of enantiomers of PPIs have led to considerable interest in the stereoselective pharmacokinetics of PPI enantiomers.[11,12,14,17] For example, the pharmacokinetics of the enantiomers of omeprazole,[14] lansoprazole,[11] E3810,[12] and PAN[17] have been investigated either in humans or experimental animals.

It has been reported that chiral inversion of the sulfoxide drug flosequinan occurred in rats via formation of the sulfide metabolite. This sulfide metabolite is produced by reduction of the sulfoxide group and its subsequent oxidation results in both flosequinan enantiomers.[18] In rats, PAN undergoes extensive metabolism to form PAN-SO_2 as a major metabolite and PAN-S as a minor metabolite (unpublished data). It is, therefore, possible that reoxidation of PAN-S to PAN, similar to flosequinan occurs in vivo, resulting in the chiral inversion of PAN enantiomers. However, to date there are no published reports on the chiral

Abbreviations used: PPI, proton pump inhibitor; PAN, pantoprazole; (+)-PAN, (+)-pantoprazole; (–)-PAN, (–)-pantoprazole; PAN-SO_2, pantoprazole sulfone; PAN-S, pantoprazole sulfide; DMPAN-SO_2, 4′-O-demethylated pantoprazole sulfone; DMPAN-S, 4′-O-demethylated pantoprazole sulfide.

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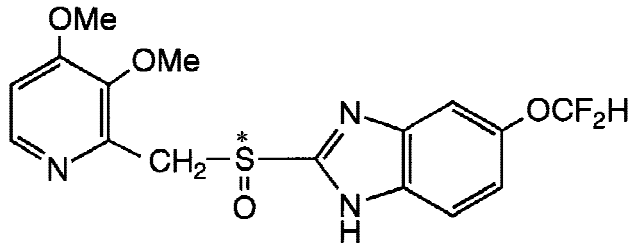
Received for publication 16 July 1997; Accepted 1 November 1997



Pantoprazole (PAN)

Fig. 1. Chemical structure of PAN. *Position of chiral center.

inversion of PAN. Another PPI, E3810, has been shown not to undergo chiral inversion in vivo in beagles.[19]

In this study, the pharmacokinetics of PAN enantiomers and their metabolites after separate intravenous or oral administration of each enantiomer (dosed at 10 mg/kg) was investigated in rats to examine the chiral inversion of the drug and its mechanism.

MATERIALS AND METHODS

Materials

PAN, PAN-SO_2, PAN-S, DMPAN-SO_2, and DMPAN-S were supplied by Byk Gulden Co., GmbH. (Konstanz, Germany). (+)-PAN and (–)-PAN were prepared in Daicel Chemical Industries, Ltd. (Tokyo, Japan). The optical purity of (+)-PAN and (–)-PAN was more than 99.0%. The absolute configurations of (+)-PAN and (–)-PAN have not been established. *N*-Butyryl-p-aminophenol was purchased from ICN Biomedicals, Inc. (Costa Mesa, CA). Phenacetin was purchased from Sigma Chemical Co., Ltd. (St. Louis, MO). All other reagents were commercially available and of analytical grade.

Kinetic Studies

Male Sprague-Dawley rats (body weight: 220–240 g) were purchased from Japan SLC (Shizuoka, Japan). All animals were maintained on commercial chow and tap water ad libitum for 1 week. Prior to drug administration animals were fasted overnight with water available ad libitum. A total of 72 rats were divided into four experimental groups of 18 each and 3 animals were assigned to each time point.

(+)-PAN and (–)-PAN were dissolved in saline (Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan) containing 0.5% 1N NaOH and 5% ethanol and administered intravenously or orally at a dose of 10 mg/2 ml/kg to rats. Blood samples (5 ml) were collected at 5, 30 min, 1, 2, 4, and 8 hr after dosing by carotid puncture. Blood samples were centrifuged at 1,500*g* for 10 min to obtain serum and samples were stored at –20°C until analysis.

Chiral HPLC Analysis for Enantiomers

The concentrations of (+)-PAN and (–)-PAN in serum samples were determined using a modification of a stereospecific HPLC method as reported previously.[17] Following an on-line solid phase sample clean-up, the enantiomers were separated on a cellulose-based chiral stationary phase [Chiralcel OJ-R (150 × 4.6 mm i.d., 5 µm particle size) (Daicel Chemical Industries, Tokyo, Japan)] using a column switching device. The column was eluted with a multistep linear gradient of 50 µM sodium perchlorate mixed with acetonitrile at a flow rate of 0.5 ml/min. The mobile phase was degassed by Degasys DG-1310 (Uniflows, Tokyo, Japan). The gradient used for the analytical separation was as follows: an initial wash of 20% acetonitrile for 2 min, then acetonitrile was increased linearly to 30% at 25.0 min, increased to 100% at 25.1 min, maintained at 100% until 26.0

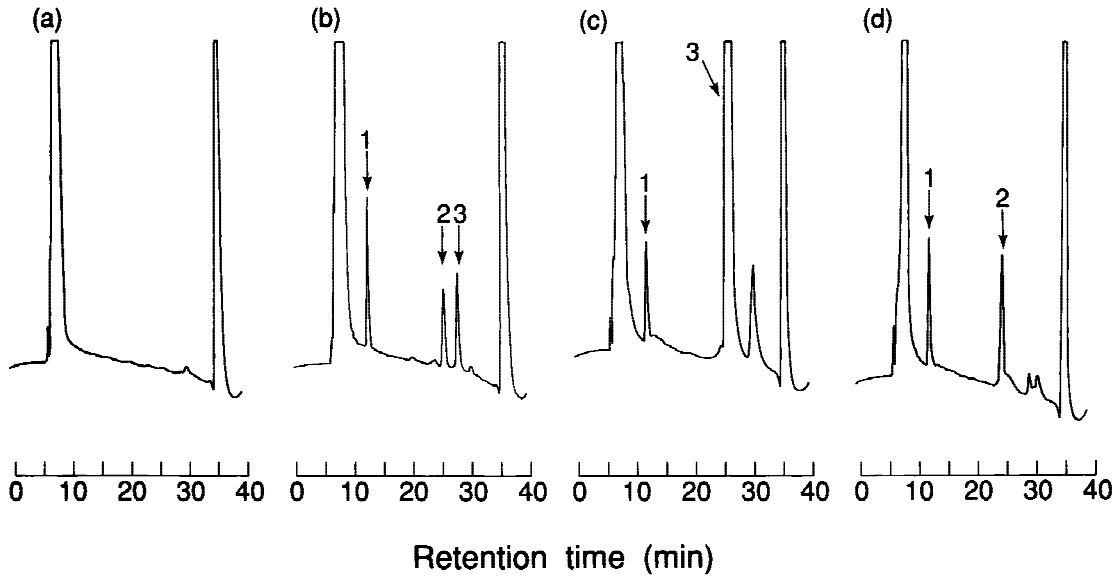


Fig. 2. HPLC chromatograms of serum samples obtained from male rats that received a single iv dose of (+)-PAN (10 mg/kg). **a:** Control serum. **b:** Control serum spiked with (+)- and (–)-PAN (1 µg/ml each). **c:** Serum samples obtained 5 min after administration. **d:** Serum samples obtained 8 hr after administration. Peak 1, IS (*N*-Butyryl-p-aminophenol); 2, (–)-PAN; 3, (+)-PAN.

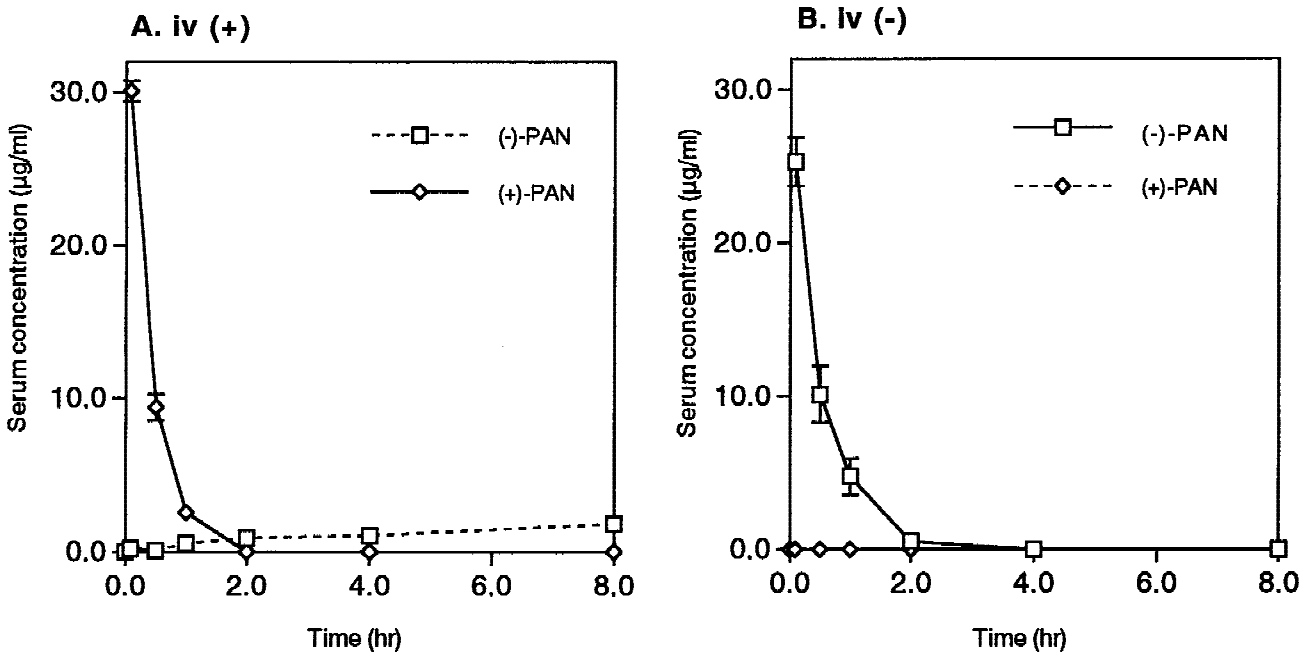


Fig. 3. Serum concentration-time profile of (+)-PAN and (–)-PAN following intravenous administration of (+)-PAN **(A)** and (–)-PAN **(B)**. Each point represents the mean ± SD of three rats.

min, reduced back to 20% at 26.1 min, and maintained there up to 40.0 min. *N*-Butyryl-*p*-aminophenol was used as an internal standard (IS). PAN enantiomers and the IS were detected by monitoring UV absorption of the column effluent at 290 nm.

HPLC Analysis for Metabolites

The concentrations of PAN metabolite in rat serum were determined by a column-switching HPLC method. The HPLC system consisted of two pumps (Model L-6200 and L-6000, Hitachi, Tokyo, Japan) and a UV detector (Model L-4000, Hitachi) with the detection wavelength set to 290 nm. An autosampler (Model AS-4000, Hitachi) and column switching module (Model, E1E010, Senshu Scientific Co., Tokyo, Japan) were used for the introduction of samples. Serum samples were injected into the precolumn (LiChroprep RP-2, 25–40 µm particle size, 10 × 6.0 mm i.d.) (E. Merck, Darmstadt, Germany), which was washed with 150 mM acetate buffer (pH 5.0)/acetonitrile (80:20, v/v) at a flow rate of 1.0 ml/min for 2 min. Then, by valve operation, the analytical mobile phase was introduced in back-flush mode to the precolumn, which was in line with the analytical column. In addition, a LiChrospher 100, RP-18 (4 × 4 mm i.d., 5 µm particle size) (E. Merck, Darmstadt, Germany) was employed as a guard column ahead of the analytical column. A TSK-GEL ODS-80TM (150 × 4.6 mm I.D, Tosoh) was used as the analytical column. The column temperature was maintained at 40°C by a column oven (model U-620, Type 30, SugaiChemy Co. Ltd., Tokyo, Japan).

A mixture of 10 mM phosphate buffer (diammonium hydrogen phosphate-ammonium dihydrogen phosphate) (pH 6.8) and acetonitrile/methanol (4:1) was used as the mobile phase at a flow rate of 1.0 ml/min. The mobile phase was degassed by Degasys DG-1310. The gradient used for the analytical separation was as follows: 19% acetonitrile/methanol for 2 min, then acetonitrile/methanol was increased linearly to 28% at 8.0 min, maintained at 28% up until 14 min, increased to 46% at 22.0 min, 68% at 33.0 min, 100% at 33.1 min, kept at 100% until 34.0 min, reduced back to 19% at 34.1 min, and maintained there up to 40.0 min. The content of acetonitrile in the mobile phase was increased in order to elute non-polar endogenous com-

TABLE 1. Pharmacokinetic parameters of (+)-PAN and (–)-PAN after intravenous administration of each enantiomer to male rats (10 mg/kg)*

Parameters		(+)-PAN	(–)-PAN
AUC_{0-8hr}	(µg · hr/ml)	15.2	16.5
$T_{1/2}$	(hr)	0.258	0.345
MRT	(hr)	0.310	0.482
Cl_{tot}	(ml/min/kg)	11.2	10.3

*$AUC_{0/-8hr}$, area under the curve of serum concentration from 0–8 hr after dosing; $T_{1/2}$, serum elimination half-life; MRT, mean residence time; Cl_{tot}, serum total clearance.

TABLE 2. AUC_{0-8hr} of PAN-SO_2, PAN-S, DMPAN-SO_2, and DMPAN-S after oral and intravenous administration of each enantiomer to male rats (10 mg/kg)*

	AUC_{0-8hr} (µg · hr/ml)		
Dose	PAN-SO_2	PAN-S	DMPAN-SO_2
(+)-PAN (po)	15.6	ND	1.20
(–)-PAN (po)	17.6	0.09	1.02
(+)-PAN (iv)	13.4	ND	0.676
(–)-PAN (iv)	20.3	ND	1.45

*ND, not detected; DMPAN-S, ND.

TABLE 3. AUC_{0-8h} of (+)-PAN and (–)-PAN after oral and intravenous administration of each enantiomer to male rats (10 mg/kg)

Dose	AUC_{0-8h} (μg · hr/ml)		Apparent inversion ratio (%)[a]
	(+)-PAN	(–)-PAN	
(+)-PAN (po)	9.38	3.66	28.1
(–)-PAN (po)	ND	9.87	ND
(+)-PAN (iv)	15.2	8.66	36.3
(–)-PAN (iv)	ND	16.5	ND

[a]Apparent inversion ratio (%) = AUC_{0-8h} of (–)- or (+)-PAN/(AUC_{0-8h} of (–)-PAN + AUC_{0-8h} of (+)-PAN) × 100.

pounds, which caused an increase in column pressure following repeated analyses. Phenacetin was used as an internal standard (IS). The retention times of DMPAN-SO_2, DMPAN-S, PAN-SO_2, PAN, PAN-S, and IS were 10.5, 19.7, 21.7, 23.7, 29.2, and 15.0 min, respectively.

Pharmacokinetic and Statistical Analysis

The software used for the pharmacokinetic analysis was TopFit[20] and the pharmacokinetic parameters for PAN were determined using a model independent method. Maximum serum concentration (Cmax) and the time to reach Cmax (tmax) were obtained directly from the observed values. The area under the concentration-time curve (AUC) was calculated by the linear trapezoidal rule using the mean serum concentrations from three animals. The mean residence time (MRT) was calculated as the ratio of the area under the first moment curve (AUMC; 0–8 hr) to AUC (0–8 hr). The total body clearance (Cltot) after iv administration was calculated by using the equation Cltot = Dose/AUC (0–8 hr). AUC after iv administration from 0 to the first data point was extrapolated by linear regression. The apparent total body clearance (Cltot/F) after po administration was calculated by using the equation Cltot/F = Dose/AUC (0–∞ hr), where F is the unknown fraction of drug available to systemic circulation. The AUC (0–8 hr) was used to calculate the apparent inversion ratio.

If the serum concentrations of PAN enantiomers and their metabolites were below quantitation limit, they are reported as ND. The mean and standard deviation of individual values were calculated by regarding ND as zero. Statistical differences between the serum concentrations were determined by employing the Student's *t*-test and a *P* value of less than 0.05 was considered statistically significant.

RESULTS

Pharmacokinetics After Intravenous Administration of Enantiomers

The lower limit of quantitation for both (+)-PAN and (–)-PAN in rat serum was found to be 0.25 μg/ml. The intra-day and inter-day accuracy and precision, as indicated by relative error (RE) (%) and CV (%) were within 15% (n = 3). No racemization of either enantiomer was observed in serum during the time required for assay. The lower limit of quantitation for DMPAN-SO_2, DMPAN-S, PAN-SO_2, PAN, and PAN-S was determined to be 0.20 μg/ml. The intra-day and inter-day accuracy and precision were within 17% above quantitation limit and within 22% at the limit of quantitation. HPLC chromatograms of serum samples obtained from rats that received an intravenous dose to male rats (10 mg/kg) of (+)-PAN are shown in Figure 2.

The mean serum concentrations of (+)- and (–)-PAN are shown in Figure 3. The pharmacokinetic parameters for the PAN enantiomers and metabolites are shown in Tables

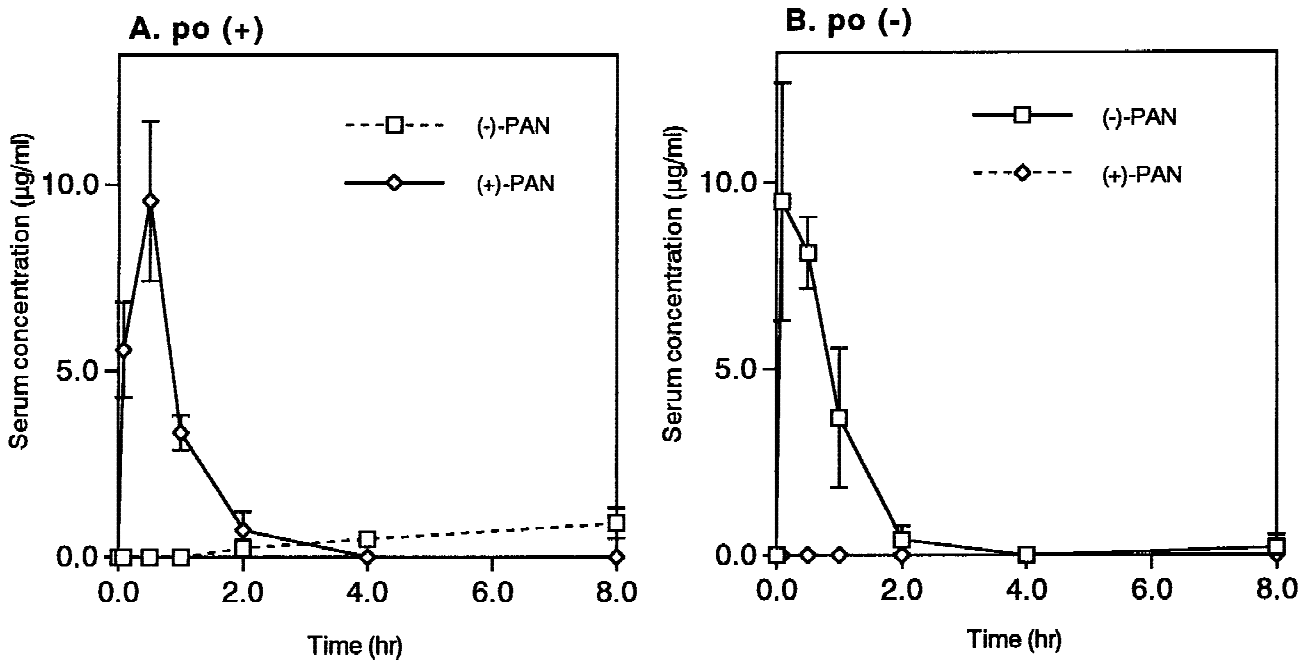


Fig. 4. Serum concentration-time profile of (+)-PAN and (–)-PAN following oral administration of (+)-PAN **(A)** and (–)-PAN **(B)**. Each point represents the mean ± SD of three rats.

TABLE 4. Pharmacokinetic parameters of (+)-PAN and (–)-PAN after oral administration of each enantiomer to male rats (10 mg/kg)*

Parameters		(+)-PAN	(–)-PAN
T_{max}	(hr)	0.50	0.08
C_{max}	(μg/ml)	9.56	9.50
$AUC_{0–8hr}$	(μg · hr/ml)	9.38	9.87
MRT	(hr)	0.748	0.935
Cl_{tot}/F	(ml/min/kg)	18.4	16.1

*T_{max}, time of peak serum concentration; C_{max}, peak serum concentration; AUC_{0-8hr}, area under the curve of serum concentration from 0–8 hr after dosing; MRT, mean residence time; Cl_{tot}/F, serum total clearance.

1 and 2, respectively. Serum concentrations of both enantiomers declined very rapidly with a $t_{1/2}$ of 0.258 and 0.345 hr, respectively (Fig. 3). The change in the serum concentration of (+)-PAN was similar to that of (–)-PAN and there was no significant difference in AUC (0–8 hr) between the two enantiomers (15.2 for (+)-PAN vs. 16.5 μg · hr/ml for (–)-PAN) (Table 1). In addition, there was no significant difference in serum levels of (+)- and (–)-PAN at any time point.

The major metabolite of both (+)- and (–)-PAN was PAN-SO_2, while DMPAN-SO_2 was found as a minor metabolite. Serum levels of PAN-S and DMPAN-S were not quantifiable after intravenous administration of either enantiomer. After dosing of (+)-PAN and (–)-PAN, the AUCs of PAN-SO_2 were 13.4 and 20.3 μg · hr/ml, respectively, and the AUCs of DMPAN-SO_2 were 0.676 and 1.45 μg · hr/ml, respectively. The AUCs of PAN-SO_2 were comparable to those obtained for the parent drug (Fig. 5).

Significant chiral inversion occurred after the intravenous administration of (+)-PAN, resulting in an AUC of (–)-PAN of 8.66 μg · hr/ml. The apparent inversion ratio, defined as the ratio of AUC of (–)-PAN to the sum of the AUCs of (+)- and (–)-PAN, was 36.3% (Table 3). On the other hand, after intravenous administration of (–)-PAN, (+)-PAN could not be detected in serum. These data suggest a stereoselective inversion from (+)-PAN to (–)-PAN in rats.

Pharmacokinetics After Oral Administration of (+)- and (–)-PAN

Changes in the serum concentrations of (+)- and (–)-PAN after a single oral administration of (+)- or (–)-PAN (10 mg/kg) to male rats are shown in Figure 4. The pharmacokinetic parameters for the PAN enantiomers and their metabolites are shown in Tables 4 and 2, respectively.

After oral dosing of (+)- or (–)-PAN, the enantiomers were rapidly absorbed with tmax values of 0.5 hr and 5 min, respectively. The serum concentration profile over time of (+)-PAN was similar to that of (–)-PAN and no differences in Cmax and AUC (0–8 hr) of (+)- and (–)-PAN were observed (9.56 vs. 9.50 μg/ml and 9.38 vs. 9.87 μg · hr/ml, respectively) (Table 4). There was no significant difference in serum levels of the enantiomers at any time point.

The major metabolite of both (+)- and (–)-PAN was PAN-SO_2, and DMPAN-SO_2, was only detected as a minor metabolite. Serum levels of PAN-S and DMPAN-S were not quantifiable following oral administration of either enantiomer. The AUCs of PAN-SO_2 were 15.6 and 17.6 μg · hr/ml, respectively, and the AUCs of DMPAN-SO_2 were 1.20 and 1.02 μg · hr/ml, respectively. The AUCs of PAN-SO_2 were greater than those of the parent drug following oral dosing of either enantiomer (Fig. 6).

As was observed for intravenous administration of (+)-PAN, a significant chiral inversion occurred after oral administration of (+)-PAN. After administration of (+)-PAN, the AUC of (–)-PAN was 3.66 μg · hr/ml and the apparent inversion ratio was 28.1% (Table 3). On the other hand, serum levels of (+)-PAN were not quantifiable after oral dosing of (–)-PAN. Therefore, the chiral inversion was observed only after administration of (+)-PAN, again suggesting a stereoselective chiral inversion from (+)-PAN to (–)-PAN occurs in rats. The extent of inversion after oral dos-

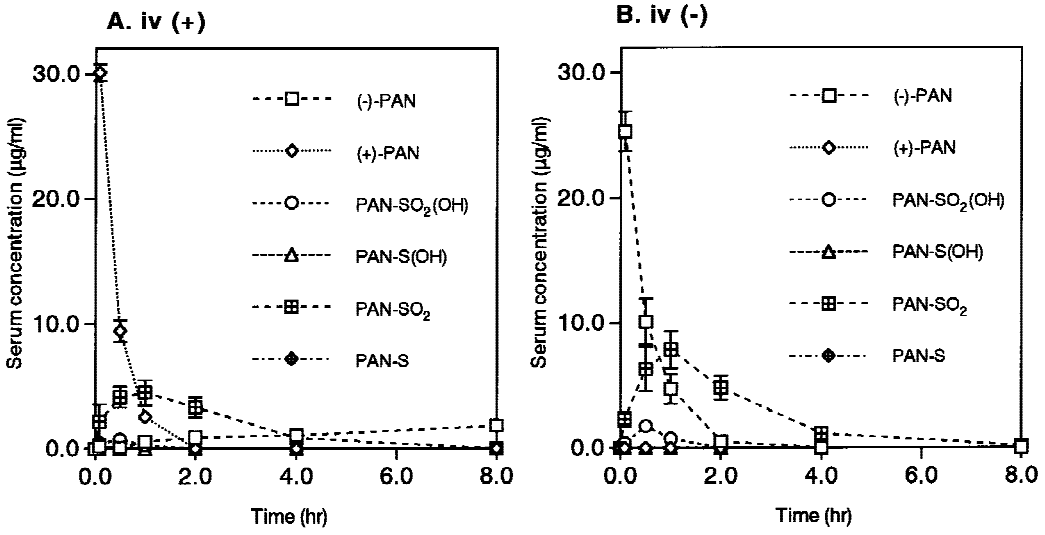


Fig. 5. Serum concentration-time profile of (+)-PAN and (–)-PAN and their metabolites following intravenous administration of (+)-PAN **(A)** and (–)-PAN **(B)**. Each point represents the mean ± SD of three rats.

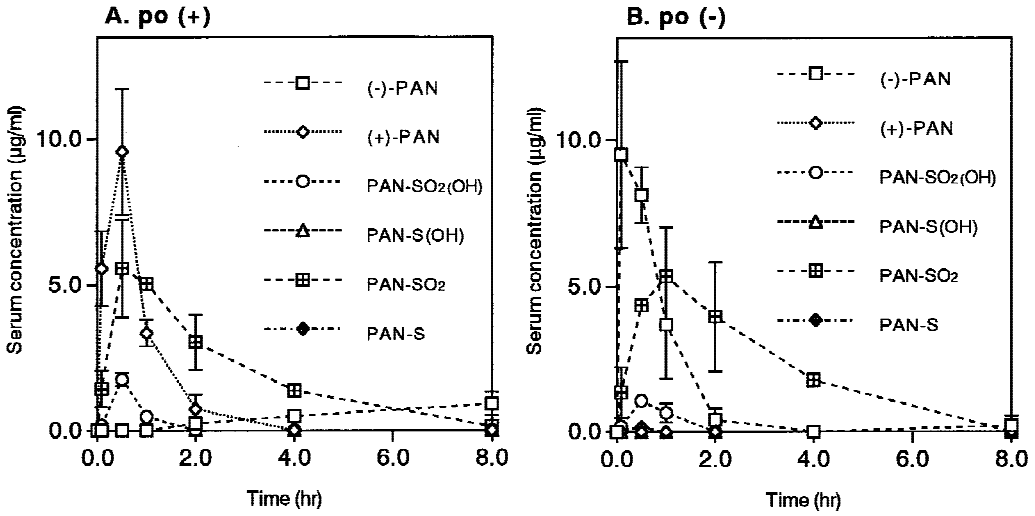


Fig. 6. Serum concentration-time profile of (+)-PAN and (–)-PAN and their metabolites following oral administration of (+)-PAN **(A)** and (–)-PAN **(B)**. Each point represents the mean ± SD of three rats.

ing was slightly lower than that seen after intravenous administration.

DISCUSSION

We have previously reported that the metabolic disposition of PAN is under pharmacogenetic control of S-mephenytoin 4′-hydroxylase (CYP2C19).[21] CYP2C19 is polymorphically expressed, meaning that a few individuals, i.e., poor metabolizers (PMs), within the population lack this enzyme activity.[22] The clearance of PAN in PMs of S-mephenytoin 4′-hydroxylase was much lower than clearance in extensive metabolizers (EMs). PMs of S-mephenytoin 4′-hydroxylase metabolize PAN more slowly than EMs.[21] The elimination half-lives in PMs were approximately 5 times longer than in EMs (6.86 vs. 1.40 hr).[21] We have also previously investigated the stereoselective pharmacokinetics of PAN enantiomers in EMs and PMs after a single oral dose of (±)-PAN.[23] In the EMs, at each dose, serum concentrations of (–)-PAN were slightly higher than those of (+)-PAN, while in the PMs, serum concentrations of both enantiomers were much higher than those in the EMs and the AUCs for (+)-PAN was greater than that for (–)-PAN. Therefore, the metabolism of (+)-PAN is impaired to a greater extent than (–)-PAN in the PMs, resulting in the stereoselective disposition of PAN enantiomers in the PMs.

In the present study, we have selected the rat as a test model for chiral inversion of the individual PAN enantiomers, because the corresponding experiment in humans is impractical. Both after intravenous or oral administration, the chiral inversion occurred only with (+)-PAN. The mechanism for the unidirectional chiral inversion from (+)-PAN to (–)-PAN is not clear at present. It is assumed to be due to stereoselective formation of (–)-PAN in either the reversible redox reaction between the sulfoxide and sulfide, or between the sulfoxide and sulfone. Inversion of the chiral sulfoxide drug flosequinan occurs in rats via reduction of the sulfoxide group to form the sulfide, followed by oxidation of the sulfide to both flosequinan enantiomers.[18,24] Sulfoxide moieties can undergo oxidative metabolism by cytochrome P450[25,26] and/or by flavin containing monooxygenase,[25,26] and can undergo reductive metabolism by aldehyde oxidase[27] and/or thioredoxin-linked enzymes.[27] Both liver and gut flora are potential sites for formation of the sulfide metabolites.[24–27] To date there are no reports regarding the microbial metabolism of PAN. Interestingly, both omeprazole[28] and lansoprazole[29] are known to be metabolized by both liver and gut flora in rats. However, chiral inversion of (+)-PAN occurred after both routes of administration, and the extent of chiral inversion was slightly higher after intravenous administration, indicating that the chiral inversion of (+)-PAN to (–)-PAN was predominantly systemic.

Three possible mechanisms for the chiral inversion of PAN enantiomers in rats are as follows: (1) chiral inversion occurred via formation of the sulfide metabolite (PAN-S)

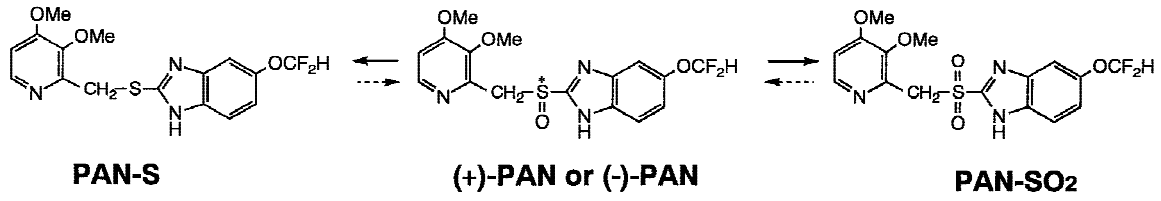


Fig. 7. Possible metabolic pathways of PAN. *Position of chiral center. A solid arrow means an identified pathway and a broken arrow means an unidentified one.

formed by reduction of the sulfoxide group of PAN, followed by a stereoselective oxidation of the sulfide to (–)-PAN; (2) chiral inversion occurred via formation of the sulfone metabolite (PAN-SO_2) formed by oxidation of the sulfoxide group of PAN, followed by stereoselective reduction of the sulfone to (–)-PAN (Fig. 7); (3) chiral inversion occurred via formation of the unknown intermediate metabolite formed from PAN, followed by a stereoselective oxidation and/or reduction of the metabolites to (–)-PAN. PAN enantiomers probably undergo enantioselective oxidation and/or reduction in rats. In the present study, the serum concentrations of PAN-S were below quantitation limits, except after oral administration of (–)-PAN. The explanation for this may be that the rate of oxidation of PAN-S to PAN enantiomers might be faster than the rate of reduction from PAN enantiomers to PAN-S. On the other hand, PAN-SO_2 was the major metabolite of both (+)- and (–)-PAN. Therefore, it is difficult to elucidate the mechanism for the chiral inversion from the results obtained in the present study.

In conclusion, the unidirectional chiral inversion from (+)- to (–)-PAN was observed after either oral or intravenous dosing of (+)-PAN. Further in vitro and in vivo studies are required to elucidate the mechanism of this unidirectional chiral inversion from (+)- to (–)-PAN.

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