Pharmacokinetics and Bioinversion of Ibuprofen Enantiomers in Humans

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An open, randomized, six-way crossover study was conducted in 12 healthy males to assess pharmacokinetics and bioinversion of ibuprofen enantiomers. The mean plasma terminal half-life ($t_{1/2}$) of R(−)ibuprofen was 1.74 hr when intravenously infused as a racemic mixture and was 1.84 hr when intravenously infused alone. The mean $t_{1/2}$ of S(+)ibuprofen was 1.77 hr when dosed as S(+)ibuprofen. Examination of values of both the absorption and disposition parameters of R(−)ibuprofen revealed that the kinetics of R(−)ibuprofen were not altered by concurrent administration of S(+)ibuprofen. In this study, there was little or no presystemic inversion of R(−)ibuprofen to its S(+)isomer. Also, 69% of the intravenous dose of R(−)ibuprofen was systemically inverted and 57.6% of the oral dose of R(−)ibuprofen lysinate was bioavailable as S(+)ibuprofen. These results indicate that the bioinversion of R(−)ibuprofen administered orally is mainly systemic. Because bioinversion of R(−)ibuprofen is not complete, S(+)ibuprofen produced higher bioavailability of S(+)ibuprofen (92.0%) than either racemic ibuprofen (70.7%) or R(−)ibuprofen (57.6%). However, bioavailability of R(−)ibuprofen (83.6%) when dosed alone was not significantly different from when dosed as racemic mixture (80.7%).

KEY WORDS: ibuprofen enantiomers; pharmacokinetics; bioinversion; bioavailability.

INTRODUCTION

Ibuprofen is an effective and well-tolerated nonsteroidal anti-inflammatory agent which is marketed commercially as the racemic mixture of R(−) and S(+)enantiomers. In 1973, Mills *et al.* reported that metabolites in human urine were dextrorotatory after oral administration of R(−)ibuprofen (1). Subsequently, it was shown in humans that 70% of the intact and hydroxylated ibuprofen was recovered in urine as S(+)enantiomers following a racemate dose, 80% of intact and 54% of hydroxylated ibuprofen was recovered in urine as S(+)enantiomers following an R(−)ibuprofen dose, and 100% of intact and hydroxylated ibuprofen was recovered in urine as S(+)enantiomers following an S(+)ibuprofen dose (2,3). Later, based on plasma data and assuming that the bioavailability of ibuprofen is complete, Lee *et al.* (4) showed that 63% of the dose of R(−)ibuprofen administered orally to humans was bioinverted to the S(+)enantiomer and bioinversion of the S(+) to R(−)ibuprofen was not measurable. These findings (1–4) indicate that the bioinversion of R(−) to S(+)ibuprofen is unidirectional in humans. Similar stereoselective (R to S) chiral inversion has also been observed for many other 2-arylpropionic acid anti-inflammatory agents in humans and laboratory animals (5–13).

Because the pharmacological activities of ibuprofen and other 2-arylpropionates are mainly, if not entirely, associated with the S(+)enantiomer (14–16), the kinetics and pathway of bioinversion of R(−)ibuprofen and its analogues are not only of pharmacokinetic and biochemical interest but also assume therapeutic importance (16,17).

An enzymatic mechanism by which R(−)ibuprofen and other chiral 2-arylpropionate undergo unidirectional bioinversion has been proposed by Nakamura *et al.* (18). According to this proposal, R(−)ibuprofen is first converted to its coenzyme A thioester, which subsequently undergoes epimerization and hydrolysis to yield S(+)ibuprofen. Not being a substrate for acyl-CoA synthetases, S(+)ibuprofen, however, is unable to undergo bioinversion. This mechanism is reinforced by the findings that *in vivo* incorporation of ibuprofen into "hybrid" triglycerides and *in vitro* formation of the CoA derivatives were highly stereoselective for R(−)enantiomer (19,20). Despite these advances in our knowledge of the bioinversion of R(−)ibuprofen, little is known about the bioinversion and its locality. Whether the bioinversion of R(−)ibuprofen in humans is systemic or presystemic remains controversial (21–23). That is to say, kinetic studies to date fail to provide definitive information on relative contribution between the rate and extent of presystemic and systemic bioinversion of R(−)ibuprofen to S(+)ibuprofen and to address the potential for interaction between the isomers (4).

Martin *et al.* (24) conducted a pharmacokinetic study of ibuprofen in humans receiving racemic ibuprofen lysine. Results of this study indicate that the pharmacokinetics of ibuprofen are linear in the dosage range of 200–400 mg and that the oral absorption of ibuprofen is complete. Although, from the results of this study, it can be deduced that the oral absorption of each enantiomer of ibuprofen is also complete, the bioavailability of ibuprofen enantiomers remains to be determined following oral administration of each enantiomer or the racemic mixture.

The objectives of this study are: (i) to determine the oral bioavailability of R(−) and S(+)ibuprofen following separate oral administration of racemic ibuprofen and each enantiomer; (ii) to evaluate the potential enantiomer–enantiomer interaction between the R(−) and S(+)ibuprofen; (iii) to investigate whether the bioinversion of R(−)ibuprofen to its S(+) isomer occurs systemically and/or presystemically; and (iv) to estimate the rate and extent of systemic bioinversion of R(−)ibuprofen.

THEORETICAL

Assuming that the disposition of R(−)ibuprofen obeys linear kinetics and is subject to presystemic and systemic metabolic inversion to its S(+) isomer (Figure 1), the rates of change of the R(−) and S(+)ibuprofen plasma concentrations [$dC_R(t)/dt$ and $dC_S(t)/dt$] can be described by the following equations:

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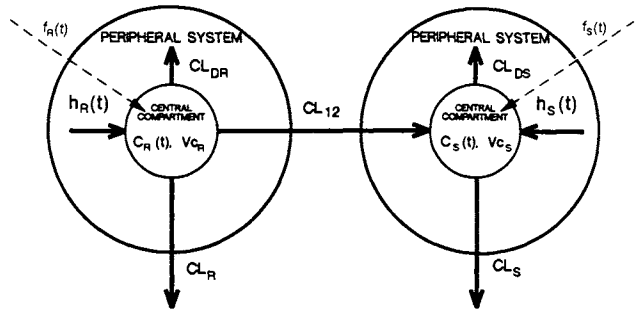

Figure 1. R(−)Ibuprofen–S(+)Ibuprofen System. $f_R(t)$ and $f_S(t)$ are input functions of R(−)ibuprofen and of S(+)ibuprofen; $C_R(t)$ and $C_S(t)$ are plasma concentrations of R(−)ibuprofen and of S(+)ibuprofen at time t; Vc_R and Vc_S are central volumes of distribution of R(−)ibuprofen and of S(+)ibuprofen; CL_{12} is the formation clearance of S(+)ibuprofen; CL_{DR} and CL_{DS} are the distribution clearances of R(−)ibuprofen and of S(+)ibuprofen; $CL_R + CL_{12}$ and CL_S are the systemic clearances of R(−)ibuprofen and of S(+)ibuprofen; and $h_R(t)$ and $h_S(t)$ are the distribution functions of R(−)ibuprofen and of S(+)ibuprofen.

$$Vc_R \cdot dC_R(t)/dt = -[CL_R + CL_{DR} + CL_{12}] \cdot C_R(t) + Vc_R \cdot C_R(t) * h_R(t) + f_R(t) \quad (1)$$

and

$$Vc_S \cdot dC_S(t)/dt = -[CL_S + CL_{DS}] \cdot C_S(t) + CL_{12} \cdot C_R(t) + Vc_S \cdot C_S(t) * h_S(t) + f_S(t) \quad (2)$$

where the subscripts R and S denote the measured R(−)ibuprofen and S(+)ibuprofen, respectively, the asterisk denotes convolution, and the other symbols are defined and depicted in Figure 1. Following oral administration of a dose, D, of R(−)ibuprofen, it follows (from Eq. 1 and 2) that:

$$CL_{11} \cdot AUC_R^{R,po} = F_R^R \cdot D^{R,po} \quad (3)$$

and

$$CL_S \cdot AUC_S^{R,po} = CL_{12} \cdot AUC_R^{R,po} + F_S^S \cdot f_{presys} \cdot D^{R,po} \quad (4)$$

where the superscripts, R and S, denote the compound dosed and the superscript po denotes oral administration, f_{presys} is the fraction of oral dose of R(−)ibuprofen inverted presystemically, and F_R^R and F_S^S are the bioavailability of R(−) and S(+)ibuprofen, respectively. From Figure 1, the total clearance of R(−)ibuprofen CL_{11} is the sum of its formation clearance to S(+)ibuprofen, CL_{12} and by other routes, CL_R. Combining Eq. 3 and 4 yields:

$$AUC_S^{R,po} = D^{R,po} \cdot [F_R^R \cdot (CL_{12}/CL_{11}) + F_S^S \cdot f_{presys}]/CL_S \quad (5)$$

Also, F_R^R and F_S^S can be calculated by

$$F_R^R = \frac{AUC_R^{R,po} \cdot D^{R,if}}{AUC_R^{R,if} \cdot D^{R,po}} \quad (6)$$

and

$$F_S^S = \frac{AUC_S^{S,po} \cdot D^{S,if}}{AUC_S^{S,if} \cdot D^{S,po}} \quad (7)$$

where the subscript if denotes intravenous infusion. From Eq. 1 and 2, it can be readily shown that:

$$AUC_S^{R,if} = D^{R,if} \cdot (CL_{12}/CL_{11})/CL_S \quad (8)$$

and

$$AUC_S^{S,if} = D^{S,if}/CL_S \quad (9)$$

Dividing Eq. 5 by Eq. 9 yields:

$$\frac{AUC_S^{R,po} \cdot D^{S,if}}{AUC_S^{S,if} \cdot D^{R,po}} = F_R^R \cdot (CL_{12}/CL_{11}) + F_S^S \cdot f_{presys} \quad (10)$$

Let F_S^R be the bioavailability of S(+)ibuprofen following the oral administration of R(−)ibuprofen. By definition,

$$F_S^R = \frac{AUC_S^{R,po} \cdot D^{S,if}}{AUC_S^{S,if} \cdot D^{R,po}} \quad (11)$$

From Eq. 10 and 11, it follows that:

$$F_S^R = F_R^R \cdot (CL_{12}/CL_{11}) + F_S^S \cdot F_{presys} \quad (12)$$

Combining Eq. 8 and 9 yields:

$$\frac{AUC_S^{R,if} \cdot D^{S,if}}{AUC_S^{S,if} \cdot D^{R,if}} = CL_{12}/CL_{11} \quad (13)$$

By definition, the fraction of the dose of R(−)ibuprofen inverted systemically to S(+)ibuprofen is (25).

$$f_{sys} = \frac{AUC_S^{R,if} \cdot D^{S,if}}{AUC_S^{S,if} \cdot D^{R,if}} \quad (14)$$

Combining Eq. 13 and 14 yields

$$f_{sys} = CL_{12}/CL_{11} \quad (15)$$

From Eq. 12 and 15, it follows that

$$f_{presys} = [F_S^R - (F_R^R \cdot f_{sys})]/F_S^S \quad (16)$$

METHODS

Clinical study

This was an open, six-period, randomized, crossover study. Treatments consisted of single oral doses of 400 mg of racemic ibuprofen, 200 mg of S(+)ibuprofen, 200 mg of R(−)ibuprofen, and separate constant, intravenous infusions of 100-ml saline solutions of racemic ibuprofen (200 mg), S(+)ibuprofen (100 mg), and R(−)ibuprofen (100 mg) over a 30-minute interval. All doses were given as the lysine salt. Each treatment was separated by washout period of at least 6 days.

Twelve male volunteers between the ages of 19 and 40, weighing between 150–199 lb, participated in the study after giving written informed consent. Subjects were judged to be in good health on the basis of history, physical examination, ECG, and routine laboratory data (hematology, blood chemistry, and urinalysis). Subjects with a history of drug and/or

alcohol abuse, asthma, thrombosis or thrombotic disease, renal or hepatic disease, psychiatric disorders, hypersensitivity precipitated by aspirin or other nonsteroidal medication, and/or multiple and/or severe allergies to drugs or foods were excluded. The use of any medication was prohibited during the period beginning 2 weeks before the study and ending after the conclusion of this study. The subjects were prohibited from ingesting any alcoholic beverages and from cigarette smoking for 48 hr before and between treatments.

After a 12-hr fast, subjects received each of the six drug treatments in this randomized crossover study. Blood samples (6 ml each) were collected in heparinized tubes prior to dosing and at 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 8, and 10 hr post dose following each oral treatment. In addition to samples obtained at these times, blood samples were also taken at 0.5 hr post dose after each intravenous treatment. Plasma was obtained from each blood sample and stored frozen at −20°C until analysis.

Assay procedure

Concentrations of R(−) and S(+)ibuprofen in plasma samples were analyzed according to a stereoselective HPLC method. The method involved extraction of the enantiomers and internal standard (2-naphthylacetic acid, Aldrich Chemical Company, Milwaukee, WI) from acidified plasma with isooctane/isopropanol (90/10, v/v) (26), derivatization with S(−)-1-(1-naphthyl)ethylamine and subsequent normal-phase determination of the resultant diastereomers (27). Standard curves of S(+) and R(−)ibuprofen in human control plasma were prepared and analyzed daily with study samples. The range of concentrations in the daily standard curve was 0.2 to 10.0 μg/ml. Coefficients of variation for replicate analysis were ≤10% at each concentration of the standard curve. The lower limit of quantitation of S(+) and R(−)ibuprofen in plasma was 0.2 μg/ml.

Data analysis

Values of AUC, mean residence time in the body (MRT), steady-state volume of distribution (V_{ss}), and plasma terminal half-life ($t_{1/2}$) were calculated by using the

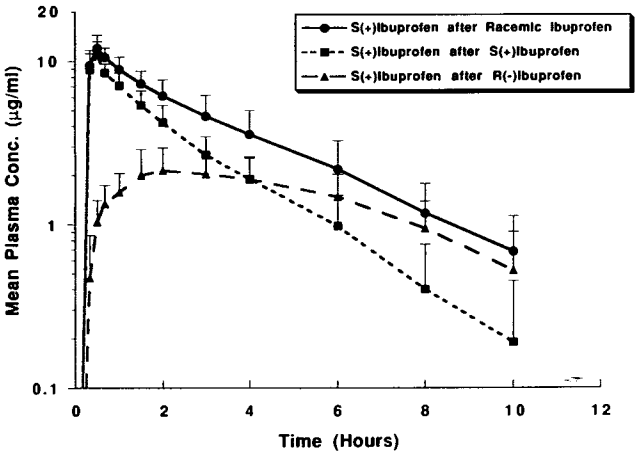

Figure 3. Mean (± S.D.; n = 12) Plasma Concentration-Time Profiles of S(+)Ibuprofen after Separate Intravenous Infusion of 200 mg of Racemic Ibuprofen And 100 mg of Each Enantiomer

LAGRAN computer program (28). Estimates of the extent of drug absorption were made using deconvolution (29). The functional forms of the rate and extent profiles have been reported previously (29) and are restated below for the convenience of the readers.

$$F(t) = \frac{D}{100}\sum_{i=1}^{L} u_i(-v_i)e^{-v_i(t-t_{lag})+} \qquad (17)$$

$$\mathrm{PCT}(t) = u_0 + \sum_{i=1}^{L} u_i e^{-v_i(t-t_{lag})+} \qquad (18)$$

where $F(t)$ is the rate of absorption, PCT(t) is the extent of absorption, t_{lag} is the lag time, u_i and v_i are results from deconvolution, u_0 is the extent of absorption as time approaches infinity, and D is the oral dose administered. Similarly, the rate and extent of systemic bioinversion of R(−)ibuprofen following i.v. infusion of R(−)ibuprofen were also calculated by deconvolution (30). In this case, $F(t)$

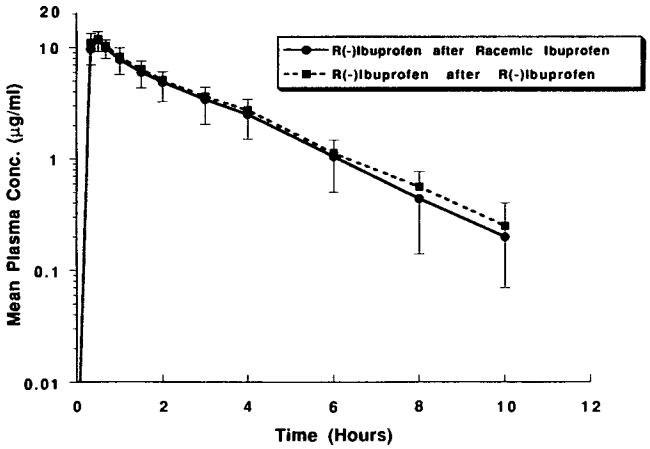

Figure 2. Mean (± S.D.; n = 12) Plasma Concentration-Time Profiles of R(−)Ibuprofen after Separate Intravenous Infusion of 200 mg of Racemic Ibuprofen And 100 mg of R(−)Ibuprofen

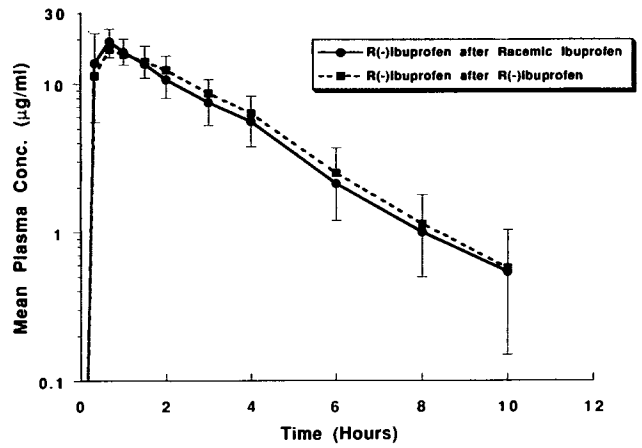

Figure 4. Mean (± S.D.; n = 12) Plasma Concentration-Time Profiles of R(−)Ibuprofen after Separate Oral Administration of 400 mg of Racemic Ibuprofen And 200 mg of R(−)Ibuprofen

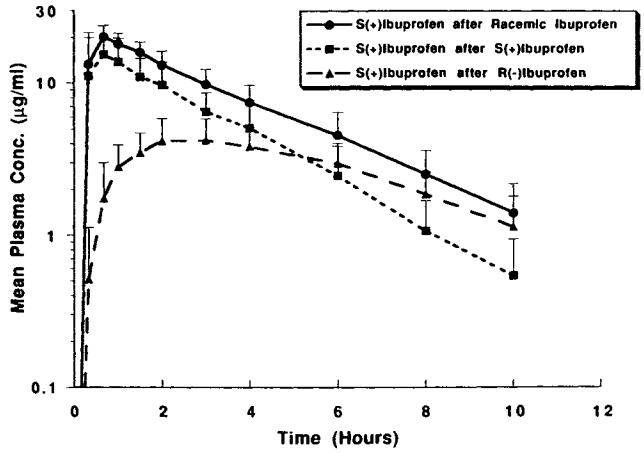

Figure 5. Mean (± S.D.; n = 12) Plasma Concentration-Time Profiles of S(+)Ibuprofen after Separate Oral Administration of 400 mg of Racemic Ibuprofen And 200 mg of Each Enantiomer

is the rate of bioinversion, PCT(t) is the extent of bioinversion, u_0 is the extent of bioinversion as time approaches infinity, and D is the intravenous dose of R(−)ibuprofen. The mean residence time of a compound in the body after i.v. administration of a bolus dose (MRT^{iv}) was obtained as the difference between MRT^{if} and $\tau/2$ (31), where τ is the intravenous infusion time and equals 0.5 hr. The mean absorption time of a compound (MAT) was obtained as the difference between MRT^{po} and MRT^{iv}. The bioavailability of R(−) or S(+)ibuprofen following oral administration of racemic ibuprofen was calculated as follows:

$$F_x^{Rac} = \frac{AUC_x^{Rac,po} \cdot D^{x,if}}{AUC_x^{x,if} \cdot D^{Rac,po}} \quad (19)$$

where x = R or S. Because R(−)ibuprofen can be considered as a prodrug of S(+)ibuprofen, a dose for racemic ibuprofen of 200 mg was used when calculating F_R^R, and a dose of racemic ibuprofen of 400 mg was used when calculating F_S^{Rac}. Statistical significance of the observed differences between pharmacokinetic parameters of R(−) and S(+)ibuprofen or of R(−) and R(−)ibuprofen following different mode of administration as tested by Student's paired t test. A p value of 0.05 or less was considered to be statistically significant.

RESULTS

Mean plasma concentration-time profiles of the individual enantiomers following separate oral and i.v. administration of racemic ibuprofen and each enantiomer are depicted in Figures 2–5. The pharmacokinetic parameter values of R(−)ibuprofen following separate i.v. infusion of R(−)ibuprofen and racemic ibuprofen are summarized in Table 1. The mean values of CL_{11}, V_{ss}, $t_{1/2}$ and MRT^{iv} for the R(−)ibuprofen intravenously administered alone were 50.1 ml/min, 7.4 liters, 1.82 hr, and 2.49 hr, respectively. Corresponding values were 58.7 ml/min, 7.8 liters, 1.74 hr, and 2.34 hr following an intravenous dose of the racemate. Also shown in Table 1 are the mean values of CL_S, V_{ss}, $t_{1/2}$, and MRT^{iv} for S(+)ibuprofen following an intravenous infusion of S(+)ibuprofen.

As shown in Table 2, the MAT for R(−)ibuprofen averaged 0.29 hr when dosed as racemic mixture and averaged 0.44 hr when dosed alone. The mean absorption time for S(+)ibuprofen averaged 0.64 hr when dosed alone. The bioavailability of S(+)ibuprofen was 92.0% when dosed orally as S(+)ibuprofen, 70.7% when dosed as racemic mixture, and 57.6% when dosed as R(−)ibuprofen (Table 3). The bioavailability of R(−)ibuprofen was 80.7% when dosed as racemic ibuprofen and was not significantly different from 83.6% when administered as R(−)ibuprofen.

The mean time courses of absorption for R(−)ibuprofen and S(+)ibuprofen following separate oral administration of racemic ibuprofen and of the individual enantiomer are depicted in Figure 6. The absorption of ibuprofen enantiomers was essentially over within 2 hours.

Fractional bioinversion of R(−)ibuprofen, presystemically (f_{presys}) or systemically (f_{sys}), in 12 subjects are presented in Table 3. On average, f_{sys} is 0.69 while f_{presys} is −0.01. The mean profiles of systemic inversion are depicted in Figure 7. On average, the maximal rate of bioinversion of R(−)ibuprofen was 23.0 mg/hr, which occurred at 0.3 hr.

DISCUSSION

Following either i.v. infusion or oral administration of R(−)ibuprofen, substantial amounts of S(+)ibuprofen were detected. No measurable amount of R(−)ibuprofen was found after administration of S(+)ibuprofen. Thus, the bioinversion of R(−)ibuprofen was unidirectional. This result is totally consistent with all previous findings (1–4) and the mechanism proposed by Nakamura *et al.* (18).

Table 1. Mean Disposition Parameter Values of S(+) and R(−)Ibuprofen in Humans

	CL (ml/min)			V_{ss} (l)			$t_{1/2}$ (hr)			MRT^{iv} (hr)		
	Rac[a]	R(−)[b]	S(+)[c]	Rac	R(−)	S(+)	Rac	R(−)	S(+)	Rac	R(−)	S(+)
Mean[d]	58.7	50.1	65.1	7.8	7.4	8.8	1.74[e]	1.82[e]	1.77[e]	2.34	2.49	2.40
S.D.	24.3	11.1	21.1	2.0	1.3	1.6	—	—	—	0.43	0.38	0.71
p value	0.157		0.010	0.426		0.010	0.220		0.699	0.146		0.527

[a] Value of R(−)ibuprofen after intravenous infusion of racemic ibuprofen
[b] Value of R(−)ibuprofen after intravenous infusion of R(−)ibuprofen
[c] Value of S(+)ibuprofen after intravenous infusion of S(+)ibuprofen
[d] n = 12
[e] Harmonic mean

Table 2. Mean Absorption Times for R(−)Ibuprofen and S(+)Ibuprofen Following Separate Oral Administration of Racemic Ibuprofen and Each Enantiomer

	MAT_R^{Rac} (hr)	MAT_R^R (hr)	MAT_S^S (hr)
Mean[a]	0.29	0.44	0.64
S.D.	0.30	0.44	0.75
p value	0.24	0.36	

[a] n = 12

Following separate intravenous infusions of S(+) and R(−)ibuprofen, the mean systemic clearance and V_{ss} for the preformed S(+)ibuprofen were significantly larger than those for the R(−)ibuprofen. However, no significant differences in mean $t_{1/2}$ and MRT^{iv} were observed between both isomers. Similarly, there were no significant differences in CL_{11}, V_{ss}, $t_{1/2}$, and MRT^{iv} for R(−)ibuprofen between intravenous infusion of racemic ibuprofen and intravenous infusion of R(−)ibuprofen. Also, there was no significant difference in MAT or F for R(−)ibuprofen between these two modes of administration. Thus, the kinetics of R(−)ibuprofen were not altered by concurrent administration of S(+)-ibuprofen. Inasmuch as the presence of S(+)ibuprofen is unavoidable following the administration of the R(−)ibuprofen, the effect of the R(−)isomer on the absorption and disposition of the S(+) antipode cannot be determined definitively.

Oral absorption of either R(−) or S(+)ibuprofen was rapid and essentially over within 2 hours post dose in most of the subjects regardless of whether these enantiomers were dose individually or as the racemic mixture. Kinetically, the fraction of dose absorbed should increase monotonically with time and reach a plateau when absorption ceases. Slight oscillation in fractions of dose absorbed, after the absorption is complete, is to be expected. This is not an error of the deconvolution process but is simply a result of the sensitivity of this process to errors present in the data and strict compliance with the assumption of invariance in disposition between treatments.

The bioavailability of S(+)ibuprofen is nearly quantitative (92.0%) when dosed as S(+)ibuprofen. S(+)ibuprofen, however, is less bioavailable when dosed as either racemic mixture or R(−)ibuprofen because the bioinversion of R(−)ibuprofen is incomplete. The bioavailability of R(−)ibuprofen is 83.6% when dosed alone and is 80.7% when dosed as the racemic mixture. This high bioavailability (83.6%) indicates that the mean fraction of the oral dose of R(−)ibuprofen inverted presystemically to S(+)ibuprofen (f_{presys}) is less than 0.17. Indeed, in this study, the mean value of f_{presys} was close to zero. Thus, in humans, there was little or no presystemic inversion of R(−)ibuprofen to its S(+)isomer. On the other hand, 69% of an intravenous dose of R(−)ibuprofen was systemically inverted and 57.6% of the oral dose of R(−)ibuprofen was bioavailable as S(+)ibuprofen. These results indicate that the bioinversion of R(−)ibuprofen administered orally is mainly systemic. This finding is consistent with the results reported by Cox (21) and Hall *et al.* (23).

In theory, assessment of f_{sys} requires plasma data from two independent sources; namely, separate intravenous doses of R(−) and S(+)ibuprofen. Previous estimates of 63% (4) have been reported following only oral administrations of individual ibuprofen enantiomers and 67% (21) wherein only R(−)ibuprofen was administered intravenously. Recently, using a stable isotope method involving coadministration of racemic ibuprofen and d_4-S(+)ibuprofen, Hall *et al.* (23) estimated f_{sys} to be approximately 60%. For all practical purposes, these estimates are all identical to the 69% derived from intravenous doses of R(−) and S(+) isomers. The congruence is possible because of the complete oral absorption of ibuprofen enantiomer(s), no significant R(−)ibuprofen–S(+)ibuprofen interaction, and negligible presystemic bioinversion of R(−) to S(+)ibuprofen.

The disposition kinetics of a generated metabolite may be different from those of the preformed metabolite owing to the presence of a diffusion barrier in the body, caused by

Table 3. Bioavailability of S(+) and R(−)Ibuprofen and Fractions of Dose of R(−)Ibuprofen Inverted

Subj.	F_S^{Rac} (%)	F_S^S (%)	F_S^R (%)	F_R^{Rac} (%)	F_R^R (%)	f_{sys}	f_{presys}
1	77.2	92.9	63.3	105	78.8	0.75	0.04
2	75.1	91.4	48.3	96.9	111	0.52	−0.11
3	66.3	80.4	43.6	88.7	91.5	0.39	0.10
4	52.0	103	51.0	77.9	57.6	0.54	0.19
5	89.6	107	52.9	77.1	103	0.94	−0.41
6	55.6	70.5	57.1	94.5	110	0.58	−0.10
7	76.2	95.0	54.6	58.3	59.5	0.76	0.10
8	72.0	106	56.5	80.0	78.6	0.98	−0.20
9	87.2	94.1	75.3	78.6	70.0	0.69	0.28
10	68.0	84.2	61.8	62.2	86.0	0.84	−0.12
11	59.4	97.1	68.9	69.5	80.1	0.62	0.20
12	80.5	89.2	66.0	96.0	101	0.69	−0.04
	70.7[a]	92.0[a]	57.6[a]	80.7[a]	83.6[a]	0.69[b]	−0.01[b]
						0.17[c]	0.20[c]

[a] Geometric mean
[b] Arithmetic mean
[c] Standard deviation

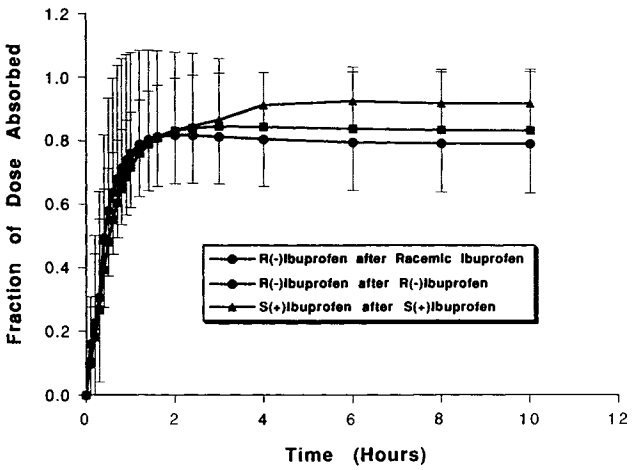

Figure 6. Mean (± S.D.; n = 12) Cumulative Absorption Profiles of Ibuprofen Enantiomers after Separate Oral Administration of Racemic Ibuprofen and Each Enantiomer. The lines were generated by connecting every two adjacent data points.

large differences in polarity between metabolite and parent drug (32,33). Estimations of f_{presys} and f_{sys} by Eq. 16 and 14 assume that no diffusion barrier for the generated S(+)ibuprofen is present in the body. The validity of this assumption seems likely in that the polarity of the metabolite, S(+)ibuprofen is not different from the parent, R(−)ibuprofen. Similarly, the absence of a pharmacokinetic interaction between R(−) and S(+)ibuprofen is a necessary condition for the valid estimations of f_{presys} and f_{sys}.

Discontinuous absorption processes have previously been reported for drugs such as cimetropium bromide (34), sulfisoxazole (35) and griseofulvin (36). The mean profile of the rate of systemic inversion showed peaks at 0.3 and 1.5 hr, suggesting that the inversion process might be discontinuous. Indeed, examination of the individual plasma concentration profiles and time courses of change in the extent and rate of systemic inversion (profiles not shown) revealed discontinuities in four out of 12 subjects.

Although little or no information is available so far on what factors may perturb the bioinversion of R(−)ibuprofen, it is possible that the irregular rate of inversion of R(−)ibuprofen observed in this study is caused by stereoselective biliary recycling of ibuprofen enantiomers. As reported previously (37), in dogs, S(+)ibuprofen undergoes biliary excretion and enterohepatic recycling, while R(−)ibuprofen does not. Also, in humans, formation of ibuprofen glucuronide conjugates favors the S(+)enantiomer (38). Thus, it is possible that biliary excretion and recycling of these conjugates favors the S(+)enantiomer.

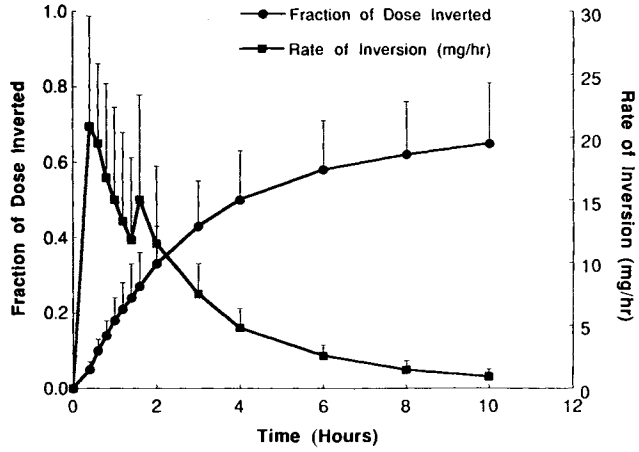

Figure 7. Profiles of Mean (± S.D.; n = 12) Rate and Extent of Systemic Inversion of R(−)Ibuprofen in Humans. The lines were generated by connecting every two adjacent data points.

Although it has been reported previously that the bioinversion of R(−)ibuprofen in rats (39), dogs (37), and humans (21,23) occurs systemically, presystemic and systemic inversions of R(−)ibuprofen have not been isolated and quantified separately in any species. In this report, equations were derived to separately quantify the presystemic and systemic components of bioinversion of R(−)ibuprofen and applied to data obtained from a clinical study. Also, the rate and extent of systemic inversion of R(−)ibuprofen were obtained by deconvolution. Methods and approaches used in this study should be generally applicable to the pharmacokinetic evaluation of drug–metabolite, prodrug–drug, or precursor–successor pairs.

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