Stereoselective Systemic Disposition of Ibuprofen Enantiomers in the Dog

Hae-Young Ahn,[1] Gordon L. Amidon,[1] and David E. Smith[1,2]

Received October 31, 1990; accepted March 28, 1991

The pharmacokinetics of ibuprofen are complicated by the unidirectional metabolic inversion of the (−)-R- to (+)-S-enantiomer. Chiral inversion is of therapeutic significance since the drug's pharmacologic activity has been shown to depend upon the (+)-S-isomer. As a result, the present study was undertaken to determine if chiral inversion occurs systemically and to elucidate further the kinetics of the inversion process. Experiments were performed in the beagle dog after intravenous bolus injections of ibuprofen enantiomers separately [100 mg (−)-R, $n = 4$; 100 mg (+)-S, $n = 4$] and as admixtures of varying proportions [100 mg (−)-R + 100 mg (+)-S, $n = 4$; 100 mg (−)-R + 200 mg (+)-S, $n = 2$]. Plasma samples of (−)-R- and (+)-S-enantiomers were measured by a stereospecific HPLC assay after all drug administrations. Based on the area under the plasma concentration–time curves for (+)-S after administration of each enantiomer alone, chiral inversion was 70 to 75%. A progressive reduction in total plasma clearance of (−)-R-ibuprofen is also observed as increasing amounts of (+)-S-enantiomer are added to the system. The results demonstrate that chiral inversion occurs to a significant extent in the systemic circulation in dog and that R-to-S inversion of ibuprofen may be inhibited by its (+)-S-enantiomer.

KEY WORDS: ibuprofen enantiomers; systemic inversion; chiral inversion; kinetics.

INTRODUCTION

The 2-arylpropionic acid class of nonsteroidal antiinflammatory drugs (NSAIDs) is of clinical importance in the treatment of rheumatoid and osteoarthritis. However, despite their widespread use, the relationship between response (i.e., analgesia) and blood levels of NSAIDs is poorly understood. This may, in part, be due to the fact that NSAIDs are usually administered as racemates even though the pharmacological activities of these mixtures are associated primarily with the S-isomer; the R-isomers are either inactive or have reduced activity (1,2). NSAIDs also have a complex pharmacokinetic profile (3–9). As a result, stereoselective differences in metabolism, protein binding, and the unidirectional metabolic inversion of (−)-R- to (+)-S-enantiomer can complicate the dose–response relationship.

Ibuprofen is a prototype NSAID of the arylpropionic acid class. Although detailed information is available concerning the drug's pharmacokinetics, certain aspects of its stereochemical disposition are still unclear (6–8). In particular, it has been proposed that the R-to-S inversion of ibuprofen takes place in the gastrointestinal tract during first-pass transit through the presystemic circulation (7,10–12). This conclusion must be viewed as tentative, however, since these authors evaluated only extravascular doses. In fact, systemic inversion cannot be ruled out because no definitive studies have characterized the stereoselective kinetics/inversion of ibuprofen after intravenous dosing. Given that chiral inversion can account for 60–70% of the elimination of the (−)-R-enantiomer or add 60–70% more of the active (+)-S-enantiomer, it is important to clarify whether systemic inversion occurs and to more fully elucidate the kinetics of the inversion process. Therefore, we studied the stereoselective disposition of ibuprofen after intravenous bolus injections of each enantiomer separately and as admixtures of varying proportions in the beagle dog.

MATERIALS AND METHODS

Chemicals

Racemic ibuprofen (Lot No. 117F-0797) was purchased from the Sigma Chemical Company (St. Louis, MO). (−)-*R*-Ibuprofen (Lot No. 0198-KWF-008; 99.9% purity, HPLC) and (+)-*S*-ibuprofen (Lot No. 0198-KWF-012; 97.5% purity, HPLC) were kindly donated by The Upjohn Company (Kalamazoo, MI). The internal standard, (±)-2-(4-benzoyl phenyl)butyric acid (Lot No. LJP 2806), was supplied by Rhone-Poulenc Pharma Inc. (Montreal, Canada). Ibuprofen doses were prepared by dissolving drug in a small amount of ethanol, diluting it with normal saline, and then adjusting the final solution for injection to pH 7.4 with dibasic sodium phosphate solution.

Experimental Design

Following an overnight fast, beagle dogs (15.8 ± 1.9-kg body weight) received a single intravenous bolus injection of ibuprofen enantiomer or admixture in a crossover fashion. Doses were administered as 100 mg (−)-*R*-ibuprofen ($n = 4$), 100 mg (+)-*S*-ibuprofen ($n = 4$), 100 mg (−)-*R*- + 100 mg (+)-*S*-ibuprofen (i.e., racemic mixture; $n = 4$), and 100 mg (−)-*R*- + 200 mg (+)-*S*-ibuprofen ($n = 2$). Food was not allowed during the study period. Blood samples (2 ml) were collected from a cephalic vein contralateral to the site of drug administration via an indwelling heparinized catheter into tubes containing EDTA. Serial blood samples were then drawn prior to and over a 10-hr period after dosing. Blood samples were centrifuged immediately after collection and the plasma was harvested and stored frozen at −20°C until analyzed.

Assay

Ibuprofen enantiomers were assayed in plasma using a stereospecific HPLC method, as previously reported (13).

Kinetics

Plasma concentration–time curves of (−)-*R*-ibuprofen [after dosing of 100 mg (−)-R, 100 mg (−)-R + 100 mg (+)-S, or 100 mg (−)-R + 200 mg (+)-S] and (+)-*S*-ibuprofen [after dosing of 100 mg (+)-S] were fit to a

[1] College of Pharmacy, The University of Michigan, Ann Arbor, Michigan 48109-1065.

[2] To whom correspondence should be addressed.

0724-8741/91/0900-1186$06.50/0

general polyexponential equation (14) using the nonlinear least-squares regression program RSTRIP (15) and a weighting factor of unity, $1/y$, or $1/y^2$. Model Selection Criterion (15) was used to determine the number of exponents needed for each data set. The quality of the fit was determined by evaluating the coefficient of determination (r^2), the standard error of parameter estimates, and by visual inspection of residuals.

Pharmacokinetic parameters were calculated using standard equations (14,16) in which V_c is the volume of the central compartment, V_{dss} is the volume of distribution steady-state, AUC is the area under the plasma concentration–time curve from time 0 to infinity, CL is the total plasma clearance, $T_{1/2}$ is the terminal-phase half-life, and K_{10} is the elimination rate constant from the central compartment.

Plasma concentration–time curves of (+)-*S*-ibuprofen [after dosing of 100 mg (−)-R, 100 mg (−)-R + 100 mg (+)-S, or 100 mg (−)-R + 200 mg (+)-S] were fit in a manner analogous to that performed previously (17). However, in these cases, the only parameters that were calculated were AUC and $T_{1/2}$.

The fraction of an intravenous bolus dose of (−)-*R*-ibuprofen inverted to (+)-*S*-ibuprofen (F_{rs}) was calculated as (18): $[F_{rs} = (AUC_{s:r}/AUC_{s:s}) \cdot (D_s/D_r)]$, where $AUC_{s:r}$ is the area under the plasma concentration–time curve (from time 0 to infinity) of the (+)-S-enantiomer after dosing the (−)-R-enantiomer; $AUC_{s:s}$ is the area under the plasma concentration–time curve (from time zero to infinity) of the (+)-S-enantiomer after dosing the (+)-S-enantiomer; and D_s and D_r are the respective 100 mg doses of (+)-*S*- and (−)-*R*-ibuprofen. The clearance of R-to-S inversion (CL_{rs}) was calculated as $[CL_{rs} = F_{rs} \cdot CL_r]$, where CL_r is the total plasma clearance of (−)-*R*-ibuprofen after dosing of 100 mg (−)-R. The clearance of (−)-*R*-ibuprofen by pathways other than inversion (CL_{rnons}) was calculated as $[CL_{rnons} = CL_r - CL_{rs}]$.

Statistics

Unless otherwise indicated, data are expressed as the mean ± SD. Statistical differences between multiple treatment groups were determined using a single-factor analysis of variance (ANOVA) and Scheffé F test. Statistical differences between two treatment groups were determined using a paired t test. A P value ≤ 0.05 was considered significant.

RESULTS

Plasma concentrations of ibuprofen enantiomers were fit to a monoexponential equation for 3 data sets, to a biexponential equation for 20 data sets, and to a triexponential equation for 1 data set. The data were described reasonably well using a compartmental analysis; r^2 values averaged 0.977 ± 0.026. In addition, the area under the plasma concentration–time curve (AUC) was calculated for all data sets using the trapezoidal rule. Absolute differences between these two methods were less than 5%, on average, indicating no significant deviations due to methodological preference. The average extrapolated AUC was less than 18% for all treatment groups except that of (+)-*S*-ibuprofen (33%) when measured after dosing the 100 mg (−)-R + 200 mg (+)-S admixture.

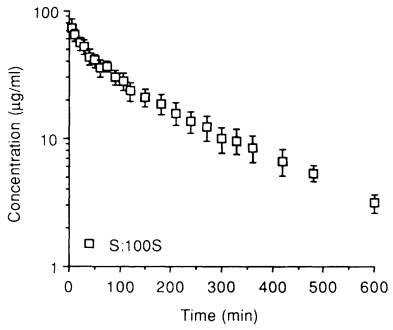

Fig. 1. Mean (±SE) plasma concentration–time curve of (+)-S-enantiomer (S:100S) after a bolus intravenous injection of 100 mg (+)-*S*-ibuprofen.

The plasma concentration–time profile of (+)-*S*-ibuprofen is displayed after administration of 100 mg (+)-S-enantiomer (Fig. 1). The data are characterized by a biexponential decline, and as indicated, no (−)-*R*-ibuprofen was observed in the plasma. In contrast, substantial amounts of (+)-*S*-ibuprofen were detected in the plasma along with (−)-*R*-ibuprofen after administration of 100 mg (−)-R-enantiomer (Fig. 2). The (−)-R data typically show a biexponential decline and the (+)-S data are biexponential due to metabolite formation and disappearance.

As observed in Table I, significant differences are evident between the total plasma clearance of (+)-S- and (−)-R-enantiomers, resulting in significant differences in area under the curve. Since the volume of distribution (V_c and V_{dss}) is not different between treatments, the three to four times greater clearance of (−)-*R*-ibuprofen is due to differences in elimination. In particular, K_{10} is about four times larger for (−)-*R*-ibuprofen as opposed to (+)-*S*-ibuprofen, reflecting the contribution of chiral inversion to the overall elimination of (−)-R drug (overall elimination is the sum of inversion and noninversion routes). Chiral inversion is lacking for the (+)-*S*-enantiomer, thus the much smaller value for K_{10} (and total clearance).

The plasma concentration–time profiles of (+)-*S*- and (−)-*R*-ibuprofen are displayed after administration of 200 mg of the racemic mixture (Fig. 3). The disappearance of (−)-R-enantiomer is consistent with that observed previously after administration of (−)-R alone and shows a biexponential decline. On the other hand, (+)-*S*-ibuprofen data were best fit to a monoexponential equation for three of the

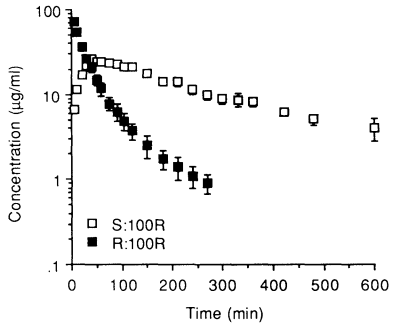

Fig. 2. Mean (±SE) plasma concentration–time curves of (+)-S-enantiomer (S:100R) and (−)-R-enantiomer (R:100R) after a bolus intravenous injection of 100 mg (−)-*R*-ibuprofen.

Table I. Pharmacokinetic Parameters of Ibuprofen Enantiomers After Intravenous Bolus Administration of 100 mg (+)-*S*-Ibuprofen and 100 mg (−)-*R*-Ibuprofen[a]

Parameter	S:100S		R:100R		Paired *t* test
V_c (liters)	1.43	(0.41)	1.24	(0.22)	NS ($P > 0.20$)
V_{dss} (liters)	2.24	(0.53)	2.78	(0.75)	NS ($P > 0.05$)
AUC (μg · min/ml)	10,741	(3,573)	2,893	(656)	S ($P < 0.05$)
CL (ml/min)	10.1	(3.1)	36.1	(9.0)	S ($P < 0.02$)
$T_{1/2}$ (min)	192	(30)	162	(63)	NS ($P > 0.20$)
K_{10} (min^{-1})	0.00702	(0.00059)	0.0296	(0.0075)	S ($P < 0.01$)

[a] Data from S:100S represent the kinetics of (+)-S-enantiomer after the administration of 100 mg (+)-*S*-ibuprofen ($n = 4$); data from R:100R represent the kinetics of (−)-R-enantiomer after the administration of 100 mg (−)-*R*-ibuprofen ($n = 4$).

four dogs tested. This finding is probably due to the compensating effects, which occur on similar time scales, of drug distribution after dosing (+)-S and of R-to-S inversion after dosing the (−)-R-enantiomer.

In Table II, the pharmacokinetic parameters of (−)-*R*-ibuprofen are displayed as a function of increasing amounts of (+)-S-enantiomer (from 0 to 200 mg). Also displayed are the AUC and $T_{1/2}$ estimates of (+)-*S*-ibuprofen after similar treatments. As indicated in this table, a significant amount of (−)-R-enantiomer is inverted to its active S-form after bolus administration of (−)-*R*-ibuprofen into the systemic circulation. Based on the AUC values of (+)-S after administration of each enantiomer alone, it is estimated that, on average, chiral inversion is on the order of 70–75% in the dog. Given this finding, the total plasma clearance of (−)-*R*-ibuprofen (36.1 ml/min) can now be separated into its parallel elimination pathways, the R-to-S chiral inversion clearance (25.2 ml/min) and the clearance by other routes (10.9 ml/min). Interestingly, the values for CL_{rnons} (after dosing *R*-ibuprofen) and the clearance of (+)-S (after dosing *S*-ibuprofen) are remarkably similar (10.9 vs 10.1 ml/min, respectively). Although no significant difference is observed for volume of distribution (V_c and V_{dss}), the volume of distribution steady state of (−)-*R*-ibuprofen is reduced by 16 and 37% when administered with 100 and 200 mg of (+)-S-enantiomer, respectively. More importantly, there is a substantial increase in the (−)-R AUC when the two enantiomers are administered together. This increase is a result of the progressive reduction (19 and 53%) in total plasma clearance of the (−)-R-enantiomer as increasing amounts of (+)-*S*-ibuprofen are present in the plasma. A concomitant 14 and 49% reduction in K_{10} also occurs when 100 and 200 mg of (+)-S-enantiomer are added to 100 mg of (−)-R-ibuprofen. Despite the trend for the half-life of (−)-*R*-ibuprofen to decrease in the presence of (+)-S-enantiomer, the changes observed were not statistically significant. In contrast, the half-life of (+)-*S*-ibuprofen was significantly higher after dosing 100 mg (−)-*R*- + 200 mg (+)-*S*-ibuprofen than after 100 mg of the (−)-R- or (+)-S-enantiomer alone ($P \leq 0.05$; ANOVA/Scheffé).

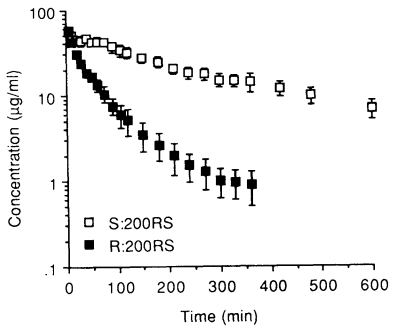

Fig. 3. Mean (±SE) plasma concentration–time curves of (+)-S-enantiomer (S:200RS) and (−)-R-enantiomer (R:200RS) after a bolus intravenous injection of 200 mg racemic ibuprofen.

It should be appreciated that the nonstatistical differences between treatments for V_{dss} and half-life may be due to the limited number of animals studied, particularly in the 100 mg (−)-R + 200 mg (+)-*S* group. Unfortunately, the investigators were limited by the availability of pure enantiomer and thus the number of experiments that could be run.

DISCUSSION

It has been suggested (7,10–12) that the major site for R-to-S inversion of ibuprofen is in the gastrointestinal tract during presystemic contact. This conclusion is based primarily on data obtained while evaluating the kinetics of ibuprofen enantiomers in humans following oral administration of racemic ibuprofen tablets with different absorption rates (12). In this study, it was observed that the S:R ratio of plasma concentration at the peak time of (+)-S and the S:R ratio of area under the curve were significantly different between the slower- and the faster-absorbing dosage forms. Thus, the slower-absorbing product had a greater residence time in the gut and a greater inversion was possible. Further, one would expect a continuous inversion of R-to-S enantiomer if the process were systemic; this outcome was not observed by these authors (12) as demonstrated by the similar half-lives of (−)-*R*- and (+)-*S*-ibuprofen after racemic dosing.

However, alternate hypotheses can also account for these results. For example, if metabolite formation is rate-limiting in the overall elimination process for ibuprofen, then one would expect similar terminal-phase half-lives. In this case, the absence of the expected slower half-life of (+)-S disappearance [after (+)-S dosing] could be the result of an assay limitation or the lack of a sufficiently extended sampling schedule. One can also speculate that a saturable systemic inversion after administration of the faster-absorbing dosage form would result in the S:R differences cited previously for concentration and AUC. Although the authors' conclusions may be reasonable (12), they are not substanti-

Table II. Pharmacokinetic Parameters of Ibuprofen Enantiomers After Intravenous Bolus Administration of 100 mg (−)-*R*-Ibuprofen, 100 mg (−)-*R*- + 100 mg (+)-*S*-Ibuprofen, and 100 mg (−)-*R*- + 200 mg (+)-*S*-Ibuprofen[a]

Parameter	R:100R	R:100R + 100S	R:100R + 200S	ANOVA/Scheffé[b]
V_c (liters)	1.24 (0.22)	1.17 (0.22)	1.13 (0.08)	NS
V_{dss} (liters)	2.78 (0.75)	2.34 (0.57)	1.75 (0.25)	NS
AUC (μg · min/ml)	2,892 (656)*	3,469 (546)†	5,944 (757)*†	S
CL (ml/min)	36.1 (9.0)*	29.4 (4.5)	17.0 (2.2)*	S
$T_{1/2}$ (min)	162 (63)	102 (47)	90.2 (22.3)	NS
K_{10} (min^{-1})	0.0296 (0.0075)*	0.0254 (0.0032)	0.0151 (0.0030)*	S
F_{rs}	0.723 (0.128)			
CL_{rs} (ml/min)	25.2 (1.8)			
CL_{rnons} (ml/min)	10.9 (7.8)			
AUC_s (μg · min/ml)[c]	7,484 (1,545)	13,951 (4,057)	30,588 (9,286)	
$T_{1/2s}$ (min)[c]	178 (31)	206 (43)	436 (241)	

[a] Data from R:100R represent the kinetics of (−)-R-enantiomer after the administration of 100 mg (−)-*R*-ibuprofen (n = 4); data from R:100R + 100S represent the kinetics of (−)-R-enantiomer after the administration of 100 mg (−)-*R*- + 100 mg (+)-*S*-ibuprofen (n = 4); data from R:100R + 200S represent the kinetics of (−)-R-enantiomer after the administration of 100 mg (−)-*R*- + 200 mg (+)-*S*-ibuprofen (n = 2).

[b] Treatments R:100R, R:100R + 100S, and R:100R + 200S were compared and significant differences are designated using common superscripts (* or †).

[c] AUC_s and $T_{1/2s}$ represent the area under the plasma concentration–time curve and terminal-phase half-life, respectively, of (+)-S-enantiomer after the administration of 100 mg (−)-*R*-ibuprofen (n = 4), 100 mg (−)-*R*- + 100 mg (+)-*S*-ibuprofen (n = 4), and 100 mg (−)-*R*- + 200 mg (+)-*S*-ibuprofen (n = 2).

ated by the data. Only extravascular doses were evaluated and much of the supporting discussion about a lack of systemic inversion after intravenous dosing of racemate was based upon a "personal communication" (10–12).

In the present study, (−)-*R*-ibuprofen is inverted to the (+)-S-enantiomer to a significant extent in the systemic circulation. After 100-mg intravenous bolus doses of each enantiomer, chiral inversion was calculated as 72.3 ± 12.8% in the dog. This value is in close agreement with the 63 ± 6% estimate reported in humans after oral dosing (19). These results also support a preliminary report in which the authors state that chiral inversion of (−)-*R*-ibuprofen occurred in healthy volunteers at 50-, 100-, 200-, 400-, and 600-mg intravenous doses, based on urinary excretion data (20); numerical values were not provided. Thus it is apparent that systemic inversion of R-to-S enantiomers cannot be ignored. Likewise, these results do not rule out that a concomitant gastrointestinal inversion may occur with oral dosing.

Little is known about the effect of one ibuprofen enantiomer on the disposition of its optical antipode. Evans and co-workers (21,22) have reported that not only do ibuprofen enantiomers have a concentration-dependent and stereoselective binding to plasma proteins, but also they compete with one another for binding sites. As a result, the free fraction of (−)-*R*- and (+)-*S*-ibuprofen was increased about 20–40% by the presence of equal concentrations (50 μg/ml) of the other enantiomer (22). In the present study, protein binding experiments were not performed due to the sensitivity limit of the assay and the unavailability of radiolabeled drug.

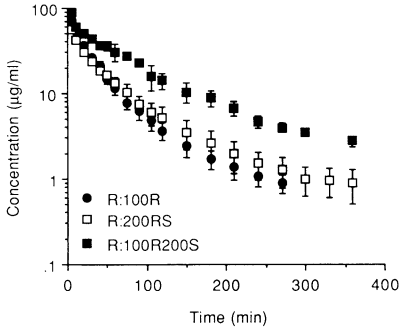

Fig. 4. Mean (±SE) plasma concentration–time curves of (−)-R-enantiomer after a bolus intravenous injection of 100 mg (−)-*R*-ibuprofen (R:100R), 200 mg racemic ibuprofen (R:200RS), and 100 mg (−)-*R*- + 200 mg (+)-*S*-ibuprofen (R:100R200S).

The data in Table II suggest that nonlinear kinetics may be operative. In particular, a progressive reduction in total plasma clearance of (−)-*R*-ibuprofen is noticed as increasing amounts of (+)-S-enantiomer are added to the system. As a result, the AUC of (−)-R-enantiomer is significantly increased even though the amount of (−)-R dosed is unchanged (Fig. 4). Since the clearance for R-to-S inversion predominates over the other clearance routes for (−)-R, it appears that the presence of (+)-S may be inhibiting chiral inversion. In fact, if one assumes that the clearance of (+)-*S*-ibuprofen is unchanged between the 100-mg dose of (+)-S and the 200-mg dose of racemic mixture (based on similar $T_{1/2}$ values), then R-to-S inversion can be estimated for the racemate [$F_{rs} = (AUC_{s:rs}/AUC_{s:s} - 1) \cdot (D_s/D_r)$] as 31.6 ± 15.2%, where $AUC_{s:rs}$ is the AUC of (+)-S after dosing the racemic mixture. This estimate was significantly different from the 72.3 ± 12.8% inversion of R-enantiomer ($P < 0.005$).

Further support for an inhibition of chiral inversion is afforded by comparing the clearance data of R:100R vs R:100R + 200S. As shown in Table II, the CL of (−)-*R*-ibuprofen (17.0 ml/min) after dosing 100R + 200S is much smaller than the CL_{rs} (25.2 ml/min) after dosing 100R. Since [$CL = CL_{rs} + CL_{rnons}$], this reduction should not be

possible even in the absence of alternate elimination pathways for drug (i.e., $CL_{rnons} = 0$; $CL = CL_{rs}$). As a result, an inhibition of R-to-S inversion would be required for this reduction in CL to occur. An increase in free fraction would result in an increase in CL_{rnons} since ibuprofen and other NSAIDs are compounds of low hepatic extraction (4,6,23,24). If there had been no change in free fraction, then CL_{rnons} should also remain unchanged. These last two scenarios, although speculative, would mean that a greater than anticipated inhibition of R-to-S inversion had occurred. Regardless, all three examples demonstrate that the data are consistent with an inhibitory effect of the (+)-S-enantiomer on chiral inversion. What is uncertain is whether or not this effect is due to product inhibition, perhaps through a feedback mechanism, or to higher free concentrations of (−)-R which are in the range of capacity-limited transport. The latter hypothesis is less likely, however, since an increase in free fraction should result in either a proportional (i.e., linear kinetics) or a nonproportional (i.e., nonlinear kinetics) increase in clearance.

In conclusion, this study demonstrates that (−)-*R*-ibuprofen is inverted significantly to (+)-*S*-ibuprofen in the systemic circulation. Although R-to-S inversion is approximately 70–75% in the dog after dosing the (−)-R-enantiomer, chiral inversion may be inhibited by the presence of increasing amounts of (+)-S-isomer.

ACKNOWLEDGMENTS

This work was supported in part by National Institutes of Health Grant GM 35498 and Food and Drug Administration Grant FD01462. The authors would like to thank John W. Wlodyga for his help with the experimental setup and data collection aspects of the study.

REFERENCES

1. S. S. Adams, P. Bresloff, and C. G. Mason. Pharmacological differences between the optical isomers of ibuprofen: Evidence for metabolic inversion of the (−)-isomer. *J. Pharm. Pharmacol.* **28**:256–257 (1976).
2. A. J. Hutt and J. Caldwell. The importance of stereochemistry in the clinical pharmacokinetics of the 2-arylpropionic acid nonsteroidal anti-inflammatory drugs. *Clin. Pharmacokinet.* **9**:371–373 (1984).
3. R. K. Verbeeck, J. L. Blackburn, and G. R. Loewen. Clinical pharmacokinetics of nonsteroidal anti-inflammatory drugs. *Clin. Pharmacokinet.* **8**:297–331 (1983).
4. R. K. Verbeeck. Pathophysiologic factors affecting the pharmacokinetics of nonsteroidal antiinflammatory drugs. *J. Rheumatol.* **15** (Suppl. 17):44–57 (1988).
5. D. C. Brater. Clinical pharmacology of NSAIDs. *J. Clin. Pharmacol.* **28**:518–523 (1988).
6. R. O. Day, G. G. Graham, K. M. Williams, G. D. Champion, and J. de Jager. Clinical pharmacology of non-steroidal anti-inflammatory drugs. *Pharmacol. Ther.* **33**:383–433 (1987).
7. F. Jamali, R. Mehvar, and F. M. Pasutto. Enantioselective aspects of drug action and disposition: Therapeutic pitfalls. *J. Pharm. Sci.* **78**:695–715 (1989).
8. M. D. Murray and D. C. Brater. Nonsteroidal anti-inflammatory drugs. *Clin. Geriatr. Med.* **6**:365–397 (1990).
9. D. G. Kaiser, G. J. VanGiessen, R. J. Reischer, and W. J. Wechter. Isomeric inversion of ibuprofen (R)-enantiomer in humans. *J. Pharm. Sci.* **65**:269–273 (1976).
10. F. Jamali. Research methodology in NSAID monitoring: plasma concentrations of chiral drugs. *J. Rheumatol.* **15** (Suppl. 17):71–74 (1988).
11. F. Jamali. Pharmacokinetics of enantiomers of chiral nonsteroidal antiinflammatory drugs. *Eur. J. Drug Metab. Pharmacokin.* **13**:1–9 (1988).
12. F. Jamali, N. N. Singh, F. M. Pasutto, A. S. Russell, and R. T. Coutts. Pharmacokinetics of ibuprofen enantiomers in humans following oral administration of tablets with different absorption rates. *Pharm. Res.* **5**:40–43 (1988).
13. R. Mehvar, F. Jamali, and F. M. Pasutto. Liquid-chromatographic assay of ibuprofen enantiomers in plasma. *Clin. Chem.* **34**:493–496 (1988).
14. J. G. Wagner. Pharmacokinetic parameters estimated from intravenous data by uniform methods and some of their uses. *J. Pharmacokin. Biopharm.* **5**:161–182 (1977).
15. *RSTRIP. Exponential Curve Stripping and Parameter Estimation,* MicroMath Scientific Software, Salt Lake City, UT, 1989.
16. M. Gibaldi and D. Perrier. *Pharmacokinetics,* 2nd ed., Marcel Dekker, New York, 1982.
17. J. G. Wagner. Linear pharmacokinetic equations allowing direct calculation of many needed pharmacokinetic parameters from the coefficients and exponents of polyexponential equations which have been fitted to the data. *J. Pharmacokin. Biopharm.* **4**:443–467 (1976).
18. P. J. Meffin, B. C. Sallustio, Y. J. Purdie, and M. E. Jones. Enantioselective disposition of 2-arylpropionic acid nonsteroidal anti-inflammatory drugs. I. 2-Phenylpropionic acid disposition. *J. Pharmacol. Exp. Ther.* **238**:280–287 (1986).
19. E. J. D. Lee, K. Williams, R. Day, G. Graham, and D. Champion. Stereoselective disposition of ibuprofen enantiomers in man. *Br. J. Clin. Pharmacol.* **19**:669–674 (1985).
20. S. R. Cox, G. L. Royer, and E. L. Murrill. Pharmacokinetics of ibuprofen enantiomers following i.v. administration of racemic ibuprofen. *Pharm. Res.* **3** (Suppl. 5):111S (1986).
21. A. M. Evans, R. L. Nation, and L. N. Sansom. Lack of effect of cimetidine on the pharmacokinetics of R(−)- and S(+)-ibuprofen. *Br. J. Clin. Pharmacol.* **28**:143–149 (1989).
22. A. M. Evans, R. L. Nation, L. N. Sansom, F. Bochner, and A. A. Somogyi. Stereoselective plasma protein binding of ibuprofen enantiomers. *Eur. J. Clin. Pharmacol.* **36**:283–290 (1989).
23. G. F. Lockwood, K. W. Albert, W. R. Gillespie, G. G. Bole, T. M. Harkcom, G. J. Szpunar, and J. G. Wagner. Pharmacokinetics of ibuprofen in man. I. Free and total area/dose relationships. *Clin. Pharmacol. Ther.* **34**:97–103 (1983).
24. J. H. Lin, D. M. Cocchetto, and D. E. Duggan. Protein binding as a primary determinant of the clinical pharmacokinetic properties of non-steroidal antiinflammatory drugs. *Clin. Pharmacokinet.* **12**:402–432 (1987).