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Effects of absorption rate on the pre-systemic chiral inversion of ibuprofen in rabbits

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Abstract

The chiral inversion kinetics of ibuprofen was evaluated after intraduodenal administration of racemic ibuprofen in conventional powder form and sustained-released granules compared with intravenous administration in rabbits. The AUC ratios of the *S*-(+) and *R*-(−) enantiomers remained almost constant values with time up to 2 h after administration of sustained-release formulation, while those after administration of the powder increased with time. *R*-(−) enantiomer to *S*-(+) enantiomer inversion ratios after intraduodenal administration of the powder form and the sustained-release form, and after intravenous injection were calculated to be 1.63, 1.94 and 1.19, respectively, indicating that pharmacological effects may depend on the absorption rate in rabbits.

Introduction

Ibuprofen is a 2-arylpropionic acid marketed as a non-steroidal anti-inflammatory drug and is readily available in many dosage forms (Davies 1998). Although the *S*-(+) enantiomer of ibuprofen is the eutomer with respect to inhibition of prostaglandin synthesis (Adams et al 1976; Geisslinger et al 1989), the marketed products containing ibuprofen are almost all supplied as the racemate. The *R*-(−) enantiomer, the distomer of ibuprofen, has been reported to undergo unidirectional conversion to the *S*-(+) enantiomer via formation of the acyl CoA thioester of ibuprofen (Lee et al 1985; Jamali et al 1992) and other 2-arylpropionic acids (Hutt & Caldwell 1983; Nagashima et al 1984; Rubin et al 1985). Kinetic analysis of the chiral inversion of ibuprofen (Lee et al 1985; Jamali et al 1992; Vos et al 1996; Scheuerer et al 1998; Tan et al 2002) and other 2-arylpropionic acids (Fournel & Caldwell 1986; Caldwell et al 1988; Chen et al 1991) has shown that the rate and extent of the chiral inversion in-vivo varies from species to species.

Chiral inversion of ibuprofen and other 2-arylpropionic acids involves systemic and pre-systemic processes (Jamali et al 1988; Berry & Jamali 1991; Jeffrey et al 1991). A significant positive correlation between the t_{max} and the ratio of the plasma S/R concentration has been reported after oral administration of racemic ibuprofen in man (Jamali et al 1988), whereas other investigators have found no significant difference in pre-systemic inversion in man and dogs (Beck et al 1991; Hall et al 1993). Although the S/R AUC ratios were unaffected by dose, those after oral administration in tablet form were significantly greater than those following administration in solution form (Jamali et al 1992). This indicates that a longer residence time in the gastrointestinal tract can change the degree of pre-systemic inversion to the *S*-(+) enantiomer. The S/R AUC ratios in sustained-release granules were reported to be significantly higher than those in suspension or solution and a significant positive linear correlation was found between the S/R AUC ratios and t_{max} for *R*-(−)-ibuprofen in rats (Sattari & Jamali 1994). However, these studies did not include an evaluation of the S/R AUC ratios after administration of sustained-release preparations in rabbits.

This work was aimed at evaluating the pre-systemic chiral inversion after intraduodenal administration of ibuprofen in conventional powder form and sustained-released

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granules compared with after intravenous injection in rabbits to determine species difference in relation to a previous study employing sustained-release preparations in rats (Beck et al 1991).

Methods

Materials

Racemic ibuprofen and ibufenac were kindly supplied by Kaken Pharmaceuticals (Tokyo, Japan). Ibuprofen powder (Lamidon Kowa Fine Gr., lot GG1A, 50% powder; Kowa, Nagoya, Japan) and ibuprofen sustained-release granules in capsules (Fenbid, lot 01020274, 100-mg capsules; Tianjin Smith Kline & French Laboratories, Tianjin, China) were available commercially. Other chemicals were of HPLC or analytical grade.

Animal protocols

Japanese white male rabbits, 2.8–3.4 kg (n = 5), were purchased from Sankyo Laboratory Service (Tokyo, Japan) and acclimatized in their cages for at least 1 week before any experimental work was undertaken. In a three-way crossover design the rabbits were given 150 mg ibuprofen powder or sustained-release granules intraduodenally. They were also given 1 mL of 100 mg mL^{-1} ibuprofen in solution intravenously. The duration of the washout period between administrations was at least 2 weeks. No significant change in hepatic and renal function was found during monitoring using standard laboratory tests in either the intraduodenal or the intravenous study. Treatment of rabbits adhered to the guiding principles for the care and use of experimental animals and the study was approved by the Ethical Committee of the Hokkaido College of Pharmacy.

Intraduodenal administration of ibuprofen was performed as described previously by Perreault et al (1993) and Sekikawa et al (1995) with some modifications. Rabbits were given a gastric lavage in the conscious state and then fasted overnight with free access to water (Perreault et al 1993; Sekikawa et al 1995). The rabbits were then anaesthetized with sodium pentobarbital (44 mg kg^{-1}) via intravenous administration into an ear vein, and maintained unconscious for the duration of the experiment. After making a 5- to 6-cm incision of the abdomen below the xiphoid process, the lower duodenum, at about 50 cm below the pylorus, was cannulated with silicon tubing (4 mm i.d.). Ibuprofen powder and sustained-release granules in capsules were suspended in 20 mL of saline. Ibuprofen preparations were administered through the catheter, which was then flushed with 6 mL saline. After administration and extubation, the administration site was closed and a check was made to ensure that there was no leakage of drug at the site. The abdomen was closed with surgical sutures. Blood samples (0.5 mL) were withdrawn from the marginal ear vein before and 0.167, 0.333, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5 and 6 h after dosing. Specimens were centrifuged immediately at 1360 *g* for 15 min. Serum was transferred into stoppered polyethylene tubes and stored at −20 °C until analysis.

The solution of ibuprofen for injection was prepared by dissolving 1.0 g racemic ibuprofen. The powder was first dissolved in 3 mL ethanol, then 4 mL propylene glycol was added and the volume made up with distilled water to give a final concentration of 100 mg mL^{-1}. Rabbits received an intravenous bolus dose of ibuprofen solution into a marginal ear vein. Then, 0.5-mL blood samples were withdrawn from the opposite marginal ear vein before and 0.083, 0.167, 0.333, 0.5, 0.75, 1 and 1.5 h after dosing because the concentrations of ibuprofen enantiomers over 1.5 h after administration were found to be below the limit of quantitation in preliminary experiments. Specimens were treated in the same way as for the intraduodenal administration.

Analytical method

Serum concentrations of *R*-(−)- and *S*-(+)-ibuprofen were measured by the stereospecific HPLC procedure described by Hoult et al (1999) with some modifications. Complete resolution of *R*-(−)- and *S*-(+)-ibuprofen was observed and they were eluted at 12.6 and 15.1 min after injection of racemic ibuprofen. Calibration curves, made for each set of studies, were linear over the range 0.25–250 μg mL^{-1} with a correlation coefficient of 0.999. Coefficients of variation at 5 and 50 μg mL^{-1} were found to be less than 9.9% and 4.4% for both *R*-(−)- and *S*-(+)-ibuprofen, respectively. Ibufenac was employed as an internal standard and a chiral separation was achieved by normal-phase HPLC with Chiralcel OD (250 mm length × 4.6 mm i.d., particle size 10 μm; Daicel Chemical Ind., Tokyo, Japan). The HPLC mobile phase consisted of hexane–isopropanol–trifluoroacetic acid (100:1:0.1, v/v/v) and the flow rate was set at 1.0 mL min^{-1} at ambient temperature. The UV detector was operated at 225 nm.

Data analysis

The maximum serum concentration (C_{max}) and time to reach C_{max} (t_{max}) were obtained graphically. The time-course of the ratio of the serum concentration of *S*-(+)- and *R*-(−)-ibuprofen (*S*/*R* ratio) was calculated by dividing the value of the serum concentration of *S*-(+)-ibuprofen by the corresponding value of *R*-(−)-ibuprofen at each time point. Moment analysis (Yamaoka et al 1978) was employed to calculate the area under the concentration–time curve (AUC) and the mean residence time (MRT) with standard extrapolation to infinity. The mean absorption time (MAT) from the gastrointestinal tract after intraduodenal administration was calculated from $MRT_{i.d.}$ minus $MRT_{i.v.}$. The bioavailability (EBA) was calculated from the expression:

$$EBA = [(AUC_{R,i.d.} + AUC_{S,i.d.}) \times Dose_{i.v.}]/[(AUC_{R,i.v.} + AUC_{S,i.v.}) \times Dose_{i.d.}]$$

Compartment model analyses were carried out using simultaneous non-linear regression by the simplex method

according to Equation 1 for ibuprofen powder and Equation 2 for ibuprofen sustained-release granules after intraduodenal administration and Equation 3 for ibuprofen solution after intravenous administration. The rate of ibuprofen release was first-order from the powder and zero-order from the sustained-release granules following preliminary experiments (not shown).

$$C_S = \frac{\text{Dose} \cdot \text{ka} \cdot F_{pow}}{\text{Vd} \cdot (\text{ka} - \text{kel})} \cdot (e^{-\text{kel} \cdot t} - e^{-k_a \cdot t}) \quad (1)$$

$$C_S = \begin{cases} \frac{k_0 \cdot F_{sus}}{\text{Vd} \cdot \text{ka}} \cdot (1 - e^{-\text{kel} \cdot (t - t_{lag})}) & t < \tau \\ \frac{k_0 \cdot F_{sus}}{\text{Vd} \cdot \text{ka}} \cdot (1 - e^{-\text{kel} \cdot (\tau - t_{lag})}) \cdot e^{-\text{kel} \cdot (t - \tau)} & t > \tau \end{cases} \quad (2)$$

$$C_S = \frac{\text{Dose}}{\text{Vd}} \cdot e^{-\text{kel} \cdot t} \quad (3)$$

where C_S represents the serum concentration of ibuprofen, ka and kel the first-order absorption and elimination rate constants, respectively, k_0 the zero-order release rate constant, t the time after administration, τ the period of zero-order absorption, Vd the volume of distribution, t_{lag} the lag time and F_{pow} and F_{sus} the fraction of the dose absorbed from ibuprofen powder and sustained-release granules, respectively. Vd was assumed to be constant over the experimental period. The estimated AUC from compartmental model analysis was also calculated from the following equation:

$$\text{estimated AUC} = \text{Dose}/(\text{kel} \times \text{Vd}/F) \quad (4)$$

Statistical analysis

The results calculated for each rabbit are expressed as means ± s.d. Statistical analysis for the comparisons of the pharmacokinetic properties of enantiomers was performed by a two-way analysis of variance using a statistical package, StatMate II (Nankodo, Tokyo, Japan). Individual differences between groups were then examined using Fisher's protected least significant difference test. The differences between the *R* and *S* enantiomers were evaluated using an unpaired *t*-test. A value of $P < 0.05$ denoted significance in all cases.

Results

The serum concentration–time profiles of *S*-(+)- and *R*-(−)-ibuprofen following intraduodenal administration of racemic ibuprofen powder are shown in Figure 1A, while those after intraduodenal administration of sustained-release granules are shown in Figure 1B. Model-independent parameters obtained from the serum concentration profiles are shown in Table 1. Longer t_{max}, MRT and MAT values of serum *S*-(+)- and *R*-(−)-ibuprofen after administration of sustained-release granules were observed compared with those after powder administration. The C_{max} and AUC values of *S*-(+)-ibuprofen were significantly greater than those of *R*-(−)-ibuprofen after intraduodenal administration of powder and sustained-release formulations. The *S*/*R* AUC ratio following administration of sustained-release granules was significantly greater than that following administration of powder ($P < 0.05$). The total AUC and EBA values were not significantly different between the powder and sustained release granules.

Figure 2 shows the serum concentration–time profiles of *S*-(+)- and *R*-(−)-ibuprofen after intravenous administration, and the model-independent parameters obtained from the serum concentration profiles are shown in Table 1. The serum concentration of *S*-(+)-ibuprofen was significantly lower than that of *R*-(−)-ibuprofen initially (5 min after i.v. administration), whereas the serum concentrations of *S*-(+)-ibuprofen were significantly greater than those of *R*-(−)-ibuprofen 0.5 h after administration and thereafter. The *S*/*R* AUC ratios after intravenous administration were significantly lower than those after intraduodenal administration of both the powder form and sustained-release granules.

Pharmacokinetic parameters computed from simultaneous non-linear regression analysis are listed in Table 2. The Vd and elimination half-life of *S*-(+)-ibuprofen were significantly greater than those of *R*-(−)-ibuprofen ($P < 0.05$). The fraction of the dose absorbed from sustained-release granules was lower than that from the powder, but the difference was not significant ($P > 0.05$).

The *S*/*R* ratios after administration of sustained-release granules up to 0.5 h after administration were almost constant (Figure 3). They were generally greater than those for the powder, but lower 1.5 and 2 h after administration ($P < 0.05$). There were no significant differences in the *S*/*R* ratio between the powder and sustained-release granules 3 h after administration and thereafter.

Discussion

An inversion difference in the absorption phase was recently demonstrated after oral administration of a suspension and a conventional tablet in 12 healthy subjects (Aiba et al 1999). The *S*/*R* AUC ratios after intraduodenal administration of powder and sustained-release granules were significantly greater than those after intravenous administration, indicating the pre-systemic inversion of ibuprofen in rabbits (Table 1). Although Beck et al (1991) reported that unidirectional inversion of *R*-(−)-ibuprofen after intraduodenal administration, compared with intravenous administration, appeared to occur systemically rather than pre-systemically in beagles, they employed a fast-dissolving preparation to evaluate pre-systemic inversion.

Sattari & Jamali (1994) reported that the *S*/*R* AUC ratios after oral administration of sustained-released granules to rats significantly increased, compared with the values for the solution and suspension. Our results indicate that the prolonged absorption of ibuprofen increased the extent of pre-systemic inversion in rabbits.

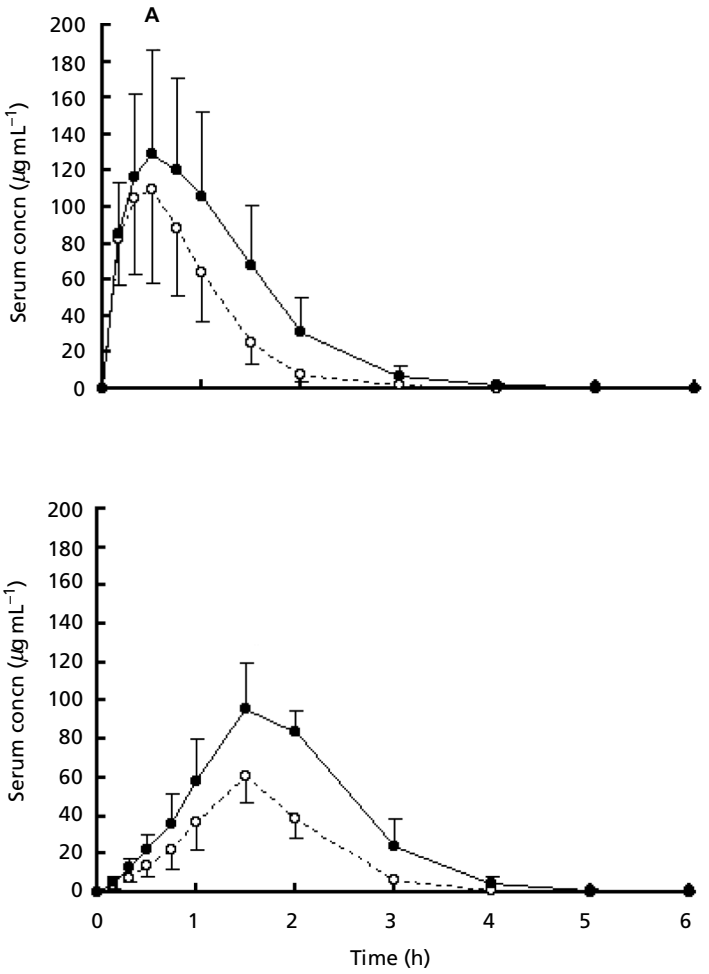

Figure 1 Serum concentration–time profiles of *S*-(+)-ibuprofen (●) and *R*-(−)-ibuprofen (○) after intraduodenal administration of 150 mg racemic ibuprofen in powder form (A) and sustained-release granules (B) to 5 rabbits, mean ± s.d. *$P < 0.05$, *S*-(+)-ibuprofen vs *R*-(−)-ibuprofen.

Table 1 Model-independent parameters of ibuprofen after intraduodenal administration of powder or sustained-release granules and intravenous administration of solution to rabbits.

Parameter	Powder (150 mg)		Sustained-release granules (150 mg)		Intravenous (100 mg)	
	R-ibuprofen	*S*-ibuprofen	*R*-ibuprofen	*S*-ibuprofen	*R*-ibuprofen	*S*-ibuprofen
C_{max} ($\mu g\,mL^{-1}$)	111.1 ± 47.9	130.7 ± 55.7	64.1 ± 6.7	101.1 ± 13.0*		
t_{max} (h)	0.43 ± 0.009	0.57 ± 0.18	1.60 ± 0.22***	1.60 ± 0.22***		
MRT (h)	0.79 ± 0.04	1.10 ± 0.11*	1.64 ± 0.22***	1.83 ± 0.22***	0.38 ± 0.04	0.51 ± 0.07*
MAT (h)	0.41 ± 0.07	0.59 ± 0.09*	1.26 ± 0.22***	1.32 ± 0.22***		
AUC ($\mu g\,h\,mL^{-1}$)	120.5 ± 49.6	197.6 ± 87.4	92.0 ± 8.9	179.6 ± 30.4*	97.4 ± 28.0	113.6 ± 24.4
AUC total ($\mu g\,h\,mL^{-1}$)	318.1 ± 136.8		271.6 ± 38.7		211.0 ± 51.2	
S/R AUC ratio	1.63 ± 0.09**		1.94 ± 0.18*****		1.19 ± 0.13	
EBA (%)	104.9 ± 53.2		89.5 ± 23.5			

MRT, mean residence time; MAT, mean absorption time; EBA, bioavailability. Each value is the mean ± s.d. of results from 5 rabbits. *$P < 0.05$, vs value for *R*-ibuprofen. **$P < 0.05$ vs corresponding value for intravenous administration. ***$P < 0.05$ vs corresponding value for powder.

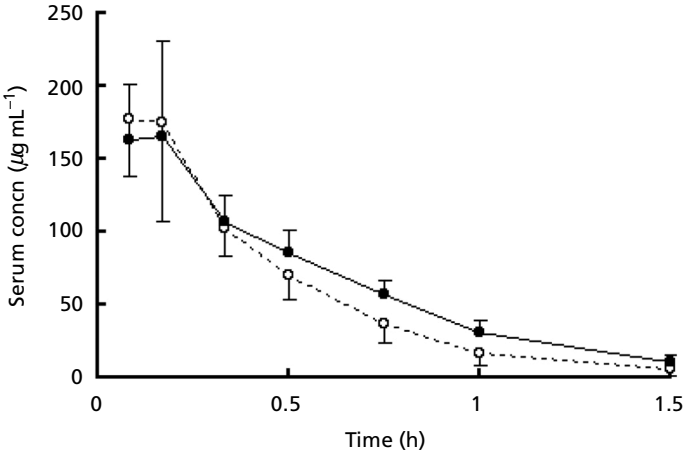

Figure 2 Serum concentration–time profiles of *S*-(+)-ibuprofen (●) and *R*-(−)-ibuprofen (○) after intravenous administration of 100 mg racemic ibuprofen to 5 rabbits, mean ± s.d. **P* < 0.05, *S*-(+)-ibuprofen vs *R*-(−)-ibuprofen.

The EBA for sustained-release granules is considered to be incomplete; however, this was not significantly different after intraduodenal administration of the two preparations. The total AUC values were not significantly different between powder and sustained-release granules and were mainly affected by the lower AUC values in one rabbit (not shown).

Evans et al (1989) reported stereoselective plasma protein binding of ibuprofen, and showed that the mean unbound *R*-(−)-ibuprofen was significantly lower than that of the *S*-(+)-ibuprofen after oral administration of 800 mg racemic ibuprofen in healthy male subjects. Lower serum concentrations of *S*-(+)-ibuprofen in the initial serum specimens are considered to be due to the increased clearance of unbound S-(+)-ibuprofen, although no evidence for this was obtained in the animal studies.

The *S*/*R* ratios in the sustained-release granules were significantly higher than those in the powder up to 0.5 h, whereas the values were not significantly different up to 1.5 h after administration of the powder and were almost unchanged up to 1.5 h after administration of the sustained released granules, indicating that ibuprofen constantly inverted during the pre-systemic phase after administration of the sustained-release granules, and there was little pre-systemic inversion after administration of the powder. Glowka (2000) found that there was no pre-systemic inversion following administration of suppositories of ibuprofen, or its lysinate, in rabbits and that the serum *S*/*R* ratios of ibuprofen did not increase during the absorption phase. The absorption rate after administration of suppositories is considered to be fast, similar to that after administration of the powder in this study. Chiral inversion of ibuprofen after administration of the powder mainly involves systemic inversion. These observations suggest that pre-systemic inversion of ibuprofen is saturated in the intestine or liver, due to the fast absorption of ibuprofen from the powder. The serum *S*/*R* ratios during the elimination phase after administration of each ibuprofen preparation were increased by the systemic inversion of ibuprofen.

Further studies to evaluate the pre-systemic and systemic inversion system of 2-arylpropionic acids are needed to obtain a better understanding of the pharmacological and pharmacodynamic effects in relation to species differences.

Table 2 Pharmacokinetic parameters of *S*- and *R*-ibuprofen in rabbits.

Parameter	*R*-ibuprofen	*S*-ibuprofen
ka (h^{-1})	3.30 ± 2.06	2.73 ± 1.57
Absorption t½ (h)	0.255 ± 0.090	0.303 ± 0.112*
t_{lag} (h)	0.215 ± 0.025	0.227 ± 0.036
k_d ($mg\,h^{-1}$)	77.5 ± 11.0	92.3 ± 11.9
τ (h)	2.06 ± 0.38	2.14 ± 0.31
Vd (L)	0.462 ± 0.116	0.544 ± 0.134*
kel (h^{-1})	2.31 ± 0.34	1.59 ± 0.38*
Elimination t½ (h)	0.305 ± 0.045	0.454 ± 0.098*
F_{pow}	0.868 ± 0.436	1.086 ± 0.501*
F_{sus}	0.662 ± 0.217	0.838 ± 0.199

ka and kel, the first-order absorption and elimination rate constants, respectively; τ, the period of zero-order absorption; Vd, the volume of distribution; t_{lag}, the lag time; F_{pow} and F_{sus}, the fractions of the dose absorbed from ibuprofen powder and sustained-release granules, respectively. Each value is the mean ± s.d of results from 5 rabbits. **P* < 0.05, vs value for *R*-ibuprofen.

Conclusions

The pharmacological effect may depend on the absorption rate. The dose of ibuprofen needed to determine the pharmacokinetic behaviour of each enantiomer, including the degree of chiral inversion, depends on the dosage form of ibuprofen in rabbits.

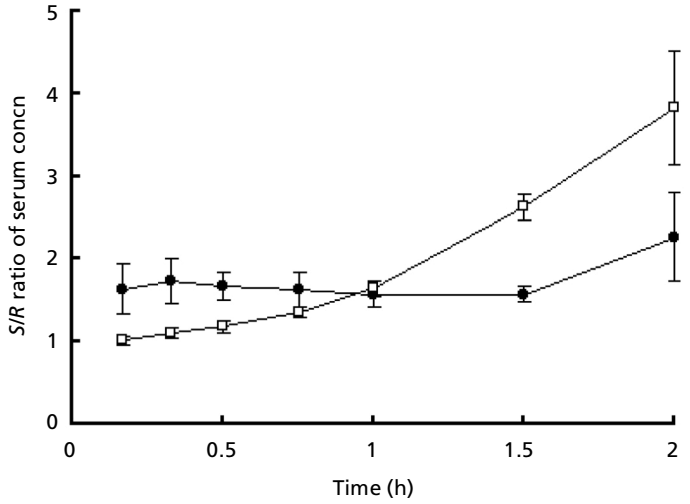

Figure 3 Serum S/R ratio profiles after intraduodenal administration of racemic ibuprofen as powder (□) or sustained-release granules (●) to 5 rabbits, mean ± s.d. $*P < 0.05$, intraduodenal vs sustained-release.

References

Adams, S. S., Bresloff, P., Mason, C. G. (1976) Pharmacological differences between the optical isomers of ibuprofen: evidence for metabolic inversion of the (−)-isomer. *J. Pharm. Pharmacol*. **28**: 256–257

Aiba, T., Tse, M. M., Lin, E. T., Koizumi, T. (1999) Effect of dosage form on stereoisomeric inversion of ibuprofen in volunteers. *Biol. Pharm. Bull*. **22**: 616–622

Beck, W. S., Geisslinger, G., Engler, H., Brune, K. (1991) Pharmacokinetics of ibuprofen enantiomers in dogs. *Chirality* **3**: 165–169

Berry, B. W., Jamali, F. (1991) Presystemic and systemic chiral inversion of R(-)-fenoprofen in the rat. *J. Pharmacol. Exp. Ther*. **258**: 695–701

Caldwell, J., Hutt, A. J., Fournel-Gigleux, S. (1988) The metabolic chiral inversion and dispositional enantioselectivity of the 2-arylpropionic acids and their biological consequences. *Biochem. Pharmacol*. **37**: 105–114

Chen, C. S., Shieh, W. R., Lu, P. H., Harriman, S., Chen, C. Y. (1991) Metabolic stereoisomeric inversion of ibuprofen in mammals. *Biochim. Biophys. Acta* **1078**: 411–417

Davies, N. M. (1998) Clinical pharmacokinetics of ibuprofen. The first 30 years. *Clin. Pharmacokinet*. **34**: 101–154

Evans, A. M., Nation, R. L., Sansom, L. N., Bochner, F., Somogyi, A. A. (1989) Stereoselective plasma protein binding of ibuprofen enantiomers. *Eur. J. Clin. Pharmacol*. **36**: 283–290

Fournel, S., Caldwell, J. (1986) The metabolic chiral inversion of 2-phenylpropionic acid in rat, mouse and rabbit. *Biochem. Pharmacol*. **35**: 4153–4159

Geisslinger, G., Stock, K. P., Bach, G. L., Loew, D., Brune, K. (1989) Pharmacological differences between R(−)- and S(+)-ibuprofen. *Agents Actions* **27**: 455–457

Glowka, F. K. (2000) Stereoselective pharmacokinetics of ibuprofen and its lysinate from suppositories in rabbits. *Int. J. Pharm*. **199**: 159–166

Hall, S. D., Rudy, A. C., Knight, P. M., Brater, D. C. (1993) Lack of presystemic inversion of (R)- to (S)-ibuprofen in humans. *Clin. Pharmacol. Ther*. **53**: 393–400

Hoult, J. R., Jackson, B. R., Benicka, E., Patel, B. K., Hutt, A. J. (1999) Chromatographic resolution, chiroptical characterization and preliminary pharmacological evaluation of the enantiomers of butibufen: a comparison with ibuprofen. *J. Pharm. Pharmacol*. **51**: 1201–1205

Hutt, A. J., Caldwell, J. (1983) The metabolic chiral inversion of 2-arylpropionic acid – a novel route with pharmacological consequences. *J. Pharm. Pharmacol*. **35**: 693–704

Jamali, F., Singh, N. N., Pasutto, F. M., Russell, A. S., Coutts, R. T. (1988) Pharmacokinetics of ibuprofen enantiomers in humans following oral administration of tablets with different absorption rates. *Pharm. Res*. **5**: 40–43

Jamali, F., Mehvar, R., Russell, A. S., Sattari, S., Yakimets, W. W., Koo, J. (1992) Human pharmacokinetics of ibuprofen enantiomers following different doses and formulations: intestinal chiral inversion. *J. Pharm. Sci*. **81**: 221–225

Jeffrey, P., Tucker, G. T., Bye, A., Crewe, H. K., Wright, P. A. (1991) The site of inversion of R(−)-ibuprofen: studies using rat in-situ isolated perfused intestine/liver preparations. *J. Pharm. Pharmacol*. **43**: 715–720

Lee, E. J., Williams, K., Day, R., Graham, G., Champion, D. (1985) Stereoselective disposition of ibuprofen enantiomers in man. *Br. J. Clin. Pharmacol*. **19**: 669–674

Nagashima, H., Tanaka, Y., Watanabe, H., Hayashi, R., Kawada, K. (1984) Optical inversion of (2R)- to (2S)-isomers of 2-[4-(2-Oxocyclopentylmethyl)-phenyl]propionic acid (loxoprofen), a new anti-inflammatory agent, and its monohydroxy metabolites in the rat. *Chem. Pharm. Bull. (Tokyo)* **32**: 251–257

Perreault, S., Dumont, L., Villiere, V., Ong, H., Adam, A., du Souich, P. (1993) Hepatic and extrahepatic metabolism of salbutamol in anesthetized rabbits. *Drug Metab. Dispos*. **21**: 485–491

Rubin, A., Knadler, M. P., Ho, P. P., Bechtol, L. D., Wolen, R. (1985) Stereoselective inversion of (R)-fenoprofen to (S)-fenoprofen in humans. *J. Pharm. Sci*. **74**: 82–84

Sattari, S., Jamali, F. (1994) Evidence of absorption rate dependency of ibuprofen inversion in the rat. *Chirality* **6**: 435–439

Scheuerer, S., Hall, S. D., Williams, K. M., Geisslinger, G. (1998) Effect of clofibrate on the chiral inversion of ibuprofen in healthy volunteers. *Clin. Pharmacol. Ther*. **64**: 168–176

Sekikawa, H., Yagi, N., Oda, K., Kenmotsu, H., Takada, M., Chen, H. F., Lin, E. T., Benet, L. Z. (1995) Biliary excretion of furosemide glucuronide in rabbits. *Biol. Pharm. Bull.* **18**: 447–453

Tan, S. C., Patel, B. K., Jackson, S. H. D., Swift, C. G., Hutt, A. J. (2002) Stereoselectivity of ibuprofen metabolism and pharmacokinetics following the administration of the racemate to healthy volunteers. *Xenobiotica* **32**: 683–697

Vos, M. R., Mayer, J. M., Etter, J.-C., Testa, B. (1996) Clofibric acid increases the unidirectional chiral inversion of ibuprofen in rat liver preparations. *Xenobiotica* **26**: 571–582

Yamaoka, K., Nakagawa, T., Uno, T. (1978) Statistical moments in pharmacokinetics. *J. Pharmacokinet. Biopharm.* **6**: 547–558