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Effect of absorption rate on pharmacokinetics of ibuprofen in relation to chiral inversion in humans

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Abstract

The effect of absorption rate on the pharmacokinetics of ibuprofen enantiomers was investigated in 12 healthy Han Chinese male volunteers following oral administration of immediate-release (IR) and sustained-release (SR) preparations containing racemic ibuprofen (rac-ibuprofen). The area under the curve of the plasma concentration–time curve (AUC; (mean ± s.d.) values for rac-ibuprofen were 192.90 ± 43.47 for the SR preparation and 195.90 ± 31.69 μg h mL^{-1} for the IR preparation. AUC values for the enantiomers after administration of the SR formulation were 55.38 ± 17.79 and 92.51 ± 30.68 μg h mL^{-1} for R- and S-ibuprofen, respectively, and were 65.94 ± 20.06 and 100.81 ± 32.28 μg h mL^{-1} for R- and S-ibuprofen after administration of the IR preparation. These values did not differ significantly. C_{max} values were significantly decreased with the SR preparation: 25.11 ± 5.71, 12.24 ± 3.79 and 12.38 ± 3.55 μg mL^{-1} for rac-, R-, and S-ibuprofen, respectively, after administration of the SR preparation, vs 46.21 ± 8.20, 20.82 ± 5.90 and 23.46 ± 7.30 μg mL^{-1} for rac-, R-, and S-ibuprofen, respectively, after administration of the IR preparation. Mean residence time was significantly increased: 7.01 ± 1.29, 5.52 ± 1.25 and 7.04 ± 1.30 h for rac-, R-, and S-ibuprofen, respectively, after administration of the SR preparation vs 4.34 ± 0.89, 3.43 ± 0.64 and 4.51 ± 0.79 h for rac-, R-, and S-ibuprofen, respectively, after administration of the IR preparation. AUC values for S-ibuprofen were significantly larger than those for R-ibuprofen in both preparations, indicating unidirectional chiral inversion. The S/R ratio of serum concentrations of enantiomers was 1.78-fold higher at 6 h after administration of the SR preparation compared with the IR preparation ($P < 0.01$).

These results indicate that ibuprofen undergoes pre-systemic chiral inversion in parallel with a systemic process and that the clinical effects of rac-ibuprofen in humans depend on the absorption rate.

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Introduction

Ibuprofen is a popular non-steroidal anti-inflammatory drug (NSAID) that is usually dispensed as a racemate. Ibuprofen contains one chiral centre, and R-ibuprofen undergoes a species-dependent unidirectional conversion to S-ibuprofen in-vivo (Lee et al 1985; Caldwell et al 1988; Jamali et al 1992). The mechanism of unidirectional chiral inversion of R-ibuprofen in-vitro has been investigated (Knihinicki et al 1989; Chen et al 1991; Shieh et al 1993). The eutomer of ibuprofen, S-ibuprofen, has been marketed in Europe and Australia (Adams et al 1976; Geisslinger, 1989).

The slow absorption of ibuprofen changes the ratio of S/R enantiomers in the serum in humans and other animals (Jamali et al 1988, 1992; Sattari & Jamali 1994). However, another report found no evidence of pre-systemic inversion of ibuprofen following intravenous or oral administration (Hall et al 1993). The pharmacokinetics of S- and R-ibuprofen should be characterized at different absorption rates with respect to inversion processes. Unidirectional chiral inversion of ibuprofen has been assessed in the Caco-2 incubation model (Hao et al 2005). Pre-systemic chiral inversion of R-ibuprofen to S-ibuprofen has been confirmed in rabbits after intraduodenal administration of the racemate as both immediate-release (IR) and sustained-release (SR) preparations (Doki et al 2003). Thus, the pharmacological effects of ibuprofen in the rabbit depend on absorption rate.

Pharmacokinetic interactions between the two enantiomers occur after intravenous administration of ibuprofen in rabbits, the clearance of both enantiomers being reduced when they are administered together (Lin et al 2004). This interaction is considered to be the result of an alteration in the metabolic and/or excretion phase rather than stereoselective protein binding during systemic distribution.

Clinical studies including intravenous administration provide the most suitable reference with which to evaluate the effect of input rate on the serum ratio of S/R ibuprofen concentrations. However, NSAIDs are not usually injected intravenously because of the risk of life-threatening adverse reactions (intravenous administration is restricted to infants with patent ductus arteriosum). The oral administration of NSAIDs is also limited by the potential side effect of gastric bleeding under fasting conditions.

The present study assesses the pre-systemic inversion of ibuprofen relative to the input rate, to clarify the clinical effects of this NSAID in healthy humans.

Materials and Methods

Chemicals

Rac-ibuprofen was purchased from Wako Pure Chemicals (Osaka, Japan). R-ibuprofen (optical purity >98%) was purified chromatographically from rac-ibuprofen using a preparative Chiralcel OD column supplied by Daicel Chemical Industries (Tokyo, Japan). S-ibuprofen (optical purity >98.64%) and ibufenac (internal standard) were gifts from Nagase & Co. (Osaka, Japan) and Kaken Pharmaceuticals (Tokyo, Japan), respectively. The optical purity of R- and S-ibuprofen was confirmed at our laboratory as >98% and >98.64%, respectively.

We also used an IR preparation of rac-ibuprofen (Lot 20030103, 100 mg tablets; Hubei Baikexiangdi Medicine Co., Hubei, China) and an SR preparation (Lot 2004032441, Fenbid, 100 mg capsules; Tianjin Smith Kline and French Lab., Tianjin, China) containing rac-ibuprofen. All other chemicals were of analytical or HPLC grade.

Clinical study

Twelve healthy male Han Chinese volunteers (age range 22–48 years; body weight 64–78 kg) provided written informed consent to participate in this open, two-way randomized crossover study. All participants were judged healthy from their medical history, complete physical examinations and laboratory tests conducted before and after enrollment. Laboratory parameters did not differ significantly before and after the study.

The volunteers fasted overnight and were then assigned to two groups. Each group was given the oral dose equivalent of 600 mg IR or SR preparation, with 200 mL of tap water, 1 h after a standard hospital breakfast. No other food or liquids were allowed over the next 4 h. Participants then ate a standard hospital lunch, and had a standard dinner 10 h after ibuprofen administration. Caffeine-free drinks were allowed at any time. This regimen was repeated with the other preparation 2 weeks later.

Blood samples (approximately 5 mL each) were collected by direct venipuncture before and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14 and 24 h after drug ingestion. Serum was separated from the blood by centrifugation and stored at –20°C.

The Independent Ethics Committee of the Public Health Ministry of Heilongjiang Province, China approved the study protocol and consent forms.

Assays

Serum concentrations of the racemate and of each enantiomer of ibuprofen were analysed by HPLC as described by Doki et al 2003 with slight modifications. The chromatographic system consisted of a system controller (SCL-6A; Shimadzu, Kyoto, Japan), an automatic sampler (SIL-6A, Shimadzu), two pumps (LC-10AD, Shimadzu) and a UV detector (SPD-10AV, Shimadzu). Achiral measurements were made using a column containing achiral C18 as the stationary phase (LiChrospher 100RP18, 250×4.0 mm, particle size 5 μm; Cica Merck, Tokyo, Japan); chiral measurements were made using a chiral stationary phase (Chiralcel OD, 250×4.6 mm, particle size 10 μm; Daicel Chemical Industries, Tokyo, Japan). The mobile phase was acetonitrile:water:phosphoric acid (50:50:0.1) for the achiral assay and hexane:2-propanol:trifluoroacetic acid (100:1:0.1) for the chiral assay. Both mobile phases were delivered at a rate of 1.0 mL min^{-1}. Ibuprofen and ibufenac were detected at 220 and 225 nm in the achiral and chiral assays, respectively. Calibration curves were linear over the range 0.25–250 μg mL^{-1}, with correlation coefficients of 0.999.

Relative standard deviation values for the method to determine rac-ibuprofen at concentrations of 1, 10 and 50 μg mL^{-1} were 5.66%, 1.35% and 3.92%, respectively, for intra-day variation and 3.44%, 2.91% and 1.84%, respectively, for inter-day variations (n=5). The relative standard deviation values for intra-day variation in the enantioselective assay at racemic concentrations of 5, 50 and 100 μg mL^{-1} were 4.91%, 1.18% and 1.41%, respectively, for R-ibuprofen, and 7.28%, 1.51%, and 1.59%, respectively, for S-ibuprofen. Values for inter-day variation were 4.36%, 3.03% and 2.06% for R-ibuprofen, and 7.75%, 3.67% and 1.79% for S-ibuprofen at the same concentrations (n=6). Recovery values for R-ibuprofen at racemic concentrations of 5, 50 and 100 μg mL^{-1} were 81.8±2.2%, 87.8±2.6% and 89.2±2.5%, respectively, and 81.5±4.3%, 87.9±2.2% and 88.4±3.6%, respectively, for S-ibuprofen at the same concentrations (n=6).

Pharmacokinetic analysis

We used moment analysis to calculate the area under the concentration–time curve (AUC) and the mean residence time (MRT) with standard extrapolation to infinity.

Rapid dissolution characteristics of the IR and SR preparations were examined using a dissolution tester. The rate of ibuprofen release from the SR granules was fitted to zero-order kinetics after preliminary experiments (data not shown). Compartment model analyses for the IR and SR preparations were performed using simultaneous non-linear regression by the simplex method using equations 1 and 2, respectively (Yamaoka et al 1981):

$$C(t) = \frac{Dose \cdot k_a}{(V_{d_T} / F_T) \cdot (k_a - k_{el})} \cdot (e^{-k_{el} \cdot (t - t_{lagT})} - e^{-k_a \cdot (t - t_{lagT})}) \quad (1)$$

$$C(t) = \begin{cases} \dfrac{k_0}{(V_{dG} / F_G) \cdot k_{el}} \cdot (1 - e^{-k_{el} \cdot (t - t_{lagG})}) & t < tau \\ \dfrac{k_0}{(V_{dG} / F_G) \cdot k_{el}} \cdot (1 - e^{-k_{el} \cdot (tau - t_{lagG})}) \cdot e^{-k_{el} \cdot (t - tau)} & t > tau \end{cases} \quad (2)$$

where C(t) represents the serum concentration of ibuprofen, k_a and k_{el} are the first-order absorption and elimination rate constants, respectively, k_0 is the zero-order release rate constant, t is the time after administration, tau is the period of zero-order absorption, V_{dT} and V_{dG} are the volumes of distribution, t_{lagT} and t_{lagG} are the lag times, and F_T and F_G are the fractions of the dose absorbed after administration of the IR and SR preparations, respectively.

We evaluated the data using a one-compartment model because we obtained minimum Akaike information criterion values. All results are expressed as mean ± s.d.

The ratio of the serum concentration profiles 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.

Statistical analysis

The pharmacokinetic properties of any form of ibuprofen were statistically analysed by one-way analysis of variance using the statistical package in Microsoft Excel. We assessed S- and R-ibuprofen at each time point using Student's *t*-test. Statistical significance was defined as $P < 0.05$.

Results

Serum concentration–time profiles

Figure 1 shows the mean serum concentration–time curves of rac-ibuprofen after oral administration of the IR and SR preparations. Concentrations of rac-ibuprofen were significantly higher after administration of the IR than the SR preparation before reaching the time of the maximum serum concentration, t_{max}. However, these values were significantly lower than those of the SR preparation in the subsequent elimination phase.

Figures 2 and 3 show the serum concentration profiles of ibuprofen enantiomers after the administration of the IR and SR preparations, respectively. The mean serum concentration profile of S-ibuprofen was significantly higher than that of R-ibuprofen during the elimination phase with both formulations, but particularly with the SR preparation.

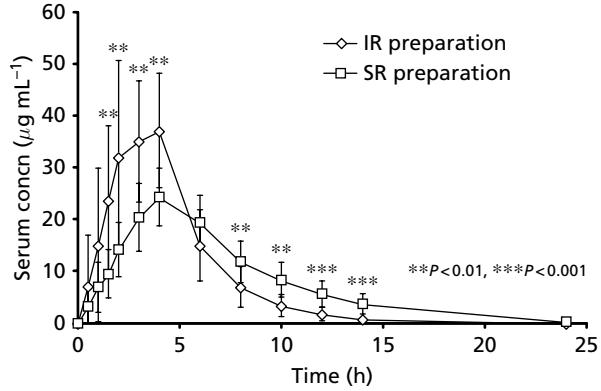

Figure 1 Serum concentration profiles of rac-ibuprofen after oral administration of 600 mg of immediate (IR) and sustained-release (SR) preparations to 12 male volunteers. Results are shown as mean ± s.d.

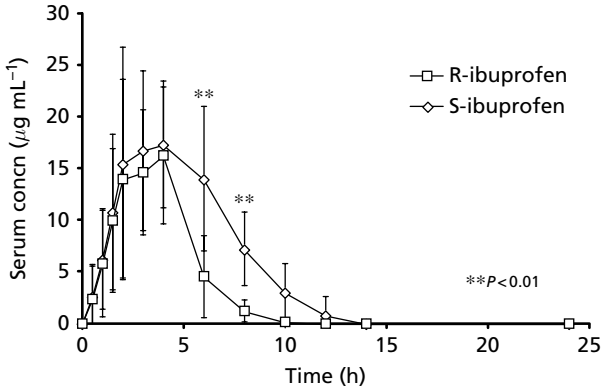

Figure 2 Serum concentration profiles of R-ibuprofen and S-ibuprofen after oral administration of 600 mg of immediate-release preparation to 12 male volunteers. Results are shown as mean ± s.d.

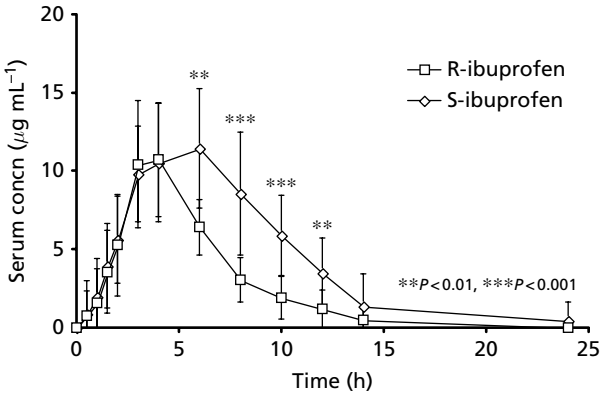

Figure 3 Serum concentration profiles of R-ibuprofen and S-ibuprofen after oral administration of 600 mg of sustained-release preparation to 12 male volunteers. Results are shown as mean ± s.d.

Pharmacokinetic parameters

The mean serum concentration profiles were fitted to an open one-compartment model by non-linear least-squares regression. Table 1 summarizes the pharmacokinetic parameters of rac-, S- and R-ibuprofen.

The t_{max} value was significantly longer for S-ibuprofen than for R-ibuprofen after administration of the SR, but not the IR preparation. The AUC and MRT values of S-ibuprofen were significantly higher than those of R-ibuprofen with both preparations. The tau value of S-ibuprofen was significantly higher and the CL/F_G value, involving chiral inversion and metabolic clearance, significantly lower, than those of R-ibuprofen after administration of the SR preparation. The k_{el} values and lag times of S-ibuprofen were significantly smaller than those of R-ibuprofen after administration of the IR preparation.

The t_{max} value of the IR tablets was much shorter than that of the SR preparation, and C_{max} values for rac- and S- and R-ibuprofen were significantly higher with the IR preparation than with the SR preparation. The AUC values of rac-, R- and S-ibuprofen with the different preparations did not significantly differ, but the MRT values of the SR preparation were significantly longer than those of the IR preparation.

S/R ratios

The S/R ratio of the AUC values of ibuprofen enantiomers did not differ significantly between the preparations (Table 1). The S/R ratios of the serum concentrations of S- and R-ibuprofen after 6 h were significantly higher with the SR than the IR preparation (Figure 4).

Discussion

The pharmacokinetic profiles of rac-ibuprofen after the oral administration of IR and SR preparations to humans have been reported (Siemon et al 1997; Li et al 1998). Our profiles were similar to these, despite the different doses. The AUC values did not differ significantly after the oral administration of either preparation, although k_{el} values were lower with the SR preparation than with the IR preparation. A recent study has shown that the elimination rate constants of both R- and S-ibuprofen are slower after the administration of single isomers than with rac-ibuprofen (Lin et al 2004). We found here that pharmacokinetic interaction between the ibuprofen enantiomers proceeded at different magnitudes after the oral administration of SR and IR preparations.

Different R/S ratios have been demonstrated after the administration of some racemic drugs with different absorption rates. The plasma R/S ratios of oral verapamil formulations differ significantly, together with substantially different input rates from those of racemic verapamil (Bhatti et al 1995; Karim et al 1995). The S/R ratios for plasma metoprolol concentrations also differ significantly between absorption and the terminal phase, with fast input of racemic metoprolol (Mistry et al 2002). Based on these facts, we attributed the different S/R ratios to the input-rate-dependent processes of drugs with high hepatic extraction ratios, such as verapamil and metoprolol.

The site of unidirectional chiral inversion in-vivo remains controversial. One group has found no significant differences in chiral inversion ratios after administering intravenous and oral ibuprofen (Hall et al 1993). Conversely,

Table 1 Pharmacokinetic parameters of racemic and R-(−)- and S-(+)-ibuprofen following oral administration of 600 mg immediate-release (IR) and sustained-release (SR) preparations to 12 male volunteers

	SR preparation			IR preparation		
	Racemate	R	S	Racemate	R	S
C_{max} (μg mL^{-1})	25.11 ± 5.71	12.24 ± 3.79	12.38 ± 3.55	46.21 ± 8.20***	20.82 ± 5.90**	23.46 ± 7.30**
t_{max} (h)	4.08 ± 0.67	3.58 ± 0.51	5.08 ± 1.38$^{\#\#}$	2.83 ± 1.03*	2.96 ± 1.18	3.00 ± 1.35*
AUC (μg h mL^{-1})	192.90 ± 43.47	55.38 ± 17.79	92.51 ± 30.68$^{\#\#}$	195.90 ± 31.69	65.94 ± 20.06	100.81 ± 32.28$^{\#\#}$
MRT (h)	7.01 ± 1.29	5.52 ± 1.25	7.04 ± 1.30$^{\#\#}$	4.34 ± 0.89***	3.43 ± 0.64***	4.51 ± 0.79***$^{\#\#}$
k_0 (h^{-1})	85.09 ± 46.60	61.84 ± 33.55	72.82 ± 35.15	–	–	–
k_a (h^{-1})	–	–	–	1.37 ± 2.12	1.32 ± 2.00	1.62 ± 2.06
Vd_G/F_G (L)	8.96 ± 5.09	9.74 ± 4.56	15.35 ± 9.45	–	–	–
Vd_T/F_T (L)	–	–	–	6.46 ± 2.13	6.45 ± 1.73	4.57 ± 2.47
k_{el} (h^{-1})	0.24 ± 0.09	0.28 ± 0.11	0.27 ± 0.13	0.54 ± 0.16	0.58 ± 0.14	0.41 ± 0.12$^{\#\#}$
Tau (h)	4.80 ± 0.41	3.91 ± 0.80	6.31 ± 1.54$^{\#\#\#}$	–	–	–
Lag $time_G$ (h)	0.36 ± 0.39	0.79 ± 0.59	0.50 ± 0.37	–	–	–
Lag $time_T$ (h)	–	–	–	0.95 ± 0.97	0.90 ± 0.82	1.10 ± 1.08$^{\#}$
$CL/(F_G$ or $F_T)$ (L h^{-1})	3.25 ± 0.71	6.04 ± 2.28	3.54 ± 1.05$^{\#\#}$	3.14 ± 0.55	5.02 ± 1.81	3.40 ± 1.68
S/R AUC ratio			1.73 ± 0.45			1.57 ± 0.45

C_{max}, the maximum serum concentration; t_{max} the time to reach C_{max}; AUC, area under the plasma concentration–time curve; MRT, mean residence time; k_0, zero order absorption rate constant; k_a, first-order absorption rate constant; Vd_G/F_G, volume of distribution / fraction absorbed of SR preparation; Vd_T/F_T, volume of distribution / fraction absorbed of IR preparation; k_{el}, elimination rate constant; Tau, drug release time of SR preparation; $Lagtime_G$, absorption lagtime of SR preparation; Lag $time_T$, absorption lag time of IR preparation; $CL/(F_G$, or $F_T)$, total body clearance / fraction absorbed SR or IR preparation.

Each value is the mean ± s.d. of results from 12 volunteers.

*$P < 0.01$; **$P < 0.001$; ***$P < 0.0001$ vs value for SR preparation; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$ vs value for R-enantiomer.

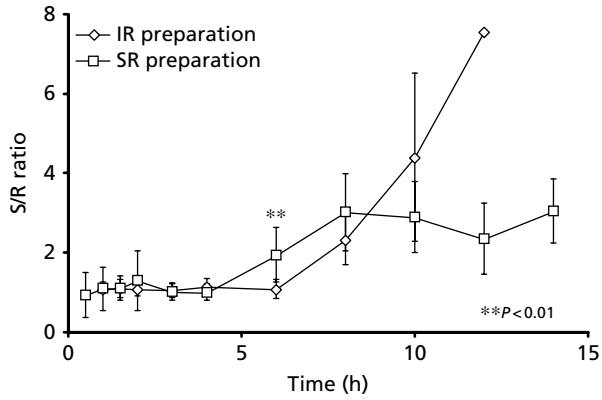

Figure 4 S/R ratio following oral administration of 600 mg of immediate-release (IR) and sustained-release (SR) preparations to 12 male volunteers. Results are shown as mean ± s.d.

pre-systemic inversion during the absorption phase has been demonstrated following the oral administration of suspensions and conventional tablets to 12 healthy individuals (Aiba et al 1999). Enantiomer–enantiomer interaction does not result in mutual inhibition in rabbits (Lin et al 2004). The S/R AUC ratios of SR granules are significantly greater after intraduodenal administration than after intravenous administration in rabbits (Doki et al 2003). The results of the current study in humans were similar to those of our experimental studies using rabbits (Lin et al 2004). One report has indicated that chiral inversion ratios in humans increase after the administration of SR granules compared with conventional tablets, although chiral inversion of ibuprofen has been proposed to vary between species (Chen et al 1991).

Conclusion

The results of the current study indicate that the clinical efficacy of ibuprofen can be increased by administering SR preparations, although the pharmacodynamic parameters remain undefined. The importance of input rates on clinical effects requires further investigation.

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