CHIRALITY 9:297–302 (1997)

Preliminary Pharmacokinetic Study of Ibuprofen Enantiomers After Administration of a New Oral Formulation (Ibuprofen Arginine) to Healthy Male Volunteers

GIANFRANCO FORNASINI,[1] NUNZIA MONTI,[1] GIANDOMENICO BROGIN,[1] MADDALENA GALLINA,[1] MARIO EANDI,[2] STEFANO PERSIANI,[1]* MASSIMO BANI,[1] CARLO DELLA PEPA,[2] GIANPAOLO ZARA,[2] AND MARGHERITA STROLIN BENEDETTI[1]

[1]*Zambon Group S.p.A., Bresso, Italy*

[2]*Institute of Pharmacology and Experimental Therapeutics, University of Turin, Turin, Italy*

ABSTRACT The pharmacokinetics of ibuprofen enantiomers were investigated in a crossover study in which seven healthy male volunteers received single oral doses of 800 mg racemic ibuprofen as a soluble granular formulation (sachet) containing L-arginine (designated trade name: Spedifen®), 400 mg (–)R-ibuprofen arginine or 400 mg (+)S-ibuprofen arginine.

Plasma levels of both enantiomers were monitored up to 480 minutes after drug intake using an enantioselective analytical method (HPLC with ultraviolet detection) with a quantitation limit of 0.25 mg/l.

Substantial inter-subject variability in the evaluated pharmacokinetic parameters was observed in the present study. After (+)S-ibuprofen arginine, the following mean pharmacokinetic parameters ±SD were calculated for (+)S-ibuprofen: t_{max} 28.6 ± 28.4 min; C_{max} 36.2 ± 7.7 mg/l; AUC 86.4 ± 14.9 mg · h/l; $t_{½}$ 105.2 ± 20.4 min. After (–)R-ibuprofen arginine, the following mean pharmacokinetic parameters were calculated for (+)S-ibuprofen and (–)R-ibuprofen, respectively: t_{max} 90.0 ± 17.3 and 50.5 ± 20.5 min; C_{max} 9.7 ± 3.0 and 35.3 ± 5.0 mg/l; AUC 47.0 ± 17.2 and 104.7 ± 27.7 mg · h/l; $t_{½}$ 148.1 ± 63.6 and 97.7 ± 23.3 min. After racemic ibuprofen arginine, the following mean pharmacokinetic parameters were calculated for (+)S- and (–)R-ibuprofen, respectively: t_{max} 30.7 ± 29.1 and 22.9 ± 29.8 min.; C_{max} 29.9 ± 5.6 and 25.6 ± 4.4 mg/l; AUC 105.1 ± 23.0 and 65.3 ± 15.0 mg · h/l; $t_{½}$ 136.6 ± 20.7 and 128.6 ± 45.0 min. T_{max} values of S(+)- and (–)R-ibuprofen after a single dose of 400 mg of each enantiomer did not differ significantly from the corresponding parameters obtained after a single dose of 800 mg of racemic ibuprofen arginine, indicating that the absorption rate of (–)R- and (+)S-ibuprofen is not different when the two enantiomers are administered alone or as a racemic compound. An average of 49.3 ± 9.0% of a dose of the (–)R-ibuprofen arginine was bioinverted into its antipode during the study period (480 minutes post-dosing). The percent bioinversion during the first 30 minutes after (–)R-ibuprofen arginine intake averaged 8.1 ± 3.9%. The mean AUC of (+)S-ibuprofen calculated after 800 mg racemic ibuprofen arginine (105.1 ± 23.0 mg · h/l) was lower than the mean AUC value obtained by summing the AUCs of (+)S-ibuprofen after administration of 400 mg (+)S-ibuprofen arginine and 400 mg (–)R-ibuprofen arginine (133.4 ± 26.6 mg · h/l).

In conclusion, the administration of Spedifen® resulted in very rapid absorption of the (+)S-isomer (eutomer) with t_{max} values much lower than those observed for this isomer when conventional oral solid formulations such as capsules or tablets of racemic ibuprofen are administered. This characteristic is particularly favourable in those conditions in which a very rapid analgesic effect is required. *Chirality 9:297–302, 1997.*

Nunzia Monti's address is I.P.A.S. SA, Via Mastri, 6853, Viganello, Switzerland.

*Correspondence to: Dr. S. Persiani, Department of Pharmacokinetics and Metabolism, Zambon Group S.p.A., Via L. Del Duca 10, 20091, Bresso, (MI), Italy.

Received 1 July 1996; Accepted 13 September 1996

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KEY WORDS: anti-inflammatory drugs; ibuprofen; clinical pharmacokinetics; bioinversion; enantiomers

Ibuprofen (2-(4-isobutyl-phenyl)propionic acid) is an effective and well-tolerated non-steroidal anti-inflammatory drug (NSAID) widely used for the treatment of acute and chronic pain.[1] Ibuprofen exists as (–)R- and (+)S-enantiomers (Figure 1) and the anti-inflammatory activity is thought to reside almost exclusively in the (+)S-enantiomer (eutomer).[2,3] It has been shown that (–)R-ibuprofen is bioinverted unidirectionally to (+)S-ibuprofen in humans.[3–6] (–)R-ibuprofen is first converted to its Coenzyme-A (Co-A) thioester, which subsequently undergoes racemization and hydrolysis to yield a mixture of (–)R- and (+)S-ibuprofen. Since (+)S-ibuprofen is not a substrate for acyl-Co-A synthetases cannot undergo bioinversion.[7] Whether the bioinversion of (–)R-ibuprofen occurs presystemically or systemically remains to be established.[8–10]

(+)S-ibuprofen has been found to be more potent than the (–)R-isomer (distomer) in inhibiting prostaglandin synthesis in vitro[3] with an eudismic ratio of 160 (i.e., the ratio of activities of the eutomer vs. the distomer). Thus, the bioinversion of (–)R-ibuprofen is not only of pharmacokinetic and biochemical interest but also has therapeutic and/or toxicological importance.[3,11]

Racemic ibuprofen, when administered as oral solid formulations such as capsules or sugar-coated tablets, gave peak plasma levels at about 1–2 hours post-dosing.[12] A new oral dosage form of ibuprofen has been developed: a soluble granular sachet containing the active ingredient (racemic ibuprofen) and L-arginine (designated trade name: Spedifen®).[13]

The dosage of 400 mg was used in a clinical trial in patients suffering from chronic osteoarticular pain, to investigate whether the pharmaceutical preparation containing L-arginine allowed a quicker analgesic response compared with the reference commercial tablets (Brufen® 400 mg), while maintaining a good tolerability profile.[14] In the same study an investigation was carried out in healthy volunteers, who were treated with 200 and 400 mg Spedifen®; the aim of the investigation was to establish whether the quicker analgesic response was associated with shortening of the peak time without a decrease in bioavailability.[14] The study demonstrated that administration of Spedifen® resulted in a decrease in t_{max} values and an increase in the peak plasma concentration (C_{max}) compared to the reference formulations Nurofen® and Brufen®. The elimination half-life and bioavailability of ibuprofen when administered as soluble granular formulation were not altered compared to the commercial ibuprofen formulations.[14] The faster rate of ibuprofen absorption and the increase in C_{max}, resulting in higher plasma concentration of the drug in the first hour after administration, are particularly favourable for those clinical conditions, such as severe pain, in which a very rapid pharmacological effect is required.[14] However, in that study the pharmacokinetics of ibuprofen arginine were evaluated using a non-enantioselective analytical method. Since the kinetics of ibuprofen are known to be complex and cannot be defined satisfactorily in terms of total ibuprofen concentrations,[6] a study was carried out in healthy volunteers treated with the new formulation containing arginine, in which the kinetics of (–)R- and (+)S-ibuprofen were monitored separately using an enantioselective assay. In this study, the volunteers were treated with (–)R-, (+)S-, and racemic ibuprofen (rac-ibuprofen) as soluble granular sachets containing the active ingredient and L-arginine.

TABLE 1. Individual and mean demographic data of the subjects enrolled in the study

Subject no.	Age (years)	Height (cm)	Weight (kg)
1	30	176	72
2	21	180	75
3	20	180	75
4	25	175	62
5	33	182	83
6	20	191	83
7	30	178	68
Mean ± SD	25.6 ± 5.4	180.3 ± 5.3	74.0 ± 7.6

MATERIALS AND METHODS

Study Design

Seven male healthy volunteers participated in this crossover study, carried out at the Casa di Cura delle Suore Domenicane, Turin, Italy, after giving written informed consent. Their demographic data are shown in Table 1. Subjects were judged to be in good health on the basis of case history, physical examination, ECG, and routine laboratory data including blood pressure and pulse. Other exclusion criteria were drug and/or alcohol abuse, multiple allergies, intolerance or hypersensitivity to NSAIDs, HIV and/or hepatitis B infections. No medications were allowed during the study or in the last 2 weeks prior to study start. The treatments, which were performed in fasting conditions, were as follows:

1. Treatment A: One sachet of 400 mg of (+)S-ibuprofen arginine (dose expressed as ibuprofen equivalents) dissolved in 150 ml of tap water.
2. Treatment B: One sachet of 400 mg of (–)R-ibuprofen arginine (dose expressed as ibuprofen equivalents) dissolved in 150 ml of tap water.
3. Treatment C: Two sachets of 400 mg of racemic ibuprofen arginine (dose expressed as ibuprofen equivalents) dissolved in 300 ml of tap water.

Treatments A and C were randomized and crossed over, while treatment B was given after the other two since the formulation became available later. The optical purity of the individual isomers was greater than 99.0% by HPLC assay. The volunteers were required to fast for at least 8 hours prior to treatment and the fasting state was maintained for 2 hours after drug intake. A washout of at least 2 weeks separated each treatment.

Blood Sampling

Venous blood (about 6 ml) was collected prior to dosing (time 0) and 5, 10, 15, 30, 45, 60, 90, 120, 240, 360, and 480 minutes post-dosing. Blood was collected in heparinized tubes and plasma was obtained by centrifugation. Plasma samples were frozen at –20°C until analysis.

Assay Procedure

(–)R- and (+)S-ibuprofen were extracted from 250 µl of plasma (to which 150 µl of 3N HCl were added) with 5 ml of cyclohexane. After 15 minutes vortexing, the samples were centrifuged at 1,200*g* for 5 minutes and 3 ml of the organic phase were separated. The extraction was repeated once, and the organic extracts were pooled and evaporated to dryness under a nitrogen stream. The residue was then reconstituted with 250 µl of 0.1 M phosphate buffer, pH 7.4, and an aliquot of 25 µl was injected into the HPLC. The concentrations of (–)R- and (+)S-ibuprofen were determined in plasma using an HPLC method with UV detection. Separation of the enantiomers was achieved using a Chiral-AGP column (100 × 4 mm; 5 µm) fitted with a Chiral-AGP (10 × 3 mm; 5 µm) guard column. Detection was carried out at 230 nm using a Jasco (Cremella, Italy) automated HPLC system. The mobile phase was acetonitrile/0.02 M NaH_2PO_4 (10:990 v/v) containing 0.001 M dimethyloctylamine, pH 6.5, flow rate of 1.2 ml/min at a constant temperature of 18°C. Under these conditions (–)R-ibuprofen and (+)S-ibuprofen had retention times of 2.7 and 3.5 minutes, respectively. The internal standard (propyl-4-hydroxybenzoate; Figure 1) had a retention time of 5.7 minutes. The minimum quantifiable concentration of the assay was 0.25 mg/l for both enantiomers with CV% of 8.3 and 7.5% for the (–)R- and (+)S-enantiomer, respectively. Accuracy (tested at 1, 10, and 40 mg/l) ranged from 77.6 to 81.2% and from 79.5 to 83.6%; precision (tested at concentrations of 0.2, 0.5, 2.5, 5.0, 10, 20, and 25 mg/l) ranged from 3.9 to 8.3% and from 5.2 to 9.6% for the (–)R- and (+)S-enantiomer, respectively.

Pharmacokinetics

The estimation of the pharmacokinetic parameters was performed by non-compartmental analysis of ibuprofen isomer plasma concentrations vs. time curves. Maximum plasma concentrations (C_{max}) and the corresponding times (t_{max}) were read as the coordinates of the highest raw data point in each volunteer. The area under the plasma concentration vs. time curve ($AUC_{(0\text{-}t)}$) was estimated by the linear trapezoidal rule up to the last measurable time. $AUC_{(0\text{-}\infty)}$ (AUC) was obtained by adding the part of the area extrapolated to infinity (last measurable concentration/Ke) to $AUC_{(0\text{-}t)}$. The elimination half-life from plasma data ($t_{½}$) was estimated by linear regression analysis of natural log concentrations against time, $t_{½} = \ln 2/\text{slope}$.

The degree of bioinversion (i.e., the fraction of the administered dose of (–)R-ibuprofen inverted to (+)S-ibuprofen) was calculated as described by Lee et al.[6] and by Geisslinger et al.[15]

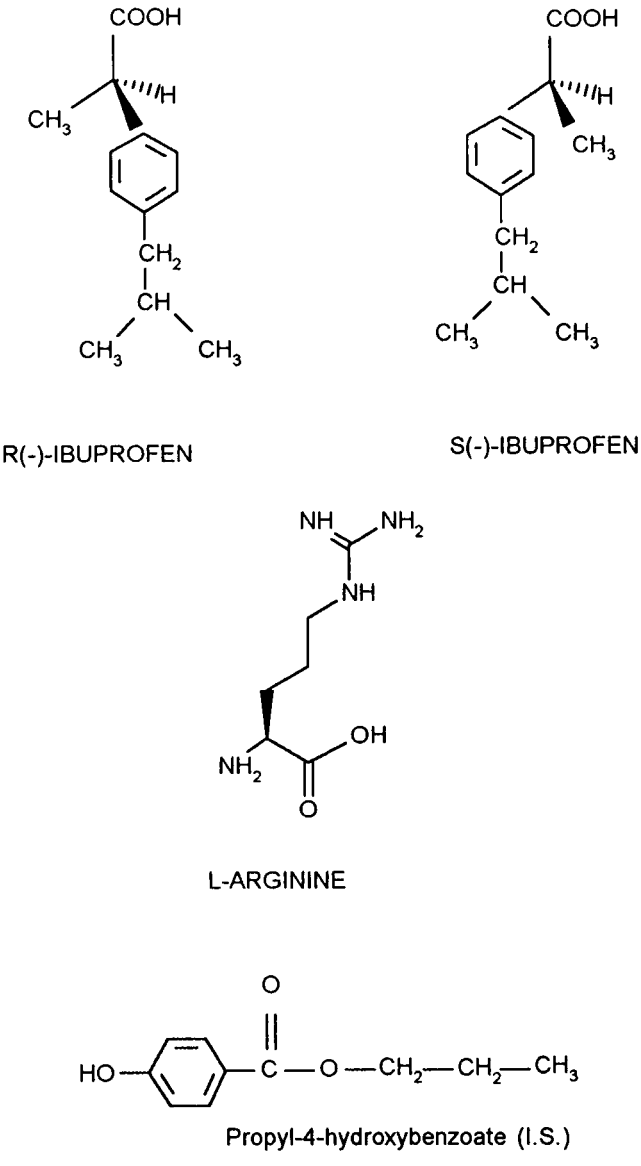

Fig. 1. Structural formulae of (–)R-ibuprofen, (+)S-ibuprofen, L-arginine, and the internal standard (I.S.) propyl-4-hydroxybenzoate.

$$\%\ \text{of the dose inverted} = \frac{AUC_1 \cdot \text{Dose (+)S}}{AUC_2 \cdot \text{Dose (–)R}} \cdot 100$$

were AUC_1 and AUC_2 are the AUCs of (+)S-ibuprofen after administration of (–)R-ibuprofen arginine and (+)S-ibuprofen arginine, respectively.

Statistical Analysis

C_{max}, AUC, t_{max}, and $t_{1/2}$ calculated for (–)R- and (+)S-ibuprofen after treatment with the racemic compound and after treatment with the corresponding enantiomer were compared using the Student's *t*-test for paired data. T_{max} values were compared using the non-parametric Wilcoxon signed rank test. The value of $P < 0.05$ was considered statistically significant.

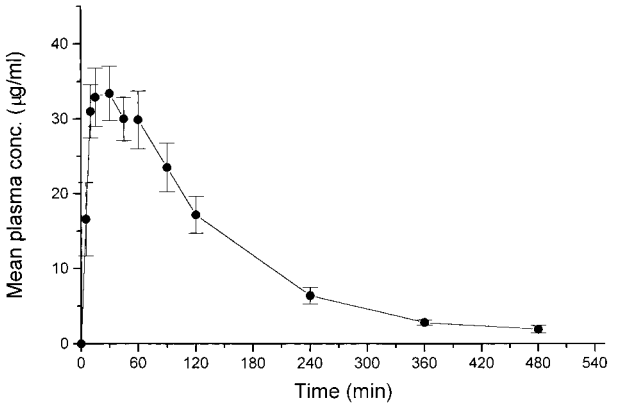

Fig. 2. Mean plasma concentration-time curve (n = 7) of (+)S-ibuprofen after a single oral dose of 400 mg (+)S-ibuprofen arginine. Standard error of the mean is shown by vertical bars.

RESULTS

All treatments were well tolerated by all subjects. (–)R- and (+)S-ibuprofen were above the minimum quantifiable concentration in plasma from all the volunteers up to the last sampling time (480 minutes after dosing), indicating that the limit of quantitation of the analytical method employed was sufficient to monitor the analytes at the dose levels administered. This allowed a satisfactory evaluation of the pharmacokinetics of both ibuprofen enantiomers after all treatments.

Marked inter-subject variability in the evaluated pharmacokinetic parameters was observed in the present study. AUC, t_{max}, and C_{max} values differed up to threefold among subjects receiving the same treatment; $t_{1/2}$ values also varied among subjects to a lesser extent.

The plasma levels of the individual enantiomers following a single oral dose of 400 mg (+)S-, 400 mg (–)R-, and 800 mg rac-ibuprofen arginine are shown in Figures 2, 3, and 4, respectively. The pharmacokinetic parameters are shown in Table 2. C_{max} and $t_{1/2}$ but not t_{max} and AUC value of (+)S-ibuprofen after 400 mg (+)S-ibuprofen differed significantly from the corresponding parameters after 800 mg rac-ibuprofen arginine ($P < 0.05$ for C_{max} and < 0.025 for $t_{1/2}$). For (–)R-ibuprofen C_{max} and AUC values calculated after 400 mg (–)R-ibuprofen arginine differed significantly from the corresponding parameters calculated after 800 mg rac-ibuprofen arginine ($P < 0.01$ for C_{max} and < 0.05 for AUC). T_{max} and $t_{1/2}$ values did not differ significantly. The mean AUC value of (+)S-ibuprofen calculated after 800 mg rac-ibuprofen arginine (105.1 ± 23.0 mg · h/l) was not statistically different from that obtained by summing the AUCs of (+)S-ibuprofen after administration of 400 mg of the optically pure enantiomers (133.4 ± 26.6 mg · h/l) although a tendency toward a lower value was found.

The mean cumulative percentage of the administered dose of (–)R-ibuprofen bioinverted by the seven volunteers as a function of time is shown in Figure 5. An average of 49.3 ± 9.0% of the (–)R-ibuprofen arginine dose was bioinverted to the (+)S-isomer in 480 minutes post-dosing. The percent of the administered dose of (–)R-ibuprofen bioinverted during the first 30 minutes after (–)R-ibuprofen arginine intake averaged 8.1 ± 3.9%.

DISCUSSION

The pharmacokinetic study previously carried out in healthy volunteers[14] after 200 or 400 mg rac-ibuprofen arginine (Spedifen®) showed a reduction in t_{max} and an increase in C_{max} values compared to the corresponding values calculated after the administration of the same doses as Nurofen® (200 mg) and Brufen® (400 mg), which were chosen as reference formulations.

In that study t_{max} values averaged 90 ± 70 min (C_{max} 16 ± 4 mg/l) and 64 ± 30 min (C_{max} 43 ± 9 mg/l) after Nurofen® and Brufen®, respectively. The corresponding values after 200 and 400 mg Spedifen® were 17 ± 8 min (C_{max} 26 ± 6 mg/l) and 24 ± 16 min (C_{max} 56 ± 14 mg/l), respectively. Even though the analytical method employed was not enantioselective, the data indicated that, compared to the reference formulations, the new oral formulation of rac-ibuprofen resulted in faster absorption of the active component accompanied by an increase in C_{max} values.

In the present study the pharmacokinetics of each ibuprofen enantiomer were evaluated separately by the use of an enantioselective analytical method. The data obtained in

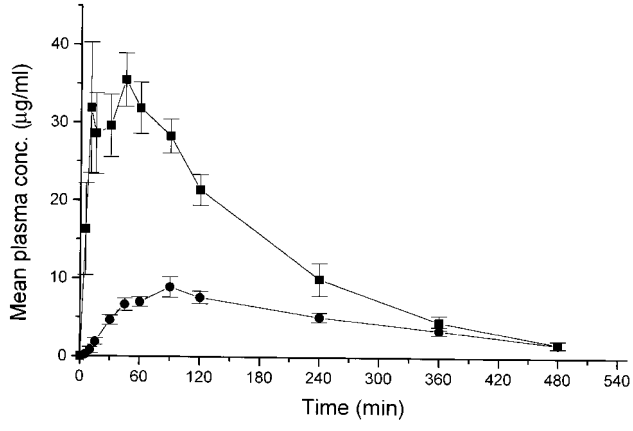

Fig. 3. Mean plasma concentration-time curve (n = 7) of (+)S-ibuprofen (●) and (–)R-ibuprofen (■) after a single oral dose of 400 mg (–)R-ibuprofen arginine. Standard error of the mean is shown by vertical bars.

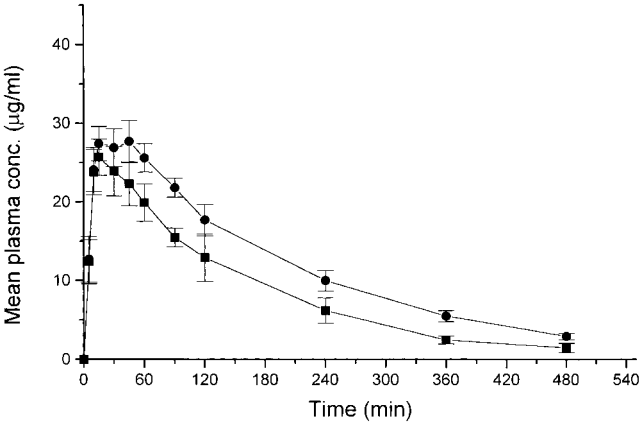

Fig. 4. Mean plasma concentration-time curve (n = 7) of (+)S-ibuprofen (●) and (–)R-ibuprofen (■) after a single oral dose of 800 mg rac-ibuprofen arginine. Standard error of the mean is shown by vertical bars.

TABLE 2. Mean pharmacokinetic parameters ± SD of ibuprofen enantiomers after a single oral administration of 400 mg (+)S-ibuprofen arginine, 400 mg (–)R-ibuprofen arginine, and 800 mg rac-ibuprofen arginine (n = 7)

	(+)S-ibuprofen arginine (400 mg)		(–)R-ibuprofen arginine (400 mg)			rac-ibuprofen arginine (800 mg)	
	(+)S-ibuprofen	*P**	(+)S-ibuprofen	(–)R-ibuprofen	*P***	(+)S-ibuprofen	(–)R-ibuprofen
Pharmacokinetic parameter							
t_{max} (min)	28.6 ± 28.4	NS***	90.0 ± 17.3	50.0 ± 20.5	NS***	30.7 ± 29.1	22.9 ± 29.8
C_{max} (mg/l)	36.2 ± 7.7	<0.05	9.7 ± 3.0	35.3 ± 5.0	<0.01	29.9 ± 5.6	25.6 ± 4.4
AUC (mg · h/l)	86.4 ± 14.9	NS	47.0 ± 17.2	104.7 ± 27.7	<0.05	105.1 ± 23.0	65.3 ± 15.0
$t_{½}$ (min)	105.2 ± 20.4	<0.025	148.1 ± 63.6	97.7 ± 23.3	NS	136.6 ± 20.7	128.6 ± 45.0

*Comparison of (+)S-ibuprofen parameters after administration of 400 mg (+)S-ibuprofen arginine and 800 mg rac-ibuprofen arginine.
**Comparison of (–)R-ibuprofen parameters after administration of 400 mg (–)R-ibuprofen arginine and 800 mg rac-ibuprofen arginine.
***Using the Wilcoxon signed rank test.

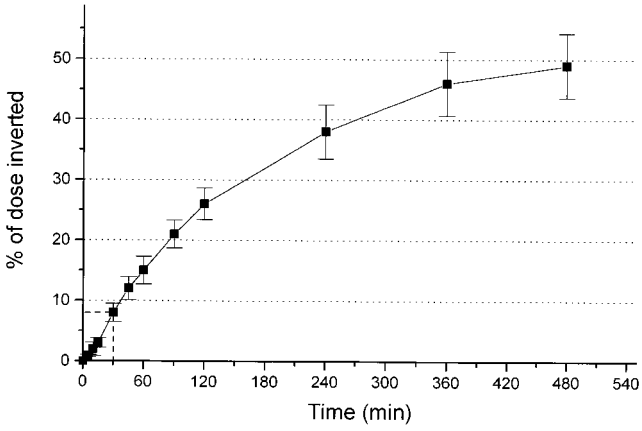

Fig. 5. Profile of mean (n = 7) rate of bioinversion of (–)R-ibuprofen. The extent of bioinversion at 30 minutes after drug intake is highlighted (dashed line). Standard error of the mean is shown by vertical bars.

the present study are reasonably in line with previous findings[14] (mean t_{max} of (+)S- and (–)R-ibuprofen were 31 ± 29 min and 23 ± 30 min, respectively after a single dose of 800 mg of rac-ibuprofen arginine).

Similar mean t_{max} values were found for (–)R- and (+)S-ibuprofen after a single dose of 400 mg of each enantiomer. These results indicate that the rate of absorption of (–)R- and (+)S-ibuprofen is not different when the two enantiomers are administered separately or as a racemic compound, and are in agreement with the results obtained by Geisslinger et al. after the administration of 300 mg (+)S-ibuprofen, 300 mg (–)R-ibuprofen, and 600 mg rac-ibuprofen capsules.[15]

In the present study the percentage of (–)R-ibuprofen arginine dose that was inverted into its antipode in the time interval from 0 to 8 hours after drug intake averaged 49.3 ± 9.0% whereas it averaged 54.4 ± 16.9% when extrapolated to infinity. The latter result is in line with the data obtained by Geisslinger et al.[15] who found a bioinversion of 52% (up to infinite time) following the administration of capsules, and by Lee et al.[6] who found a bioinversion of 63% (up to infinite time) following the administration of a dilute alkaline solution.

Although the number of volunteers enrolled in the present study was small it would appear that the extent of bioinversion of (–)R-ibuprofen is not affected by this new oral formulation.

The AUC values of (+)S-ibuprofen after (+)S-ibuprofen arginine, although lower, did not differ significantly from the AUC values of (+)S-ibuprofen after rac-ibuprofen arginine. This result, which is apparently in contrast with the percent of bioinversion of the distomer (54%), suggests that different and complex mechanisms contribute to the clearance of each enantiomer due to the concurrent presence of the opposite enantiomer.[6]

In the present study, during the first 30 minutes post dosing, the percent of the (–)R-ibuprofen arginine dose, which was bioinverted, averaged 8.1 ± 3.9%. In a previous study,[14] 30 minutes after drug intake, the analgesic effect of Spedifen® in patients suffering from chronic osteoarticular pain was significantly higher than the reference formulation Brufen.® These findings suggest that the analgesic effect observed during the first 30 minutes after Spedifen® administration should be mainly due to the rapid absorption and the corresponding high plasma concentrations of the eutomer rather than to the bioinversion of the distomer, which is also rapidly absorbed (see Table 2 for t_{max} values of ibuprofen enantiomers).

The AUC value of (+)S-ibuprofen calculated after administration of rac-ibuprofen arginine was not statistically different from that obtained by summing the AUC values of (+)S-ibuprofen calculated after the separate administration of (–)R- and (+)S-ibuprofen arginine, although a tendency toward a lower value calculated after rac-ibuprofen was seen in the present study. This observation has been described already but the difference was found to be statistically significant.[6]

In conclusion, Spedifen® administration resulted in a very rapid absorption of the (+)S-isomer (eutomer) with t_{max} values much lower than those observed for this isomer when conventional oral solid formulations such as capsules or tablets of rac-ibuprofen are administered.[10,11,15,16] This characteristic is particularly favourable in those conditions in which a very rapid analgesic effect is required.

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