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Report

Pharmacokinetics of Ibuprofen Enantiomers in Humans Following Oral Administration of Tablets with Different Absorption Rates

Fakhreddin Jamali,[1,3] Nikhilesh N. Singh,[1] Franco M. Pasutto,[1] Anthony S. Russell,[2] and Ronald T. Coutts[1]

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Ibuprofen (IB) is a racemic drug and is administered as such. While activity is due mainly to the S enantiomer, pharmacokinetic interpretations, as well as criteria to assess the bioequivalence of IB formulations, are based on measurements of the total (S + R) drug concentrations. IB enantiomers possess different disposition properties mainly as a result of R-to-S isomeric bioinversion. Inversion is maximal during the absorption phase, suggesting, perhaps, involvement of a presystemic process. This concept was evaluated in healthy subjects by crossover administration of four IB tablets having different absorption rates. The plasma concentrations of the individual isomers were measured using a stereospecific gas chromatographic assay. Differences among the products were insignificant with respect to the extent to the absorption. The S:R concentration ratios rose for 4 to 6 hr and then remained relatively unchanged. This observation was consistent with equal terminal $t_{1/2}$ values for the enantiomers. There were significant differences between the peak times (T_{max}) of the products. The S:R ratios of the concentrations at T_{max} of S and AUC also differed; significant positive correlations were found between T_{max} and the S:R ratios of C_{max}. Thus the extent of R-to-S inversion, and hence the potency of a racemic dose of IB, may be absorption rate dependent.

KEY WORDS: ibuprofen enantiomers; enantiomeric inversion; presystemic inversion; gut metabolism.

INTRODUCTION

The 2-arylpropionic acid (APA) nonsteroidal antiinflammatory drugs (NSAIDs) are usually marketed and administered as racemates. However, the pharmacological properties of these mixtures are mainly, if not entirely, associated with the S isomer (1). The two enantiomers may also have different disposition kinetics due partly to the unidirectional metabolic inversion of R-APA to S-APA. Nevertheless, thus far only limited data on the pharmacokinetics of the enantiomers of chiral NSAIDs in humans are available. For example, for ibuprofen (IB), the literature contains only one article (2) reporting the time course of the drug enantiomers in four healthy subjects. It has been shown that after oral administration of racemic ibuprofen (IB) as dilute alkaline solutions to humans, the inactive R isomer inverts to the active S isomer (2). The process appears to be very rapid and maximal during the absorption phase, suggesting the potential involvement of presystemic inversion. However, in the rat, Cox *et al.* (3) noticed negligible inversion of R- to S-IB upon the first pass through the perfused isolated liver. Simmonds *et al.* (4), on the other hand, detected substantial amounts of S-benoxaprofen when the R isomer was exposed to everted rat gut. From these observations, we hypothesized that the R-to-S inversion of APAs may take place mainly in the gut upon the first pass. If so, then prolonging the residence time of the racemate in the gut should favor R-to-S bioinversion. This concept was evaluated in two groups of healthy volunteers who, on different occasions, took two tablets of racemic IB having different absorption rates. The other intention of this paper is to report data on the pharmacokinetics of ibuprofen enantiomers following the administration of commercially available dosage forms to a relatively large group of subjects.

MATERIALS AND METHODS

Products

Tablets were available from commercial sources as Motrin (Upjohn of Canada, Don Mills, Ontario) or Apo-Ibuprofen (Apotex Inc., Weston, Ontario, Canada).

Products I (Motrin, Lot No. P889I) and II (Apo-Ibuprofen, Lot No. 56151) were 600-mg film-coated tablets, while products III (Motrin, Lot No. P864) and IV (Apo-Ibuprofen, Lot No. 441651) were 300-mg sugar-coated tablets.

[1] Faculty of Pharmacy & Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada T6G 2N8.

[2] Division of Rheumatology, University of Alberta, Edmonton, Alberta, Canada.

[3] To whom correspondence should be addressed.

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Subjects

Fourteen healthy volunteers were recruited from the Pharmacy and Medical student bodies at the University of Alberta. Subjects were 19–37 years old and all were within 10% of ideal body weight. They were interviewed to assure normal health and absence of significant indigestion or previous sensitivity to other NSAIDs. With the exception of subject 5 (Table I), the participants were nonsmokers.

Eight volunteers took film-coated tablets, while the remaining six took sugar-coated tablets. Subjects were required to abstain from any other medications for at least 7 days before and during the study.

The investigation was approved by the Medical Ethics Review Committee of the University of Alberta Hospital. The objectives of the study and the possible side effects of the treatment were explained to the subjects and written consent forms were signed.

Dosing

In a crossover fashion and following a 12-hr fast, single doses of the products (two 300-mg sugar-coated tablets or one 600-mg film-coated tablet) were swallowed with 200 ml of water. Food was not allowed for 2hr after dosing. A "washout" period of at least 5 days was enforced prior to the administration of each product. The order in which the products were given was decided based on the toss of a coin.

Blood Sample Collection

Blood samples (4–6 ml) were collected from a forearm vein through an indwelling cannula or directly into a heparinized Vacutainer. Immediately after collection the samples were centrifuged, and the plasma was separated, divided into two portions, and stored at −20°C until analyzed.

Blood samples were collected at 0.0, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, and 12.0hr after dosing. From two subjects (Nos. 6 and 8, Table I) samples were taken only up to 8hr.

Assay

The enantiomers of IB in plasma were assayed according to a previously reported stereospecific gas chromatographic (GC) assay (5–7).

Treatment of Data

The plasma concentration–time curves were plotted for each enantiomer. The $t_{1/2}$ values of the log-linear terminal phase of the curves were estimated by linear least-squares regression except in some cases (film-coated tablets, Table I) where, due to fluctuations, only the last two points could be utilized in calculation. The areas under plasma enantiomers concentration–time curves (AUC) were estimated by employing the linear trapezoidal rule. To include all of the subjects in the statistical assessment without introducing errors associated with the estimation of the slope of the terminal phase of some of the curves, only AUC values from 0 to 8hr were considered. Nevertheless, relatively small concentrations of the enantiomers were found in plasma 8hr after dosing of the products. In some cases the enantiomers reached their maximum concentration (C_{max}) at different times; consequently the peak time of the S enantiomer [T_{max}(S)] and the concentration ratio at T_{max}(S) were utilized

Table I. Bioavailability Indices Following Administration of Single 600-mg Oral Doses of Ibuprofen as One Film-Coated Tablet

		C_{max}, mg/liter			AUC, (mg/liter) hr			$t_{1/2}$, hr	
Subject No.	T_{max}, hr[a]	S	R	S/R at T_{max}	S	R	S/R	S	R
Product I									
1	1	31.13	28.43	1.09	88.66	63.94	1.39	1.97[c]	2.05[c]
2	1	16.37	16.65	0.98	59.51	42.80	1.39	2.74	4.70
3	1	27.24	28.62	0.95	162.84	96.79	1.68	1.67	1.58
4	3	26.39	16.52	1.60	108.73	59.30	1.83	4.08	4.02
5	3	63.60	56.74	1.12	150.71	112.89	1.33	1.50	1.43
6	1	22.00	18.58	1.18	63.69	38.65	1.65	2.31[c]	2.69[c]
7	1	28.56	26.96	1.06	125.29	92.18	1.36	4.62	2.74
8	0.5	25.00	27.12	0.92	95.54	87.16	1.10	2.15	2.31
Mean	1.44	30.04	27.45	1.11	106.87	74.21	1.47	2.63	2.69
SD	0.92	13.36	12.12	0.20	35.29	25.19	0.22	1.06	1.07
Product II									
1	2	19.98	15.88	1.77	77.71	38.95	1.99	2.16[c]	2.32
2	3	33.32	22.43	1.58	107.07	64.20	1.67	2.63[c]	5.49[c]
3	4	33.58	32.35	2.14	164.04	109.51	1.50	2.15	1.37
4	3	44.75	24.14	1.45	148.26	74.35	1.99	5.58[c]	5.45[c]
5	3	43.23	33.13	1.31	99.04	65.83	1.50	1.88	1.37[c]
6	3	17.38	13.31	1.31	77.90	48.02	1.62	1.96[c]	2.82[c]
7	1	35.30	28.70	1.23	172.84	106.73	1.62	2.31	1.88
8	3	25.50	18.40	1.39	126.92	83.37	1.52	2.01	2.04
Mean	2.75[b]	31.50	23.54	1.52[b]	121.72	73.87	1.68[b]	2.58	2.84
SD	0.83	9.36	6.96	0.28	34.86	23.68	0.19	1.15	0.58

[a] Time to attain C_{max} of the S isomer.
[b] Significantly different from product I.
[c] Based only on the two last data points on the log-linear terminal phase.

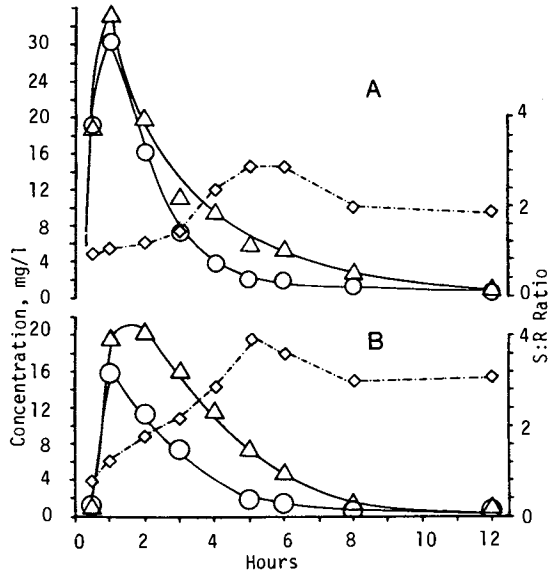

Fig. 1. Typical plasma S (△) and R (○) ibuprofen concentrations and the corresponding S:R concentration ratios versus time curves in subject 1 following single 600-mg oral doses of products I (A) and II (B).

in the calculations. Negligible differences were noticed when T_{max}(R) was used.

Statistical significance of the observed differences between the paired products and among all products were tested by paired Student's *t* test and Duncan's new multiple-range test ($\alpha = 0.05$), respectively. Significance of the correlation between indices was also examined at $\alpha = 0.05$. Data are expressed as the mean ± SD.

RESULTS AND DISCUSSION

Figure 1 depicts the plasma time course of IB enantiomers in subject 1 following 600-mg racemic doses as film-coated tablets. Tables I and II contain the estimated pharmacokinetic indices after crossover administration of single doses of the film-coated and sugar-coated tablets, respectively. There was no significant difference in the extent of absorption of the products. However, products II [T_{max}(S), 2.75 ± 0.83] and IV [T_{max}(S), 2.83 ± 0.37] were absorbed significantly slower than products I [T_{max}(S), 1.44 ± 0.92] and III [T_{max}(S), 1.42 ± 0.61]. As expected, the plasma concentrations and AUCs were generally greater for S-IB than for R-IB.

When the S:R concentration ratios were plotted against time, a general trend similar to what is shown in Fig. 1 was observed. This ratio increased progressively until 4–6hr postdosing and then leveled off. This observation, although not conclusive, leads us to propose that the R-to-S inversion of IB takes place presystemically. A systemic inversion is expected to be a continuous process and proceed until entire circulating R is eliminated. Hence, in the presence of a systemic inversion, one expects the concentration gap between the two isomers to broaden as long as there remains R in the body (9). We noticed a parallel decline in the plasma concentrations of the enantiomers (Tables I and II). The data of Lee *et al.* also are in agreement with ours. Despite their statement that plasma concentrations of S-IB declined "more slowly" than those of the other enantiomer (2), a paired *t* test performed by us on their reported data failed to find a significant difference in the $t_{1/2}$ values of the enantiomers after racemic doses (*t* calculated, 2.82; *t* table, 3.18 at $\alpha = 0.05$).

Alternatively, one may suggest that in the absence of R, S may have a very rapid rate of elimination and attribute the

Table II. Bioavailability Indices Following Administration of Single 600-mg Oral Doses of Ibuprofen as Two 300-mg Sugar-Coated Tablets

		C_{max}, mg/liter			AUC, (mg/liter) hr			$t_{1/2}$, hr	
Subject No.	T_{max}, hr[a]	S	R	S/R at T_{max}	S	R	S/R	S	R
Product III									
1	2	25.63	26.69	0.96	97.79	74.96	1.30	4.14	3.90
2	2	26.99	25.42	1.06	70.56	46.98	1.50	1.50	1.67
3	0.5	18.24	23.40	0.94	69.71	69.95	1.00	3.01	2.15
4	1	25.89	27.99	0.92	121.93	68.54	1.79	2.15	1.67
5	1	22.90	20.34	1.13	90.77	56.86	1.60	2.01	1.31
6	2	24.95	23.60	1.09	101.19	70.00	1.45	1.69	1.43
Mean	1.42	23.90	20.34	1.13	90.77	56.86	1.60	2.42	2.02
SD	0.61	2.87	2.49	0.08	18.12	9.58	0.24	0.91	0.88
Product IV									
1	3	20.22	14.84	1.66	93.36	49.10	1.90	2.15	2.31
2	3	20.90	11.92	1.77	69.08	32.67	2.11	1.88	1.88
3	3	26.38	17.17	1.54	98.27	53.29	1.84	2.15	2.16
4	3	24.12	14.03	1.65	80.67	42.38	1.90	1.68	1.88
5	3	29.56	22.47	1.32	97.45	61.14	1.59	3.54	2.51
6	2	39.07	23.48	1.76	162.27	70.48	2.30	1.88	2.74
Mean	2.83[b]	26.71	17.32	1.62[b]	100.18	51.51	1.94[b]	2.21	2.24
SD	0.37	6.37	4.29	0.15	29.61	12.25	0.22	0.62	0.31

[a] Time to attain C_{max} of the S isomer.
[b] Significantly different from product III.

similarity of the enantiomers $t_{1/2}$ after racemic doses to continuous formation of S from R. The limited data reported for IB enantiomers in human seem to be contrary to this suggestion. Although Lee *et al.* (2) suggest different terminal $t_{1/2}$'s for S-IB when given alone or along with R-IB, our interpretation of their data proves otherwise. A paired Student's *t* test performed by us on their data (2) failed to reveal a significant difference in the $t_{1/2}$ values reported for S-IB given alone or as a racemate (*t* calculated, 2.67; *t* table, 3.18), i.e., the $t_{1/2}$ remained unchanged despite 56–71% inversion. Furthermore, very recently Cox *et al.* (9), who gave iv doses of racemic IB to 30 healthy volunteers, noticed only negligible differences between the disposition kinetics of the enantiomers. All these indicate a presystemic process for the R-to-S inversion.

Drugs may undergo presystemic biotransformation in the gastrointestinal tract (GIT) and/or the liver. The liver first-pass metabolisms are always followed by substantial systemic metabolisms due to the efficient circulation through the organ. However, because of the limited circulation through the GIT, this will not be the case when this organ is the site of the presystemic biotransformation. Hence, the absence of evidence suggestive of significant systemic (continuous) inversion supports the notion that the formation of R-IB from S-IB takes place in the GIT.

Despite considerable inter- and intrasubject variations, and with only a few exceptions, the S:R concentration ratios at T_{max} and the S:R AUC ratios (Tables I and II) were found to be significantly greater after the administration of products II and IV (longer T_{max} values) compared to products I and III (shorter T_{max} values). This may suggest absorption rate dependence for the inversion. Interestingly, positive and linear relationships were observed when the S:R concentration ratios were plotted versus their corresponding T_{max} values. The highest correlation coefficient was found when the concentration ratios at T_{max} were considered (*r* calculated, 0.74; *r* required, 0.37). Similarly, AUC(S)/AUC(R) appears to be linked significantly to the rate of absorption. The relationship was, however, curvilinear, as they tend to increase proportionally with prolongation of T_{max} up to a certain point (T_{max} of 2hr) and then level off as if a saturation level has been reached. These may indicate that, up to a time limit, the longer R-IB resides in the absorption site, the greater will be its extent of inversion to the active S-isomer.

Our observation does not exclude the possibility of a systemic enantiomeric inversion for IB. However, if it is considered along with the negligible differences between the enantiomers' concentration observed following iv doses (9) and also with the observations that the R-benoxaprofen is inverted at the rat gut wall (4), it may indeed suggest that the major site of R-to-S inversion for IB is the gastrointestinal tract.

The observations presented in this article further emphasize the importance of differentiating between the enantiomers of chiral drugs when assessing bioavailability and when correlating efficacy with drug concentration (10). For APA derivatives that undergo substantive R-to-S inversion, this consideration is even more critical since factors such as absorption rate, route of administration, disease state, and presence of other drugs may influence the time course of the pharmacologically active portion of the dose.

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