Pharmacokinetics of Two Enteric-Coated Ketoprofen Products in Humans with or Without Coadministration of Omeprazole and Comparison with Dissolution Findings

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INTRODUCTION

Generally, comparative bioavailability studies are conducted in healthy humans not taking any medications in whom the stomach pH is usually around 1–2 (1). Therefore, potential effects of concurrent administration of drugs, such as enteric-coated products with anti-ulcer drugs or of clinical situations resulting in higher stomach pH, on the bioavailability would be missed.

To assess such an interaction, Verbeeck et al (2) concluded that concurrent administration of cimetidine did not alter the pharmacokinetics of the enteric-coated ketoprofen products. The lack of observable effect of cimetidine on the pharmacokinetics of ketoprofen could also be due to changes in hepatic blood flow-rate. As cimetidine is known to reduce hepatic blood flow (3), the mechanism might counter the effect of reduced acidity. Therefore, it would be difficult to extract the effect of earlier release of drug in the stomach from the plasma concentration profiles alone.

As omeprazole does not effect the hepatic flow rate (4), and is also a more direct agent for inhibiting gastric acid production, it appears to offer advantages in studying effect of low gastric acidity on the release of enteric-coated products.

The purpose of this study was to evaluate the effect of a single dose of omeprazole on the pharmacokinetics of two enteric-coated ketoprofen tablet products to determine if there are influences on the absorption of the drug, and if such influences could cause a differentiation between products which have previously been shown to meet bioequivalence standards in a usual bioavailability study in healthy human volunteers. Dissolution differences were also assessed.

MATERIALS AND METHODS

MATERIALS: Samples of racemic ketoprofen and the calcium salt of fenoprofen were purchased from Sigma (St. Louis, MO). A sample of the individual enantiomers of ketoprofen was kindly supplied by Rhone-Poulenc Rorer (Montreal, Canada). The dosage forms administered were enteric-coated 100 mg tablets of ketoprofen, designated A and B, and omeprazole capsules (20 mg, Losec, Astra Pharma Inc., Canada) which were obtained from the local (Canadian) market.

Pharmacokinetic Study Protocol: The study protocol was approved by the institutional Human Ethics Committee (Hospital Maisonneuve, Rosemont, Montreal) and volunteers gave informed consent for their participation. The study was conducted as a double-blinded randomized trial according to a randomized single oral dose 4 × 4 cross-over (Latin square) design.

Twelve healthy non-smoker male volunteers of 18–28 years of age (24.2 ± 3.0, mean ± SD) participated and completed the study. Their mean (±SD) body weight and height were 77.3 ± 11.2 kg and 175.7 ± 8.2 cm, respectively. They were instructed to abstain from alcohol for at least 2 days prior to the study and received no other drug for at least 14 days before the study.

All volunteers received a single 100 mg oral dose, with 100 ml of water, of ketoprofen tablets (A or B) following an overnight fast. In each phase of the study half the subjects received a capsule of omeprazole 1 hour prior to the administration of ketoprofen dose also with 100 ml of water. Volunteers who did not receive omeprazole consumed no extra water. A light lunch was eaten 4 hours following the ketoprofen dose.

Blood samples (7 ml) were drawn from the antecubital vein into EDTA containing 10 ml Vacutainer tubes, immediately before (0) and at 0.25, 0.50, 0.75, 1, 1.25, 1.50, 1.75, 2.0, 2.25, 2.50, 3, 4, 5, 8, 12, 16 and 24 h following each ketoprofen dose. The plasma was separated and stored frozen at −20°C until analyzed.

Concentrations of ketoprofen in plasma were determined by a stereospecific HPLC assay with UV detection described by Foster and Jamali (5). The calibration curves were linear over the range (0.078 to 2.5 μg/ml) used with high coefficient of determination (R^2) > 0.998. The curves for individual enantiomers were obtained by weighted (1/peak-height ratio) regression analysis of peak height ratios of respective ketoprofen vs IS enantiomers against ketoprofen concentrations. Coefficient of variation (%) of the analytical method was less than 6% while accuracy was better than 97% based on predicted values for the quality control samples.

Drug Dissolution Studies: The dissolution test system (Hanson Research, CA) consisted of 6-vessel paddle unit (Model #72 RL) with detached water bath, a temperature controller and a speed controller. The temperature of the water bath was set at 37°C while the paddle speed was set at 50 rpm. Solution was drawn from the vessel through a VanderKamp Full Flow 10 μm filter using a peristaltic pump connected to a HP 8451A diode array detector (Hewlett-Packard, CA) with a 100 μl flow-through cell. The detector was connected to an HP computer system to run the dissolution software as well as to store the data. Absorbance was measured at 300 nm at five or ten minute intervals up to 2 hours. The dissolution media employed were 0.1 M phos-

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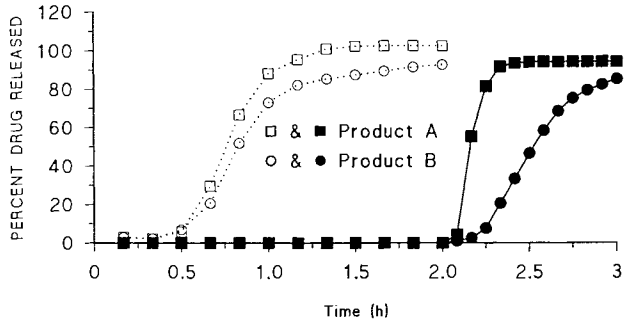

Figure 1 Dissolution profiles of 100 mg ketoprofen tablets in different dissolution media using USP apparatus 2 (volume 900 ml, paddle rotation speed = 50 rpm). (· · · · ·) phosphate-citrate buffer (pH 4.5); (——) 0.1 N NCl (2h) followed by pH 6.8 phosphate buffer (1 h).

phate and acetate buffer solutions, prepared as described in the literature (6, 7).

Although no specific monograph is available in the USP for enteric-coated ketoprofen products, the dissolution experiments were conducted as described in the USP under the general procedure for dissolution studies of delayed-release products (7). The drug release from the tested products was, therefore, monitored using 900 ml of phosphate buffer at pH 6.8, following exposure of tablets for 2 hours in 0.1 N HCl. In addition to the USP general conditions, release characteristics under different conditions of pH and types of buffer, were also studied in phosphate-citrate and acetate buffers of pH 4 to 5.0 for two hours. If the tablets and the coating remained visibly intact, dissolution experiments were continued using phosphate buffer at pH 6.8.

Data and Statistical Analysis: Pharmacokinetic parameters were calculated according to standard methods based on non-compartmental methods (10). Statistical evaluations were performed by analysis of variance (ANOVA) for the cross-over design using SAS (SAS Institute Inc., Cary, USA) with periods and sequences treated as fixed effects. Differences in the individual enantiomer concentrations within subjects were assessed using a paired t-test. Differences between means were considered significant at $p < 0.05$.

RESULTS AND DISCUSSION

DISSOLUTION STUDIES: Representative dissolution profiles are shown in figure 1. As expected for enteric-coated products, the tested products were found to be resistant to the low acidic environment and no appreciable quantity of the drug was released in HCl medium. However, drug was released using the phosphate buffer (pH 6.8) within the generally accepted tolerance of more than 75% dissolved.

On the other hand, both in phosphate and acetate buffers at pH 4.5 or higher, drug was released from the tested products. As an example, the release characteristics of the tested products using phosphate/citric acid buffer (pH 4.5) are also shown in figure 1. Although, the rank order of the release profiles for the tested products was the same under both experimental conditions, drug release was slower using phosphate buffer at pH 4.5 compared with phosphate buffer at pH 6.8. Table I summarizes the data from the dissolution experiments using media of pH 5 or using phosphate buffer (pH 6.8) following dissolution in a buffer at pH 4.

In general, under the experimental conditions used, drug release was faster from the product A than B with the dissolution media of different pH values. The differences were more pronounced when only phosphate or acetate buffer (pH 5) was used as compared to the phosphate buffer (pH 6.8) following exposure to HCl or pH 4 buffer. Therefore, the *in vitro* experiments suggest that not only could the drug be released from the products at relatively low acidic pH (e.g., 4.5) values, but that the release profiles could be different than those obtained at higher pH (6.8) values.

CLINICAL STUDY: At 15 out of 44 sampling points (all 4 phases), concentrations of R(−) enantiomer were significantly higher than those of S(+). These results are in agreement with the observation reported by Foster and Jamali (8) in which they also observed higher concentrations of R(−) than S(+) enantiomer following the administration of ketoprofen tablets to healthy humans. However, as also described by Foster and Jamali (8) this observation does not concur with the general trend of higher concentration of S(+) enantiomer of NSAIDs as reported by Hutt and Caldwell (9). These investigators reported that in many cases including carprofen, fenoprofen, flurbiprofen, ibuprofen, in-

Table I. Percent (mean ± SD from n = 6) Ketoprofen Released at Different Times in; (Upper Table) Phosphate Buffer (pH 6.8) Following Dissolution Using a Buffer of pH 4 for Two Hours (Lower Table) Phosphate-citrate or acetate Buffer at pH 5 for Two Hours. Apparatus 2 (Paddle Method), Paddle Speed = 50 rpm, Medium Volume = 900 ml, Run-Time = 3 Hours (Upper Table), 2 Hours (Lower Table)

Buffers	Product	5	15	30	60 (min)*
(i) Phosphate-Citrate (pH 4)	A	14.2 ± 6.9	81.4 ± 18.5	89.0 ± 8.9	89.9 ± 8.9
(ii) Phosphate (pH 6.8)	B	5.2 ± 1.7	51.6 ± 10.8	87.0 ± 6.8	102.0 ± 3.4
(i) Acetate (pH 4)	A	33.3 ± 12.6	98.7 ± 7.3	103.3 ± 0.9	103.2 ± 0.8
(ii) Phosphate (pH 6.8)	B	3.53 ± 1.6	45.0 ± 8.3	87.0 ± 7.4	103.4 ± 1.25

* Times following two hours of dissolution in the first buffer.

Buffer	Product	10	20	30	60	120 (min)
Phosphate-Citrate (pH 5)	A	11.9 ± 18.1	16.6 ± 11.8	56.0 ± 27.4	108.6 ± 7.5	111.9 ± 2.0
	B	4.4 ± 5.2		10.0 ± 5.5	67.1 ± 8.4	96.3 ± 3.8
Acetate (pH 5)	A	5.8 ± 2.2	50.9 ± 7.0	89.8 ± 7.9	104.3 ± 4.0	104.4 ± 4.0
	B	3.0 ± 2.4	11.3 ± 7.1	32.4 ± 13.0	84.0 ± 10.0	101.4 ± 1.9

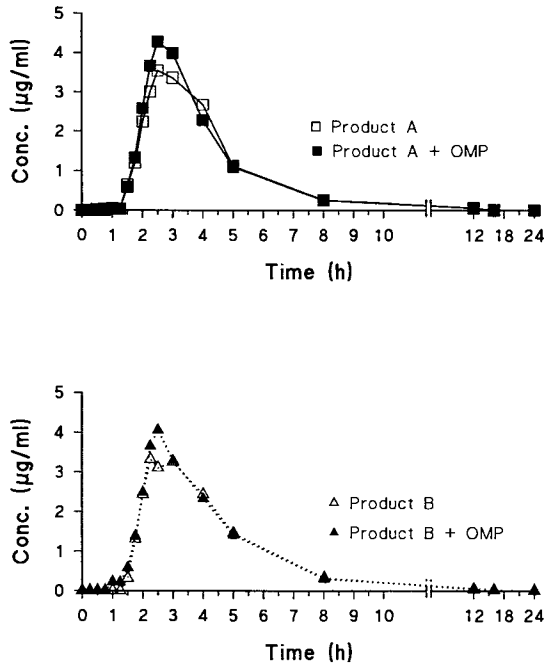

Figure 2 Mean (n = 12) plasma concentrations-time profiles of R(−) enantiomer after administration of 100 mg ketoprofen tablet with or without omeprazole (OMP).

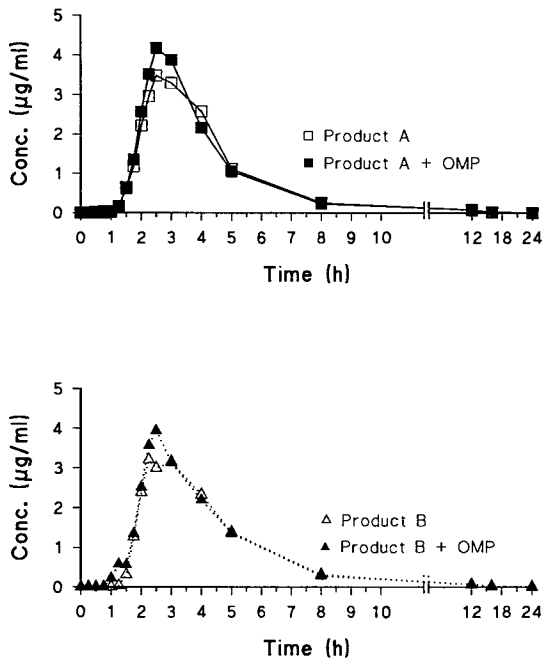

Figure 3 Mean (n = 12) plasma concentrations-time profiles of S(+) enantiomer after administration of 100 mg ketoprofen tablet with or without omeprazole (OMP).

doprofen, naproxen and pirprofen, in relation to the enantiomeric composition of the material present in plasma, R-antipode is in general more rapidly eliminated than the S(+) enantiomer which results in higher plasma concentrations of S(+). In the present investigation, the differences in individual enantiomer concentrations were also reflected in the over-all pharmacokinetic parameters such as C_{max} and AUCs. Although a trend of longer half-lives was apparent for R(−) enantiomer than the S(+), this difference did not achieve significance.

The mean plasma concentration-time profiles of ketoprofen are shown in figures 2 and 3. As expected the t_{max} values were longer than those reported for non enteric-coated formulations (8). Our findings of apparent higher t_{max} values than reported in literature (2) can be attributed to more frequent sampling times (every 15 min vs 30 min).

The derived pharmacokinetic parameter values of AUC, t_{max}, C_{max} etc. are given in Tables II and III. Foster et al (8, 11) have shown, both in young healthy and young and elderly arthritic volunteers, that the differences in the enantioselective disposition of ketoprofen were negligible. In one of the reports (8), as in our case ($p < 0.05$), the authors reported small but significantly higher AUC values for R(−) vs S(+) enantiomer.

If the enteric-coating of the tested ketoprofen tablets had released in the stomach, the expected outcome would be shorter t_{max} values similar to those reported for non-enteric coated capsules, with a t_{max} of around 1 hour (8). Although there are no substantial differences in t_{max} or C_{max}, the trend to shorter t_{max} and higher, with less variable (smaller SD), C_{max} values with omeprazole treatments is in this direction. The possible explanation of no statistically significant differences may be that the rise in stomach pH would be only for a short duration, which may not be sufficient to alter the release characteristic of the enteric-coated products.

In summary, in vitro release experiments showed that drug from enteric-coated products may be released at pH values that have been found in the stomach. Overall systemic bioavailabilities from the two enteric-coated ketoprofen products, with or without single dose omeprazole administration, showed no significant differences. A trend in higher plasma concentrations with omeprazole indicates a possibility of drug release from enteric-coated products at potentially elevated stomach pH values.

Table II. Pharmacokinetic Parameters (Mean ± SD) Derived from the Plasma Concentration-Time Curves for R(−) Enantiomer Following Administration of a 100 mg Ketoprofen Tablet With or Without a 20 mg Omeprazole (OMP) Capsule

	$AUC_{(0-t)}$ (µg · h/ml)	Cl_f (l/h)	C_{max} (µg/ml)	t_{max} (h)	k_e (h^{-1})	$t_{(1/2)}$ (h)
Product A	11.7 ± 3.9	4.51 ± 1.09	5.4 ± 1.8	2.8 ± 0.8	0.392 ± 0.145	2.16
Product A + OMP	12.2 ± 3.1	4.25 ± 1.04	6.1 ± 1.6	2.6 ± 0.6	0.393 ± 0.141	2.02
Product B	12.2 ± 3.4	4.29 ± 1.00	5.8 ± 1.8	3.0 ± 1.0	0.408 ± 0.115	1.83
Product B + OMP	12.8 ± 3.8	4.12 ± 0.92	6.2 ± 1.4	2.7 ± 1.0	0.396 ± 0.109	1.87
p Value	0.277	0.268	0.563	0.687	0.980	

$AUC_{(0-t)}$ = AUC to last quantifiable sampling time, Cl_f = (Dose/$AUC_{0-\infty}$).

Table III. Pharmacokinetic parameters (Mean ± SD) Derived from the Plasma Concentration-Time Curves for S (+) Enantiomer Following Administration of a 100 mg Ketoprofen Tablet With or Without 20 mg Omeprazole (OMP) Capsule

	$AUC_{(0-t)}$ (μg · h/ml)	Cl_f (l/h)	C_{max} (μg/ml)	t_{max} (h)	k_e (h^{-1})	$t_{(1/2)}$ (h)
Product A	11.4 ± 3.7	4.59 ± 1.07	5.3 ± 1.8	2.8 ± 0.8	0.393 ± 0.148	2.27
Product A + OMP	11.8 ± 3.1	4.43 ± 1.10	5.9 ± 1.6	2.6 ± 0.6	0.400 ± 0.138	1.97
Product B	11.8 ± 3.3	4.47 ± 1.00	5.7 ± 1.7	3.0 ± 1.0	0.427 ± 0.124	1.77
Product B + OMP	12.2 ± 3.6	4.29 ± 0.94	6.0 ± 1.4	2.7 ± 1.0	0.396 ± 0.091	1.82
p Value	0.520	0.560	0.627	0.697	0.826	

$AUC_{(0-t)}$ = AUC to last quantifiable sampling time, Cl_f = $(Dose/AUC_{0-\infty})$.

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