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Report

Pharmacokinetics of Ketorolac and *p*-Hydroxyketorolac Following Oral and Intramuscular Administration of Ketorolac Tromethamine

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Ketorolac tromethamine (KT), a potent analgesic with cyclooxygenase inhibitory activity, was administered in an open, randomized, single-dose study of Latin-square design to 12 healthy male volunteers. Doses of 30 mg oral (po) and 30, 60, and 90 mg intramuscular (im) KT were administered in solution. Plasma samples were analyzed for ketorolac (K) and its inactive metabolite, *p*-hydroxyketorolac (PHK), by reversed-phase high-performance liquid chromatography (HPLC). The 30-mg im dose was found to be similar to the 30-mg po dose with respect to total AUC values for both K and PHK. The amount of PHK circulating in plasma was very low as judged by AUC ratios (PHK/K × 100) of 1.9 and 1.5% for the 30-mg po and im doses, respectively. The rate of absorption of K and formation of PHK, as determined by C_{max} and T_{max} values, was significantly slower following the im doses. Total AUC and C_{max} for K and PHK increased linearly with dose after im administration of 30, 60, and 90 mg of KT. The mean plasma half-life of K was remarkably consistent between po and im administration and was independent of dose, ranging from 5.21 to 5.56 hr. The plasma metabolic profile was similar following both routes of administration and graded im doses.

KEY WORDS: ketorolac; *p*-hydroxyketorolac; oral; intramuscular; pharmacokinetics; dose proportionality.

INTRODUCTION

Ketorolac tromethamine (KT) is an orally and parenterally active nonnarcotic analgesic agent with cyclooxygenase inhibitory activity (1–4). KT has been studied in a broad spectrum of pain states such as postpartum and postoperative pain, cancer pain, and pain from dental extraction (5–9). These clinical trials have shown it to be safe and efficacious as an oral tablet at a dose of 10 mg up to four times daily and as intramuscular or intravenous injections of 10 or 30 mg.

The purpose of this study was to assess the pharmacokinetics and bioequivalence of ketorolac (K) and its inactive metabolite, *p*-hydroxyketorolac (PHK) after oral and intramuscular doses of KT. In addition, the dose proportionality of K and PHK following graded intramuscular doses of KT was assessed. It was also of interest to establish that no major differences occurred in the metabolism of K as assessed by plasma metabolic profiles following both routes of administration.

MATERIALS AND METHODS

Subjects

Twelve healthy male volunteers ranging in age from 24 to 38 years (mean, 29.9 years) and weighing within 10% of normal body weight for their height (mean, 80.7 kg) participated in this study after signing a written informed consent form. Their good health was determined by pre- and postexperiment physical examinations and laboratory tests.

Study Design

Following an overnight fast, each subject received one

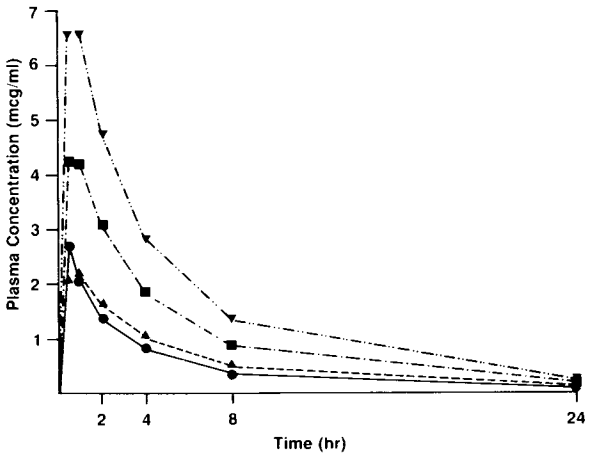

Fig. 1. Mean plasma concentrations of ketorolac vs time following a 30-mg dose of ketorolac tromethamine orally in solution (●), 30 mg im (▲), 60 mg im (■), and 90 mg im (▼).

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Table I. Pharmacokinetic Parameters of Ketorolac After po and im Doses of Ketorolac Tromethamine in 12 Healthy Subjects

Parameter	Dose			
	30 mg po	30 mg im	60 mg im	90 mg im
T_{max} (min)[a]	30.0 ± 0.0	50.0 ± 14.8	47.5 ± 15.4	45.0 ± 15.7[b]
C_{max} (μg/ml)	2.70 ± 0.36	2.24 ± 0.32	4.48 ± 0.82	6.88 ± 1.15
Total AUC (μg · hr/ml)	12.5 ± 4.2	13.7 ± 4.0	26.1 ± 5.7	40.7 ± 10.1
Half-life (hr)	5.56 ± 0.79	5.21 ± 0.68	5.42 ± 0.77	5.52 ± 0.87
F (%)[c]	100.0 ± 0.0	112.5 ± 19.3	109.8 ± 23.6	113.8 ± 27.1

[a] Mean ± SD for 12 subjects.
[b] Means underlined by the same line are not significantly different ($P \leq 0.05$).
[c] Systemic bioavailability relative to the 30-mg po solution.

of four ketorolac tromethamine doses administered in solution according to a randomized crossover schedule: 30 mg (po and im), 60 mg (im), and 90 mg (im). The im injection was administered as 3 ml of a 1, 2, or 3% solution, respectively, into the upper lateral quadrant of the gluteus maximus. The oral solution (3 ml, 1%) was administered with 100 ml water. All subjects fasted until 4 hr after dosing. No drugs, including all over-the-counter drugs, alcohol, or tobacco was allowed 72 hr prior to and 24 hr after each dose. Sequential treatments were separated by intervals of 1 week.

Venous blood samples (15 ml) were collected in heparinized Vacutainer tubes immediately prior to dosing and at 0.5, 1, 2, 4, 8, and 24 hr postdose. The samples were promptly centrifuged and the plasma was frozen at −22°C until analyzed. Plasma concentrations of K and PHK were determined by reversed-phase high-performance liquid chromatography with UV detection at 313 nm (10). Briefly, 1 ml of acidified plasma (pH 3) is extracted with 5 ml of ether and back extracted into 2 ml of 0.1 *N* NaOH following the addition of 3 ml of hexane. The resulting aqueous extract is acidified with 1 *N* HCl and extracted into 8 ml ether. The organic layer is evaporated and the residue is reconstituted in methanol and injected onto a C-18 column (Regis, 5 μm, 4.6 × 250 mm) using a mobile phase of acetonitrile:methanol:0.02 *M* phosphate buffer (pH 6) + 0.01 *M* tetrabutylammonium phosphate (15:20:65) at a flow rate of 0.8 ml/min. The sensitivity of the assay was 50 ng/ml for ketorolac and 10 ng/ml for *p*-hydroxyketorolac in plasma.

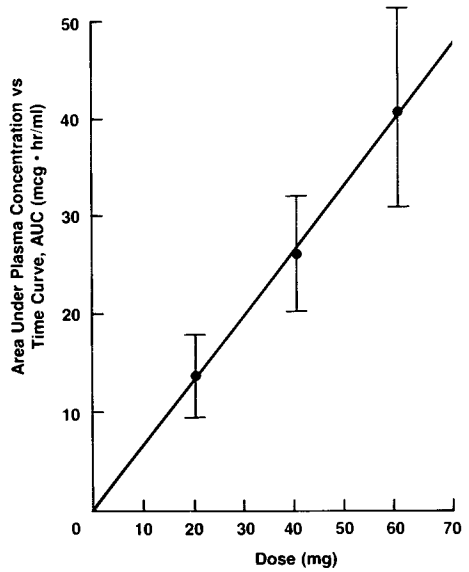

Fig. 2. Plot of the area under the plasma concentration vs time curve for ketorolac vs an intramuscular dose of ketorolac. Circles represent mean values, while vertical bars indicate standard deviations.

Data Analysis

Peak plasma concentrations (C_{max}) of ketorolac and its metabolite, *p*-hydroxyketorolac, and times to reach peak levels (T_{max}) were determined from the individual plasma concentration–time curves. The plasma half-life ($t_{1/2}$) was computed using linear regression on the log of the plasma concentrations in the terminal phase of the plasma concentration–time curve. The total area under the plasma concentration–time curve (AUC) was calculated using the linear trapezoidal rule up to the last measurable time point and addition of the term $C_{p_{last}}/\beta$. Analysis of variance (ANOVA) associated with a replicated Latin-square design was performed using the GLM procedure of the Statistical Analysis System (11). A *P* value of less than 0.05 was considered to

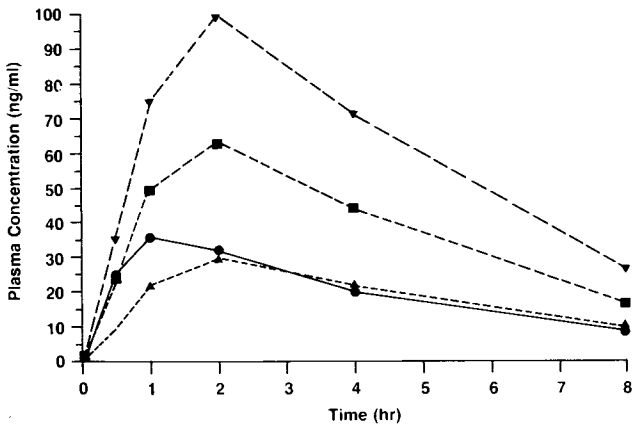

Fig. 3. Mean plasma concentrations of *p*-hydroxyketorolac vs time following a 30-mg dose of ketorolac tromethamine orally in solution (●), 30 mg im (▲), 60 mg im (■), and 90 mg im (▼).

Table II. Pharmacokinetic Parameters of *p*-Hydroxyketorolac After po and im Doses of Ketorolac Tromethamine in 12 Healthy Subjects

Parameter	Dose			
	30 mg po	30 mg im	60 mg im	90 mg im
T_{max} (min)[a]	68.2 ± 27.1	114.6 ± 49.9	114.6 ± 18.1	120.0 ± 46.5[b]
C_{max} (ng/ml)	36.9 ± 8.9	30.1 ± 10.4	63.4 ± 20.6	102.0 ± 26.0
Total AUC (ng · hr/ml)	216.8 ± 93.5	193.1 ± 79.0	371.9 ± 119.9	600.4 ± 200.5

[a] Mean ± SD for 12 subjects.
[b] Means underlined by the same line are not significantly different ($P \leq 0.05$).

be statistically significant. Duncan's multiple-range test was used to analyze pairwise comparisons (11). All results are expressed as the mean ± SD.

RESULTS AND DISCUSSION

The mean plasma ketorolac concentrations following the oral solution and the three intramuscular doses are shown in Fig. 1. The mean pharmacokinetic parameters are presented in Table I. The absorption of ketorolac tromethamine following im and po administration was rapid and essentially complete as suggested by earlier studies (13). The time to peak concentrations (T_{max}) was slightly prolonged for the intramuscular doses, suggesting slower absorption relative to the oral solution. The mean T_{max} was 30, 50, 48, and 45 min for the oral solution and the 30-, 60-, and 90-mg im doses, respectively. While all subjects given the oral solution peaked at 30 min, subjects on the im dose peaked at 30 min or 1 hr. As a result, the peak plasma level (C_{max}) following the oral solution (2.70 μg/ml) was significantly higher than following an equivalent im dose (2.24 μg/ml). The mean total AUC following the oral solution (12.5 μg · hr/ml) was not significantly different from that after an equivalent im dose (13.7 μg · hr/ml).

Mean C_{max} values for the 30-, 60-, and 90-mg im doses increased proportionally to the administered dose from 2.24 to 4.48 to 6.88 μg/ml, respectively. Also, the mean total AUC increased linearly with the dose; the mean total AUC increased 1.9-fold from 30 to 60 mg and 3.0-fold from 30 to 90 mg (Fig. 2). The mean relative bioavailabilities of the 30-, 60-, and 90-mg im doses were 112.5, 109.8, and 113.8%, respectively. The linear increase in AUC was in agreement with an earlier study (14) which demonstrated dose proportionality between 0.8- and 3.2-mg/kg oral doses. The mean plasma half-life was remarkably consistent among the oral and intramuscular doses, ranging between 5.21 and 5.56 hr. These values are in agreement with previous studies which reported half-lives of 5–6 hr for doses ranging between 10 and 120 mg (13,14).

p-Hydroxyketorolac is an essentially inactive metabolite, having less than 1/5 the antiinflammatory activity and less than 1/100 the analgesic activity of ketorolac tromethamine in animal models (15). Mean plasma *p*-hydroxyketorolac (PHK) concentrations following the oral solution and three intramuscular doses are shown in Fig. 3 and mean computed pharmacokinetic parameters are presented in Table II. Mean PHK plasma levels following both po and im doses of ketorolac tromethamine were approximately 50- to 100-fold lower than ketorolac (K). Following the 30-mg po and im doses, the relative percentage of PHK in plasma was similar, as judged by the C_{max} ratios (PHK/K × 100) of 1.4 and 1.3% and AUC ratios of 1.9 and 1.5%, respectively (Table III). The T_{max} ratios were also similar (2.3 vs 2.5) following both doses, which indicates that the more rapid appearance of PHK in plasma after the po dose

Table III. Comparison of Mean Ratios (PHK/K) for Pharmacokinetic Parameters Following po and im Doses of Ketorolac-Tromethamine

Parameter ratio	Dose			
	30 mg po	30 mg im	60 mg im	90 mg im
(PHK/K) × 100				
C_{max}[a]	1.40%	1.34%	1.39%	1.50%
AUC	1.85%	1.53%	1.46%	1.52%
(PHK/K)				
T_{max}	1.27	2.45	2.73	2.73

[a] Means underlined by same line are not significantly different ($P \leq 0.05$).

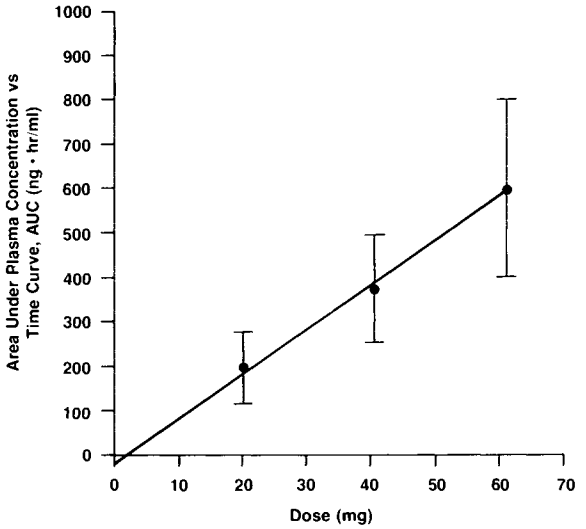

Fig. 4. Plot of the area under the plasma concentration vs time curve for *p*-hydroxyketorolac vs an intramuscular dose of ketorolac. Circles represent mean values, while vertical bars indicate standard deviations.

was due to the more rapid rate of absorption of ketorolac tromethamine following the po dose, and not to differences in the rate of metabolism. As was the case for ketorolac, the time to reach peak PHK plasma levels was shorter following the oral solution (68.2 min) compared to the intramuscular dose (115 min). As a result, significantly higher peak plasma levels were reached following the oral solution (36.9 ng/ml) than for the im dose (30.1 ng/ml). However, the extent of absorption as determined from the total AUC was not significantly different between the oral solution and the im dose (217 vs 193 ng · hr/ml). Following graded im doses of ketorolac tromethamine of 30, 60, and 90 mg, PHK plasma levels increased proportionally with the dose and this was reflected by total AUC values of 193, 372, and 600 ng · hr/ml (Fig. 4) and C_{max} values of 30.1, 63.4, and 102 ng/ml, respectively. However, T_{max} did not change with dose and averaged 115, 115, and 120 min at the three im dose levels.

PHK is the only metabolite of ketorolac found in plasma. The observations that ketorolac tromethamine was completely absorbed following po and im doses and that the PHK total AUC was similar following po and im doses present very strong evidence that the metabolism of ketorolac is similar following po and im administration. In fact, it has been demonstrated previously that the metabolism and excretion of ketorolac are similar following po and iv administration of ketorolac tromethamine to humans (15), and one would expect the same to be true for an im dose. Studies in animals (15) also indicate that the metabolism and excretion of ketorolac are similar following the iv, po, and im routes of administration.

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