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COMPARATIVE BIOAVAILABILITY OF TWO ORAL FORMULATIONS OF KETOROLAC TROMETHAMINE: DOLAC® AND EXODOL®

FRANCISCO J. FLORES-MURRIETA*‡, VINICIO GRANADOS-SOTO*, GILBERTO CASTAÑEDA-HERNÁNDEZ*, JORGE E. HERRERA*† AND ENRIQUE HONG*

*Sección de Terapéutica Experimental, Departamento de Farmacología y Toxicología, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, México, D.F., Mexico
†Departamento de Investigación Clínica y Biomédica, Hospital General 'Dr Miguel Silva', Morelia, Mich., Mexico

ABSTRACT

The bioavailability of ketorolac after administration of two oral formulations containing 10 mg of ketorolac tromethamine, Exodol® and Dolac®, to 12 healthy Mexican volunteers was compared. Subjects received both formulations according to a randomized crossover design and blood samples were drawn at selected times during 24 h. Ketorolac plasma concentrations were determined by HPLC and individual plasma-concentration-against-time curves were constructed. Maximal plasma concentration and AUC_{0-24} values were compared by analysis of variance followed by Westlake's confidence interval test. 90% confidence limits ranged from 80 to 125% for C_{max} and from 85 to 118% for AUC_{0-24}. It is concluded that the two assayed formulations are bioequivalent.

KEY WORDS Ketorolac tromethamine Bioequivalence

INTRODUCTION

Ketorolac is a potent analgesic agent currently used in the treatment of moderate to severe pain.[1] Clinical studies have shown that the potency and efficacy of ketorolac are similar to those of morphine,[2–4] but that it does not exhibit the untoward effects related to opioid drugs.[1] There is evidence suggesting that the analgesic activity of ketorolac could be due to prostaglandin synthesis inhibition;[1,5] however, it has been suggested that endogenous opioid release could also be involved.[6] Animal studies have shown that ketorolac is about 100 times more potent than aspirin as an analgesic agent, although its anti-inflammatory activity is limited.[5] Comparative clinical studies have confirmed that ketorolac is remarkably more potent in pain relief than currently used non-steroidal anti-inflammatory drugs.[7] One major advantage of ketorolac over

‡Addressee for correspondence.

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other non-steroidal anti-inflammatory drugs is that the salt ketorolac tromethamine can be administered either intravenously, intramuscularly, or orally.[8,9] Therefore, it can be used in a wide variety of clinical situations.

It has been reported that ketorolac is completely and rapidly absorbed after oral administration of ketorolac tromethamine,[8] resulting in fast pain relief.[7] However, it must be considered that bioavailability is determined by the pharmaceutical formulation. In this study, we compared the bioavailability of ketorolac after administration of ketorolac tromethamine in two formulations manufactured in Mexico.

METHODS

Subjects

Twelve young healthy male Mexican volunteers participated in the study. No abnormalities were detected in routine clinical and laboratory (biochemical and haematological) tests. Demographic data are given in Table 1. None of the subjects was an alcohol or drug abuser nor taking any concomitant medication at the time of the study. All subjects read the protocol approved by the hospital ethics committee and gave written consent for participation before entering the study.

Study plan

The study was carried out according to the recommendations of the Declaration of Helsinki. All subjects received two oral pharmaceutical

Table 1. Demographic data and sequence of administration of ketorolac subjects who volunteered for participation in the comparison of two oral formulations of ketorolac tromethamine

Volunteer	Age (years)	Height (cm)	Weight (kg)	Sequence of administration	
				First session	Second session
UGA	24	179	74·3	A	B
JCC	34	178	71·5	B	A
ATF	20	186	87·0	B	A
RMN	20	172	65·6	A	B
EGM	26	164	66·5	B	A
ATF	23	185	85·8	A	B
NBB	25	163	60·5	A	B
MGM	20	172	63·5	B	A
JRG	23	165	63·0	B	A
NCM	27	164	63·0	A	B
JAM	21	168	68·0	A	B
MCH	27	160	59·0	B	A
Mean	24·16	171·33	68·98	—	—
SEM	1·17	2·56	2·66	—	—

formulations containing 10 mg of ketorolac tromethamine in two separate trial sessions according to a randomized crossover design. A one-week washout period was allowed between sessions. At each session, volunteers, who had abstained from alcohol and caffeine-containing beverages for at least 24 h, came to the hospital at 8:00 p.m. After an overnight fast (10 h), they received a tablet of 10 mg ketorolac tromethamine with 200 ml water. The studied formulations were Dolac® (formulation A) and Exodol® (formulation B); the treatment sequence for each subject is indicated in Table 1. The study was started at 7:00 a.m. Before medication, an indwelling catheter with a heparin lock was placed in a suitable forearm vein and blood samples were drawn at 0, 10, 20, 30, and 45 min and at 1, 1·5, 2, 4, 6, 8, 12, 16, and 24 h after drug administration. Plasma was obtained by centrifugation, immediately frozen in liquid nitrogen and stored at −20 °C until analysed. Subjects remained fasting for 4 h after medication. Lunch was given at noon.

Determination of ketorolac in plasma

Ketorolac plasma concentrations were determined by a high-performance liquid chromatographic (HPLC) method developed in our laboratory. 1 ml plasma samples were spiked with 100 ng sodium tolmetin, which was used as an internal standard. Samples were then acidified by addition of 0·2 ml of a 0·1 M solution of sodium acetate (pH 4) and extracted twice with 5 ml diethyl ether. The organic layers of both extractions were pooled in a conical glass tube and evaporated until dry at 50 °C under a gentle nitrogen stream. The dry residue was redissolved in 0·2 ml deionized water and 80 μl aliquots were injected into the chromatographic system.

The chromatographic system consisted of a 510 solvent delivery system, a U6K injector, a 150×3·9 mm Novapak C-18 column (particle size 4 μm), and a 490 multiwavelength detector (Waters Assoc., Milford, MA, U.S.A.). Chromatograms were recorded using a 4270 integrator (Varian, Palo Alto, CA, U.S.A.). The column was eluted with a mixture of acetonitrile and 1 mM phosphoric acid (pH 3) 32:68 v/v at a constant flow rate of 1 ml min^{-1}. The effluent from the column was detected at 313 nm. Analyses were performed at room temperature. Since ketorolac tromethamine dissociates into the anion form of ketorolac at physiological pH after absorption, the measured concentrations are referred to ketorolac.

Drugs and reagents

Exodol® tablets as well as ketorolac tromethamine standards were provided by Laboratorios Senosiain S.A. de C.V. (Mexico City, Mexico). Sodium tolmetin was a gift of Laboratorios Cilag S.A. de C.V. (Mexico City, Mexico). Commercially available Dolac® tablets were manufactured by Syntex Mexico S.A. de C.V. (Mexico City, Mexico). Deionized water was prepared using

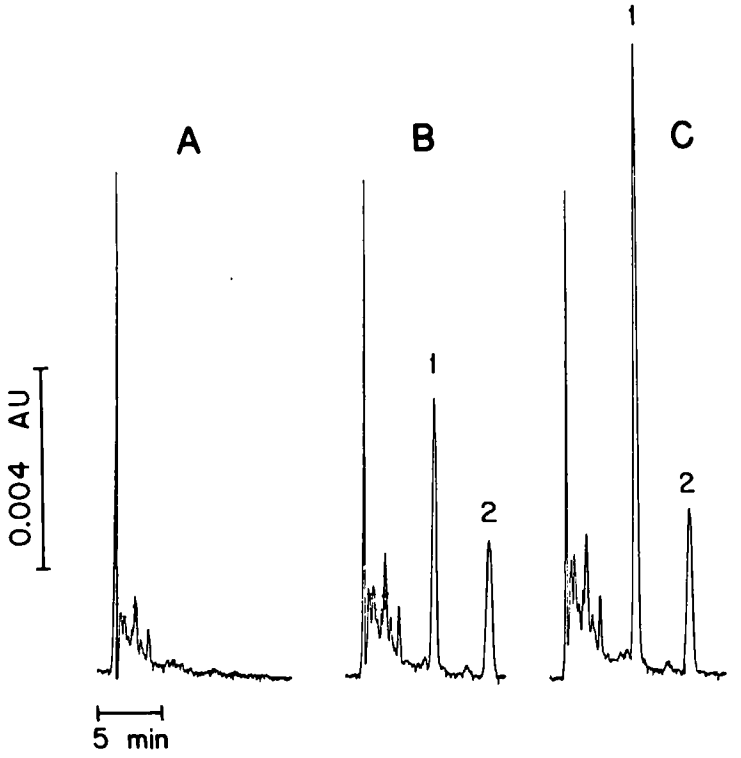

Figure 1. Typical chromatograms resulting from the injection of plasma extracts into the chromatographic system for drug-free plasma (A), plasma spiked with 100 ng of ketorolac (1) and 100 ng of the internal standard (2) (B), and plasma obtained from a volunteer 4 h after administration of an oral dose of 10 mg ketorolac tromethamine, spiked with 100 ng of the internal standard (C)

a Milli-Q system (Continental Water Systems, El Paso, TX, U.S.A.). Acetonitrile chromatographic grade was obtained from Merck (Darmstadt, Federal Republic of Germany). All other reagents were of analytical grade.

Pharmacokinetic analysis and statistics

Individual plasma concentration versus time curves were constructed using semilog coordinates. Maximal plasma concentration (C_{max}) and time to reach the maximal concentration (t_{max}) were directly determined from these plots. Half-life ($t_{½}$) was calculated by least-squares linear regression of the terminal concentration decay phase. Area under the curve (AUC) was determined by the trapezoidal rule. The area under the last point to infinity was determined by dividing the last detectable plasma concentration by the terminal slope. Data are presented as mean ± SEM. Formulations were compared by analysis of variance for a crossover design.

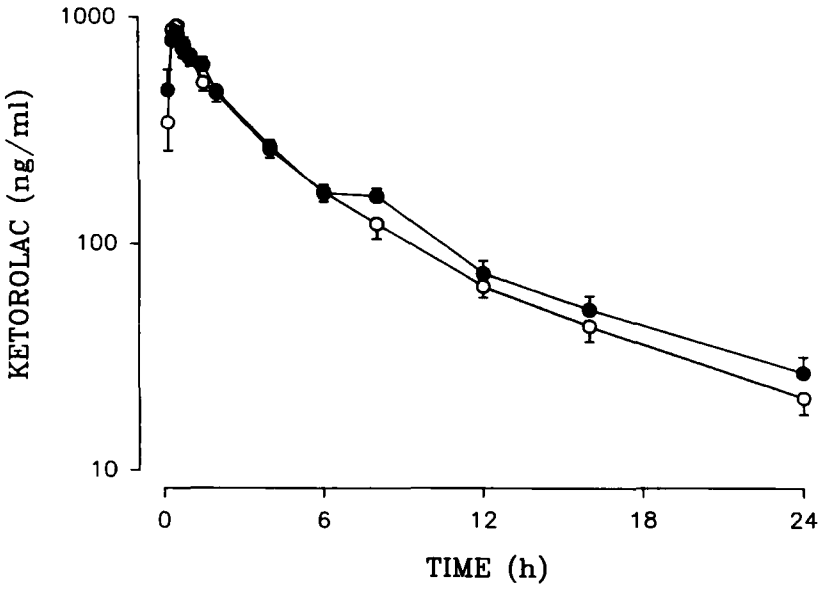

Figure 2. Mean (±SEM) plasma-concentration-against-time curves of ketorolac after administration of two oral formulations containing 10 mg ketorolac tromethamine to 12 healthy volunteers. Formulations tested were Dolac® (○) and Exodol® (●)

In order to examine the bioequivalence of the studied formulations, logarithmic transformation of AUC from 0 to 24 h (AUC_{0-24}) and C_{max} were compared by analysis of variance for a crossover design followed by Westlake's confidence interval test; limits of acceptance were fixed at 80–125%.[10-12] A decision in favour of bioequivalence was taken if the 90% confidence interval was fully contained within the limits of acceptance.[12]

RESULTS

Figure 1 shows typical chromatograms obtained after the injection of plasma extracts. Retention times were 6·82 and 10·07 min for ketorolac and tolmetin respectively; no interferring peaks occurred at these times. Calibration curves were constructed over a range of 10–1500 ng ml^{-1}. A linear relationship ($r = 0·9992$) was obtained when the ratio of the peak areas of ketorolac and tolmetin was plotted against ketorolac concentration. The coefficient of variation was always lower than 8%. The method had a precision of 99·8 ± 1·8% and its detection limit was 5 ng ml^{-1}. The HPLC method thus proved to be suitable for pharmacokinetic studies.

Figure 2 depicts mean plasma concentrations of ketorolac observed in the 12 healthy volunteers studied with two oral pharmaceutical formulations:

Table 2. Pharmacokinetic parameters of ketorolac after administration of 10 mg ketorolac tromethamine in two different oral formulations to 12 healthy volunteers. Data are shown as mean ± SEM

Parameter	Formulation A	Formulation B
C_{max} (ng ml^{-1})[a]	1026·4 ± 86·1	934·0 ± 66·7
t_{max} (h)	0·48 ± 0·07	0·57 ± 0·10
AUC_{0-24} (ng h ml^{-1})[a]	3459·8 ± 287·8	3659·7 ± 268·2
$AUC_{0-\infty}$ (ng h ml^{-1})	3674·2 ± 311·1	3969·7 ± 324·1
$t_{½}$ (h)	6·62 ± 0·48	7·16 ± 0·57

[a]Geometric means for formulations A and B were 987·9 ng ml^{-1} and 907·1 ng ml^{-1} for C_{max} and 3318·6 ng h ml^{-1} and 3541·1 ng h ml^{-1} for AUC_{0-24}, respectively.

Exodol® and Dolac®. Ketorolac kinetics exhibited a similar pattern after administration of either formulation. Interindividual variability in ketorolac plasma concentrations was small. For all subjects, there was a very fast absorption, a peak concentration of about 1 μg ml^{-1} being attained in about 30 min. Then, plasma concentrations decayed with a half-life of about 7 h. Pharmacokinetic parameters calculated from individual plasma-level–time curves are shown in Table 2. No statistically significant difference was observed in pharmacokinetic parameters when both formulations were compared by analysis of variance.

In order to determine bioequivalence, individual log C_{max} and log AUC_{0-24} were calculated and compared by analysis of variance for a crossover design. Geometric means were determined (see Table 2), and then a further comparison according to Westlake's confidence interval test, considering Dolac® as the reference formulation, was performed. Westlake's 90% confidence limits for Exodol® ranged from 80 to 125% for C_{max} and from 85 to 118% for AUC_{0-24}. Since the confidence interval was fully contained within the limits of acceptance, it is concluded that the two formulations are bioequivalent.

DISCUSSION

We studied the bioequivalence of two pharmaceutical formulations of ketorolac tromethamine manufactured in Mexico by comparing plasma level *versus* time curves. In order to measure ketorolac concentrations in plasma, we developed a novel HPLC method. A HPLC procedure for ketorolac determination in human and animal plasma has been previously described by Mroszczac and colleagues.[13] However, in this procedure the internal standard is *p*-fluoroketorolac, a compound that is not easily obtainable since it is not commercially available. Therefore, we decided to develop our own method using

tolmetin as internal standard. Tolmetin is also a commercially available analgesic agent; hence it can be easily obtained. Our method proved to be suitable for pharmacokinetic studies having sensitivity, precision, and accuracy similar to that of Mroszczac and colleagues.[13]

It has been reported that ketorolac bioavailability after oral administration of ketorolac tromethamine is 100%, as absorption from the gastrointestinal tract is complete and there is practically no first-pass effect.[8] Since interindividual variability in bioavailability was small, few subjects were required to detect significant differences.[14] The sample size was calculated according to the equation proposed by Stolley and Strom,[15] considering the variability reported by Jung and coworkers.[8] It appeared that a 20% difference could be detected with 12 subjects with an α value of 0·05 and a β value of 0·2. We observed a variability similar to that previously reported[16] and the α and β values obtained were consistent with the experimental design. The experimental design allowed the conclusion that the two assayed formulations are bioequivalent.

Our results allow us to conclude that two oral formulations containing 10 mg of ketorolac tromethamine, Exodol® and Dolac®, manufactured in Mexico are bioequivalent.

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