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RESEARCH PAPERS

KETOROLAC TROMETHAMINE BIOAVAILABILITY VIA TABLET, CAPSULE, AND ORAL SOLUTION DOSAGE FORMS

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ABSTRACT

The single-dose mean pharmacokinetic characteristics and relative bioavailability of 10-mg ketorolac tromethamine tablet, capsule, and oral solution dosage forms were evaluated in 12 healthy volunteers in a randomized study of Latin square design. The tablet and the capsule formulations used were shown to have similar *in vitro* dissolution profiles. Ketorolac tromethamine was rapidly absorbed from all three dosage forms. The tablet and capsule were not significantly different with respect to any of the mean pharmacokinetic parameters: time to maximum plasma concentration (T_{max}) (35 and 42 min for the tablet and capsule, respectively), peak plasma concentration (C_{max}) (0.865 and 0.809 μg/ml for the tablet and capsule, respectively), area under the curve (AUC) (3.50 and 3.43 μg/ml x hr for the tablet and capsule, respectively), and half-life ($t_{1/2}$) (5.2 and 4.8 hr for the tablet and capsule, respectively). Ninety-five percent fiducial (confidence) limits supported the equivalence of all of the tablet and capsule pharmacokinetic characteristics except for T_{max}, because of the higher variability of this parameter. The solution was absorbed significantly faster than the tablet (the time to maximum plasma concentration was 23 min for the solution versus 35 min for the tablet), but was not significantly different from the tablet in any other pharmacokinetic aspect. The fiducial intervals supported these tablet versus solution findings. Therefore, when functional or anatomical abnormality make tablet administration inadvisable, the

solution or capsule formulations employed in this study may be used as alternatives to the commercially marketed tablet without adversely impacting the absorption profile of the drug substance.

INTRODUCTION

Ketorolac tromethamine (Toradol®, Syntex) is a member of the pyrrolo-pyrrole group of nonsteroidal anti-inflammatory drugs. Ketorolac tromethamine exhibits analgesic, anti-inflammatory, and antipyretic activity, and is indicated for use in the short term management of pain. It inhibits the synthesis of prostaglandins and may be considered a peripherally acting analgesic. As such, its rate of absorption is critical, because slow absorption might delay the onset of pain relief. Ketorolac tromethamine was approved by the FDA for administration as an oral tablet in 1991. It has been demonstrated that ketorolac tromethamine is completely absorbed following oral administration, and that the pharmacokinetic profiles of intramuscular and oral tablet doses are very similar, although some individuals actually have faster absorption when taking tablets (1, 2, 3, 4). The impact of different oral dosage forms on the absorption of ketorolac tromethamine has not been examined previously. This information is desirable for when an alternative oral dosage form is needed because functional or anatomical abnormality make tablet administration inadvisable, such as in elderly patients who may have difficulties swallowing tablets (5,6,7), or in a hospital setting where a nasogastric tube is in place.

The purpose of this open, randomized study of Latin square design was to assess the pharmacokinetics and compare the bioavailability of ketorolac following a dose of the 10-mg ketorolac tromethamine marketed formulation tablet, a 10-mg capsule, and a 10-mg oral solution. Additionally, by using the oral solution as a reference treatment, the *in vivo* effects from dosage form disintegration and drug substance dissolution from the capsule and tablet formulations can be seen.

MATERIALS AND METHODS

Subjects - The study subjects were 12 healthy male volunteers between 24 and 35 years of age. They were within 17% of the average weight for their age and height as determined by the Metropolitan Life Insurance Company weight tables. They were between 58.5 kg and 88.1 kg in body weight.

Healthy subjects were selected for this study on the basis of medical history, physical examination, and routine laboratory work, which demonstrated no clinically relevant abnormalities. Laboratory work consisted of red blood cell count, white blood cell count, hemoglobin, hematocrit, differential, urinalysis, calcium, phosphorus, glucose, blood urea nitrogen, uric acid, cholesterol, total protein, albumin, bilirubin, alkaline phosphatase, lactic dehydrogenase, and serum glutamic oxaloacetic transaminase.

No hypnotics, sedatives, antihistamines, or other enzyme-inducing drugs were used for 1 month prior to or during this study. No other drugs or alcohol were allowed 72 hr before or during the entire study period. The subjects did not use tobacco in any form. Subjects with a history of ulcers were excluded from the study. Institutional Review Board approval was obtained, and all subjects signed a written informed consent.

Dosage Form Preparation - The 10-mg ketorolac tromethamine tablet was the marketed formulation (Syntex, lot # 37619-00-31-3-439). The 10-mg ketorolac tromethamine capsule was manufactured by passing 350 g of ketorolac tromethamine (Syntex, lot # 4747-143-1) through a 60 mesh screen, blending it in a Kitchen Aid mixer for 10 min with 1,575 g of corn starch, NF (Hubinger Co., lot # 38-9974), via geometric dilution, passing the mixture through a 40 mesh screen, blending it with 13,746 g of spray dried lactose, USP (Foremost Whey Products, lot # 4RM103), in an AMF planetary mixer for 15 min, mixing in 79 g of magnesium stearate, NF (Mallinckrodt Specialty Chemicals Co., lot # 2255P8), for 2 min, and then filling 450 mg of the powder blend into size 0 opaque blue GB two-piece hard gelatin capsule shells (Elanco Qualicaps, lot # C1KG38) using a Zanasi RM63 filling machine. The ketorolac tromethamine oral solution (1 mg/ml, with the dose being 10 ml) was manufactured by dissolving with stirring 500 mg of ketorolac tromethamine (Syntex, lot # 4747-143-1) and 500 mg of sodium benzoate, NF (J.T. Baker Chemical Co., lot # 837360), in 250 ml of purified water (Syntex, material # 830725), adjusting the pH to 7.4 with 0.5 N sodium hydroxide solution, NF (Mallinckrodt Specialty Chemicals Co., lot # KPPM), adjusting the final volume to 500 ml by adding purified water while stirring, and then filtering it through a 0.4 micron Nuclepore membrane filter. Because the drug in solution is light-sensitive, the solution was protected from light by filling it into amber glass vials which were sealed with grey butyl siliconized stoppers with aluminum caps. All of the formulations were tested for stability of content after manufacturing and were found to exhibit no changes in potency for the length of the study.

Study Procedure - The study was conducted at the Syntex Clinical Studies Unit in Palo Alto, California. All subjects received a single dose of the study drug (1 tablet, 1 capsule or 10.0 ml of the solution) with 200 ml of water at 8:00 a.m. following an overnight fast. The order of drug administration was randomized. Each subject received all three drug formulations, with approximately a 1-week interval between drug administrations. After each dose, the study subjects remained fasting until the 4-hr blood sample had been obtained.

Fifteen milliliters of whole blood were collected in heparinized vacutainer tubes on study days at baseline (immediately before dosing), 20 and 40 min after dosing, and 1, 2, 4, 8, and 24 hr after dosing. Blood samples were taken from alternate arms. Because the drug is light-sensitive, blood samples were centrifuged in the dark. The plasma was separated and stored frozen until assayed for ketorolac levels by HPLC (8).

Bioavailability Parameters - The following bioavailability parameters were analyzed statistically: 1) plasma concentrations of ketorolac at each sampling time (C_p); 2) time to maximum plasma concentration (T_{max}); 3) maximum plasma concentration (C_{max}); 4) area under the plasma curve (AUC) computed using the trapezoidal rule from 0-24 hr and extrapolated to infinity by addition of the term C_p (24 hr)/β, where β is the terminal rate constant of plasma level decline; and 5) plasma half-life ($t_{1/2}$) determined by log-linear regression of plasma concentrations between 4 and 24 hr.

Statistical Analysis - Wilk's criterion was used in a multivariate analysis of variance (9) to test for differences among the formulations in both blood levels and calculated parameters while keeping the overall probability of a Type I error at the desired level. Univariate analysis of variance appropriate for a replicated Latin square design (10) was then performed on each variable using PROC GLM of the Statistical Analysis System (SAS) (11). When the F-test for a formulation effect was statistically significant at the 0.05 level, the ANOVA was followed by Duncan's multiple range test (10) to further define the differences among the formulations. For each variable, 95% fiducial intervals were calculated using Fieller's Theorem (12) on the ratios of the means for the tablet and the capsule to the mean for the solution, and on the ratio of the mean for the tablet to the mean for the capsule.

When the fiducial limits for a variable fell within (or very close to) the interval (0.80, 1.20), then the means for the two formulations differed by approximately 20%

or less with 95% confidence and they were deemed to be bioequivalent with respect to that variable.

***In Vitro* Dissolution** - Dissolution of the ketorolac tromethamine tablets and capsules was determined using USP XXI Apparatus II. The medium was 600 ml of deionized water maintained at 37.0 ± 0.5°C. The paddles rotated at 50 rpm. Automated sampling equipment removed the samples through a filter and analyzed them spectrophotometrically at 322 nm, sampling every 15 min for 45 min. The dissolution values reported were the mean of 6 tablets or capsules for each formulation.

RESULTS AND DISCUSSION

The *in vitro* dissolution profiles of the tablets and capsules are shown in Table 1. The dissolution profiles of the tablets and capsules were essentially identical, and both products were completely dissolved within 45 min.

Mean plasma concentrations are shown in Figure 1 for the 0-8 hr time interval. Table 2 shows that plasma levels of ketorolac from the three formulations were not statistically significantly different from each other except at 20 min after dosing. The mean plasma level at 20 min was highest for the solution (0.935 µg/ml), followed by the tablet (0.663 µg/ml) and then the capsule (0.288 µg/ml). Table 3 shows that at the first sampling time (20 min), the 95% fiducial limits comparing each formulation pair were wide, and therefore equivalence was not demonstrated at that time point. The fiducial limits demonstrated equivalent plasma levels between the tablet and the solution at 40 min and 1, 2, and 8 hr (but not at 4 and 24 hours since plasma levels at these times were too variable to demonstrate equivalence); between the capsule and the solution at 40 min and 1 and 2 hr (but not at 4, 8, and 24 hours); and between the tablet and the capsule at 40 min and 1, 2, and 8 hr (but not at 4 and 24 hours).

Table 4 demonstrates that the time to maximum plasma concentration (T_{max}) values averaged 35, 42, and 23 min for the tablet, capsule and solution respectively. Individual T_{max} values ranged between 20 and 60 min for the tablet and capsule, and between 20 and 40 min for the solution. The average T_{max} was significantly shorter for the solution ($p = 0.0015$), but was not significantly different between the tablet and capsule. The fiducial intervals are presented in Table 5, and since they were wide, they provide strong support for the significance

TABLE 1
***In Vitro* Dissolution Profiles for the Ketorolac Tromethamine 10-mg Solution, Tablets, and Capsules**

	% Dissolved ± S.D. at 10 Min	% Dissolved ± S.D. at 20 Min	% Dissolved ± S.D. at 30 Min	% Dissolved ± S.D. at 45 Min
Solution	NA[a]	NA[a]	NA[a]	NA[a]
Tablets	24 ± 6	68 ± 13	88 ± 8	98 ± 3
Capsules	31 ± 3	71 ± 2	91 ± 1	100 ± 1

[a] Not Applicable, 100% dissolved by definition

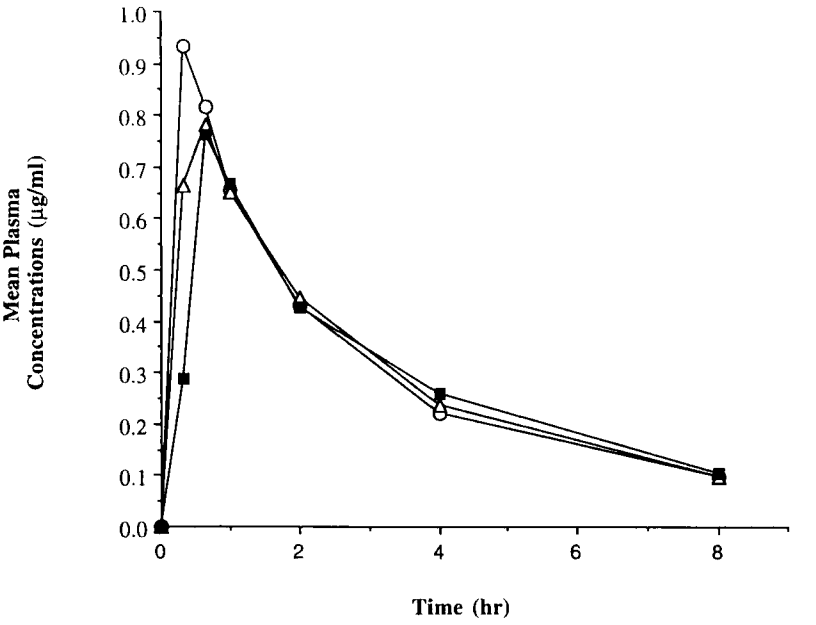

FIGURE 1
Mean ketorolac plasma concentrations versus time, following oral administration of a ketorolac tromethamine 10-mg oral solution (○), tablet (△), or capsule (■).

TABLE 2
Multiple Comparisons[a] Between Mean Plasma Concentrations (μg/ml) Following Oral Administration of a Ketorolac Tromethamine 10-mg Tablet, Capsule, or Solution

Sample Time	Formulation Means (± Standard Deviation)			F-test p-value[b]
	Tablet	Capsule	Solution	
20 min	0.663 ± 0.366	0.288 ± 0.267	0.935 ± 0.287	0.0003
40 min	0.782 ± 0.223	0.764 ± 0.191	0.817 ± 0.160	0.6562
1 hr	0.652 ± 0.171	0.667 ± 0.089	0.656 ± 0.124	0.8720
2 hr	0.447 ± 0.140	0.427 ± 0.100	0.431 ± 0.059	0.7412
4 hr	0.236 ± 0.071	0.259 ± 0.089	0.222 ± 0.056	0.3722
8 hr	0.097 ± 0.035	0.104 ± 0.025	0.098 ± 0.026	0.5952
24 hr	0.015 ± 0.007	0.012 ± 0.005	0.013 ± 0.006	0.1612

[a] Duncan's multiple range test - means underlined by the same line are not significantly different at $p < 0.05$.

[b] Analysis of variance model comparing the three formulations at each time point. Manova P-value for formulation effect = 0.0136 and period effect = 0.1635.

TABLE 3

Ratios and 95.0% Fiducial (Confidence) Limits[a] on Ratios for Ketorolac Plasma Concentrations for a 10-mg Ketorolac Tromethamine Tablet, Capsule, and Solution

Parameter	Ratio of Tablet/Solution x 100%	95% Fiducial Limits	Ratio of Capsule/Solution x 100%	95% Fiducial Limits	Ratio of Tablet/Capsule x 100%	95% Fiducial Limits
20 min	70.9	7.4%, 274.0%	30.8	--[b], 178.1%	230.1	15.4%, 288.5%
40 min	95.7	81.9%, 111.7%	93.5	79.8%, 109.3%	102.4	87.2%, 120.2%
1 hr	99.4	90.3%, 109.4%	101.6	92.4%, 111.7%	97.8	89.0%, 107.6%
2 hr	103.7	91.4%, 117.8%	99.2	87.1%, 112.9%	104.6	92.2%, 118.9%
4 hr	106.4	84.1%, 135.1%	116.8	93.5%, 147.3%	91.1	73.0%, 113.1%
8 hr	98.9	84.6%, 115.5%	105.9	91.2%, 123.3%	93.4	80.1%, 108.5%
24 hr	119.9	95.0%, 154.1%	97.4	74.5%, 126.7%	123.1	97.3%, 159.3%

[a]Computed using Fieller's Theorem

[b]Could not be calculated; variance too large.

TABLE 4
Multiple Comparisons[a] Between Means of Various Computed Parameters Following Oral Administration of a Ketorolac Tromethamine 10-mg Tablet, Capsule, or Solution

Computed Parameter	Formulation Means (+ Standard Deviation)			F-test p-value[b]
	Tablet	Capsule	Solution	
$t_{1/2}$ (hr)	5.23 ± 0.68	4.77 ± 0.47	4.93 ± 0.77	0.1386
C_{max} (μg/ml)	0.865 ± 0.231	0.809 ± 0.121	0.976 ± 0.228	0.0279
T_{max} (min)	35.0 ± 15.1	41.7 ± 10.3	23.3 ± 7.8	0.0015
AUC (μg/ml x hr)	3.50 ± 0.98	3.43 ± 0.63	3.51 ± 0.75	0.9123

[a] Duncan's multiple range test - means underlined by the same line are not significantly different at $p < 0.05$.

[b] Analysis of variance model comparing the three formulations for each computed parameter. Manova P-value for formulation effect = 0.1060 and period effect = 0.8068.

TABLE 5

Ratios and 95.0% Fiducial (Confidence) Limits[a] on Ratios for Computed Pharmacokinetic Parameters for a 10-mg Ketorolac Tromethamine Tablet, Capsule, and Solution

Parameter	Ratio of Tablet/Solution x 100%	95% Fiducial Limits	Ratio of Capsule/Solution x 100%	95% Fiducial Limits	Ratio of Tablet/Capsule x 100%	95% Fiducial Limits
$t_{1/2}$	106.1	97.9%, 116.2%	96.7	88.0%, 106.3%	109.7	100.1%, 120.3%
T_{max}	150.0	111.4%, 210.8%	178.6	135.2%, 248.7%	84.0	66.6%, 104.9%
C_{max}	88.5	77.7%, 100.5%	82.7	72.2%, 94.4%	106.9	92.9%, 123.3%
AUC	99.8	89.1%, 111.9%	97.9	87.2%, 109.8%	102.0	90.9%, 114.5%

[a]Computed using Fieller's Theorem

of the differences in T_{max} between the tablet and solution (111%-211%), and between the capsule and solution (135%-249%). The T_{max} values were too variable to support equivalence between the tablet and capsule (67%-105%).

The maximum plasma concentration (C_{max}) values averaged 0.865, 0.809, and 0.976 μg/ml for the tablet, capsule, and solution doses, respectively (Table 4). The tablet was not significantly different from the solution or the capsule with respect to C_{max}; however, the mean C_{max} for the capsule was significantly lower than that for the solution. The results were supported by the fiducial intervals for the ratio of tablet to solution (78%-101%), tablet to capsule (93%-123%) and capsule to solution (72%-94%) (Table 5).

With respect to the area under the curve (AUC), there was no statistically significant difference among the three formulations in the AUC (Table 4). The AUC averaged 3.50, 3.43, and 3.51 μg/ml x hr for the tablet, capsule and solution, respectively. The ratio of mean AUC (Table 5) was 100% for the tablet and 98% for the capsule relative to the solution. The 95% fiducial intervals confirmed equivalent AUC between the tablet and solution (89%-112%), the capsule and solution (87%-110%), as well as between the tablet and capsule (91%-115%).

The $t_{1/2}$ averaged 5.23, 4.77, and 4.93 hr for the tablet, capsule, and solution doses, respectively (Table 4). There was no significant difference in half-life among the three formulations. This was confirmed by the fiducial intervals (Table 5).

CONCLUSIONS

This study demonstrates that the commercially marketed ketorolac tromethamine 10-mg tablet and the capsule formulation used in this study (which had an *in vitro* dissolution profile similar to the tablet) were clearly equivalent with respect to the C_{max}, AUC, and $t_{1/2}$. The T_{max} was not significantly different between the tablet and the capsule, although the fiducial limits were too wide to demonstrate equivalence. In general, the data indicate that the tablet and the capsule were similar with respect to the rate and extent of ketorolac absorption. The solution, when compared to the tablet, demonstrated a slightly although significantly faster rate of absorption. Hypothesis testing illustrated that the tablet and solution were equivalent with respect to the C_{max}, AUC, and $t_{1/2}$. These data indicate that the

solution or the capsule formulations utilized in this study may be used as alternatives to the commercially marketed tablet without adversely impacting the absorption profile of the medicament.

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