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Pilot Study of Relative Bioavailability of Two Oral Formulations of Ketoprofen 25 mg in Healthy Subjects. A Fast-Dissolving Lyophilized Tablet as Compared to Immediate Release Tablet

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ABSTRACT The pharmacokinetics of ketoprofen from a fast-dissolving lyophilized tablet (LT), which need not be swallowed, as compared to an immediate release (IR) tablet as reference after single oral dose (25 mg) administration was determined in six healthy subjects aged between 25–40 years using a randomized crossover design. In this study, the rate and extent of absorption of ketoprofen were found to be very different after administration of the LT and the IR tablet. The rate of absorption of ketoprofen from LT was significantly faster than that of IR tablet and had significantly higher C_{max} (by about 50%) and earlier t_{max} (by 15 min), whereas the extent of absorption expressed by AUC was about 68% higher as compared to the IR tablet. The relative bioavailability (f_{rel}) of the LT compared with the IR tablet was 168%. The difference between the two formulations for half-life and MRT were statistically significant ($p < 0.05$). The tolerance of the two tested formulations was excellent. Ketoprofen LT remained physically and chemically stable for 12 months at 25°C and 60% relative humidity.

KEYWORDS Fast-dissolving tablet, Ketoprofen, Lyophilized tablet, Bioavailability

INTRODUCTION

Ketoprofen is a non-steroidal anti-inflammatory (NSAID) drug and its (S)-(+)-enantiomer (dexketoprofen) is one of the most potent in vitro inhibitors of prostaglandin synthesis (Barbanoj et al., 2001). It is mainly used in the treatment of inflammation and pain associated with rheumatic disorders (Fossgreen, 1976; Kantor, 1986; Airaksinen, 1993) and in postoperative pain and fever in children (Nikanne et al., 1999; Keinänen-Kiukaanniemi et al., 1980; Kokki et al., 2000). Ketoprofen is also known to cause local gastrointestinal (GI) side effects which may require withdrawal of treatment. Ketoprofen is poorly water soluble,

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however, once dissolved it is rapidly absorbed from the GI tract with maximal concentration in plasma achieved within 0.5–1 hr after administration (Ishizaki et al., 1980). Bioavailability of ketoprofen is improved by increasing its solubility and dissolution rate which also results in reducing its ulcerative side effects (Solanker & Jagtap, 2005). Ketoprofen has a short half-life of about 1–3 hr (Stiegler et al., 1995) and is metabolized in the liver to an unstable, inactive glucuronic ester that is excreted in the urine (Debruyne et al., 1987). The pharmacokinetics of ketoprofen in young children after intravenous infusion, intramuscular and oral administration were found to be quite similar to those reported in adults (Kokki et al., 2001; Kokki et al., 2002). Administration of ketoprofen after a heavy meal delays the onset of absorption but does not modify the extent of absorption of the drug (Nievel et al., 1987), however, in one study the maximum concentration and the area under the curve over one 24-hr dosage period were found to be significantly higher with a low calorie/low fat diet (LCFD) compared to a high calorie/high fat diet (HCFD; Le Liboux et al., 1994).

When a fast-dissolving ketoprofen tablet, which dissolve rapidly in the mouth and need not be swallowed, is absorbed rapidly and efficiently from the buccal mucosa, the bioavailability would be expected to improve compared with that of an immediate release formulation due to reduction of first-pass effect of ketoprofen. The aim of this study was to compare the rate and extent of absorption and pharmacokinetic characteristics of ketoprofen following administration of a single dose (25 mg) of ketoprofen in a fast-dissolving lyophilized tablet (Ahmed et al., 2006) and an immediate release (IR) marketed tablet as a reference in six healthy volunteers using a crossover design under fasting conditions.

MATERIALS AND METHODS

Subjects

Six healthy male volunteers (ages 25 to 40 years; mean age, 33.5 ± 6.2 years) participated in the study. All were within 20% of their ideal body weights (weights, 68 to 79 kg; mean weight, 72.6 ± 4.3 kg and heights, 165–178 cm, mean height, 171.8 ± 4.9 cm). All subjects were not taking any medication including ketoprofen products and all were non-smokers. All subjects showed no clinically relevant positive findings from a standard physical examination at entry; normal clinical and laboratory tests within 24 hr prior to the first administration. No febrile illness within 7 days prior to entry; no history of gastrointestinal, cardiovascular, renal or hepatic disease and no history of hypersensitivity, asthma, urticaria or other allergic symptoms. Study protocol was approved by Cairo University Institutional Review Board (IRB) for the protection of human subjects. Each subject read, understood, and signed an informed written consent. All subjects were well informed about the risks and objectives of the study.

Study Design

The study was performed to compare the pharmacokinetics of two ketoprofen tablet formulations following administration of single doses of 25 mg each using a nonblind, two-treatment, two-period, randomized, crossover design. Under this design half of the subjects were given the IR treatment first and the LT treatment second and the other half were given the treatments in opposite order. The subjects were received in the facility at 8:00 AM of the day of the study after an overnight fast (at least 10 hr) as instructed before the study. From this time on they remained at the study site under controlled dietary and liquid intake until the end of the study day. No food was allowed for 4 hr after dosing. The washout time was one week. The subjects were under medical supervision during the study day and were watched for any adverse events such as GI disturbances, nausea, vomiting, diarrhea, allergic reactions, headache, etc.

Drugs

The two tested ketoprofen formulations were a new fast-dissolving ketoprofen tablet prepared by a freeze-drying in blister technique (Ahmed et al., 2006) and a commercially available immediate release tablet (Ketofan-25 mg, Amriya, Egypt). The fast-dissolving lyophilized tablet (LT) was administered orally without water. Each subject was asked to keep the LT in the mouth for few minutes until completely dissolved in the saliva (Treatment A). Water was allowed after 30 min. The immediate release tablet (IR) was ingested with 200 mL of water (Treatment B).

Collection of Blood Samples

For blood sampling an indwelling catheter was inserted in a forearm vein in the morning before administration which generally remained in place until the last sampling point. Venous blood samples (10 mL) were collected into heparinized tubes at the following time points: 0 (predose), 5, 10, 15, 30 min, 1, 2, 3, 4, 5, 6, 8, 10, and 12 hr after administration of the LT. Samples were collected at 0, 15, 30 min, 1, 2, 3, 4, 5, 6, 8, 10, and 12 hr after administration of the IR tablets. The 5 and 10 min blood samples were omitted from the IR treatment based on a preliminary study in one subject to determine sampling times. In this study no ketoprofen was detected in the plasma at the 5 and 10 min time points following IR administration. Plasma was obtained by centrifugation at 2000 *g* for 10 min. The plasma was pipetted into glass tubes and stored at –20°C until the analytical determination of ketoprofen.

Assay Methods

Chromatographic Conditions

Plasma concentrations of unchanged racemic ketoprofen were determined following the HPLC procedure outlined by Rifai (Rifai et al., 1997) apart from the fact that diclofenac sodium (Sigma chemicals, St. Louis, MO) was used instead of ibufenac as the internal standard and the UV absorbance was detected at 260 nm instead of the 220 nm used by Rifai. The mobile phase mixture was prepared by dissolving 4 mL concentrated phosphoric acid in 600 mL deionized water and 400 mL acetonitrile (HPLC grade, Fisher chemicals, NJ). The HPLC column was Hypersil BDS C_{18} 5 μm, 25 cm × 4.6 mm (Altek).The HPLC system consisting of Waters Alliance 2695 separation module, autosampler, empower software and Waters 2996 photodiode array detector (Waters Associates, Milford, MA). The flow rate was 1 mL/min.

Standard Solutions

Ketoprofen standard stock solutions were prepared to contain 50 mg/L of reference standard by dissolving ketoprofen in methanol (HPLC grade, Fisher chemicals, NJ). Stock solutions were diluted with blank plasma to contain 0.04, 0.08, 0.2, 1, 2, 4, 8, and 10 μg/mL of ketoprofen. Standards were prepared by spiking 0.5 mL of blank plasma with 100 μL of stock solutions and 50 μL of internal standard (100 μg/mL). The analytical method consisted of a single step extraction of ketoprofen from plasma samples with 1.5 mL 95% acetonitrile. The samples were vortexed for 30 sec and centrifuged at 3000 *g* for 10 min. A portion of the supernatants were transferred to glass HPLC tubes and 50 μL injected onto the HPLC column. Retention times of ketoprofen and internal standard were about 5 and 9 min, respectively. A standard curve was constructed by plotting the peak-area ratios of ketoprofen to internal standard against ketoprofen concentrations in plasma. All assays were performed in triplicate. During the assay of the study samples, the intra-batch precision and accuracy of the analytical procedure were evalutated after replicate analysis ($n = 6$) of control plasma samples spiked at four concentration levels: 0.04, 0.2, 2, and 10 μg/mL. The lower limit of quantification was 0.04 μg/mL with a linear response across the full range of concentrations from 0.04 to 10 μg/mL ($R^2 = 0.999$). The analysis of quality control samples showed a precision below 3% relative standard variation and accuracy below ±5% for intra-batch analysis. The coefficient of variation for inter-batch analysis was less than 10%.

Plasma Analysis

Half a milliliter of subject plasma was added to 1.5 mL 95% acetonitrile containing 50 μL of the internal standard (10μg/mL), mixed by vortex for 30 sec and centrifuged at 3000 *g* for 10 min. Portions of supernatant were transferred to HPLC tubes and assayed as described above.

Pharmacokinetic Analysis

Pharmacokinetic characteristics from plasma data following administration of the two treatments were estimated for each subject by using a computer program, WinNonlin® (version 1.5, Scientific consulting, Inc., NC). Noncompartmental analysis was used. C_{max} (μg/mL) and t_{max} (min) were the observed maximal drug concentration and its time, respectively. The area under the curve, $AUC_{(0-t)}$ (μg.h/mL), was calculated using the linear trapezoidal rule from zero time to the last time of blood sample. The area under the curve from zero to infinity, $AUC_{(0-\infty)}$ (μg.h/mL), was calculated as $AUC_{(0-\infty)} = AUC_{(0-t)} + C_t/k$, where C_t is the

last measured concentration at the time t, and k is the terminal elimination rate constant estimated by log-linear regression analysis on data visually assessed to be a terminal log-linear phase. Apparent terminal elimination half-life ($t_{1/2}$) was calculated as $t_{1/2} = 0.693/k$. Mean residence time (MRT) was calculated from AUMC/AUC. The relative bioavailability (f_{rel}) was calculated as AUC_{LT}/AUC_{IR}.

Statistical Analysis

Descriptive statistics were provided for all pharmacokinetics parameters for completers. An analysis of variance (ANOVA) was performed on untransformed and log-transformed data for the pharmacokinetic parameters, C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ and untransformed data for $t_{1/2}$ using the software SPSS 11.0 (SPSS Inc., Chicago). Statistical inferences were based on both untransformed and log-transformed values for the C_{max} and AUC parameters and observed values for $t_{1/2}$. The two-sided 90% confidence intervals (CI) for the ratio of average AUC and C_{max} between each test formulation (LT) and the reference formulation (IR) were constructed (FDA, 1993). The nonparametric Signed Rank Test was used to compare the t_{max} for test and reference. The level of significance was $\alpha = 0.05$. A p-value of ≤ 0.05 was considered statistically significant. The sample size ($n = 6$) was not selected based on statistical consideration but rather on economic consideration.

Storage Stability

Ketoprofen lyophilized tablets (LT) were stored at 25°C and 60% relative humidity in a stability chamber (Hoffman Manufacturing Inc., Oregon) during a period of 12 months. Stability was assessed by comparing initial dissolution profiles and DSC thermograms with those obtained after 3, 6, and 12-month storage. The results of dissolution experiments were checked for statistical significance using the one-way analysis of variance (ANOVA) F-test for testing the equality of several means. A p-value of >0.05 was considered statistically insignificant.

RESULTS AND DISCUSSION

The study was completed by the six subjects who were included in the pharmacokinetic analysis. The volunteers tolerated very well the two treatments and did not complain of any adverse effects during the course of the study. No signs of GI disturbances or allergic reactions were observed from any of the subjects during the study. The mean plasma concentration-time courses for ketoprofen following administration of LT and IR tablets are shown in Fig. 1. Remarkable differences in the shape of the concentration-time courses between the two treatments were found, expressed by higher C_{max} (by about 50%) and earlier t_{max} (by 15 min) values for the LT. The mean C_{max} estimates from the LT and IR tablets were 1.49 ± 0.316 μg/mL and 1.02 ± 0.24 μg/mL, respectively (90% CI for the ratio from 116% to 175%). The differences between the two treatments for C_{max} and t_{max} were statistically significant. The higher C_{max} and earlier t_{max} obtained following administration of LT is expected due to rapid disintegration in the mouth and dissolution of the drug in the saliva resulting in very fast absorption. These in vivo results correlate well with in vitro dissolution results obtained from previous work (Ahmed et al., 2006). Ketoprofen was detected in plasma as soon as the 5-min sampling time in the six subjects following administration of the LT indicating very rapid absorption by this route of administration. The extent of absorption from LT expressed by $AUC_{(0-t)}$ was determined to be 68% larger and statistically significantly different as compared to the IR tablet. The improved bioavailability of ketoprofen from the LT obtained in this study, suggests that absorption from the buccal mucosa resulted in reduction of first-pass hepatic effect of ketoprofen. The relative bioavailability (f_{rel}) of the LT compared with the IR tablet was

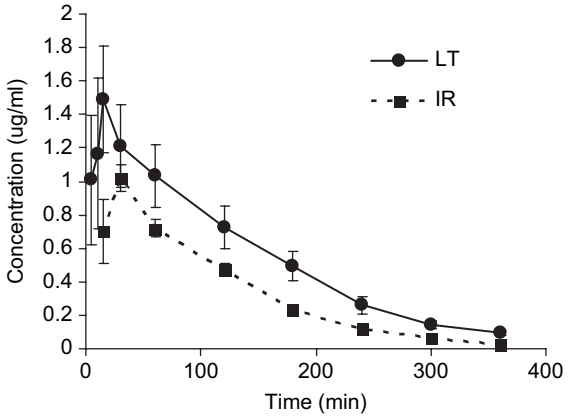

FIGURE 1 **Mean (±SD) plasma ketoprofen concentrations (μg/mL) following administration of 25 mg ketoprofen in LT or IR tablets in six subjects.**

estimated to be on average 168% (90% CI from 138 to 196%). The percentage of extrapolation required to calculate $AUC_{(0-\infty)}$ from $AUC_{(0-t)}$ was low, amounting to 5.4 and 2.1% on average for the LT and IR tablets, respectively. The mean ketoprofen half-life estimate from LT (83.7 ± 4.3 min) was determined to be about 36% larger and statistically significantly different relative to the mean half-life following administration of IR tablets (61.5 ± 9.7 min). Although the significant increase in ketoprofen half-life from LT is inconsistent with the pharmacokinetic theory, in which an increase in absorption should not affect elimination, this result could be attributed to the higher variability in the mean half-life parameter observed with IR treatment. It has been reported that drugs that show low extraction ratios and are eliminated primarily by metabolism (such as ketoprofen) demonstrate marked variation in over-all elimination half-lives within a population (half-life of ketorpofen is about 1–3 hr). This variation in half-life is thought to be mainly due to genetic differences in intrinsic hepatic enzyme activity along with some other factors such as age and nutrition (Shargel & Yu, 1985). The variability in mean half-life parameter from LT is far less than that observed from IR treatment (less than half), which is consistent with the findings that the observed increase in bioavailability of ketoprofen from LT compared to IR tablets could be due to a decreased first-pass effect. Statistical comparison of MRT parameter also indicated a significant difference between LT (109.2 ± 3.7 min) and IR tablet (98.8 ± 2.5 min). The mean non-compartmental MRT of ketoprofen estimate from LT was about 11% larger relative to MRT estimate from IR tablet. The estimates of the mean untransformed pharmacokinetic parameters obtained by non-compartmental fitting of the concentration-time data from the biostudy along with the 90% CI for the ratio (LT/IR) of average parameters C_{max} and AUC_{0-t} are given in Table 1. The statistical analysis comparing the pharmacokinetic parameters between the two treatments is also summarized in Table 1 with *p*-values.

With regard to the extent parameters for ketoprofen from the two treatments, the ANOVA model for log-transformed data indicated significant treatment effects for C_{max} and $AUC_{(0-t)}$ with $p = 0.024$ and $p = 0.002$, respectively. The ANOVA model also indicated no significant sequence effect. The 90% CI for C_{max} and $AUC_{(0-t)}$ were outside the predetermined range for bioequivalence of 80–125% (FDA, 1993). The estimates of the geometric mean of C_{max} and $AUC_{(0-t)}$ parameters along with the 90% CI for the ratio of the C_{max} and AUC_{0-t} of LT/IR are presented in Table 2. The mean C_{max} estimate from the LT was determined to be about 147% that obtained from IR treatment (90% CI is 113 to 190%). The bioavailability of ketoprofen from LT determined from log-transformed data was about 169% relative to the IR (90% CI is from 134 to 211%). Due to the small variability encountered in the study both untransformed and log-transformed analyses for C_{max} and $AUC_{(0-t)}$ gave similar results and conclusions. The conclusions based on the confidence interval approach are identical to the two one-sided *t*-tests each performed at the 5% level (Schuirman, 1987).

Based on these results, it can be concluded that the greater bioavailability obtained from the LT, which

TABLE 1 **The Mean (±SD) Pharmacokinetic Parameters of Ketoprofen After Administration of 25 mg in Fast-Dissolving Lyophilized (LT) or Immediate Release (IR) Tablets to Six Fasted Volunteers and 90% Confidence Intervals (in Parentheses) for the Ratio (LT/IR) of Averages for C_{max} and AUC_{0-t}**

Parameter	LT	IR	Statistical tests
C_{max} (μg/mL)	1.49 ± 0.316	1.02 ± 0.24	$p = 0.02$
		(116–175%)	
AUC_{0-t} (μg*min/mL)	200.8 ± 36.3	119.9 ± 26.6	$p = 0.002$
		(138–196%)	
$AUC_{0-\infty}$ (μg*min/mL)	212.5 ± 38.3	122.3 ± 25.9	$p = 0.001$
t_{max}* (min)	15.0	30.0	$p = 0.002$
$t_{1/2}$ (min)	83.7 ± 4.3	61.5 ± 9.7	$p = 0.001$
MRT (min)	109.2 ± 3.7	98.8 ± 2.5	$p = 0.0001$
% Bioavailability = 168%			

Data are mean values ($n = 6$) ± SD.
*medians.

TABLE 2 **Geometric Mean (±SD) and 90% Confidence Intervals (in Parentheses) for Log-Transformed Pharmacokinetic Parameters of Ketoprofen After Administration of 25 mg in Fast-Dissolving Lyophilized (LT) or Immediate Release (IR) Tablets to Six Fasted Volunteers**

Parameter	LT	IR	Statistical tests
C_{max} (μg/mL)	0.38 ± 0.21	–0.008 ± 0.25	$p = 0.024$
		(113–190%)*	
AUC_{0-t} (μg*min/mL)	5.29 ± 0.18	4.76 ± 0.22	$p = 0.002$
		(134–211%)*	
% Bioavailability = 169%			

*90% CI for LT/IR.

was about 68% larger than that measured after administration of the IR tablet, with higher C_{max}, shortened t_{max} and longer half-life may be attributed to rapid and efficient absorption of ketoprofen from the buccal mucosa resulting in decreased presystemic biotransformation due to either first-pass hepatic extraction or metabolism in the epithelium and/or lumen of GI tract, or by a combination of these processes.

Since the oral administration of conventional dosage forms of ketoprofen is reported to cause serious local and systemic side effects mainly gastric disturbances (Chi & Jun, 1991; Jachowicz et al, 2000; Topaloglu et al, 1999 ; Solanker & Jagtap, 2005), ketoprofen LT as a drug delivery system ensure less irritation of the GI tract and a lower risk of side effects, however, because of the nature of the study design and the small number of subjects included in the study the results can only be considered preliminary and further studies with a larger number of subjects under different conditions such as varying conditions of food intake should be conducted in order for doing an adjustment in dose with the advantage of lesser potential adverse effects. Because LT need not be swallowed, it could also be convenient for pediatric and geriatric patients and may replace intramuscular and rectal administration especially in children.

Stability studies indicated that ketoprofen LT maintained the initial properties with respect to dissolution characteristics and amorphous state after one year storage at 25°C and 60% relative humidity. The percentages of ketoprofen dissolved at 2 min were slightly lower after 3, 6, and 12-month storage when compared to freshly prepared tablets; however the difference is not statistically significant ($p > 0.05$). The percentage of ketoprofen released from the tablets after 3, 6, and 12-month storage is presented in Table 3. DSC thermograms of ketoprofen LT after 3, 6, and 12-month storage showed the absence of the endothermic peak characteristic of ketoprofen suggesting absence of crystallinity and maintenance of amorphous state of the drug upon storage.

CONCLUSION

Our results indicated that ketoprofen LT is a promising formulation resulting in ketoprofen being rapidly and effectively absorbed into the blood stream with significantly higher bioavailability when compared to standard immediate release oral dosage form. The results are only preliminary and a definitive clinical trial would be required with the new formulation for any subsequent approval of LT formulation. The stability of ketoprofen LT is satisfactory.

TABLE 3 **Percentages of Dissolved Ketoprofen From LT After 0, 3, 6, and 12-Month Storage at 25°C and 60% Relative Humidity**

	Months				
Time	0	3	6	12	*p*-value (min)
2	76.0 ± 3.1	72.7 ± 2.8	73.6 ± 3.1	73.9 ± 2.7	>0.05
5	93.6 ± 1.6	95.1 ± 1.7	92.4 ± 2.5	94.2 ± 2.1	>0.05
8	96.2 ± 2.4	98.2 ± 2.6	96.3 ± 1.8	96.0 ± 0.8	>0.05
10	100.3 ± 1.4	99.0 ± 0.7	97.8 ± 1.1	98.6 ± 1.3	>0.05

Data are mean values ($n = 6$) ± SD.

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