ISSN: 0975-0851
Journal of Bioequivalence & Bioavailability

OPEN ACCESS Freely available online

Research Article

Ketorolac Tromethamine Sublingual Tablet: A Randomized, Single-Dose, Two-Sequence, Two-Period, Crossover Study to Assess the Bioequivalence between Two Formulations

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ABSTRACT

Ketorolac Tromethamine is a non-hormonal anti-inflammatory drug, with potent analgesic action, used to short-term treatment of moderate to severe acute pain. In order to register a generic product in Brazil, it was performed a bioequivalence study under fasting conditions between two ketorolac tromethamine sublingual tablets. The study was designed and conducted in accordance with ethical principles and current legislation, presenting an open, randomized, with two treatments, two periods and two sequences crossover design. For this study, 32 healthy men and women were selected; however, 30 participants completed the study. Blood samples were collected serially up to 24 h post-drug administration and plasma concentrations of ketorolac were obtained by a validated bioanalytical method, using ketorolac-d5 as an internal standard. A non-compartmental model was used to determine the pharmacokinetic parameters. Bioequivalence between test and reference formulation was demonstrated by constructing the 90% confidence intervals calculated for the corresponding ratios of the transformed data of the pharmacokinetic parameters C_{max}, AUC_{0-t} and AUC_{0-inf}. The point estimates and 90% confidence intervals obtained were 101.195 (96.12%-106.53%), 99.43% (95.27%-103.78%) and 98.93% (94.86%-103.16%), respectively. Considering these values are within the range of 80% to 125%, it is possible to conclude that the two formulations are bioequivalent in terms rate and extent of absorption and, therefore, are interchangeable. Both formulations showed to be safe and well tolerated.

Keywords: Ketorolac; Anti-inflammatory agents; Non-steroidal; Bioequivalence; Pharmacokinetics; Bioavailability; Bioanalytical method

INTRODUCTION

When it comes to the management of acute pain, it is important to ensure that the drug presents a potent and rapid onset of action to meet patient's needs. In this sense, opioids agents and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are the most common therapeutic options for the treatment of acute pain, considering the magnitude of analgesia these agents offer [1]. Sublingual dosage forms are good candidates for the treatment of acute pain, since it contributes for a rapid absorption of the drug through passive mechanism to reach systemic circulation, being 3 to 10 times greater when compared to oral route. Additionally, facilitates drug administration to patients that presents difficulty to swallow tablets, such as pediatric, geriatric, and psychiatric patients [2].

Ketorolac tromethamine is a potent analgesic agent of the class of NSAIDs that acts inhibiting prostaglandin synthesis through the inhibition of the cyclooxygenase enzyme system [3]. It is present as a racemic mixture of enantiomers, in which the (-) S form is responsible for the analgesia [3]. Ketorolac is available as its tromethamine salt as injectable solution, topical ophthalmic

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Received: 06-Aug-2022, Manuscript No. JBB-22-17694; **Editor assigned:** 10-Aug-2022, PreQC No. JBB-22-17694 (PQ); **Reviewed:** 24-Aug-2022, QC No. JBB-22-17694; **Revised:** 01-Sep-2022, Manuscript No. JBB-22-17694 (R); **Published:** 08-Sep-2022, DOI:10.35248/0975-0851.22.14.484

Citation: Meulman J, Davanço MG, Costa F, Pacheco FBC, Teixeira KVS, Carandina SAC, et al. (2022) Ketorolac Tromethamine Sublingual Tablet: A Randomized, Single-Dose, Two-Sequence, Two-Period, Crossover Study to Assess the Bioequivalence between Two Formulations. J Bioequiv Availab. 14:484.

solution, sublingual tablets, and nasal spray dosage forms [4].

Due to its potent analgesic action, ketorolac tromethamine sublingual tablet is indicated for the short-term treatment of moderate to severe acute pain. It is rapidly and completely absorbed after oral administration, presenting a bioavailability of 81% to 100%. Peak plasma concentration increases linearly with dose, and it is expected to occur between 30 to 60 minutes after drug administration [3]. Approximately 40% of dose is metabolized, preferably by the liver. The major route of excretion is urinary, with more than 90% of the drug unchanged, in addition to metabolites. A small percentage of the dose (10%) is excreted in feces. Ketorolac presents very similar half-lives for the different routes of administration (intravenous, intramuscular, and oral) ranging from 4.5 hours to 5.6 hours, with a mean of 5.4 hours. The most common adverse reactions associated with this drug are abdominal pain with cramping, diarrhea, dizziness, drowsiness, dyspepsia, edema, headache, and nausea [3].

The aim of the present study was to assess the bioequivalence and safety of two ketorolac tromethamine 10 mg sublingual tablet formulations according to ANVISA regulatory requirements to register the test product in Brazil [5]. Two products are considered bioequivalent when the 90% confidence intervals for the ratio between the means of the data transformed into natural logarithms of C_{max} and AUC_{0-t} are between 80% to125% [5]. In this sense, it can be concluded that both test and reference products present the same rate and extent of absorption and therefore are therapeutically equivalents, possessing the same efficacy and safety profiles.

MATERIALS AND METHODS

Ethical aspects

This study was designed and conducted in accordance with the standards established by the ICH Guidelines for Good Clinical Practice, Good Clinical Practices - Document of the Americas, Declaration of Helsinki and all applicable regulatory requirements, as ANVISA Resolution 1170/2016 and 466/2012 [6-9]. The data and biological materials obtained were used only for the purposes determined in this research, maintaining the confidentiality of the data and results obtained, ensured by the controlled access of people responsible for its evaluation and execution.

The study was performed at Centro Avançado de Estudos e Pesquisas in Campinas, São Paulo, Brazil and was approved by Research Ethics Committee Investiga–Instituto de Pesquisa with protocol number 4.416.552. All participants agreed to participate in the study by signing the informed consent form.

Products under evaluation

The test formulation is ketorolac tromethamine 10 mg sublingual tablet (batch No. 92820, expiry date: August 2022) manufactured by Zodiac Produtos Farmacêuticos S.A. (Pindamonhangaba, São Paulo, Brazil) and the reference is Toragesic® 10 mg sublingual tablet (batch No. 1L1974, expiry date: November 2021) manufactured by EMS S.A. (São Bernardo do Campo, São Paulo, Brazil).

Subjects and study design

It was performed a single-center, open-label, randomized, crossover bioequivalence study with two periods, two treatments and two sequences, balanced, in which the subjects received in each distinct period the test drug or the reference drug, with a washout of seven days. Thirty-two healthy participants were selected to participate in the study, being equally divided between men and women to guarantee gender balance. The sample size assessment was based considering a within-subject coefficient of variation of 15% for the drug, in addition to an excess number of participants predicting possible dropouts to ensure greater reliability of the statistical results. Among the inclusion criteria in the study are a minimum age of 18 years and a maximum of 50 years, presenting a body mass index between 18.5 kg/m^2 and 29.9 kg/m^2, being in good health or being free from significant illness through assessment of clinical history, vital signs, anthropometric data, physical examination, ECG, and laboratory tests. Regarding the exclusion criteria, it can be cited the participation in any experimental study or the intake of any experimental drug within the six months prior to the start of this study, present history of liver, gastrointestinal, or other conditions that may interfere with drug absorption, distribution, metabolism, or excretion. Table 1 presents the demographic characteristics of the 32 study participants enrolled in the study.

Table 1: Demographic characteristics of the participants enrolled in study.

	Mean	Range
Age (years)	35.96	19-50
Weight (kg)	73.3	55.0-93.0
Height (m)	1.69	1.51-1.88
BMI (Kg/m^2)	24.46	18.86-28.61

Drug administration and sampling times

In each period of the study, the participants received one sublingual tablet of ketorolac tromethamine 10 mg (test or reference product) after eight hours of fasting. At the correct time of administration, the sublingual tablet was placed under the tongue, in the deepest cavity. The drug should not be swallowed but dissolved completely in the oral cavity without being chewed. Participants were monitored every two minutes until drug dissolution was complete.

Fluid and food intake was standardized among all participants in the two study periods. Fasting conditions were maintained for 4 hours after drug administration and water was not allowed two hours before and two hours after drug administration. Twenty-one (21) blood samples were collected beginning at 0 h (before drug administration) and then 0.17, 0.33, 0.50, 0.67, 0.83, 1.00, 1.25, 1.50, 1.75, 2.00, 2.33, 2.67, 3.00, 4.00, 5.00, 6.00, 8.00, 10.0, 12.0 and 24.0 hours after drug administration, in tubes containing EDTA K3 as anticoagulant. Immediately after collection, blood samples were centrifuged at 3,500 rpm for 10 min at 4°C. Plasma was separated, transferred to amber cryogenic tubes, and stored in ultra-freezers at -20°C with appropriate labeling until analysis.

Bioanalytical method

For the quantification of ketorolac in plasma it was used a properly validated reversed-phase ultra-performance liquid chromatography coupled to mass spectrometry (UPLC-MS/MS) method, using electrospray ionization source in positive mode and Multiple Reaction Monitoring (MRM) as the detection method. Ketorolac-d5 was used as an Internal Standard (IS), and the detection parameter was the m/z ratio between the product and precursor ion. The quantification parameter was the area under the peak of the chromatogram identified in the retention time and the transitions monitored were m/z 256.4>104.9 and m/z 261.4>110.0 for ketorolac and ketorolac-d5, respectively. The extraction method consisted in protein precipitation with methanol. The analytic concentrations in the subject's samples were calculated through interpolation on the calibration curve, and the linearity range

used was from 10 ng/mL to 2,000 ng/mL. All samples from the same participant were evaluated in the same run, in order to avoid inter-assay influence. The bioanalytical method validation followed the requirements of ANVISA, including evaluation of selectivity, concomitant medication interference, matrix effect, carry-over, calibration curve, precision, accuracy, reinjection reproducibility and stabilities of ketorolac under different conditions [10].

Pharmacokinetic and statistical analysis

The pharmacokinetic and statistical analysis was performed through the software R©. In this study, it was obtained the pharmacokinetic parameters $AUC_{0\text{-}t}$ (area under the curve from zero to the last quantifiable concentration), $AUC_{0\text{-}inf}$ (area under the curve from zero to infinity), C_{max} (maximum plasma drug concentration), tmax (time to reach the maximum plasma drug concentration C_{max}), $t_{1/2}$ (half-life) and kel (elimination constant). It was performed an analysis of variance (ANOVA) for the evaluation of sequence, treatment, and period effects for the pharmacokinetic parameters C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$. The pharmacokinetic parameters were determined through a non-compartmental model. According to the requirements of ANVISA, the bioequivalence is achieved when the 90% confidence intervals for the ratio of test and reference products for the log-transformed data of $AUC_{0\text{-}t}$ and C_{max} are within the acceptance range of 80% to 125% [5].

Safety

The safety of the participants was assessed throughout the entire study. In the pre- and post-study periods, laboratory exams (electrocardiogram, hematological, biochemical, serological and urine tests), assessment of clinical history and clinical examination were performed. Vital signs (temperature, blood pressure and heart rate) were measured during the admission of the research participant, before drug administration in both periods, and periodically at pre-determined intervals. Participants were instructed about potential adverse events, as well as the need to immediately report them to the nursing and medical staff. At pre-determined times participants were questioned about their well-being. Adverse events were graded as mild, moderate, or intense, and their causality to the drug was determined by the medical staff as defined, unlikely, possible, probable, conditional/not classified or not accessible/not classifiable.

RESULTS AND DISCUSSION

Bioanalytical phase

The bioanalytical method was validated and covered all required tests, including evaluation of the selectivity, concomitant medication interference, matrix effect, carry-over, calibration curve, precision, accuracy, reinjection reproducibility and stabilities. Ketorolac (parent drug) and IS were extracted from human plasma by protein precipitation. The selectivity of the method was adequate since substances in the blank plasma samples did not interfere at the retention times of ketorolac and IS. Regarding precision and accuracy, the method was adequate, considering the samples prepared in the same assay (intra-run) and in distinct assays (inter-run). The stability assays showed that samples were stable (variation less than 15% in relation to the nominal value) up to 23 hours at room temperature (15°C to 25°C) and can remain for a period of up to 144 hours between (room temperature) after being extracted. For stability in freeze-thaw cycles, samples proved to be stable after 5 cycles of freezing in a regular freezer (-20°C) and in ultra-freezer (-70°C) and thawing at room temperature. In addition, samples were proved to be stable and were able to remain frozen for a period of up to 44 days in a regular freezer or ultra-freezer. These tests are important to guarantee that the storage of the samples is adequate until the moment of analysis, ensuring the reliability of the data obtained. The washout period proved to be adequate since Ketorolac was not detected in any participant's plasma samples in the pre-dose sampling time of the second period, indicating the absence of carryover effects. All validation parameters met the acceptance criteria required by ANVISA [10].

Pharmacokinetic and statistical analysis

In the present study, 32 healthy men and women were included, however, the number of participants who completed the study was 30, of which 14 were female. According to the curves of Ketorolac mean plasma concentration versus time presented in Figure 1, it is possible to observe that the pharmacokinetic profiles of both test and reference products are very close. The sampling time proved to be adequate since the absorption and elimination phases were clearly evidenced.

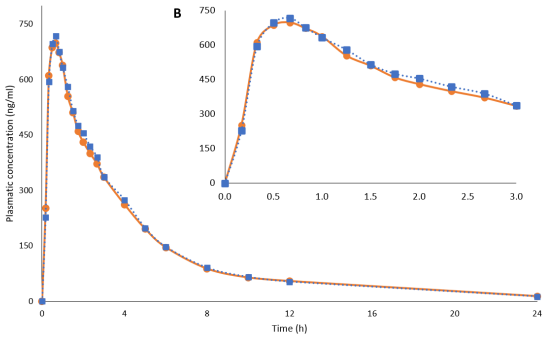

Figure 1: Mean ketorolac plasma concentrations vs. time curves after administration of test and reference formulations in healthy subjects under fasting conditions. (A) concentration-time curve from zero to 24 h; (B) concentration-time curve focused on the range from zero to 3 h (N=30, healthy male and non-pregnant female subjects). **Note:** (—●—) test; (···■···) Reference

The pharmacokinetic parameters obtained for both test and reference sublingual formulations are presented in Table 2. It is possible to observe that the values obtained in this study are consistent with the data available in literature for ketorolac tromethamine 10 mg oral formulations, as described by Gordon and collaborators during the evaluation of the relative bioavailability of ketorolac tromethamine 10 mg tablets, capsules, and oral solutions, concluding that these formulations were not significantly different with respect to the main pharmacokinetic parameters [11]. Flores-Murrieta and collaborators performed a relative bioavailability study with twelve healthy Mexican volunteers comparing two immediate release tablets of ketorolac tromethamine 10 mg [12]. The C_{max} obtained for the formulation A was 1026.4 ng/m L ± 86.1 ng/mL and for formulation B 934.0 ng/mL ± 66.7 ng/mL, the tmax 0.48 h ± 0.07 h and 0.57 h ± 0.10 h and t1/2 6.62 h ± 0.48 h and 7.16 h ± 0.57 h, respectively. Jung and collaborators presented a bioequivalence study in twenty-four healthy volunteers following oral administration of 10 mg of ketorolac tromethamine immediate release tablet [13]. It was found a C_{max} of 1,174.28 ng/mL ± 273.46 ng/mL, a t_{max} of 0.5 h ± 0.1h and a t1/2 of 6.36 h ± 1.85h for the reference product. For the test product it was found a C_{max} of 1,187.06 ng/mL ± 228.37 ng/mL, a tmax of 0.5 h ± 0.1 h and a t1/2 of 6.17 h ± 2.22 h.

Table 2: Pharmacokinetic parameters of ketorolac for the test and reference formulations.

Parameter	Test (mean ± standard error) N=30	Reference (mean ± standard error) N=30
C_{max} (ng/mL)	840.974 ± 38.271	816.373 ± 52.345
AUC_{0-t} (ng/mL· h)	3,113.594 ± 143.722	3,034.555 ± 174.637
AUC_{0-inf} (ng/mL· h)	3,284,772 ± 147,499	3,223.832 ± 184.749
t_{max} (h)	0.739 ± 0.096	0.755 ± 0.091
$t_{1/2}$ (h)	6.201 ± 0.348	6.009 ± 0.361
kel (1/h)	0.128 ± 0.011	0.133 ± 0.010

Galán-Herrera and collaborators, in turn, performed a relative bioavailability study with two 30 mg sublingual tablet formulations in 26 healthy Mexican adult subjects [14]. The mean values obtained for C_{max} of the test formulation was 3610 ng/mL and for the reference formulation 3440 ng/mL, for tmax it was found 0.66 h and 0.94 h and for t1/2 4.27 h and 3.71 h, respectively.

Geometric mean ratios for the pharmacokinetic parameters C_{max}, AUC_{0-t} and AUC_{0-inf} of test and reference products are presented in Table 3, along with the respective 90% confidence intervals for the bioequivalence analysis. The dispersion of test/reference ratio for C_{max} and AUC_{0-t}, are presented in Figures 2 and 3, respectively. It is possible to observe the homogeneity of the data obtained in this study, demonstrating the low intra-subject variability of ketorolac, which is confirmed by the values of CV within-subject of 11.7% for C_{max} and 9.76% for AUC_{0-t}.

Table 3: Statistical comparison for the pharmacokinetic parameters C_{max}, AUC_{0-t} and AUC_{0-inf}.

Parameter*	Geometric mean ratio%	90% CI	Power%	CVws%
C_{max}	101.19	96.12-106.53	100	11.74
AUC_{0-t}	99.43	95.27-103.78	100	9.76
AUC_{0-inf}	98.93	94.86-103.16	100	9.57

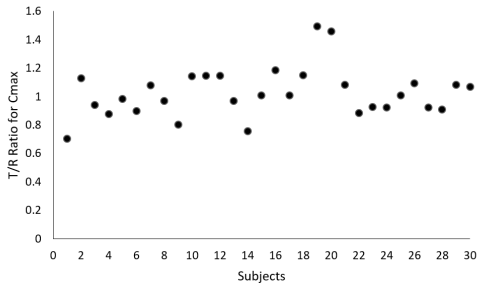

Figure 2: Dispersion of results for test/reference ratio for C_{max} between subjects (N=30).

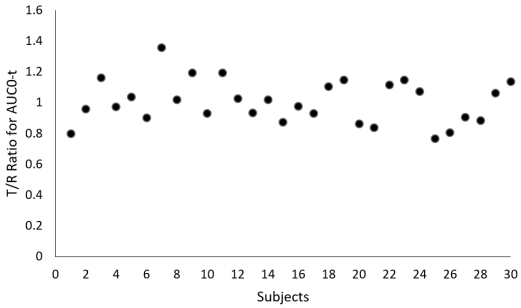

Figure 3: Dispersion of results for test/reference ratio for AUC_{0-t} between subjects (N=30).

The assessments of bioequivalence between test and reference products were estimated by the Analysis of Variance (ANOVA) for a two-way crossover design. During the statistical analysis, it was not detected any significant effect of sequence, treatment, or period. The 90% confidence interval for the ratio between the means of the data transformed into natural logarithm (Test/Reference) of C_{max}, AUC_{0-t} and AUC_{0-inf} were 96.12-106.53, 95.27-103.78 and 94.86-103.16, respectively. The results obtained in this study are within the acceptance range of 80% to 125%, according to ANVISA requirements, therefore it can be concluded that the two formulations ketorolac tromethamine 10 mg sublingual tablet (Zodiac Produtos Farmacêuticos S.A) and the reference (Toragesic®, EMS Sigma Pharma Ltda.) are bioequivalent in terms of rate and extent of absorption.

Safety

From the 32 participants enrolled in the study, six of them reported a total of seven adverse events during hospitalization period. The most common adverse events were headache, equivalent to 42.86% of the total events, and malaise with 28.57%, reported for both test and reference formulations. Table 4 describes the adverse events reported during hospitalization period and the classification according to the causality and intensity. According to the prescribing information of the reference formulation, these adverse events are characterized by a common adverse reaction. The remaining adverse events did not present a significant impact on the quality of life of subjects. No serious adverse events were reported in this study.

Table 4: Adverse Events reported during hospitalization.

Adverse Event	N (%)	Causality	Intensity
Headache	3 (42.86%)	Probable	Mild
Malaise	2 (28.57%)	Possible	Mild
Hypotension	1 (14.29%)	Probable	Mild
Hypertension	1 (14.29%)	Possible	Mild

CONCLUSION

Two drugs are considered bioequivalent when the 90% confidence intervals for the ratio of geometric means (test/reference) of logarithmically transformed C_{max}, AUC_{0-t} and AUC_{0-inf} are within the acceptance range of 80% to 125%. Since the results of this study are in accordance with the required specifications, it can be concluded that the two formulations Toragesic®, sublingual tablet 10 mg, manufactured by EMS S/A., and ketorolac tromethamine, sublingual tablet-10 mg from Zodiac Produtos Farmacêuticos S.A., are bioequivalent, showing that there is no statistical difference in behavior between these formulations. Both formulations were well tolerated and showed no relevant differences in safety profiles. Thus, these products may be considered interchangeable in medical practice since they present the same efficacy and safety profile.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article. The authors were fully responsible for all content and editorial decisions.

ACKNOWLEDGMENTS

The authors appreciate CAEP- Centro Avançado de Estudos e Pesquisas (Brazil) team for technical support in Clinical, Analytical and Statistical phases of the bioequivalence study.

FUNDING DETAILS

The bioequivalence study was financially supported by Zodiac Produtos Farmacêuticos S.A.

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