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Bioequivalence of 150 mg Extended-Release Ketoprofen from Laboratories LETI S.A.V. Test, vs ProfenidBI® of Laboratories Sanofi-Aventis Pharmaceuticals LTDA, Prolonged Release, Reference, in Healthy Volunteers*

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Abstract

Objective: To evaluate the bioequivalence between two formulations of ketoprofen after administration of a 150 mg extended release tablet (L.P. ProfenidBI®), 150 mg modified release tablets. **Methods**: A single-dose cross-over, randomized study was performed under fasting conditions with two treatments, two periods, two sequences (2 × 2) with a 7-day washout period between each dose in 28 healthy volunteers. Subjects were randomly assigned to each of the administration sequences. The pharmacokinetic parameters evaluated were: C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. For the bioequivalence analysis, the AUC_{0-t} was calculated from the time of administration to the 12th hour, posology requested for the medication test, by the trapezoidal method; Software: Excel. The means and Confidence Intervals were compared between 80% - 125% for the quotient of C_{max}, T_{max}, AUC_{0-t} and $AUC_{0-\infty}$. **Results**: C_{max} 8.3529 ± 1.9176 µg/mL vs. 7.7175 ± 2.1751 µg/mL, T_{max} 0.75 h vs. 1.25 h, AUC_{0-12} 25.9560 ± 4.9846 µg/mL/hr vs. 24.9015 ± 5.1507 µg/mL/ hr and $AUC_{0-\infty}$ 27.0147 ± 5.1099 µg/mL/hr vs. 25.6400 ± 5.1144 µg/mL/h, respectively. 95% IC: C_{max} 106.26% - 107.85%, AUC_{0-12} 101.11% - 101.78% and $AUC_{0-\infty}$ 100.53% - 102.94%. **Conclusion**: The test formulation Ketoprofen 150 mg LP, manufactured by LETI S.A.V. Laboratories, is bioequivalent with respect to the reference product ProfenidBI® 150 mg controlled release tablets, manufactured by Sanofi-Aventis Pharmaceuticals LTDA Laboratories, as the Values obtained from AUC and C_{max} were maintained in the range of 80% - 125%.

*The research product was prepared by Biocontrolled Laboratory for Leti Laboratories, S.A.V., Venezuela.

Subject Areas

Clinical Trials, Pharmacology, Rheumatology

Keywords

Ketoprofen, Extended Release, Tablets, Bioequivalence

1. Introduction

Ketoprofen is a non-steroidal anti-inflammatory drug (NSAID), not COX-2-selective, derived from arylcarboxylic acid, belonging to the propionic group. It has anti-inflammatory, analgesic, antipyretic activity and also acts as a platelet antiaggregant [1].

Ketoprofen acts on pain peripherally by a potent antiinflammatory effect associated with inhibition of cyclooxygenase (COX), and therefore the prostaglandins synthesis (PGs) from arachidonic acid. At the central level acts on the pain by an effect directly at the spinal level or at the suprasegmental level. This mechanism explains the analgesic, antipyretic and anti-inflammatory properties of ketoprofen. Other actions contribute to reinforce these effects, such as antagonism of bradykinins and of platelet aggregation, as well as stabilization of lysosomal membranes [1] [2].

Ketoprofen (KP) is rapidly and completely absorbed from the gastrointestinal tract. Pharmacokinetic studies in human subjects showed that orally administered KP is rapidly absorbed, metabolized and excreted. It is almost completely absorbed from the GIT. Total bioavailability is dose proportional in the range of 75 - 200 mg [3]. The plasma half-life is approximately 2 - 4 hours in healthy young volunteers. Absorption is more than 90% complete; peak plasma levels (Tmax) are reached within 1 - 2 hours. At a single dose of 150 mg, KP plasma concentration reaches values up to 15 - 25 μg/ml, which are much higher than the therapeutic levels(therapeutic range 0.4 - 6 μg/ml) [4]. KP concentrations in the synovial fluid peak approximately 2 hours after the peak plasma levels and decrease more slowly, so that synovial fluid levels exceed plasma levels from 4 hours after PO administration. When taken with meal, KP's bioavailability is not altered, but food intake reduces Cmax by approximately one half, and increases the mean time to peak concentration. The fluctuation of plasma peaks may also be influenced by circadian changes in the absorption process, 99% of administered ketoprofen binds to plasma proteins. It diffuses in the synovial fluid and in the intraarticular, capsular, synovial and tendon tissues; in the synovial fluid persists at concentrations higher than the serum concentrations, after the fourth hour of oral intake. It crosses blood-brain and placental barriers [3] [4] [5] [6] [7].

The plasma elimination half-life is short, with an average of 3.6 hours [5] [6] [7]. The volume of distribution is approximately 7 L. The biotransformation of

ketoprofen is performed according to two processes: Conjugation with glucuronic acid (predominant) and hydroxylation (secondary). Less than 1% of the administered dose of ketoprofen is found unchanged in the urine, whereas glucuroconjugation accounted for about 65% - 75% of the administered dose [5] [6] [7] [8].

Excretion, mainly urinary, is rapid; a 50% elimination of the administered dose is observed within 6 hours following administration of the drug, irrespective of the route of administration. Within 5 days after oral administration, approximately 75% - 90% of the dose is excreted, mainly in the urine. Fecal excretion is very low (1% to 8%) [5] [8].

Ketoprofen is generally well tolerated, however in isolated cases epigastralgia, nausea and vomiting may occur [1].

Ketoprofen is a widely known product with good indices of effectiveness in the treatment of conditions associated with inflammatory and painful processes such as rheumatic diseases, musculoskeletal conditions, postoperative surgery, dysmenorrhea, renal colic and traumatic affections [1] [7].

Objective of the Study

The objective of the present study was to evaluate the bioequivalence between the two formulations, the Ketoprofen test formulation of Laboratories Leti, S.A.V., after the administration of a 150 mg prolonged release tablet and PROFENID BI®, from Sanofi-Aventis Pharmaceuticals LTDA, 150 mg controlled-release tablets, reference formulation, in healthy volunteers under fasted conditions.

2. Methods

A single-dose cross-over study was performed under fasting conditions with two treatments, two periods, two sequences (2 × 2) with a 7-day washout period between each dose in 28 healthy adult volunteers of both genders. In this study subjects were randomly assigned to each of the administration sequences.

Inclusion criteria:

Subjects with ages between 18 and 55 years, of both sexes, with good health were included, based on the results of a complete clinical history, valid for 6 months prior to the start of the study.

Subjects with normal laboratory values: hepatic transaminases, hepatitis B and C tests, HIV and VDRL. Normal 12-lead EKG values, no greater than 6 months prior to the start of the study. Normal chest radiography, with negative result in urine drug tests. Female subjects with negative urine pregnancy test. Subjects with a Body Mass Index (BMI) with a range of 19 to 26.5 Kg/m^2.

Subjects with diastolic pressure between 50 and 89 mmHg and systolic pressure between 90 and 139 mmHg, pulse frequency between 55 and 100 beats per minute, respiratory rate between 17 to 24 breaths per minute and temperature of 35.0˚C to 37.5˚C. Non-smoking subjects or smokers who had not smoked at

least 10 hours before the start of the study. All the patients signed the signed informed consent, after informing about the possible risks and benefits of their participation, as well as their willingness and availability to participate during the entire study, being able to leave the study at the time they decided.

Exclusion criteria:

Subjects with a history of hypersensitivity to the study medication or to any other medication belonging to the study group.

Subjects with a history of cardiovascular, renal, hepatic, metabolic, gastrointestinal, neurological, endocrine, hematopoietic, psychiatric or other organic abnormalities. Subjects that require some other medication that interferes with the quantification and/or kinetics of the medication under study. Subjects exposed to agents known as inducers or inhibitors of liver enzyme systems. Subjects who had taken potentially toxic medications within 30 days prior to the start of the study. Subjects who have taken any medication within 14 days or 7 half-lives prior to the start of the study. Subjects who were hospitalized for any reason or who were seriously ill within the 60 days prior to the study. Subjects who have received a research medication within 60 days prior to the start of the study. Subjects who have donated or lost 450 mL or more of blood within 45 days prior to the start of the study. Subjects with recent history of drug abuse, including alcohol. Subjects who have consumed products containing xanthines: caffeine, cola drinks, theobromine, theophylline in the 10 hours prior to the study. Subjects with grapefruit juice consumption in the 10 hours prior to the study. Subjects with inability to understand or willingness to sign informed consent.

Volunteers were given a single oral dose of Ketoprofen 150 mg Prolonged Release from Leti Laboratories S.A.V., or one tablet or the reference product ProfenidBI® 150 mg controlled release tablets manufactured by Sanofi-Aventis Pharmaceuticals LTDA.

The following parameters were calculated from the plasma concentrations: C_{max}, Area under the curve from zero to 12 hours (AUC_{0-12}), and Area under the curve from zero to infinity (AUC_{0-inf}), as well as time in which the maximum concentration (T_{max}) occurs.

The area under the plasma concentration-time curve was calculated from the administration to the t_{12}, posology requested for the medication test (AUC_{0-t}), by the trapezoidal method. Software: Excel.

For the quantification of Ketoprofen in human plasma an analytical method was used by UV/VIS liquid chromatography, using a Zorbax Eclipse XDB-C18, 4.6 × 150 mm, 5 μm columns. The analytes were extracted from plasma samples by means of a liquid-liquid extraction technique. The analytical method was validated in a concentration range of 0.4 to 24.0 μg/mL.

We compared the means and the confidence intervals accepted values between 80.00% to 125.00%, for the quotient of the averages of the pharmacokinetic parameters C_{max} and ABC_{0-t} and $ABC_{0-\infty}$.

3. Results

The study ended with 27 volunteers as patient # 23 did not present during the second study period.

The T_{max} of the Test product was reached at 0.75 h and with the reference product at 1.25 h. Table 1 demonstrates no statistically significant differences were evident between the two formulations in any of the parameters evaluated at 12 h (therapeutic interval).

Table 2 demonstrates that the relationships between the means of both products and their 95% confidence intervals remain within accepted limits for similar products. (80% - 120%)

There were no reports of significant Adverse Events related to medication. During both periods 9 volunteers presented mild adverse effects that did not merit stopping the project or treatment (pain at the puncture site, mild gastrointestinal disorders, and short-term headache).

4. Discussion

One of the greatest expectations of researchers and clinicians when researching a new drug is to find evidence of superiority of the new drug over the standard treatment being used so that the new product allows a breakthrough in drug therapy for the patients [9]. However, it is also increasingly common for studies to focus on demonstrating that the drug being investigated is just as effective as another drug being considered as a reference.

This type of research related to the establishment of therapeutic equivalence has now taken a great impulse and has acquired importance from the clinical and management point of view [10]. Clinically, it is possible to establish if it is necessary to have several therapeutic equivalents in the pharmacotherapeutic guide, thus considering second treatment options; or to have only one of them. And from the management point of view, these studies show whether it is worthwhile to have only one equivalent or to be able to define them as homologous medicines, which allows the inclusion of several drugs whose active principles are defined as therapeutic equivalents and which will be used interchangeably, depending on the costs or availability in the market (Table 3).

Laguna *et al.* mention that in many countries, before marketing the medicines, manufacturers are required to guarantee their quality, safety and efficacy. Medications called multisource or generics, should demonstrate safety and efficacy

Table 1. Values of C_{max}, AUC_{0-12} and $AUC_{0-\infty}$ for the Test and the Reference KP and the p of the difference for each value.

	Ketoprofen AP 150 mg (Test)	Ketoprofen AP 150 mg (Reference)	p (LN transformed)
C_{max}	8.3529 ± 1.9176 µg/mL	7.7175 ± 2.1751 µg/mL	0.11
AUC_{0-12}	25.9560 ± 4.9846 µg/mL/h	24.9015 ± 5.1507 µg/mL	0.10
$AUC_{0-\infty}$	27.0147 ± 5.1099 µg/mL/h	25,6400 ± 5.1414 µg/mL/h	0.046

Table 2. Mean % of the relationships between the Reference and the Test KP (R/T) for the parameters C_{max}, AUC_{0-12} and $AUC_{0-\infty}$ and their 95% confidence intervals.

	Mean %	CI 95 % minimum	CI 95 % maximum
C_{max}	107.06	106.26	107.85
AUC_{0-12}	101.45	101.11	101.78
$AUC_{0-\infty}$	101.74	100.53	102.94

Table 3. Demographics description.

Items	N˚	Average	SD	CV%	Min-Max
Age (years)	28	29.71	8.18	27.52	22 - 54
Weight (Kg)	28	62.35	7.52	12.06	50.3 - 78
High (m)	28	1.63	0.09	5.23	1.5 - 1.8
IMC	28	23.56	2.03	8.61	19.62 - 26.93
Gelder		**N˚**		**%**	
Woman		16		57.14	
Men		12		42.8	

through the studies of therapeutic equivalence in contrast to the original drug, in order to guarantee its interchangeability [11].

According to the results obtained in this study, carried out according to the current National and International regulations, both products showed a similar amount and rate of absorption, which guarantees their interchangeability.

5. Conclusion

Based on the results obtained in the statistical analyzes performed on the data collected for the bioequivalence study, it can be concluded that the test formulation Ketoprofen tablets L.P. (Prolonged Release) of 150 mg, manufactured by LETI Laboratories, S.A.V., is bioequivalent with respect to the reference product ProfenidBI® 150 mg controlled release tablets, manufactured by Sanofi-Aventis Pharmaceuticals LTDA, since the values obtained for AUC and C_{max} were within the range of 80% - 125%.

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