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Bioequivalence of 250 mg lysine clonixinate tablets after a single oral dose in a healthy female Mexican population under fasting conditions

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Abstract. Objective: To evaluate the bioequivalence between two 250 mg-tablets of lysine clonixinate, Dorixina Forte® (Siegfried Rhein, México) as reference product, and Prestodol® (Farmaceúticos Rayere, S.A., México) as test formulation. Methods: 26 healthy adult female Mexican volunteers received a single oral dose of 250-mg lysine clonixinate under fasting conditions. The drug was administered following a randomized, two-period, two-sequence, cross-over design. Twelve serial blood samples were collected up to 8 h after dosing, and clonixin (CLX) was measured by ultra-performance liquid chromatography (UPLC) coupled with tandem mass spectrometry. Decimal logarithm values of C_{max} and area under the curve (AUC) were used to construct a classic confidence interval at 90% (90% CI). Bioequivalence was established if 90% CI of mean ratios (test/reference) fall within the 0.8 – 1.25 range. Results: Volunteers formed a homogeneous population in terms of age (27.2 ± 6.3 years), weight (55.9 ± 6.5 kg), height (1.6 ± 0.04 m), and body mass index (BMI) (22.91 ± 2.03 kg/m^2). Reference formulation exhibited the following pharmacokinetics: C_{max} (32.39 ± 8.32 µg/ml); t_{max} (0.64 ± 0.2 h); AUC_{0-8h} (48.92 ± 16.51 µg.h/ml); $t_{1/2}$ (1.3 ± 0.24 h); CL_{app} (5.64 ± 1.99 l/h), and Vd_{app} (10.22 ± 2.9 l). Concerning bioequivalence, 90% CI were: C_{max} (82.32 – 98.79), AUC_{0-t} (94.59 – 106.29), and AUC_{0-inf} (94.61 – 106.42), with a statistical power of > 0.90 at every tested interval. Conclusions: This single-dose study found that both 250-mg immediate-release tablets of lysine clonixinate met the Mexican regulatory criteria for bioequivalence in these volunteers.

Introduction

Clonixin (CLX) is an anti-inflammatory non-steroidal analgesic drug without narcotic effects (NSAIDs) that belongs to the fenamates family; its salt, lysine clonixinate (Chemical Abstracts Society (CAS) registry no. 55837-30-4) is an amorphous white powder soluble in organic solvents. It is used to relieve middle to severe episodes of dental pain [11], dysmenorrhea [3], post-operative pains [2], and migraine [10].

The mechanism of action of CLX relies on the blunting of 5-lipoxygenase with diminishing in the synthesis of the pro-inflammatory 5-HETE [6], and it has also been reported that CLX exerts an inhibitory effect on the expression of nitric oxide synthase (NOS) induced, which participate during inflammation [5]. This selectivity of CLX in 5-lipoxygenase over cyclooxygenases may explain the lack of effect on platelet number and function during its therapeutic use associated with common NSAIDs [9].

Pharmacokinetic data of CLX are succinct. The first attempt to determine the metabolic pathways of CLX in humans employed the tritium-labeled drug [8]. It showed three main metabolites both in plasma and urine: 5-OH-clonixin; 4′-OH-clonixin and 2′-ethoxyclonixin. Erratic values of plasma concentrations have been previously reported following an intravenous (IV) dose of lysine clonixinate solution in 10 children post-surgery [7]. These authors reported a distribution volume of ca. 1.3 l/kg, and a dose-dependent elimination half-life between 30 and 50 min. Serum concentrations were quite similar between IV and oral administration after 45 min post-dose; and areas under the curve were also similar, demonstrating high degree of bioavailability by oral route.