A Single-Dose, Three-Period, Six-Sequence Crossover Study Comparing the Bioavailability of Solution, Suspension, and Enteric-Coated Tablets of Magnesium Valproate in Healthy Mexican Volunteers Under Fasting Conditions

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ABSTRACT

Background: Valproic acid has been associated with a highly variable intersubject absorptive phase; therefore, magnesium salt (magnesium valproate [MgV]) was developed to diminish variation during enteric absorption.

Objectives: The aims of this study were to assess the pharmacokinetics of single oral doses of MgV 500-mg solution, suspension, and enteric-coated tablets in a healthy Mexican population, and to compare formulation-related differences.

Methods: This was a randomized, single-dose, 3-period, 6-sequence crossover study in healthy Mexican volunteers aged 18 to 45 years. In each period, subjects received single oral doses of 500-mg MgV solution, suspension, and enteric-coated tablet formulations, with a 7-day washout period between each dosing period. Serial blood samples were collected at 0 hour (prior to MgV administration) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 9, 12, 24, 48, and 72 hours after dosing. Valproate was measured by a new method of ultraperformance liquid chromatography coupled with mass spectrometry. Pharmacokinetic parameters of interest were C_{max}, T_{max}, AUC_{0-72}, $AUC_{0-\infty}$, $t_{1/2}$, V_d/F, CL/F, and mean residence time (MRT). Formulation-related differences were assayed in accordance with the Mexican regulatory bioequivalence criteria. Log-transformed values of C_{max} and AUC were used to construct a classic 90% CI. Bioequivalence was established if the 90% CI for the mean test:reference ratio of log-transformed C_{max} and AUC were within the range of 0.80 to 1.25. Tolerability was assessed based on subject interview, vital sign monitoring, and clinical assessment.

Results: A total of 24 healthy volunteers (12 women and 12 men; mean [SD] age, 28.79 [6.5] years; height, 164 [9.8] cm; weight, 65.42 [8.95] kg; and body mass index, 24.28 [2.11] kg/m^2) were included. For the MgV solution, the mean (SD) pharmacokinetic parameters of C_{max}, T_{max}, AUC_{0-72}, $AUC_{0-\infty}$, $t_{1/2}$, V_d/F, CL/F, and MRT were 59.75 (8.24) μg/mL, 0.542 (0.14) hours, 1099.67 (241.70) μg · h/mL, 1156.30 (264.01) μg · h/mL, 16.19 (2.36) hours, 9633.68 (1892.70) mL, 418.35 (92.01) mL/h, and 18.36 (1.44) hours, respectively. For the MgV suspension, the mean (SD) pharmacokinetic parameters of C_{max}, T_{max}, AUC_{0-72}, $AUC_{0-\infty}$, $t_{1/2}$, V_d/F, CL/F, and MRT were 55.04 (7.72) μg/mL, 0.773 (0.51) hour, 1057.76 (223.37) μg · h/mL, 1111.09 (245.07) μg · h/mL, 16.32 (2.20) hours, 1069.05 (1775.64) mL, 435.43 (99.59) mL/h, and 18.41 (1.43) hours, respectively. For the MgV enteric-coated tablets, the mean (SD) pharmacokinetic parameters of C_{max}, T_{max}, AUC_{0-72}, $AUC_{0-\infty}$, $t_{1/2}$, V_d/F, CL/F, and MRT were 54.88 (6.73) μg/mL, 2.79 (0.89) hours, 1100.79 (216.70) μg · h/mL, 1163.61 (238.36) μg · h/mL, 16.48 (2.10) hours, 9675.15 (1659.36) mL, 412.36 (85.24) mL/h, and 19.95 (1.53) hours, respectively. The 90% CIs for the tablets:solution ratio were 82.15 to 95.44, 94.60 to 105.39, and 95.43 to 105.95 for C_{max}, AUC_{0-72}, and $AUC_{0-\infty}$, respectively. The 90% CIs for the suspension:solution ratio were 84.79 to 98.50, 88.89 to 99.02, and 89.15 to 98.97, respectively. The 90% CIs for the tablets:suspension ratio were 89.90 to 104.43, 100.84 to 112.34, and 101.60 to 112.80, respectively.

Conclusion: This single-dose study found that the 3 formulations (solution, suspension, and enteric-

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RESEARCH ARTICLE

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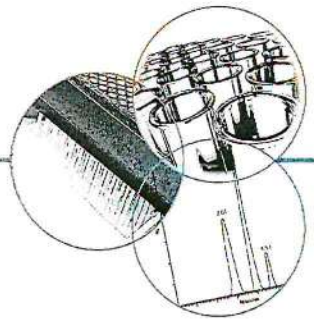

Pharmacokinetics of diphenylboroxazolidones of L-α-amino acids with activity on the CNS: quantification in rat DBS by UPLC–MS/MS

Background: A growing number of boron-containing compounds exhibit many important biological activities; of particular interest are the α-amino acid borinic derivatives with activity in the CNS. A validated, sensitive and specific UPLC–MS/MS technique for quantification of the diphenylboroxazolidones of glycine (DBPX-gly), L-aspartate (DPBX-L-asp) and L-glutamate (DPBX-L-glu) in dried blood spots (DBSs) is presented. **Results:** The most intense signal corresponds to compounds with ^{11}B. The extraction procedure was liquid elution of 3.2-mm punched DBSs with acetonitrile:aqueous formic acid 0.1% (80:20 *v/v*). Assays proved to be linear, falling accurately and precisely within the range of 0.3–50 µg/ml for DPBX-L-asp and DPBX-L-glu and 0.1–5 µg/ml for DBPX-gly. Chromatograms exhibit clean 2.0-min running time peaks and S/N ratios for the LLOQ were approximately 15:1. The technique was used to evaluate the pharmacokinetics of the molecules and to correlate these with timecourse toxic effects. **Conclusion:** DBSs represent an advantage for the collection of small volumes of samples, and also in terms of processing and storage. UPLC–MS/MS allow us not only to identify the isotopic pattern of boron in DBPX, but also to quantify them with accuracy and specificity. Pharmacokinetics of these molecules exhibit a high apparent volume of distribution; it suggests a preference of DPBX-amino acids for fatty tissues such as the CNS.

The rapid development of boron-mediated reactions in synthetic chemistry has had a huge influence on the ability to design and synthesize new types of drugs, as well as biochemical tools for therapeutics, clinical diagnosis and medicinal chemistry. Thus, a growing number of boron-containing compounds may exhibit many important biological activities and are suitable for preclinical investigation [1]. In fact, some synthetic boron-containing molecules have demonstrated biological activity as antibiotics [2], apoptotic inductors [3] and for ^{10}B-neutron capture during antineoplasic treatments [4]. A review on organo-boron compounds with biological activity has been written by Petasis [5].

Of particular interest among organoboron compounds are the α-aminoborinic acid derivatives [6]. It is hypothesized that these entities mimic amino acids and allow their entrance to the CNS by acting as enzyme inhibitors or interacting with neuronal receptors. **Diphenylboroxazolidones** (2,2-diphenyl-1,2,3-oxaborolidin-5-ones) of L-amino acids (DPBX-L-aa) are neutral complexes obtained during the reaction of α-amino acids with diphenylborinic acid. These molecules possess a coordinate boron–nitrogen bond and exhibit effects on the CNS, such as increase in globus–pallidus trigger frequency, tonic-clonic seizures and motor activity increase [7].

Synthesis of DPBX of glycine (DPBX-gly), L-aspartate (DPBX-L-asp) and L-glutamate (DPBX-L-glu) was originally a strategy to avoid the zwitterionic character of these amino acids (FIGURE 1), and to increase the bioavailability of these neurotransmitters into the CNS; allowing evaluation of their inhibitory (gly) or excitatory (L-asp and L-glu) activity, as well as their toxic profile [6].

However, despite the diverse pharmacological activity shown by these molecules, there is no pharmacokinetic information, particularly concerning mammals, due to the lack of sensitive methodology available. In this regard, a HPLC–UV technique has previously been reported for separation and quantification of α-amino acids by boroxazolidone formation [8].

Thus, the aim of the present work was to develop a micro-technique for quantification of DPBX-gly, DPBX-L-asp and DPBX-L-glu in rat dried blood spots (DBSs) by UPLC coupled with MS/MS for its use in the pharmacokinetic description of these molecules.

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Ciprofloxacin Bioavailability is Enhanced by Oral Co-Administration with Phenazopyridine

A Pharmacokinetic Study in a Mexican Population

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Abstract

Background and objective: In Mexico, urinary tract infections (UTIs) constitute the second most frequent type of infections treated at primary-care clinics. Ciprofloxacin has played a major role in the treatment of UTIs because it has a broad spectrum of antibacterial activity. In addition to antimicrobial agents, phenazopyridine has been used to alleviate symptoms that occur during episodes of UTI. Thus, the present study was designed to compare the pharmacokinetic behaviour of ciprofloxacin administered alone versus ciprofloxacin combined with phenazopyridine.

Patients and methods: Twenty-four healthy male Mexican volunteers participated in this project. The study was carried out with a single oral dose of ciprofloxacin 500mg. The double-blind, crossover, randomised, balanced trial design comprised two treatments, two periods and two sequences. After administration of the study medication, serial blood samples were collected for a period of 12 hours. The harvested plasma was analysed for ciprofloxacin by high-performance liquid chromatography. The area under the concentration-time curve to last measurable concentration (AUC_t), area under the concentration-time curve extrapolated to infinity (AUC_∞), peak plasma concentration (C_{max}), time to reach C_{max} (t_{max}), mean residence time (MRT), elimination constant (k_e) and elimination half-life ($t_{1/2}$) were determined from plasma concentrations of both treatments and considered as primary variables for statistical analysis.

Results: While there were no differences between the two treatments in terms of C_{max} and k_e, AUC_t and AUC_∞ were 35% and 29% higher, respectively, in the combined treatment arm. Moreover, a significant delay in t_{max} (from 1 to 1.5 hours) and a statistical increase of 29% in MRT were also observed with phenazopyridine co-administration.

Conclusion: Oral co-administration of phenazopyridine increases ciprofloxacin bioavailability with regard to the amount absorbed (AUC) and permanence in the body (MRT), which could be useful during treatment.

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Bioequivalence Evaluation of Two Brands of Ketoconazole Tablets (Onofin-K® and Nizoral®) in a Healthy Female Mexican Population

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ABSTRACT: A randomized, crossover study was conducted in 24 healthy female volunteers to compare the bioavailability of two brands of ketoconazole (200 mg) tablets; Onofin-K® (Farmacéuticos Rayere S.A., México) as the test and NIZORAL® (Janssen-Cilag, México) as the reference products. The study was performed at the Clinical Pharmacology Research Center of the Hospital General de México in Mexico City. Two tablets (400 mg) were administered as a single dose with 250 ml of water after a 12 h overnight fast on two treatment days separated by a 1 week washout period. After dosing, serial blood samples were collected for a period of 12 h. Plasma harvested was analysed for ketoconazole by a modified and validated HPLC method with UV detection in the range 400–14000 ng/ml, using 200 µl of plasma in a full-run time of 2.5 min. The pharmacokinetic parameters AUC_{0-t}, $AUC_{0-\alpha}$, C_{max}, T_{max} and $t_{1/2}$ were determined from plasma concentrations of both formulations and the results discussed. AUC_{0-t}, $AUC_{0-\alpha}$ and C_{max} were tested for bioequivalence after log transformation of data, and no significant differences were found either in 90% classic confidence interval or in the Anderson and Hauck test ($p < 0.05$). Based on statistical analysis, it is concluded that Onofin-K® is bioequivalent to Nizoral®. Copyright © 2004 John Wiley & Sons, Ltd.

Key words: ketoconazole; bioequivalence; HPLC; pharmacokinetics

Introduction

Ketoconazole (*cis*-1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3,-dioxolan-4-yl]methoxy]phenyl]piperazine is an imidazole derivative with antimycotic properties. Its main effect when it reaches serum levels during systemic administration is the inhibition of sterole 14-α-demethylase in fungi. This enzyme is coupled with the CYP450 complex and such an inhibition allows the accumulation of ergosterol in the cytoplasmic membrane of fungi, modifying the phospholipid arrangement and disrupting the function of ATPases and other membrane electronic transporter systems, resulting in the blocking of fungi proliferation [1].

Ketoconazole has been used clinically in the treatment of blastomycosis, histoplasmosis, coccidiomycosis and some types of candidiasis with a high degree of success [2]. Recently, there has been renewed interest in the clinical use of ketoconazole in certain opportunistic infections in immunocompromised patients [3,4] due to its effect on preventing metastases of certain kinds of cancer [5,6], and for its effect on enhancing the bioavailability of other drugs [7,8].

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