Pharmacokinetics and Bioequivalence Evaluation of Two Voriconazole tablets: an Open-Label, Single-Dose, Randomized, Two-Way Crossover Study in Healthy Chinese Male Volunteers

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Abstract

The aim of this study was to assess and compare the pharmacokinetic properties, bioavailability, and bioequivalence of a newly developed tablet of voriconazole with those of an established branded formulation in healthy Chinese adult male volunteers.

An open-label, single-dose, randomized, 2-way crossover study was conducted in fasted healthy Chinese male volunteers. Eligible participants were randomly assigned in a 1:1 ratio to receive one tablet (200 mg) of the test or reference formulation, followed by a 1-week washout period and administration of the alternate formulations. Plasma samples were collected over 36 hours and analyzed by HPLC. The Voriconazole plasma concentration–time curves were used to obtain pharmacokinetic parameters including AUC0–t, AUC0–∞, Cmax, and Tmax. The criteria for bioequivalence were 90% CIs of 80% to 125% for AUC and 70% to 143% for Cmax, and no significant differences for Tmax with a non-parametric test, according to guidelines of the SFDA of China. Tolerability was based on the recording of adverse events (AEs).

A total of 19 volunteers were included in the study. The mean (SD) Cmax, Tmax, AUC0–t and AUC0–∞ values after administration of the test and reference formulation, respectively, were as follows: 925.73(356.11) versus 1040.25(3266.86) ng/mL, 1.57(0.98) vs 1.57(0.96) hours, 5304.97(3072.25) vs 5141.63(2976.92) ng/mL/h, and 5783.21(3266.86) vs 5520.69(3148.42) ng/mL/h. The relative bioavailability of the test formulation was 103.2% by mean AUC0–t and 104.8% by mean AUC0–∞. The 90% CIs for the ratios of Cmax, AUC0–t, and AUC0–∞ were 77.3% to 122.7%, 85.7% to 114.3%, and 83.6% to 116.4%, respectively, meeting the predetermined criteria for bioequivalence. No drug-related AEs were observed.

In this study the test and reference formulations had similar PK parameters and similar plasma concentration-time profiles and the test formulations met the regulatory criteria for bioequivalence to the established reference formulations based on the rate and extent of absorption. Both formulations were well tolerated.

Keywords: Bioequivalence; Pharmacokinetics; Voriconazole; HPLC

Introduction

Voriconazole is a broad-spectrum triazole antifungal agent with activity against a wide range of yeasts and filamentous fungi [1,2] and is approved for treatment of adult and paediatric patients with invasive aspergillosis, those with fluconazole-resistant invasive Candida infections, non-neutropenic patients with candidaemia and those with emerging infections caused by Scedosporium species and Fusarium species.

Voriconazole exhibits nonlinear pharmacokinetics due to saturation of its metabolism. Although the pharmacokinetic (PK) characteristics and clinical pharmacology of voriconazole have been studied previously [3-5] insufficient data are available in a Chinese population. The present study was designed to assess and compare the PK parameters, bioavailability, and bioequivalence of the new voriconazole tablet versus the conventional tablet administered as single 200 mg doses to healthy Chinese adult male volunteers.

Subjects and Methods

Products and participants

Voriconazole tablets (Vfend™ 200 mg; lot no. B10002040), purchased from Pfizer Pharmaceuticals Co. Ltd., and voriconazole tablets (200 mg; lot no. 100302), manufactured and provided by Chengdu Huashen Pharmaceuticals Co. Ltd. (Chengdu, People’s Republic of China), were used as the reference and test products, respectively, in assessing bioequivalence.

healthy Chinese adult male volunteers participated in this study, which was conducted at Chongqing Southwest Hospital of the Third Military Medical University. Only male volunteers were enrolled because of the additional variables involved when studying women (eg, menstrual cycles and pregnancy), because guidelines of the State Food and Drug Administration (SFDA) of the People’s Republic of China recommend using male volunteers [6].

Exclusion criteria included the administration of any medication (including over-the-counter remedies) 2 weeks before or during the study period. Physical examination ascertained that all volunteers were free of significant cardiac, hepatic, renal, pulmonary, neurologic,
gastrointestinal, and hematologic diseases. Volunteers were also examined by electrocardiography and laboratory tests such as hematology (complete blood count), urinalysis, biochemistry (total bilirubin, direct bilirubin, aspartate amino transferase, alanine amino transferase, alkaline phosphatase, plasma albumin, sodium, potassium, calcium, fasting blood glucose, blood uric acid, blood urea nitrogen plasma creatinine, triglycerides, and cholesterol), hepatitis B surface antigen, and HIV antibodies.

The present study was conducted in accordance with the ethical standards for studies in humans of the Declaration of Helsinki and its amendments [7] and the Guideline for Good Clinical Principles recommended by the SFDA [6]. The study protocol and informed consent form were approved by the ethics committee of Chongqing Southwest Hospital. All participants were informed by a clinical investigator of the study's aim and risks, and each submitted written informed consent before participating in the study.

Study design

This was an open-label, single-dose, randomized, 2-way crossover bioequivalence study with a 1-week washout period between each administration. Each volunteer received a single dose of either the test or reference product of 200 mg voriconazole (one 200 mg tablet), in random order based on computer-generated tables of random numbers. Each volunteer sample had a unique number, and personnel conducting the analyses were blinded to the group assignment.

After an overnight fast of 10 hours, the volunteers received 200 mg of either product of voriconazole (reference or test), taken with 200 mL of water. Additional water intake was permitted 2 hours after treatment, and food intake was allowed 4 hours after treatment. Alcoholic beverages, intense physical activity and smoking were not allowed during the study. Chinese regulatory authorities do not require testing of food effects in bioequivalence studies (as opposed to PK testing). Smoking was not allowed during the study. Chinese regulatory authorities do not require testing of food effects in bioequivalence studies (as opposed to PK testing). Smoking was not allowed during the study.

Pharmacokinetic properties

The mean plasma concentration–time curves of two voriconazole formulations was assessed by calculating individual AUC0–t, AUC0–∞, Cmax and Tmax values. The ratios (test vs reference) of log-transformed data, together with their means and 90% CIs, were evaluated by analysis of variance (ANOVA) using Statistical Program for Social Sciences Version 16.0 (IBM, USA). If the 90% CI for AUC was located within 80% to 125%, Cmax was within 70% to 143% of the statistical interval proposed by the SFDA, and no significant differences for Tmax with a non-parameter test, the two formulations would be considered bioequivalent.

Results

Subjects

20 healthy Chinese male volunteers were enrolled in the study. One subject voluntarily withdrew during the second period. 19 participants (mean [SD] age, 22.6 [2.3] years [range, 20-27 years]; weight, 58.1 [4.6] kg [range, 53.0-78.0 kg] and height, 170.8 [4.7] cm [range, 161.0-181.0 cm]) completed the study and were included in the PK analysis at the last. No clinically significant AEs were observed during or after the study.

Methodology result

No significant interference at the retention times of voriconazole and IS was observed on chromatography of blank plasma. The observed recovery of voriconazole was within 87.22% to 105.87%. The calibration curve, established by plotting the peak area ratio (y) versus concentration (x), was linear over the range of 20 to 2000 ng/mL with the following regression equation: y = 0.6701 × -0.0009 (r = 0.9998; n = 7). The lower limit of quantification for voriconazole was 20 ng/mL.

Moreover, approximate values for intra- and interday precision were 1.90% to 4.50% and 2.05% to 4.50%, respectively. Accuracy expressed as bias ranged from -8.74% to -2.02% (Table 1).

Pharmacokinetic properties

The mean plasma concentration–time curves of two voriconazole formulations each administered a single 200 mg oral dose (one 200 mg tablet) to 19 healthy Chinese male volunteers are shown in the Figure 1. The primary PK parameters for both drugs are listed in Table 2.
In this small study in healthy Chinese adult male volunteers, a single 200 mg dose of the tablet (test) of voriconazole met the regulatory...
criteria for bioequivalence to a single 200 mg dose of the established tablet product (reference) based on the rate and extent of absorption. Both products were well tolerated.

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