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Bioequivalence of Two Oral Fluconazole Formulations in Healthy Subjects: a Single Dose, Open-Label, Randomized, Two-Period Crossover Study

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Abstract

Background: Fluconazole is a triazole antifungal agent labeled for use in the treatment of oropharyngeal and esophageal candidiasis and cryptococcal meningitis, marketed in Mexico in several generic trade names.

Objective: The aim of this study was to compare the bioavailability and determine the bioequivalence of one test formulation (fluconazole oral tablet) with its corresponding list reference-drug formulation in Mexico (a list issued by Mexican Health Authorities).

Methods: A single dose, randomized, open-label, 2-period crossover, postmarketing study was conducted. Eligible subjects was selected comprising healthy Mexican adults of either sex, and subjects were randomly assigned to receive 1 test formulation of fluconazole followed by the corresponding reference drug formulation, or viceversa, with a 1-week washout period between doses. After a 12-hour (overnight) fast, subjects received a single capsule of fluconazole 150 mg tablet formulation. For the analysis of bioequivalence, including C_{max}, AUC from time 0 (baseline) to time t (AUC_{0-t}), and AUC from baseline to infinity ($AUC_{0-\infty}$), blood samples were collected at baseline, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24, 48, 72 and 96 hours after dosing. The formulation was considered bioequivalent if the geometric mean ratios (test/reference) of the C_{max} and AUC were within the predetermined range of 80% to 125%. Tolerability was determined by clinical assessment, monitoring vital signs, laboratory analysis results, and subject interviews regarding adverse events.

Results: A total of 24 subjects were enrolled in the study The bioequivalence test drug values were C_{max} of 4.44 ± 0.79 µg/mL, t_{max} of 2.59 ± 1.03 h, AUC_{0-t} of 152.21 ± 28.89 h. µg/mL, $AUC_{0-\infty}$ of 175.13 ± 48.98 h. µg/mL, and reference drug values of C_{max} of 4.38 ± 0.83 µg/mL, t_{max} of 2.70 ± 1.15 h, AUC_{0-t} of 154.67 ± 26.10 r. µg/mL, $AUC_{0-\infty}$ of 174.33 ± 31.10 hr. µg/mL.

Conclusions: In this study in healthy Mexican adult subjects, a single dose of fluconazole 150 mg of the test formulation was found to be bioequivalent to the corresponding reference formulation according to the regulatory definition of bioequivalence based on the rate and extent of absorption. Both formulations were generally well tolerated.

Keywords: Fluconazole; Pharmacokinetics; Bioequivalence; Bioavailability; HPLC

Introduction

Fluconazole is an orally active bistriazole antifungal agent which is used in the treatment of topical and systemic candidiasis and in the treatment of cryptococcal infections in patients with AIDS. Fluconazole has a high degree (.90%) of bioavailability after oral administration, displays pH-independent absorption, and is eliminated, predominantly unchanged, by renal excretion. As a result of its beneficial lipophilic/hydrophilic profile and its low level (12%) of binding to plasmatic proteins, fluconazole readily penetrates into body tissue. Fluconazole can be given orally and intravenously and is usually well tolerated. Because of its favorable pharmacokinetic and therapeutic profiles (Koks et al., 1996).

The pharmacokinetic properties of fluconazole are similar following administration by the intravenous or oral routes. In healthy volunteers, the bioavailability of orally administered fluconazole is over 90% compared with intravenous administration. In fasted healthy volunteers, peak plasma concentrations occur between 1 and 2 hours post dose with a terminal plasma elimination half-life of approximately 30 hours (range 20-50 hours). Plasma concentrations are proportional to dose and steady-state levels are reached within 5-10 days with oral doses of 50-400 mg once daily (Debruyne and Ryckelynck, 1993; Al-Gaai et al., 2005; Jovanović et al., 2005; Portolés et al., 2004; Porta et al., 2005; Pereira et al., 2004; Manorot et al., 2000). Steady-state levels are approximately 2.5 times higher the levels achieved with single doses. Administration of loading dose (on day 1) of twice the usual daily dose enables plasma levels to approximate to 90% steady-state levels by day 2. The apparent volume of distribution approximates to total body volume. Plasma protein binding is low (11-12%).

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Although several oral generic formulations of fluconazole are available in Mexico, a MEDLINE search (1991–2007; key terms: *bioequivalence*, *bioavailability*, *Mexico*, and *fluconazole*) failed to identify published data concerning the bioavailability of each formulation in the Mexican population. Thus, the aim of this study was to compare the bioavailability of one solid oral formulation of fluconazole capsules 150 mg with its corresponding listed drug reference in Mexico.

Subjects and Methods

Study subjects

For our study, a different set of eligible healthy Mexican adult subjects aged 18 to 55 years of either sex were recruited from an outpatient records taken from a database of the Center of Scientific and Clinical Studies [Centro de Estudios Científicos y Clínicos Pharma, S.A. de C.V. (Clinical unit, CECYC Pharma)], Mexico City, Mexico. All subjects provided written informed consent prior the commencement of the study. Thereafter, the subject's medical records were documented and a physical examination was conducted. Systolic and diastolic blood pressure (BP) was measured with a digital BP monitor (HEM-712C, Omron Healthcare, Vernon Hills, Illinois), which was previously calibrated. The BP cuff was applied to the right arm and the reading was taken in the sitting position. Inclusion eligibility was also based on successful completion of a clinical health evaluation , which consisted of a personal interview; a complete physical examination (BP, pulse, weight, temperature, and respiratory rate); diagnostic testing that included a 12-lead electrocardiogram and chest radiograph; a laboratory testing that included a complete blood cell count, metabolic and hepatic tests (alanine aminotransferase [reference range, 5-55 U/L], aspartate aminotransferase [5-34 U/L]), urianalysis, pregnancy test (for female subjects), blod chemistry for glucose (70-109 mg/dL), blood urea nitrogen (7-23 mg/dL), and creatinine (0.-1.3 mg/dL), as well as serologic tests for hepatitis (B and C), and HIV antibodies. Subjects were excluded if laboratory values were significantly above or below the reference range and/or if all tests had not been performed. Testing was performed by Laboratorio de Análisis Clínicos LAPI, Salud Integral, S. A. de C. V. (Mexico City, Mexico), which has been certified by the Mexican government. In addition, the laboratory data were reviewed by the investigators of the clinical unit prior to the enrollment of the subjects. Subjects were compensated for participation.

For the study, 26 subjects were enrolled. One subject did not allow participate into the study form the first period because he did not fulfill inclusion criteria. One more subject was withdrawn because he did not attend the appointment (due to personal reasons no related to any adverse event [AE]), at the clinical unit for the second period of the study.

Study design

The protocol was approved by the ethics and research committee of the Centro de Estudios Científicos y Clínicos Pharma, S.A. de C.V. The study was carried out in accordance with the principles of the Declaration of Helsinki and its amendments (World Medical Association, 2008) and the International Conference on Harmonisation Guideline for Good Clinical Practice (59th WMA General Assembly, Seoul, October 2008).

A single-dose, randomized, open-label, 2-period crossover design was used.

The subjects for the study arrived at the clinical site the day before the beginning of the study and were randomized in a 1:1 ratio using a table of random numbers to receive fluconazole test formulation (Difusel® [Productos Medix, S. A. de C. V., Mexico City, Mexico]) followed by fluconazole reference formulation (Diflucan®, [Pfizer, S.A. de C. V., Mexico City, Mexico]) or vice versa, with a 1-week washout period between doses. To obtain accurate baseline plasma measurements, subjects underwent a 12-hour overnight fast. Blood was obtained for baseline plasma measurements in the following manner: a 20-G catheter (Jelco® Plus, Medex Medical Ltd., Ascot, United Kingdom) was inserted in a suitable forearm vein and a 6-mL blood sample was taken into a heparinized vacuum tube (Vacutainer®, Becton, Dickinson and Company, Franklin Lakes, New Jersey). Before collection of each blood sample, 1 mL of blood was drawn from the catheter and discarded. After each blood sample was drawn, 0.5 mL of sodium heparin (2.5 UI/mL) was injected into the catheter to ensure catheter permeability. Subjects received a single 150-mg tablet of the study medication, given with 250 mL of water, and additional blood samples were taken at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24, 48, 72, and 96 hours after study drug administration. Plasma was obtained by centrifugation (2000*g* for 10 minutes at room temperature) and stored frozen at –70°C until analyzed using high-performance liquid chromatography (HPLC). After a 1-week washout period, subjects returned to the clinical unit where the alternative formulation was administered and samples were drawn and analyzed as in the first treatment period.

Determination of plasma fluconazole concentrations

Analytical fluconazole plasma measurements were done blindly. Fluconazole plasma levels were determined using HPLC assay method developed by personnel of CECYC Pharma, Mexico City, Mexico, in which tinidazole was used as internal standard. Briefly, 500 µL of plasma, 20 µL of internal standard (10 µg/mL) and 4 mL of ethyle acetate:dichloromethane (75:25 v/v) were mixed by shaking in a glass test tube for 3 minutes. The tube was then centrifuged at 3500 rpm for 7 minutes. The supernatant was frozen at –70°C for 10 minutes, after removed and dried the organic phase, the extracts were reconstituted with 100 µL of mobile phase and 20 µL were injected into the chromatographic system. The separation of compounds was achieved on Zorbax XDB-C18 (150 mm x 4.6 mm, I.D.of 5 µm, Agilent) and eluted with a mobile phase consisting of 10 mM sodium acetate buffer:acetonitrile (pH 5.1 ± 0.05). The column temperature was 30°C. Flow rate was maintained constant at 1.0 mL/min, and detection was by UV detector at 260 wavelength. Under these conditions, the method was linear in the range of 0.05 to 3.20 µg/mL, accuracy was between 94.86 and 99.63%, and the relative standard deviation of the method was always lower than 6.08% (Kim et al., 2007). This method was considered suitable by the study investigators for pharmacokinetic studies of fluconazole.

Tolerability

Tolerability was assessed by monitoring vital signs (blood pressure, heart rate, body temperature) at baseline, 4.5, 11.5, and 23.5 hours, and at the end of each period, laboratory analysis results, and subject interviews regarding the potential presence

of adverse events (AEs) during the study.

Pharmacokinetic and statistical analyses

Using a power analysis (β = 0.2), it was determined that the power of the analysis of variance (ANOVA) was >0.8 at a 90% CI, indicating that a total of 24 to 25 subjects would be sufficient for the purposes of each study. Individual plasma concentration–time curves were constructed; C_{max} and T_{max} were directly obtained from these curves. AUC from time 0 (baseline) to 96 hours (AUC_{0-96}) was calculated using the trapezoidal rule (Chow and Liu, 2000; Chow and Liu, 2007). From the terminal log-decay phase, elimination rate constant (k_e) was estimated using linear regression, and $t_{½}$ was estimated using the following equation: $t_{½} = \ln 2/k_e$ where *ln* was defined as the natural logarithm. Extrapolation of AUC from baseline to infinity ($AUC_{0-\infty}$) was calculated as follows: $AUC_{0-\infty} = AUC_{0-96} + (C_{96}/k_e)$ where C_{96} was defined as concentration at 96 hours.

To compare the bioavailability (in accordance with the criteria for bioequivalence [the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action] established by the US Food and Drug Administration, in vivo bioequivalence guidelines) of the formulations tested, an ANOVA for a 2 x 2 crossover design for ln-transformed C_{max}, AUC from baseline to time t (AUC_{0-t}), and $AUC_{0-\infty}$ was carried out for each study. Ratios of ln C_{max}, ln AUC_{0-t}, and ln $AUC_{0-\infty}$ for all formulations were calculated, and 90% CIs were obtained; ANOVA was performed using the F test. Probability of exceeding the limits of acceptance (80% –125%) was obtained by the two 1-sided *t* tests described by Schuirmann (Schuirmann, 1987). The formulations were considered bioequivalent if the ln-transformed ratios of C_{max} and AUC were within the predetermined equivalence range of 80% to 125% and if *P* was ± 0.05 for the 90% CIs. All pharmacokinetic and statistical analyses were performed using WinNonlin version 5.1, (2008).

Results

Twenty-five *mestizo* subjects were enrolled in the comparison between capsules of fluconazole (12 men, 13 women; mean age, 25.16 years). Subjects in the study had the following demographics at the moment of the admission of period 1: age range, 18 to 50 years; mean weight of 60.04 ± 7.9 kg; and mean height of 1.62 ± 0.8 m; and mean body mass index of 22.93 ± 1.43 kg/m^2. Because the withdrawal of one subject during the wash-out period, the sample size for the evaluation of the PK parameters for fluconazole was reduced from 25 subjects to 24 subjects.

The bioequivalence test drug values were C_{max} of 4.44 ± 0.79 µg/mL, t_{max} of 2.59 ± 1.03 h, AUC_{0-t} of 152.21 ± 28.89 h. µg/mL, $AUC_{0-\infty}$ of 175.13 ± 48.98 h. µg/mL, and reference drug values of C_{max} of 4.38 ± 0.83 µg/mL, t_{max} of 2.70 ± 1.15 h, AUC_{0-t} of 154.67 ± 26.10 r. µg/mL, $AUC_{0-\infty}$ of 174.33 ± 31.10 hr. µg/mL.

Pharmacokinetic parameters

Figure 1 shows some chromatograms of the present study, including blank plasma, blank plasma spiked with fluconazole and internal standard, and plasma sample from one volunteer after administration of fluconazole spiked with internal standard.

Mean and SD values of C_{max}, AUC_{0-96}, and $AUC_{0-\infty}$ for each formulation are shown in Table 1 and depicted in Figure 2. No period or sequence effects were observed for the pharmacokinetic properties in the ANOVA. In addition, there was no evidence of weight-related differences in individual AUC values and C_{max} values. Table 2 shows the 90% CIs of the ratios (test/reference) for the ln-transformed values of C_{max} (as an index of rate of absorption), AUC_{0-t}, and $AUC_{0-\infty}$ (as an index of the extent of absorption); the probability of exceeding the limits of accep-

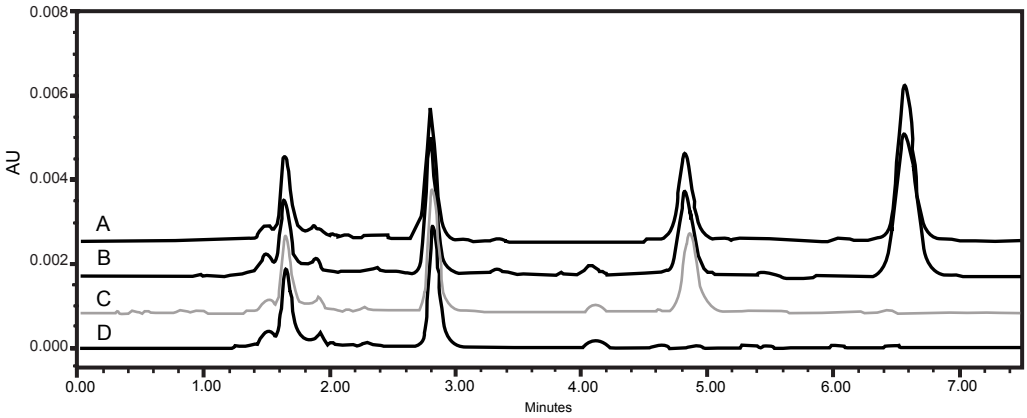

Figure 1: Chromatograms of fluconazole assay: A) Plasma sample from one volunteer spiked with internal standard and fluconazole; B) Blank plasma spiked with fluconazole and internal standard; C) Blank plasma spiked with internal standard; D) Blank plasma.

Pharmacokinetic parameter	Reference Drug A (DIFLUCAN®)				Test Drug B (DIFUSEL®)			
	Mean	Standard Deviation	CV%	n	Mean	Standard Deviation	CV%	n
C_{max} (µg/mL)	4.38	0.83	19.07	25	4.44	0.79	17.90	24
AUC_{0-t} (h. µg/mL)	154.67	26.10	16.88	25	152.21	28.89	18.98	24
AUC_{0-Inf} (h. µg/mL)	174.33	31.10	17.84	25	175.13	48.98	27.97	24
T_{max} (h)	2.70	1.15	42.77	25	2.59	1.03	39.93	24

AUC_{0-t} = AUC from time 0 (baseline) to 96 hours; AUC_{0-Inf} = AUC from baseline to infinity.

Table 1: Pharmacokinetic parameters of 2 oral formulations of fluconazole after a single dose of 150 mg. Values are mean and SD.

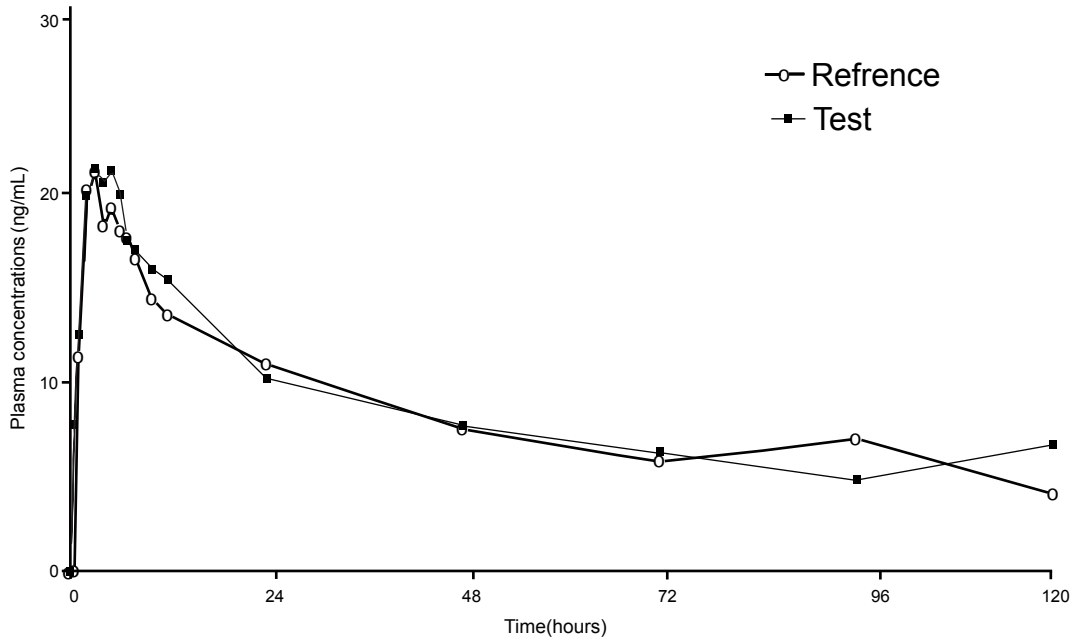

Figure 2: Mean plasma fluconazole concentration-time curve for the test (Trademark: DIFUSEL®, n = 24) and reference (Trademark: DIFLUCAN®, n = 25), oral tablet formulations of fluconazole 150 mg.

Pharmacokinetic parameter	Ratio % (Ref)	CI 90% Classical	CI 90% Westlake	Criteria for accepting Bioequivalence	Two one-sided t test Schuirmann	P	Power of the analysis	Conclusion
LnC_{max} (µg/mL)	102.24	(97.20 – 107.53)	(93.65 – 106.35)	(80%-125%)	P(θ <80%) =0.0000 P(θ>125%)=0.0000	P<0.05	1.0000	**Bioequivalent**
$LnAUC_{0-t}$ (h. µg/mL)	98.47	(93.51 – 103.68)	(94.37 - 105.63)	(80%-125%)	P(θ<80%) =0.0000 P(θ>125%)=0.0000	P<0.05	1.0000	**Bioequivalent**
$LnAUC_{0-inf}$ (h. µg/mL)	99.06	(92.23 – 106.38)	(92.79 – 107.21)	(80%-125%)	P(θ<80%) =0.0000 P(θ>125%)=0.0000	P<0.05	0.9993	**Bioequivalent**

Table 2: Ratios, 90% CIs of natural log-transformed data, the probability of exceeding the limits of acceptance (80%-125%), and power test results of 2 oral formulations of fluconazole after a single dose of 150 mg.

tance (Schuirmann's two 1-sided *t* tests); and the power of the test for fluconazole capsules (Schuirmann, 1987). The 90% CIs for the corresponding ratios of C_{max}, AUC_{0-96}, and $AUC_{0-\infty}$ were within the 80% to 125% range. All *P* values were <0.05. Similar results were found for data without a logarithmic transformation. T_{max} values were obtained, but there were not compared in the bioequivalence analysis because this parameter is not considered as a bioequivalence criteria.

Tolerability

Two subjects reported one adverse event. The first one reported mild dizziness and the second one reported mild headache, with probable association with the study drug. None of these required drug treatment.

Discussion

The results of our study suggest that the reference-test capsule formulations of fluconazole were not statistically different in terms of their PK parameters (C_{max} and AUC). Considering that all 90% CIs of the ratios of the PK parameters (C_{max} and AUC) were found to be within the predetermined range (80% -125%) and the Schuirmann two one-sided *t* test procedure (probability of exceeding limits of acceptance) found al probability values <0.05, the hypothesis that the estimated parameters exceeded limits of acceptance was rejected.

Based on the accepted regulatory requirements (Ministry of Health of Mexico, 2009), this study suggests that the test formulation was bioequivalent to the reference formulation.

Al-Gaai and colleagues (Al-Gaai et al., 2005) reported a randomized crossover study conducted on 26 healthy Arab males to compare the bioavailability of two formulations of fluconazole 150 mg capsules. The mean +/- SD maximum concentration of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were 3.17 ± 0.47 and 3.24 ± 0.59 microg/ml, 149.52 ± 29.49 and 151.36 ± 25.84 microg.h/ml, 163.57 ± 29.9 and 164.89 ± 26.46 microg.h/ml, for the test and reference drug, respectively. These values are similar to previously reported values in other ethnic groups, like Serbian population (Jovanović et al., 2005), Spanish population (Portolés et al., 2004), Brasilian people (Porta et al., 2005; Pereira et al., 2004) and Thai population (Manorot et al., 2000).

No moderate or serious AEs were reported by the investigators. Potential recall bias of AEs in this study was not likely because only one dose of each formulation was administered during each treatment period, subjects were under medical surveillance in the clinical unit, and the duration of the washout period was only 7 days.

Limitations

As with any clinical trial, and in particular for most

bioavailability/bioequivalence studies, the current studies had some limitations that should be considered. First, this was an open-label study, so it might not objectively address the effectiveness and safety profiles of the formulations tested. Also, because the data were obtained from healthy subjects who were administered a single dose, the PK parameters of fluconazole might differ in target populations.

In addition, this study was conducted under fasting conditions, because for bioequivalence studies is preferable the drug administration without food, however, to assess the food effect on the fluconazole administration, further studies would be useful for a better characterization of its PK and bioavailability in Mexican population.

Due to the limited data, we are unable to predict the response to the drug at any time after administration of alternative doses and/or administration intervals. Further studies are needed to compare the test formulation efficacy and/or tolerability with the reference formulation in Mexican patient groups.

The results of this study may serve as a reference for future controlled studies of fluconazole in the Hispanic population.

Conclusions

In this study in healthy Mexican adult subjects, a single dose of fluconazole 150 mg of the test formulation was found to be bioequivalent to the reference formulation according to the regulatory definition of bioequivalence based on the rate and extent of absorption. All formulations were generally well tolerated.

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