A Randomized, Open-Label Pharmacokinetic Comparison of Two Oral Formulations of Fluconazole 150 mg in Healthy Adult Volunteers

Dušan Jovanović, MD, PhD[1]; Vesna Kilibarda, PharmD[1]; Biljana Ćirić, BPharm[1]; Slavica Vučinić, MD, PhD[2]; Danica Srnić, MD[2]; Midhad Vehabović, MSc[3]; and Nermina Potogija, BPharm[3]

[1]Institute of Toxicology and Pharmacology, National Poison Control Centre, Belgrade, Serbia and Montenegro; [2]Clinic of Emergency and Clinical Toxicology and Pharmacology, National Poison Control Centre, Belgrade, Serbia and Montenegro; and [3]Bosnalijek d.d., Pharmaceutical and Chemical Industry, Sarajevo, Bosnia and Herzegovina

ABSTRACT

Background: Because of its systemic action, fluconazole is prescribed for a variety of fungal infections. However, therapeutic failure might result when a patient is switched between an innovator drug and a nonbioequivalent generic formulation. Pharmacokinetic (PK) studies investigating the bioequivalence of generic and innovator drugs can minimize such risks.

Objective: The aim of this study was to compare the PK profiles and relative bioavailabilities of 2 oral formulations of fluconazole: Diflucan® (reference; Pfizer Corporation Austria GmbH, Wien, Austria) and Funzol® (test; Bosnalijek d.d., Pharmaceutical and Chemical Industry, Sarajevo, Bosnia and Herzegovina), both prepared as capsules containing 150 mg of active drug.

Methods: A single oral dose of fluconazole was given under fasting conditions to healthy, white volunteers aged 18 to 55 years in this open-label, randomized, crossover study. A 3-week washout period was applied between each of the 2 doses. Serum samples were obtained before dosing and at various time points after dosing up to 144 hours and were analyzed for fluconazole concentration using a high-performance liquid chromatography–UV method. PK parameters representing the extent ($AUC_{0-\infty}$) and rate (C_{max} and T_{max}) of absorption of fluconazole were obtained. An analysis of variance, a power analysis, 90% CI, and two 1-sided tests were used for statistical analysis of relative differences between the 2 drugs. Bioequivalence was concluded if the 90% CIs for the geometric mean ratios of $AUC_{0-\infty}$ and C_{max} were between 0.80 and 1.25. A study investigator monitored the volunteers for adverse effects at 5 defined time points during the clinical part of the investigation.

Results: Thirteen men and 11 women (mean age, 33.3 years; mean weight, 73.6 kg) completed the study. The respective point estimates of the ratios of geometric means of log-transformed C_{max} and $AUC_{0-\infty}$ of fluconazole (test vs reference) were 0.985 and 1.047, with 90% CIs of 0.894 to 1.085 and 0.927 to 1.182, respectively. Differences in T_{max} also did not reach statistical significance. No adverse effects were reported by the subjects or revealed by clinical or laboratory tests.

Conclusions: The study failed to demonstrate any statistically significant differences in C_{max} and $AUC_{0-\infty}$ values between the test and reference formulations of oral fluconazole 150 mg in this small, select population of healthy volunteers. On that basis, and according to both the rate and extent of absorption, the test and reference formulations were considered bioequivalent. (*Clin Ther.* 2005;27:1588–1595) Copyright © 2005 Excerpta Medica, Inc.

Key words: bioequivalence, capsules, fluconazole, generic drugs, relative bioavailability.

INTRODUCTION

Fluconazole is a highly selective inhibitor of fungal cytochrome P450 sterol C-14 α-demethylation. The subsequent loss of normal sterols correlated with the accumulation of 14 α-methyl sterols in fungi might be responsible for the fungistatic activity of flucona-

Accepted for publication August 23, 2005.
doi:10.1016/j.clinthera.2005.10.016
0149-2918/05/$19.00

zole.[1,2] Because of its systemic action, fluconazole is prescribed for a variety of fungal infections, including cryptococcal meningitis, vaginal candidiasis in older patients, and oropharyngeal candidiasis in children.[1-4]

The pharmacokinetic (PK) properties of oral and IV fluconazole were found to be similar in a study of fasted healthy volunteers (bioavailability of oral formulation, >90%).[1,2] T_{max} after oral administration in fasted healthy volunteers was between 1 and 2 hours, with a $t_{1/2}$ of ~30 hours (range, 20–50 hours).[1,2] The apparent Vd of fluconazole approximated that of total body water.[1] Plasma protein binding was low (11%–12%). Mean body clearance in adults was reported to be 0.23 mL/kg · min.[1,5] In healthy volunteers, fluconazole was cleared primarily by renal excretion, with ~80% of the dose appearing in the urine as unchanged drug and ~11% excreted in the urine as metabolites.[1,2,5]

Pathologic conditions (eg, renal or hepatic failure) or interactions with concurrently used medications might affect the PK profile of fluconazole,[1,6] and thereby contribute to changes in therapeutic efficacy or in the adverse-events profile. Therapeutic failure might result when a patient is switched between an innovator drug and a nonbioequivalent generic formulation. PK studies investigating the bioequivalence of generic and innovator drugs can minimize such risks. The US Food and Drug Administration (FDA) has defined *bioequivalence* as "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study."[7] The aim of this study was to evaluate the bioequivalence of 2 oral formulations of fluconazole, each containing 150 mg of active drug. As a secondary objective, the tolerability of both formulations also was assessed.

SUBJECTS AND METHODS

A single-dose, open-label, randomized, 2-sequence, 2-period, crossover study design was used to evaluate the bioavailabilities of 2 oral formulations of fluconazole: Diflucan®* (reference formulation) and Funzol®† (test formulation), both prepared as capsules containing 150 mg of active drug. White volunteers aged 18 to 55 years who were determined to be in good physical condition by complete medical and laboratory examination were enrolled in the study, and written informed consent was obtained prior to any study-related procedure. The study was approved by the Drugs Commission and the Ethics Committee of the Military Medical Academy, Belgrade, Serbia and Montenegro, on September 26, 2003.

The enrolled subjects were randomly assigned to 1 of 2 sequence groups. Each subject received a single 150-mg dose (1 capsule) of the test or reference formulation with 200 mL noncarbonated mineral water after an overnight fast of at least 10 hours. Administration of the 2 drugs was separated by a 3-week washout period.

Venous blood samples (~8 mL) were collected prior to dosing (hour 0) by direct venous puncture and at 20 minutes and 1, 2, 3, 4, 12, 24, 48, 72, 96, 120, and 144 hours. The samples were allowed to clot at room temperature for 20 minutes. Within 1 hour of collection, all samples were centrifuged at 3000 rpm for 15 minutes; the serum was then separated and frozen at –20°C until assayed.

Dissolution Test

The procedure for dissolution was applied as previously described.[8] The in vitro dissolution rate in 0.1 *N*-hydrochloride medium was determined by the rotating basket method (50 rpm; replication, 6).[8] The test was performed using a dissolution apparatus (model PTWS 3CE, Pharma Test Apparatenbau GmbH, Hainburg, Germany). The amount of dissolved drug at time intervals 0, 15, and 30 minutes was determined using spectrophotometry (λ_{max}, 261 nm).[5]

Assay Method

The high-performance liquid chromatography (HPLC) set was equipped with a pump (model 2150, LKB, Bromma, Sweden), an automatic sample system (model AS-100, BioRad Laboratories, Inc., Hercules, California), a variable wavelength UV detector (model 1801, BioRad Laboratories, Inc.), and an integrator (model 2221, LKB). Separations were performed on a reverse phase column (Lichrospher 60 RP select B 250-4, 10 µm, Merck KGaA, Darmstadt, Germany), with a guard column (Lichrochart 4-4 RP select B, Merck KGaA).

*Trademark of Pfizer Corporation Austria GmbH, Wien, Austria.
†Trademark of Bosnalijek d.d., Pharmaceutical and Chemical Industry, Sarajevo, Bosnia and Herzegovina.