Comparative Pharmacokinetics of Voriconazole Administered Orally as either Crushed or Whole Tablets V

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Voriconazole is a triazole antifungal agent used to treat serious, invasive fungal infections including aspergillosis and candidemia. Limitations with existing formulations of voriconazole include restricted utility in patients with renal dysfunction (intravenous preparation) and the unavailability of an oral suspension in some countries, which makes the administration of crushed tablets desirable in many clinical scenarios. However, concerns that this approach may alter the systemic absorption of voriconazole exist. Therefore, an open-label, randomized, two-way crossover comparative pharmacokinetic (PK) study using healthy volunteers was performed to compare these methods of tablet administration. In a random sequence, subjects received voriconazole tablets either crushed or whole. The voriconazole dose was 400 mg every 12 h for 1 day orally followed by 200 mg every 12 h orally for 5.5 days. Study periods were separated by 7 days. PK parameters were determined by the noncompartmental method. An equivalence approach with no-effect boundaries of 80 to 125% was used to assess bioequivalence. Twenty healthy subjects (10 males; aged 20 to 43 years) were enrolled in and completed the study. The adjusted mean areas under the plasma concentration-time curve from 0 to τ, where τ equals 12 h, for the crushed and whole tablet groups were 9,793 and 11,164 ng · h/ml, respectively (ratio, 87.72; 90% confidence interval [CI], 80.97, 95.04). The ratio of the maximum concentration of drug in serum for the crushed tablet versus whole tablet arms was 94.94 (90% CI, 86.51, 104.22). The only difference noted between groups was a slightly faster time to maximum concentration of drug in serum when subjects received crushed tablets, 0.5 h versus 1.5 h (90% CI, −0.75, −0.25). Treatment-related adverse events occurred in 12 subjects receiving whole tablets and 9 subjects receiving crushed tablets; all were mild. The administration of crushed voriconazole tablets is bioequivalent to whole-tablet administration.

Voriconazole (Vfend; Pfizer Inc., New York, NY) is a triazole antifungal agent with potent activity against yeasts and molds. Since its release on the U.S. market in 2002, voriconazole has established itself as the first-line treatment for invasive aspergillosis (6) and proven useful in other fungal infections that are resistant and refractory to standard antifungal therapies (9). More recently, voriconazole has been indicated for treating candidemia, showing efficacy equal to that of amphotericin B followed by fluconazole (8); this includes activity against fluconazole-resistant strains of Candida spp. (5).

Voriconazole is currently available as an intravenous (i.v.) formulation and two oral preparations, tablets and suspension. The severity of infection or underlying disease state in patients with invasive fungal infections often makes intravenous antifungal therapy desirable. Due to the insolubility of the parent drug, the i.v. formulation of voriconazole includes sulfobutyl ether-β-cyclodextrin sodium as a solubilizing agent. In patients with moderate renal dysfunction (creatinine clearance of <50 ml/min), levels of the intravenous vehicle sulfobutyl ether-β-cyclodextrin sodium that are higher than those in subjects with normal renal function have been observed (4). This limits the use of the i.v. preparation in some patient populations at high risk for invasive fungal disease.

In patients with decreased renal function, oral administration of voriconazole is a feasible alternative, as bioavailability via this route exceeds 90%. Some patients (e.g., geriatric or seriously ill patients) that require voriconazole therapy may have difficulty swallowing the whole tablet formulation. Although an oral suspension is available in the United States, it is not available in all countries. Additionally, considering the viscosity of the oral suspension, it may be difficult to administer this preparation via enteral feeding tubes, particularly nasogastric tubes with a smaller diameter. Therefore, crushing the whole tablet formulation of voriconazole may be an alternative approach for oral administration.

Whenever the administration technique is altered, ensuring that adequate but not excessive plasma concentrations of voriconazole are achieved is essential. Voriconazole absorption is known to be dependent on the fasting state of the patient (11), and toxicity and treatment failure have been linked to elevated and decreased plasma concentrations, respectively (1, 3, 12). Therefore, we sought to compare the kinetics of the tablet formulation of voriconazole when administered whole versus crushed.

MATERIALS AND METHODS

Subjects. Healthy nonsmoking males and females were eligible for participation if they provided written informed consent, were between the ages of 18 and 45 years, were otherwise healthy (based on physical examination, electrocardiogram [ECG], and laboratory measurements), and were willing to comply with all study procedures, including confinement to the healthy volunteer unit at Duke University Hospital.

Potential subjects were excluded if they were pregnant, had donated blood or blood products within 30 days, had a body mass index of >30 kg/m², had consumed grapefruit-containing products within 7 days, or had positive clinical history or laboratory tests confirming any of the following entities: hepatitis B...
virus, hepatitis C virus, human immunodeficiency virus, illicit drug use, excessive alcohol consumption, or other significant diseases or procedures such as gastrectomy that would be likely to interfere with the absorption of study drug. Any subject with baseline liver function tests >1.5 times the upper limit of normal, a corrected QT interval of >430 (males) or >450 (females), or other significant laboratory abnormalities was not allowed to enroll. In addition, all medications, caffeine, alcohol, tobacco, and nutritional supplements were discontinued at an interval prior to study initiation to ensure complete elimination before the first voriconazole dose. Oral contraceptives, acetaaminophen (<2 g/day), and thyroid replacement therapies were permitted during the study.

**Design.** An open-label, randomized, two-way crossover study to compare the pharmacokinetics (PKs) of voriconazole tablets administered whole versus voriconazole administered crushed was conducted. Subjects were randomized in a one-to-one fashion to receive either crushed voriconazole or whole tablets initially followed by the opposite drug regimen after a 1-week washout period. During each dosing period, voriconazole was administered at a dose of 400 mg orally every 12 h on day 1 as loading doses, followed by 200 mg orally every 12 h beginning on the morning of day 2 through the morning of day 6. All drug administration was observed by research unit staff. This study was conducted in compliance with the ethical principles originating in, or derived from, the Declaration of Helsinki and in compliance with the Institutional Review Board, informed consent regulations, and the International Conference on Harmonization Good Clinical Practices Guidelines. The study was approved by the Duke University Health System Institutional Review Board. All study procedures were performed at the Duke General Clinical Research Center (grant M01RR30).

Subjects were admitted to the study unit on the morning prior to drug dosing for baseline laboratory and ECG assessments. The first dose of study drug was administered on the following morning by the prescribed method (crushed or whole tablet). Subjects were fasting for a minimum of 1 h prior to and until 1 h following each drug administration. In order to minimize adherence to plastic medication cups, tablets were crushed in a mortar and pestle and then transferred into a glass jar and diluted with 10 ml water for drug administration. The mortar and pestle were rinsed serially with a total of 60 ml tepid water following drug preparation, and the solution was subsequently given to the patient to ensure the complete recovery of voriconazole. Each drug dose, independent of the administration method, was administered with a total of 240 ml of tepid water.

Subjects remained as inpatients in the research unit until 1 h after the first maintenance (200-mg) dose of voriconazole was administered on the morning of the second drug dosing day. Following discharge, all subjects returned to the unit at 12-h intervals for observed drug administration and verification of drug administration conditions (i.e., fasting) and to document adverse events (AEs).

On the evening of the fifth day of drug dosing, subjects were again admitted to the research unit. Safety monitoring was performed via laboratory tests and ECG. Subjects remained in the unit until 12 h following their final dose of voriconazole on the morning of the sixth day of drug dosing to complete the pharmacokinetic analysis.

After a 7-day washout period, subjects were again admitted to the research unit. The same procedures were followed for drug dosing days 1 through 6 for the opposite method of drug administration. Following the second drug dosing period, subjects returned for a final safety assessment 7 to 10 days after the last dose of voriconazole.

During the entire study period, subjects were not allowed to consume caffeine, tobacco, alcohol, grapefruit, or grapefruit juice. While confined, they were also restricted to a standard diet of 2,500 kcal (50% carbohydrate, 35% fat, and 15% protein). In addition, physical activity was limited to no more than brisk walking prior to all pharmacokinetic and safety laboratory monitoring.

**Pharmacokinetic sampling.** During each study period, whole-blood samples were collected at the following time points: immediately prior to the first dose of drug (drug dosing day 1, time zero), immediately prior the last dose of drug (drug dosing day 6, time zero), and following the last dose of study drug (drug dosing day 6) at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 h following the voriconazole dose. Whole-blood samples were collected in heparinized tubes. Within 1 h of collection, samples were centrifuged at 1,700 x g for 10 min at 4°C. Plasma, at least 1 ml, was then transferred into polypropylene tubes and frozen at −70°C until analyzed for drug concentration.

Plasma samples were analyzed for voriconazole concentrations at PPD Laboratories in Richmond, VA, using a validated assay. Samples were extracted using a solid-phase extraction procedure and were analyzed by liquid chromatography-tandem mass spectroscopy. The dynamic range of the voriconazole assay was 10 to 5,000 ng/ml. The assay performance of the quality controls, based on relative standard deviations, used during sample analysis had an accuracy range from 1.19% to 2.67%, with a precision of ≤10.7% for the voriconazole assay. All samples were analyzed within the known established storage stability period.

**Pharmacokinetic analyses.** For each study period, steady-state PK parameters of voriconazole were calculated from plasma concentration-versus-time data. PK analyses were carried out with WinNonlin (V.3.2; Pharsight, Mountain View, CA) using standard noncompartmental methods. PK parameters calculated included area under the plasma concentration-time curve from 0 to τ (AUC<sub>τ</sub>), where τ equals 12 h in this study (AUC<sub>12h</sub> was calculated by the linear trapezoidal rule); the maximum observed concentration of drug in serum at steady state (C<sub>max</sub>); and the time to maximum observed concentration of drug in serum (T<sub>max</sub>.

**Safety evaluations.** Safety was assessed at protocol-specified time points through AE monitoring, measurement of vital signs and ECGs, and collection of blood and urine specimens for laboratory analysis.

**Statistical methods.** The sample size was calculated using the approximate formulas for the multiplicative model (2). A sample size of nine subjects per treatment sequence was required to provide 90% power to demonstrate the bioequivalence of C<sub>max</sub> at steady state with 90% confidence intervals (CI) of 80% and 125%.

To test the primary hypothesis, log-transformed AUC<sub>τ</sub> and C<sub>max</sub> at steady state for crushed (test treatment) versus whole (reference treatment) tablets were compared using the mixed-effects model for sequence, period, treatment, and random effects for subjects. Estimates of the adjusted mean differences between treatments and 90% confidence intervals around the differences were calculated. For AUC<sub>τ</sub> and C<sub>max</sub>, the anti-log (exponent) of the differences and confidence limits were used to estimate the ratios between treatments and the confidence intervals of the ratios. For T<sub>max</sub>, the confidence intervals of the mean differences were calculated. Geometric means were determined for AUC<sub>τ</sub> and C<sub>max</sub>, while arithmetic means were used for T<sub>max</sub>.

The bioequivalence of the 200-mg crushed voriconazole tablet and the 200-mg whole voriconazole tablet (both under fasted conditions) was predefined as the 90% confidence limits for AUC<sub>τ</sub> and C<sub>max</sub> ratios both falling wholly within the 80% and 125% equivalence limits.

The safety population consisted of all subjects who received the study drug. Safety data were summarized using descriptive statistics.

**RESULTS**

**Subject disposition and demographics.** Thirty subjects were screened between November 2003 and October 2004 to determine their eligibility for study entry, and of these, 20 subjects were enrolled. All 20 subjects were treated with the study medication, completed the study, and were included in the safety evaluation as well as the PK analysis. The study population included 10 males and 10 females and was predominantly Caucasian (90%), with a mean age of 27.6 years (range, 20 to 43 years). Subjects’ body mass index ranged from 19 to 28 kg/m².

**Pharmacokinetics.** The mean steady-state voriconazole concentration-time profiles on day 6 for whole and crushed tablets are shown in Fig. 1. The steady-state PK parameters for whole and crushed tablets are summarized in Table 1. C<sub>max</sub> and AUC<sub>τ</sub> values for voriconazole appeared to be...
similar following administration of the whole and crushed tablets. The median $T_{\text{max}}$ value for the crushed tablet (0.5 h) was lower than that for the whole tablet (1.5 h). Table 2 summarizes the statistical comparisons of voriconazole steady-state PK parameters of crushed versus whole tablets.

As demonstrated, crushed tablets were equivalent to whole tablets with regard to $C_{\text{max}}$ and $AUC_{\text{tr}}$. There was a difference noted in the time to maximum concentration of drug in serum. For the crushed tablet group, $T_{\text{max}}$ occurred at 0.5 h, compared to 1.5 h for the whole tablet arm (90% CI, $-0.75, -0.25$).

**Safety results.** (i) Adverse events. A total of 38 AEs were reported during the study period, 25 of which were judged by the investigators to be related to voriconazole therapy. The treatment-related AEs were distributed between the crushed and whole tablet administration arms: 12 and 13, respectively. None of these were serious adverse events or required study discontinuation.

The majority of treatment-related side effects were visual disturbances: 11/13 in whole tablet group and 10/12 in crushed tablet group. Three additional adverse events were abnormal dreams (2/13 in the whole tablet group and 1/12 in the crushed tablet group) and one report of dizziness in the crushed tablet group that was attributed to voriconazole therapy.

No clinically significant laboratory, vital sign, or ECG changes were reported.

(ii) ECG monitoring. ECGs were obtained at baseline and on the fifth and sixth days of drug dosing in each treatment period. There were no clinically significant changes in the corrected QT interval noted throughout the study.

**DISCUSSION**

The pharmacokinetics of voriconazole are nonlinear, variable between patients, and subject to genetic variations in metabolism (7, 10). Therefore, it is important to ensure that alternate methods of administration do not significantly alter plasma drug exposure.

This study showed that the systemic exposure of voriconazole following administration of the crushed tablets was not significantly altered compared to that observed after administration of the whole tablets in healthy volunteers. However, the absorption of voriconazole after administration of the crushed tablets was faster than that of the whole tablet. This is to be expected, since the disintegration and dissolution of the whole tablet in the gastrointestinal tract take time. However, the change in the rate of absorption following administration of the crushed tablets did not significantly influence the AUC, and $C_{\text{max}}$ of voriconazole.

This study demonstrated that crushing voriconazole tablets is a viable method of administration. This provides new options for clinicians who have reported difficulty in administering this drug to critically ill patients, such as those with renal dysfunction, or to patients who are unable to swallow whole tablets. The availability of an oral suspension does assist with this problem in some cases. However, the oral suspension is not available in some countries, and the viscosity of the formulation may interfere with administration via nasogastric tubing, especially tubing of smaller diameter.

In our study, the crushed tablets of voriconazole appeared to adhere to plastic medication cups based on visual examination. Therefore, glass containers were required in order to ensure that subjects received the full amount of active drug. This should be noted by practitioners who intend to administer the drug as crushed tablets.

Side effects noted in our subjects were generally similar to those reported in infected patients enrolled in clinical trials of voriconazole (6, 13). None of our subjects reported skin reactions, although this may have been avoided by careful counseling regarding the need to avoid sun exposure for the duration of study participation.

In summary, bioequivalence in systemic exposure suggests that the clinical performance of the crushed tablet would be expected to be similar to that of the whole tablet of voriconazole. Administration of either the whole or crushed tablet was generally safe and well tolerated. This provides an option for the administration of crushed voriconazole tablets to subjects unable to swallow the whole tablet or unable to tolerate the i.v. formulation.

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**REFERENCES**


