Safety and Pharmacokinetics of Oral Voriconazole in Patients at Risk of Fungal Infection: A Dose Escalation Study

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The objective of this study was to investigate the safety, tolerability, and pharmacokinetics of oral voriconazole in subjects at high risk of developing fungal infections. This was a multicenter, randomized, double-blind, double-dummy, parallel-group, dose escalation study with a fluconazole active control. Twenty-four subjects with hematological malignancies, solid tumors, or autologous bone marrow transplants were randomized to receive voriconazole 200 mg q 12 h (n = 9), voriconazole 300 mg q 12 h (n = 9), or fluconazole 400 mg OD (n = 6) for a period of 14 days. Blood samples were taken for the assessment of voriconazole pharmacokinetics in plasma on Days 1 and 14. Using a 200 mg q 12 h dosing regimen, geometric mean voriconazole peak plasma concentrations ($C_{\text{max}}$) were 904 ng/ml on Day 1 and 2996 ng/ml on Day 14. Geometric mean voriconazole exposure, as measured by the area under the curve within a dosing interval (AUC$_{\tau}$), was 4044 and 20308 ng•h/ml on Days 1 and 14, respectively. On Day 1, geometric mean $C_{\text{max}}$ and AUC were 1.80- and 1.94-fold higher in subjects receiving voriconazole 300 mg q 12 h than in those receiving 200 mg q 12 h. Similarly, on Day 14, geometric mean $C_{\text{max}}$ and AUC were 1.56- and 1.80-fold greater in the high-dose group. Although the confidence intervals are large, this trend suggests nonlinearity in pharmacokinetics with respect to dose as seen in healthy volunteers. The absorption of orally administered voriconazole was relatively rapid, with $t_{\text{max}}$ achieved in 1.7 to 3.0 hours. There was a mean 5.4- and 5.0-fold accumulation of voriconazole over the 14-day study period in the 200 mg and 300 mg q 12 h dose groups, respectively. Voriconazole was generally safe and well tolerated. Mild, reversible visual disturbances were the most commonly reported adverse event but were not associated with treatment discontinuation. No patient developed a breakthrough fungal infection. It was concluded that in this group of patients at risk of fungal infection, voriconazole pharmacokinetics was consistent with that reported in healthy volunteers.

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Invasive fungal infections remain an important cause of morbidity and mortality among the severely immunocompromised, including patients receiving cytotoxic chemotherapy for hematological malignancies or solid tumors, organ transplant recipients, and those with immunodeficiency syndromes, such as AIDS.1,2 Such patients are at particularly high risk of developing opportunistic invasive infections with Candida or Aspergillus species.3,5 Voriconazole is a new triazole antifungal agent, developed as oral and intravenous formulations, with potent activity against a broad spectrum of clinically significant pathogens, including Aspergillus and Candida species,6-8 and emerging fungal pathogens, such as Scedosporium and Fusarium species.9,10 Voriconazole has demonstrated clinical efficacy in neutropenic patients with acute invasive aspergillosis,11,12 non-neutropenic patients with chronic invasive aspergillosis,13 immunocompromised patients with esophageal candidiasis,14 and patients with infections refractory to standard antifungal treatments.15,16 Furthermore, a recent trial has indicated that empirical therapy with voriconazole was more effective than

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liposomal amphotericin B in preventing breakthrough fungal infections in persistently febrile neutropenic patients.17

Although the pharmacokinetic profile of voriconazole in healthy volunteers has been described in the literature,18-21 there have been no data published on the pharmacokinetics of voriconazole in patients for whom it is intended, such as those with compromised immune systems. Based on pharmacokinetic data from healthy subjects and in vitro fungal susceptibility data, 200 mg q 12 h is the proposed oral dose for the treatment of fungal infections in patients, with the possibility of dose escalation to 300 mg q 12 h. It is of clinical importance to confirm that the pharmacokinetic characteristics of voriconazole in such patients are consistent with those observed in healthy subjects.

In vitro and in vivo studies indicate that voriconazole is extensively metabolized by the cytochrome (CYP) P450 system, mainly by the CYP2C19 isoenzyme, by CYP2C9, and, to a lesser extent, by CYP3A4.22 There has been speculation that a previous case of photosensitivity in a patient receiving voriconazole, which was apparently associated with the drug,23 may have resulted from elevations in endogenous retinoid levels24 since metabolism of retinoic acids is mediated by the CYP3A,25 and CYP3A4 is inhibited by voriconazole. In the present study, safety assessments included retinol and retinol-binding protein assays to determine if changes in these parameters were associated with adverse events.

Patients randomized to the control group received fluconazole therapy as an active control, primarily to allow comparative assessments of the safety and tolerability of voriconazole. A placebo-controlled study design was not considered, as it would have been unethical to deprive patients at high risk of fungal infections of appropriate prophylactic antifungal therapy. Fluconazole was selected because the safety and pharmacokinetics of this drug are well reported,26-28 and it is a mainstay in the treatment of patients at risk of specific fungal infections.29

This study was designed to assess the pharmacokinetics and safety of escalating doses of voriconazole over a 14-day period in patients with hematological malignancies, solid tumors, or autologous bone marrow transplants.

METHODS

Study Subjects

Eligible subjects had a diagnosis of hematologic malignancy, other hematologic condition, or solid tumor and had either successful engraftment of an autologous bone marrow/stem cell transplant or treatment for fever during periods of prolonged granulocytopenia (≥7 days with an absolute granulocyte count ≤ 500 cells/mm³) within 4 weeks of study entry.

In addition, all subjects were to be at least 18 years of age and weigh at least 50 kg, with a Karnofsky score ≥ 70, adequate bone marrow function at screening (an absolute granulocyte count ≥ 1000 cells/mm³, hemoglobin ≥ 7.0 g/dl, or platelet count ≥ 50,000/mm³), and a life expectancy of at least 6 weeks. All subjects were to provide written informed consent prior to study entry.

Subjects were excluded if there was any histological or microbiological evidence of disseminated aspergillosis or other systemic fungal infection that required continuous IV or oral antifungal therapy during the study, or any clinical evidence of systemic infection at screening. Subjects were also excluded if it was anticipated that they would need any of the following medications during the trial: immunosuppressive agents, corticosteroids, medications metabolized predominantly by hepatic cytochrome P450 enzymes (or that reduce or inhibit these enzymes), topical ophthalmologic medications, or medications with known ophthalmologic side effects.

Study Design

This was a two-phase, multicenter, randomized, double-blind, dose escalation study with an active control group receiving fluconazole. The study was conducted in accordance with the ethical principles originating from the Declaration of Helsinki (1989), and the protocol was approved by the institutional review boards associated with the study centers. Patients were randomized to treatment at three centers (H. Lee Moffitt Cancer Center and Research Institute, University of South Florida, Tampa, FL; University Hospitals of Cleveland, Cleveland, OH; Medical College of Virginia, Bone Marrow Transplant Unit, Richmond, VA).

A screening visit, which included an ophthalmologic evaluation, was conducted prior to randomization. A total of 24 subjects were assigned in a 3:1 ratio to receive either voriconazole or fluconazole using a central randomization schedule. Treatment was initiated within 7 days of randomization.

In Phase I, subjects received either voriconazole 200 mg q 12 h and a placebo matching the fluconazole dosing regimen (n = 9) or fluconazole 400 mg OD and a placebo matching the voriconazole regimen (n = 3) for a period of 14 days. Drugs or placebo were administered at 8 a.m. and the second daily dose of voriconazole or matched placebo at 8 p.m. All doses were taken with...
water on an empty stomach at least 1 hour before or 2 hours after a meal. Phase I was considered complete once a minimum of 12 evaluable subjects had been accrued. Evaluable subjects were defined as those who had completed the full 14 days of treatment or had discontinued due to adverse events. At the end of Phase I, the blind was broken and an analysis was performed to assess the safety and tolerability of voriconazole 200 mg q 12 h. As this dose was considered to be well tolerated, Phase II was initiated in a new group of subjects who received voriconazole 300 mg q 12 h and a placebo matching the fluconazole dosing regimen \( (n = 9) \) or fluconazole 400 mg OD and a placebo matching the voriconazole regimen \( (n = 3) \) for a further 14 days.

Following the first dose, each subject was observed closely for 12 hours and multiple blood samples were collected for pharmacokinetic analysis. Three 4-hour safety and pharmacokinetic monitoring visits were scheduled for Days 4, 7, and 10, and on Day 14 (end of treatment), the subject returned for a 12-hour pharmacokinetic monitoring visit. On Day 15, the subject returned for a safety visit that included a repeat of the ophthalmologic tests originally performed at screening. On Day 21, the subject returned for a final safety monitoring visit.

**Pharmacokinetic Sampling**

On Days 1 and 14 of each study phase, blood samples were collected prior to dose and at 1, 2, 4, 8, and 12 hours postdose to assess plasma voriconazole concentrations. On the mornings of Days 4, 7, and 10, predose blood samples were collected to assess plasma voriconazole trough (\( C_{min} \)) concentrations. Blood samples sufficient to provide 4 ml of plasma were collected in heparinized tubes. Samples were centrifuged at 1300 g at 5°C for 15 minutes within 30 minutes of collection and stored upright in screw-capped polypropylene tubes at -20°C.

**Assays**

Plasma samples were assayed for voriconazole using a previously validated high-performance liquid chromatography (HPLC) assay (Huntingdon Life Sciences, Huntingdon, Cambridgeshire, UK).\(^3\) Over the calibration range 25-2500 ng/ml, the interbatch precision and inaccuracy of the assay, as assessed from the coefficients of variation and mean relative errors of the quality control samples analyzed during test sample analysis, were in the ranges of 3.8% to 7.6% and 0.6% to 4.4%, respectively. The assay had been previously validated over the concentration range of 10 to 3000 ng/ml, with the lower limit of quantification of this assay, 10 ng/ml, having a precision at this level of 0.8%.

**Study Drugs**

In this study, 50 mg and 200 mg active and placebo voriconazole tablets and 200 mg active and placebo fluconazole tablets were used. Study drug was taken with 8 ounces of water on an empty stomach at least 1 hour before or 2 hours after a meal.

**Safety Assessments**

**Adverse events.** All adverse events that occurred during treatment were recorded and documented according to their severity, time of onset and duration, and the investigator’s assessment of their relationship to study drug treatment. Events involving adverse drug reactions, illnesses with onset during the study, or exacerbations of preexisting conditions were recorded. Objective test findings (e.g., visual examination findings, abnormal 12-lead electrocardiogram, or laboratory tests) that resulted in dose change or study drug discontinuation were recorded as adverse events. All adverse events were followed up, even after treatment was discontinued, until their sequelae had resolved or stabilized. Investigators were also requested to immediately report any serious adverse events occurring during the study or events occurring up to 30 days after the last dose of study drug, regardless of treatment period or suspected relationship to drug.

**Visual tests.** To further characterize the visual adverse events that have been reported in previous voriconazole studies, the following visual tests were performed: funduscopy, visual acuity, color vision and contrast sensitivity, photostress recovery time, and fundus color photography. Subjects reporting visual disturbances at any time during the study were asked to notify the investigator. The investigator was to arrange a return to the study unit, preferably within 2 hours of onset of symptoms, to perform a complete medical evaluation. This included the completion of a comprehensive questionnaire to characterize the nature and severity of the visual disturbance.

**Routine tests and other safety parameters.** Routine hematology tests, clinical chemistry tests, urinalysis, and hepatitis screens were performed on samples taken at screening and on Days 1, 4, 7, 10, 15, and 21. Samples were processed at the study site and sent on dry ice to Covance, Inc. (Indianapolis, IN). Measurements of selected vital signs (blood pressure and pulse) were also conducted on Days 1, 4, 7, 10, 15, and 21, while a
12-lead electrocardiogram was performed at screening and on Days 7 and 15.

To evaluate whether voriconazole administration is associated with an elevation of endogenous retinoid levels, blood samples were drawn for retinol and retinol-binding protein assays. Samples for retinol determination were drawn up to 12 hours after dosing on Days 1, 4, 7, 10, and 14 and were stored frozen, protected from light, and assayed using standard HPLC techniques.

Pharmacokinetic Analysis

The maximum observed plasma voriconazole concentration (C\text{max}) and the time to the first occurrence of C\text{max} (t\text{max}) were obtained directly from the plasma concentration-time curves. The area under the plasma concentration-time curves predose to 12 hours after dosing on Days 1 (AUC\text{12}) and 14 (AUC\text{τ}) was calculated by the linear trapezoidal rule. For dose proportionality analysis, C\text{max} and AUC were dose normalized to the 200 mg dose of voriconazole (NC\text{max} and NAUC, respectively).

Statistical Analysis

Log (NC\text{max}) and log (NAUC) were compared between voriconazole and placebo groups by one-way analysis of variance (ANOVA) on Days 1 and 14 separately to assess dose proportionality after single dosing and after multiple dosing. In addition, t\text{max} values were compared among dose groups for Days 1 and 14 separately using one-way ANOVA.

RESULTS

Subjects

There were 37 subjects from three centers screened and 24 randomized to treatment. One subject in the fluconazole group discontinued due to a moderate treatment-related adverse event. All 24 subjects were evaluated for safety; 18 subjects were evaluated for voriconazole pharmacokinetics. The demographic characteristics of the voriconazole (n = 18) and fluconazole (n = 6) groups were similar with respect to age (range: 23-61 years), weight (range: 48-95 kg), and gender (11 male, 13 female).

At study entry, 17 and 23 subjects reported the presence or a history of diseases/syndromes, respectively. Eye disorders (n = 2), color vision deficiencies (n = 2), and enhanced visual acuity in one eye (n = 1) were the only visual history data reported on entry. Six subjects had a history of breast cancer, and 1 had a history of secondary neoplasm of the bone/bone marrow. Seven and 12 subjects, respectively, reported the presence or a history of malignant lymphatic or hematopoietic cancer. Four subjects were receiving treatment for hypothyroidism. The most commonly prescribed medications prior to study entry were antibacterials (n = 6) and ulcer-healing drugs (n = 6).

Pharmacokinetics

Mean study drug plasma concentration profiles for both voriconazole dose groups on Days 1 and 14 are shown in Figure 1.

On Days 1 and 14, AUC values were 1.94- and 1.80-fold higher in subjects receiving 300 mg q 12 h voriconazole than in those receiving 200 mg q 12 h, respectively. In both dose groups, individual AUC values on multiple dosing were variable, with intersubject coefficients of variation at Day 14 ranging from 45% (300 mg q 12 h) to 69% (200 mg q 12 h) (Table I).

On Days 1 and 14, mean C\text{max} was 1.80- and 1.56-fold higher in subjects receiving 300 mg q 12 h voriconazole than in subjects receiving 200 mg q 12 h, respectively (Table I). Individual C\text{max} values on multiple dosing varied more than 3-fold, with coefficients of variation ranging from 35% (300 mg q 12 h) to 51% (200 mg q 12 h). C\text{max} was reached between 1.7 and 3.0 hours, but wide intersubject variation in t\text{max} was noted on multiple dosing in each dose group, with coefficients of variation ranging from 51% (300 mg q 12 h) to 60% (200 mg q 12 h).

The accumulation index (AIAUC) indicated that there was a 5.4- and 5.0-fold accumulation of voriconazole over the 14-day study period in the 200 mg q 12 h and 300 mg q 12 h dose groups, respectively (Table I).

Figure 1. Mean plasma voriconazole concentrations on Days 1 and 14. (Error bars represent standard error margins.)
Mean plasma voriconazole $C_{min}$ was higher for 300 mg q 12 h (range: 374-4276 ng/ml) than for 200 mg q 12 h (range: 65-2685 ng/ml) dosing over the course of the 14-day treatment. For both dose groups, visual inspection of mean trough plasma concentration data (Figure 2) suggested that steady-state concentrations were achieved between Days 4 and 7.

Over the range studied, the ratios of the geometric means between doses for NAUC and NC$_{max}$ were greater than 1 on both Days 1 and 14, suggesting that voriconazole pharmacokinetics was not proportional to dose (Table II).

### Safety

**Discontinuations.** One subject discontinued fluconazole after 3 days of treatment due to moderate treatment-related abdominal pain. This symptom subsequently resolved within 5 days of treatment termination. There were no dose reductions as a result of adverse events.

**Adverse events.** A total of 6 of 9 subjects in the 200 mg q 12 h group, 8 of 9 subjects in the 300 mg q 12 h group, and 5 of 6 subjects in the fluconazole control group experienced an adverse event (Table III). Three serious adverse events were observed (fever, wound infection, upper respiratory tract infection) in the voriconazole groups, none of which was considered treatment related by the investigator. With the exception of 1 subject withdrawing from the study due to moderate abdominal pain, there were no serious adverse events in the fluconazole group. All treatment-related adverse events were mild to moderate in nature. The adverse

### Table I  Summary of Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Voriconazole</th>
<th>200 mg q 12 h (n = 9)</th>
<th>300 mg q 12 h (n = 9)</th>
<th>(300 mg q 12 h)/(200 mg q 12 h) Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 14</td>
<td>Day 1</td>
</tr>
<tr>
<td>AUC$^a$ (ng•h/ml)</td>
<td>4044  (38)</td>
<td>20,308 (69)</td>
<td>7839  (33)</td>
</tr>
<tr>
<td>$C_{max}^a$ (ng/ml)</td>
<td>904   (37)</td>
<td>2996 (51)</td>
<td>1630  (44)</td>
</tr>
<tr>
<td>$t_{max}^b$ (h)</td>
<td>2.8   (2.3)</td>
<td>1.7  (1.0)</td>
<td>1.7   (1.0)</td>
</tr>
<tr>
<td>AIAUC$^c$</td>
<td>5.4  (2.3)</td>
<td>5.0 (1.9)</td>
<td>—</td>
</tr>
</tbody>
</table>

a. Geometric mean (coefficient of variation [%]). Both parameters calculated for the period 0 to 12 hours postdose.

b. Arithmetic mean (± SD).

c. Accumulation index (AUC$_{\tau}$/AUC$_{12}$), arithmetic mean of individual values (± SD).

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### Table II  Ratios of Dose-Adjusted Geometric Means for Voriconazole 200 mg and 300 mg Doses

<table>
<thead>
<tr>
<th></th>
<th>Ratio of Means</th>
<th>Upper and Lower Limits of 90% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAUC$_{12}$ (Day 1)</td>
<td>1.292</td>
<td>0.954, 1.751</td>
</tr>
<tr>
<td>NAUC$_{14}$ (Day 1)</td>
<td>1.198</td>
<td>0.761, 1.887</td>
</tr>
<tr>
<td>NC$_{max}$ (Day 1)</td>
<td>1.203</td>
<td>0.844, 1.714</td>
</tr>
<tr>
<td>NC$_{max}$ (Day 14)</td>
<td>1.037</td>
<td>0.726, 1.483</td>
</tr>
<tr>
<td>AIAUC$^a$</td>
<td>0.927</td>
<td>0.670, 1.284</td>
</tr>
</tbody>
</table>

a. Accumulation index (AUC$_{\tau}$/AUC$_{12}$), geometric mean of individual values.

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Figure 2. Mean plasma voriconazole trough concentrations on Days 1 and 14. (Error bars represent standard error margins.)
Table III  Adverse Events Experienced by More Than 1 Subject in Any Period (all entries are numbers of subjects)

<table>
<thead>
<tr>
<th></th>
<th>Voriconazole 200 mg q 12 h (n = 9)</th>
<th>Voriconazole 300 mg q 12 h (n = 9)</th>
<th>Fluconazole 400 mg OD (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total subjects with adverse events</td>
<td>6</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Total adverse events</td>
<td>20</td>
<td>25</td>
<td>15</td>
</tr>
<tr>
<td>(Treatment related)</td>
<td>(1)</td>
<td>(13)</td>
<td>(5)</td>
</tr>
<tr>
<td>Total serious adverse events</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>(Treatment-related)</td>
<td>(1)</td>
<td>(0)</td>
<td>(0)</td>
</tr>
<tr>
<td>Most common adverse events (all causality)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Abnormal vision</td>
<td>2</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Photophobia</td>
<td>0</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

DISCUSSION

This study in patients at risk of fungal infection showed that orally administered voriconazole at both 200 mg and 300 mg doses given q 12 h was absorbed, with a \( t_{\text{max}} \) of 1.7 to 3.0 hours after dose administration, and showed fivefold accumulation on multiple dosing over 14 days of treatment.

The pharmacokinetic characteristics of voriconazole following oral administration to patients at risk of fungal infections were consistent with data from previous oral and IV-to-oral switch pharmacokinetics studies in healthy volunteers.\(^{31,32}\) These earlier studies also indicated that the use of a loading dose (two doses of 6 mg/kg IV or 400 mg PO q 12 h on Day 1) re-
results in the rapid attainment of $C_{\text{max}}$ in most subjects. It is on this basis that the clinical recommendation for the use of a loading dose is based.

In common with findings in healthy volunteers, there was a trend in this study toward nonlinear pharmacokinetics ($C_{\text{max}}$ and $AUC$) with respect to dose. Voriconazole accumulation with stable mean plasma concentrations achieved between Days 4 and 7 of multiple dosing suggests consistent absorption over time. Previous studies have indicated that voriconazole has a high level of bioavailability and that first-pass metabolism is rapidly and completely saturated, even at low doses of the drug. Therefore, it is likely that the accumulation and apparent nonlinear pharmacokinetics of voriconazole in this study are attributable to saturation of its metabolism and systemic clearance.

The similarity of the pharmacokinetic profiles of voriconazole in healthy volunteers and patients contrasts with those of itraconazole, a first-generationazole antifungal agent used for the treatment of serious fungal infections. It has been demonstrated that itraconazole has decreased oral absorption in patients with AIDS and those with hematological malignancy. Although the current study was not designed to assess the efficacy of voriconazole in these high-risk patients, it is reassuring to note that none of the patients treated with voriconazole during the study had a breakthrough fungal infection.

Voriconazole was well tolerated by patients at risk of serious fungal infection, with no discontinuations or dose adjustments. Voriconazole demonstrated tolerability comparable to fluconazole, an antifungal agent with extensive safety information accumulated from broad use. Abnormal vision and photophobia were the only treatment-related adverse events reported by more than 1 patient. These events were all mild in nature and cleared without intervention. Mild, transient visual disturbances have been widely reported following voriconazole administration. A range of additional tests was incorporated in the protocol to provide a comprehensive assessment of visual function. The results of these tests did not provide any evidence of damage to the retina or visual function following voriconazole administration.

It has been reported that patients can develop a rash following voriconazole administration. To investigate whether a mechanism for this reaction is the elevation of endogenous retinoid levels (by voriconazole competitively inhibiting hepatic CYP3A4-mediated retinoic acid metabolism), retinol and retinol-binding protein (RBP) were assayed throughout the study in both voriconazole treatment groups. The results from these assays suggest that voriconazole does not elevate endogenous retinoid concentrations compared with baseline levels. Based on the data from this study, it seems unlikely that this is the mechanism for the development of photosensitivity-associated rashes during voriconazole therapy.

In conclusion, the pharmacokinetic profile of voriconazole in patients at risk of fungal infection was consistent with that reported in healthy volunteers, in contrast to some earlier generation azoles. Voriconazole kinetics was characterized by nonlinearity in the dose range studied, relatively rapid absorption, and accumulation.

REFERENCES
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