Steady-State Pharmacokinetics of Oral Voriconazole and Its Primary Metabolite, N-Oxide Voriconazole, Pre- and Post-Autologous Peripheral Stem Cell Transplantation

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Voriconazole (VCZ) is frequently utilized for prevention and treatment of invasive fungal infections in peripheral stem cell transplant (PSCT) patients. We performed an open-label pharmacokinetic study to compare VCZ and N-oxide voriconazole (N-oxide VCZ) pharmacokinetics in patients pre- and post-PSCT. Ten patients completed both sampling periods. The pharmacokinetics of VCZ were unchanged; however, those of N-oxide VCZ were significantly different pre- and post-PSCT.

Voriconazole (VCZ) is considered first-line therapy for invasive aspergillosis and is often empirically prescribed to prevent the emergence of invasive fungal infections in patients undergoing a peripheral stem cell transplant (PSCT) (1, 2). In volunteers and patients, VCZ displays highly variable nonlinear pharmacokinetics, which are due primarily to polymorphic cytochrome P450 2C19 (CYP2C19) metabolism (3–6). Overall, the mean pharmacokinetic data of hematological-oncological patients are similar to those of healthy volunteers (7, 8). After oral and intravenous administration, VCZ is extensively metabolized to inactive metabolites, including N-oxide VCZ, 4-hydroxy-VCZ, and dihydroxy-VCZ (5, 9, 10). The primary VCZ metabolite, N-oxide VCZ, results from the N-oxidation of the fluoroypyrimidine ring and accounts for 21% of the VCZ recovered dose (9). The formation of this metabolite is catalyzed primarily by CYP2C19 and CYP3A4 (9–12). VCZ pharmacokinetics are further influenced by the genetic polymorphisms of CYP2C19, other drug-metabolizing enzymes, and age-based differences in drug metabolism (10–17). The pharmacokinetics of VCZ have been studied, but those of N-oxide VCZ remain poorly characterized in PSCT patients. Therefore, the primary objective of this study was to characterize oral VCZ and N-oxide VCZ pharmacokinetics pre- and post-adult autologous PSCT.

This was an open-label, single-center pharmacokinetic study of adults undergoing an autologous PSCT and receiving oral VCZ. Patients were >17 years old, medically stable, and prescribed VCZ for prophylactic antifungal therapy by their primary physician. All subjects in the study were diagnosed with multiple myeloma, were undergoing a melphalan-based autologous PSCT, and provided informed consent. Patients with clinical and laboratory evidence of veno-occlusive disease, aplastic anemia, liver disease (Child-Pugh classification B or C), a history of gastrointestinal illness, or surgery that may affect drug absorption or galactose intolerance were excluded from this study. Patients with a history of anaphylaxis to VCZ or other triazole antifungal agents or who received a systemic antifungal agent within 7 days of receiving VCZ as well as other drugs that are known to be substrates of CYP2C19, CYP3A4, or CYP2C9 were excluded. All subjects received 400 mg VCZ orally every 12 h on day 1, followed by 200 mg orally every 12 h on days 2 to 17. As part of their standard immunosuppression regimen, all subjects received high-dose dexamethasone. Repeated blood sampling occurred 2 days following the loading dose (study day 3) and 6 days post-PSCT (study day 12) at predose and 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, and 12.0 h after the a.m. dose. All blood samples were analyzed in singlet by PPD/Pharmaco for analysis by high-performance liquid chromatography (HPLC) and mass spectrometry according to PPD method LCMS 244 V 2.00 (18). The accuracy of the values for N-oxide VCZ was not guaranteed. Noncompartmental pharmacokinetic analysis of serum concentration data was performed using WinNonlin (Pharsight, St. Louis, MO). Statistical significance was defined a priori as an α value of ≤0.05. Statistical analysis was performed with NCSS 2001 (Number Cruncher Statistical Systems, Kaysville, UT).

In the study, 14 patients were enrolled, but only 10 patients (6 males) completed both pharmacokinetic sampling periods (day 3 and day 12), and only those are presented. The demographics of the 10 patients who completed both VCZ sampling arms are provided in Table 1, and the mean VCZ and N-oxide VCZ plasma concentration-time curves on days 3 and 12 are displayed in Fig. 1. Male and female subjects differed significantly for weight, height, mg/kg of body weight/dose, and mg/kg/day, but the body mass index (BMI) did not significantly differ between the genders. VCZ and N-oxide VCZ pharmacokinetics demonstrated considerable...
interpatient variability. Overall, on days 3 and 12, VCZ pharmacokinetic parameters were not significantly different (Table 2). On days 3 and 12, the mean VCZ concentrations at hour 12 (C₁₂) were 1.58 g/ml (range, 0.135 to 3.63 g/ml) and 1.84 g/ml (range, 0.09 to 3.89 g/ml), respectively (P = 0.4). The primary metabolite N-oxide VCZ demonstrated significant pharmacokinetic changes between days 3 and 12 (Table 2). Parent-to-metabolite (VCZ/N-oxide VCZ) ratios were also compared for the maximum concentration of the drug (Cₘₐₓ) and the area under the concentration-time curve from 0 to 12 hours (AUC₀₋₁₂) on days 3 and 12 (Table 2). Day 12 VCZ/N-oxide ratios for Cₘₐₓ and AUC₀₋₁₂ were increased by 50% and 47.5%, respectively, compared to day 3.

The pharmacokinetic values of oral VCZ in our study are consistent with those of previous multiple-dose studies that used a loading dose (19, 20). Therefore, our data suggest that the standard oral VCZ dosing regimen is sufficient to adequately maintain prophylactic VCZ serum concentrations and exposure in most patients pre- and post-PSCT. Moreover, dosages recommended by approved labeling for adults achieved adequate mean C₁₂ values on days 3 and 12 for prophylaxis (>0.5 µg/ml). However, given the range of C₁₂ values observed, standard dosing may be inadequate for the treatment of invasive infections and may even be insufficient for prophylaxis in certain patients (21, 22). Unlike VCZ, the N-oxide VCZ pharmacokinetic values were all significantly decreased on day 12 compared to day 3. Because there were no significant pharmacokinetic changes in the parent compound during the study period, the significant changes in N-oxide VCZ pharmacokinetics are intriguing and are most likely due to further metabolism via other CYP enzymes (5, 9–12).

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![FIG 1 Day 3 and day 12 mean VCZ and N-oxide VCZ serum concentrations (n = 10). Error bars represent standard deviations (SD) of the mean. ■, VCZ day 3; ●, VCZ day 12; □, N-oxide VCZ day 3; ○, N-oxide VCZ day 12.](https://aac.asm.org/)

**TABLE 1** Demographics for patients that underwent day 3 and day 12 VCZ sampling

<table>
<thead>
<tr>
<th>Demographic variable</th>
<th>Female (n = 4)</th>
<th>Male (n = 6)</th>
<th>Overall (n = 10)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>66.5 (51–76)</td>
<td>67.5 (67–69)</td>
<td>67.1 (51–76)</td>
<td>0.86</td>
</tr>
<tr>
<td>Wt (kg)</td>
<td>60.9 (53–74.7)</td>
<td>88.7 (80.3–108.9)</td>
<td>77.6 (53–108.9)</td>
<td>0.003</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>161.6 (155–168)</td>
<td>178 (165–188)</td>
<td>171.4 (155–188)</td>
<td>0.006</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.3 (20.8–28.3)</td>
<td>28.1 (23.8–32.5)</td>
<td>26.2 (20.8–32.5)</td>
<td>0.06</td>
</tr>
<tr>
<td>Dose (mg/kg)</td>
<td>3.4 (2.7–3.8)</td>
<td>2.3 (1.8–2.5)</td>
<td>2.7 (1.8–3.8)</td>
<td>0.002</td>
</tr>
<tr>
<td>Dose (mg/kg/day)</td>
<td>6.7 (5.4–7.5)</td>
<td>4.6 (3.7–5)</td>
<td>5.4 (3.7–7.5)</td>
<td>0.0015</td>
</tr>
</tbody>
</table>

*Values are means (ranges).*
able consequence of our patients receiving high-dose dexamethasone, which is known to activate glucocorticoid receptor (GR). GR activation can increase the transcription of CYP2C19 and CYP3A4 enzyme gene expression and possibly induction effects (23). Visual inspection of our VCZ serum concentrations does not suggest induction between days 3 and 12, but others have observed VCZ induction (24). To our knowledge, this is the first report of VCZ/N-oxide ratios with repeated dosing in patients without interacting medications. The day-3 ratios in this study are consistent with those of two other steady-state oral VCZ studies that compared VCZ and the N-oxide metabolite (19, 20). In a third study, the ratios for Cmax and AUC0-12 were lower than ours (25). However, that study was performed only in adult females who were considerably younger than our subjects (mean of 25.9 years versus 67.1 years, respectively). While the sex differences between the study populations may have contributed to the differences in parent-to-metabolite ratios, the effect of sex on CYP2C19 is inconclusive (26). Lastly, the reductions may reflect analytical artifact. Nonetheless, while the accuracy of the metabolite concentrations in this study cannot be guaranteed, the serum N-oxide VCZ concentrations, pharmacokinetic values, and parent drug/metabolite ratios we obtained are consistent with those measured by others employing a similar regimen (7, 8, 13, 19, 20, 25). Moreover, assay precision is not affected by sample age and was within the acceptable range for assay performance. Therefore, our data suggest that a decline in N-oxide VCZ serum concentrations occurred between days 3 and 12, but the exact values and magnitude of that decline cannot be reliably characterized by our study.

In conclusion, our data suggest that the standard VCZ oral loading and maintenance dosing regimens are sufficient to maintain prophylactic VCZ serum concentrations and exposure in most patients pre- and post-PSCT. However, we noted a significant decline in N-oxide VCZ serum concentrations and pharmacokinetic values. Although this finding is interesting, the clinical significance and metabolic implications of these changes need further study.

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