Serial Plasma Voriconazole Concentrations after Allogeneic Hematopoietic Stem Cell Transplantation

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Plasma voriconazole concentrations vary considerably between patients receiving standard dosing, and trough voriconazole concentrations are known to affect efficacy and toxicity. Temporal variations in serial plasma voriconazole concentrations through the course of therapy in hematopoietic stem cell transplantation patients has not been carefully described. Paired voriconazole concentrations in 64 patients were studied to determine the predictability of the second concentration based on the first. The difference between the two values was ≤5% in six patients. In 25 patients, the second concentration was higher by a median of 40%. In 33 patients, the subsequent concentration was lower by a median of 59%. For patients with an initial concentration of <2 μg/ml, the correlation between the two values was poor (r = 0.24; P < 0.17). For those with an initial concentration of ≥2 μg/ml, the correlation was good (r = 0.72; P < 0.0001). There was no relationship between the magnitude of the change and the time elapsing between the two measurements. Among the 43 patients who had an initial concentration of ≥1 μg/ml, the two voriconazole measurements were strongly correlated (r = 0.66, P < 0.0001), but only 67% had a voriconazole serum concentration of ≥1 μg/ml on the second measurement. No studied variables were reliable predictors in identifying concentrations above or below 1 or 2 μg/ml. Our data suggest that variations in voriconazole concentrations are unpredictable despite standard dosing, and the acceptability of a concentration on one occasion cannot be extrapolated to future concentrations in the same patient. This suggests that ongoing therapeutic drug monitoring and dose adjustment may be beneficial in patients requiring prolonged voriconazole therapy.

Invasive fungal infections are a significant source of morbidity and mortality following allogeneic hematopoietic stem cell transplantation (HSCT). Voriconazole, a triazole antifungal agent, is frequently used in the treatment of many yeast and mold infections following HSCT (2, 7). Use of voriconazole for prevention of opportunistic fungal infections has also shown merit (16). Voriconazole is metabolized by the cytochrome P450 isoenzyme system, primarily CYP 3A4, CYP 2C9, and CYP 2C19 (3). Genetic polymorphism of the CYP 2C19 isoenzyme, interactions with several drugs used during the post-transplantation period, self-induced voriconazole metabolism, and direct hepatotoxicity from the conditioning regimen can alter the metabolism and disposition of voriconazole significantly (1, 8). This may increase or decrease voriconazole exposure in an unpredictable fashion, and large inter- and intrapatient variations in voriconazole plasma concentrations have been observed in several reports (11, 12, 14). Recent studies have suggested that there is an association between voriconazole plasma concentrations and successful treatment outcomes, indicating a possible need for therapeutic drug monitoring (TDM) (5, 9, 13).

Although the optimum duration of voriconazole prophylaxis and therapy for most fungal infections has not been defined clearly, most allogeneic HSCT recipients require prolonged antifungal therapy—often for several months. Since physiology (e.g., absorption, metabolism, and protein binding) and pharmacologic (e.g., drug interactions and nonlinear kinetics) conditions change over time following HSCT, plasma voriconazole concentrations would be expected to vary. The temporal variation of plasma voriconazole concentrations through the course of therapy in HSCT patients when measured serially has not been carefully described. We report the results of paired plasma voriconazole measurements in 64 patients following allogeneic HSCT.

MATERIALS AND METHODS

Adult patients with hematologic malignancies who had undergone allogeneic HSCT at Northwestern Memorial Hospital between June 2004 and January 2007 and received voriconazole for prophylaxis of invasive fungal infection were identified. Paired voriconazole trough plasma concentrations were systematically drawn 30 min prior to the next dose from HSCT recipients. Concentrations were quantified by standardized high-pressure liquid chromatography assay at the University of Texas at San Antonio Health Science Center (6).

Patients were included in the analysis if the paired measurements fulfilled the following criteria: (i) patients were hospitalized for the entire study period, (ii) there were identical voriconazole doses for both measurements, (iii) both plasma concentrations were measured a minimum of 6 days after voriconazole therapy was initiated (to assess plasma steady-state concentrations), (iv) only oral voriconazole was administered during the study period (i.e., no intravenous voriconazole), and (v) no patient received voriconazole during the study period for treatment of invasive fungal infection (i.e., only patients receiving prophylactic voriconazole were included).

Although all patients experienced some degree of mucositis and diarrhea, documentation was not consistent enough to allow classification according to...
TABLE 1. Voriconazole plasma concentrations

<table>
<thead>
<tr>
<th>Variable</th>
<th>Plasma concn (µg/ml)</th>
<th>Initial</th>
<th>Follow-up</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>&lt;0.2–10.0</td>
<td>&lt;0.2–11.84</td>
<td>0.38</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>2.50</td>
<td>2.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>1.78</td>
<td>1.24</td>
<td>0.62</td>
<td></td>
</tr>
<tr>
<td>Undetectable (&lt;0.2 µg/ml)</td>
<td>6 (9)</td>
<td>10 (16)</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>≥1.0 µg/ml</td>
<td>43 (67)</td>
<td>38 (59)</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>≥2.0 µg/ml</td>
<td>29 (45)</td>
<td>23 (36)</td>
<td>0.28</td>
<td></td>
</tr>
</tbody>
</table>

* Percentages are given in parentheses.

World Health Organization or National Cancer Institute grading criteria, and thus these parameters could not be analyzed. A clinical pharmacist verified drug compliance with the prescribed regimen via medication administration records. Our cohort of allogeneic HSCT recipients did not receive any other drugs known to interact with voriconazole disposition or metabolism. This retrospective study was reviewed and approved by the Northwestern University Institutional Review Board.

Statistical methods. Correlation analysis was used to determine the test-retest reliability of the two voriconazole measurements and to evaluate the association between voriconazole measurements, inter-recording interval, and weight. A 95% confidence interval for proportions was constructed for the proportion of samples that fell below 1 or 2 g/ml on the second test. Optimal data analysis was used to statistically discriminate patients with voriconazole plasma concentrations that did or did not fall below 1 or 2 µg/ml on the second test (17). The reason for choosing 1 to 2 µg/ml as a threshold was evidence that this plasma concentration may influence efficacy (5, 9, 13).

RESULTS

All patients (n = 64) had hematologic malignancies (40 leukemia, 16 lymphoma, 6 myeloma, and 2 myelodysplastic syndrome). Voriconazole was given orally to all patients in the present study at a dose of 200 mg twice daily in 81% of the patients, 300 mg twice daily in 13% of the patients, and other doses in 6% of the patients. The drug dose based on the actual body weight was 2.7 to 12.0 mg/kg (median, 5.8 mg/kg). Patients received voriconazole for primary (80%) or secondary prophylaxis (20%). Thirty-six had received a conventional-intensity conditioning regimen, and twenty-eight had undergone a reduced-intensity allograft. The time interval between the two plasma concentrations was 1 to 252 days (median, 15 days).

Table 1 shows the paired plasma concentrations. The difference between the two plasma concentrations was ≤5% in six patients. In 25 patients, the plasma concentration increased by 6 to 1,865% (median, 40%). In 33 patients, the plasma concentration declined by 11 to 96% (median, 59%). This is graphically illustrated in Fig. 1 (where two increases of 1,865 and 650%—have not been charted due to constraints of scale). Positive numbers represent an increase from the first to the second level and negative numbers represent a decline.

Among the 29 patients who had a voriconazole plasma concentration of ≥2 µg/ml on the first measurement, 18 (62%; 95% confidence interval, 34 to 80%) had a voriconazole plasma concentration of ≥2 µg/ml on the second measurement. In these 29 patients, correlations did not exist between plasma concentrations and the time interval between the measured concentrations (P = 0.60) or patient weight (P = 0.49). Optimal data analysis revealed that all 10 patients with an initial voriconazole plasma concentration of ≥4.6 µg/ml had a second voriconazole plasma concentration of ≥2 µg/ml (model positive predictive value of 100%). This finding was consistent when jackknife validity analysis was conducted, suggesting that this result is likely to cross-generalize to an independent random sample.

FIG. 1. Percent change in voriconazole plasma concentration in each of the 64 patients (the two highest changes—1,865 and 650%—have not been charted due to constraints of scale). Positive numbers represent an increase from the first to the second level and negative numbers represent a decline.

change and the time elapsing between measurement of the two plasma concentrations was observed (Fig. 4A). In the entire group, the median change from the first plasma concentration was a 22% decline. Figure 4B shows the lack of any obvious relationship between the magnitude of the change and the drug dose based on patient weight.

A lack of obvious relationship between the magnitude of the...
The optimal data analysis model predicted that when a patient’s initial plasma concentration is \( \leq 4.6 \, \text{g/ml} \), the second plasma concentration will be \( \geq 2 \, \text{g/ml} \). All 11 patients who in reality had a second plasma concentration of \( < 2 \, \text{g/ml} \) were correctly predicted by the optimal data analysis model to have a second plasma concentration \( \geq 2 \, \text{g/ml} \) (model specificity of 100%). The model was, however, not perfect, and eight patients with an initial plasma concentration of \( \leq 4.6 \, \text{g/ml} \) had a second plasma concentration of \( < 2 \, \text{g/ml} \), yielding model negative predictive value of 58% and a sensitivity of 56%.

For the sample of 43 patients who had a voriconazole plasma concentration of \( \leq 1 \, \text{g/ml} \) on the first measurement, the two voriconazole measurements were strongly correlated \( (r = 0.66, P < 0.0001) \). Plasma concentration was not significantly correlated with the inter-recording time intervals \( (P = 0.21) \) or weight \( (P = 0.62) \). Of the total of 43 patients, 33 (67%) had a voriconazole plasma concentration of \( \geq 1 \, \text{g/ml} \) on the second measurement. The 95% confidence interval for the proportion of patients with a second voriconazole recording below 1 \( \mu g/ml \) regardless of the inter-recording time interval, was 10.5 to 36.0%. The initial voriconazole plasma concentration \( (P = 0.40) \), the intermeasurement interval \( (P = 0.90) \), or the weight \( (P = 0.77) \) were not statistically reliable discriminators of patients whose second voriconazole plasma concentration fell below 1 \( \mu g/ml \).

**DISCUSSION**

This report differs from previous efforts in that we assessed paired voriconazole plasma concentrations. This study confirms our previous reports of significant inter- and intrapatient variability in voriconazole disposition at standard doses used in practice (11, 12). Of the 128 obtained plasma concentrations, 30 were included in our first report of voriconazole plasma concentrations after HSCT, and 84 were included in our second report of variability in voriconazole plasma concentrations after HSCT (11, 12). Statistical techniques were applied to determine whether, despite the inter- and intrapatient variations, it was possible to predict subsequent changes in a patient’s voriconazole plasma concentration based upon the first plasma concentration. Our data suggest that with current assessed variables, it is not possible to predict subsequent voriconazole concentrations with any degree of clinical certainty.

TDM is recommended to improve the safety and efficacy of drug therapy when drugs exhibit wide inter- or intrapatient variability and there is a relationship between measured concentrations and safety or efficacy. A lack of prospective studies has hampered our understanding of the role of TDM for oral antifungal therapy. However, growing evidence suggests that there is a relationship between voriconazole plasma concentrations for efficacy as well as toxicity (5, 9, 13). Hence, these findings implicate a role for TDM at least in some patients, and recently formulated evidence-based guidelines for the management of aspergillosis now recommend voriconazole TDM, along with clinical assessment for optimal treatment efficacy and safety (15).

Two retrospective studies have shown a correlation between voriconazole plasma concentrations of \( \geq 2 \, \mu g/ml \) and successful treatment outcomes for patients with aspergillosis (9) or prevention of breakthrough *Candida glabrata* infections (13). Recently, a prospective study of 52 patients with invasive fun-
gal infections which incorporated TDM to adjust voriconazole dosing to achieve plasma concentrations between 1 and 5.5 μg/ml found significantly more favorable outcomes among patients whose plasma concentrations were maintained within the target range. All six patients with subtherapeutic voriconazole plasma concentrations and inadequate clinical response had successful outcomes when the voriconazole dose was increased to attain plasma concentrations in the target range. Increased toxicity was also seen as voriconazole plasma concentrations increased beyond 5.5 μg/ml (5).

Voriconazole may display nonlinear pharmacokinetics, and it takes approximately 5 days to reach steady-state plasma concentrations (10). We conservatively measured plasma concentrations 6 to 7 days after starting therapy. Interestingly, we found that the voriconazole plasma concentrations drawn 6 days after the initiation of therapy tend to be higher than plasma concentrations measured at a later date in the same patient. This suggests that reliance upon a single early plasma concentration could overestimate the proportion of patients in whom drug plasma concentrations are therapeutic. This undesirable change in voriconazole plasma concentrations out of the target range could not be predicted by patient weight or the time interval between the two voriconazole measurements. This report is consistent with the findings of previous studies; that there are large and unpredictable inter- and intrapatient variations in voriconazole plasma concentrations with doses commonly used in clinical practice (11, 12, 14).

Finally, consistent with prior reports (4), ca. 20% of the voriconazole plasma concentrations were undetectable, and 35% were below the MICs for mold infections. Neither of these outcomes could be predicted by dose, weight, or time interval between measurements. The cause of the decline in voriconazole plasma concentrations over time is probably multifactorial and may include changes in absorption, patient protein status, liver function, and disease modifying effects (e.g., graft-versus-host disease).

There are limitations with our study. It is quite possible that some of the changes in plasma concentrations were the result of changes in concomitant therapy or changes in patient variables. However, all concomitant therapy was solely dictated by clinical needs. Even with a prospective study, most patients would require extensive adjunct therapies due to the nature of the underlying illness and intervention. Thus, the data, despite being retrospective, were acquired under circumstances routinely seen in clinical practice. The results are from a single institution in a defined patient population and may not necessarily be entirely applicable to other patient populations.

Conclusions. Large intrapatient variability in plasma voriconazole concentrations (especially in patients with initially low measured plasma concentrations) suggests the need for repeated TDM in subjects requiring prolonged voriconazole administration.

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REFERENCES