Monitoring Plasma Voriconazole Levels May Be Necessary to Avoid Subtherapeutic Levels in Hematopoietic Stem Cell Transplant Recipients

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BACKGROUND. Low voriconazole levels have been associated with a higher failure rate in patients with confirmed fungal infections.

METHODS. Steady-state plasma trough voriconazole levels were measured after at least 5 days of therapy in 87 patients with hematologic malignancies on 201 separate occasions (1–5 levels per patient; median, 2). Most patients (90%) had undergone allogeneic hematopoietic stem cell transplantation. The daily voriconazole dose, administered in 2 divided doses, was 200 mg (n = 4), 400 mg (n = 151), 500 mg (n = 20), 600 mg (n = 18), and 800 mg (n = 8); corresponding to 2.0–16.3 (median, 5.4) mg/kg. Plasma voriconazole levels were 0–12.5 μg/mL (median, 1.2). Voriconazole was undetectable (<0.2 μg/mL) in 15%.

RESULTS. The correlation between dose and levels was weak ($r = 0.14$; $P = .045$). The median absolute daily drug dose (400 mg) was identical in groups of patients with levels of 0, 0.2 to 0.5, >0.5 to 2.0, >2.0 to 5.0, and >5.0. Whereas the daily drug dose in mg/kg was significantly higher when the levels were >5.0 μg/mL, there was no consistent relation between dose and level below that threshold. In adult patients getting standard doses of voriconazole orally, the drug levels are highly variable. Based on limited available data, between a quarter and two-thirds of these levels could potentially be associated with a lower likelihood of response or a higher likelihood of failure.

CONCLUSIONS. Future voriconazole studies should incorporate prospective therapeutic drug monitoring and consideration should be given to checking levels in patients receiving the drug for confirmed, life-threatening fungal infections. ***Cancer* 2007;109:1532–5.** © *2007 American Cancer Society.*

KEYWORDS: voriconazole, fungal infections, hematologic malignancies.

Therapeutic drug monitoring is recommended when individualization of drug dose is required to ensure safety and efficacy. There are limited data on the effects of monitoring drug levels and therapeutic success in fungal infections.[1–4] Because most of this evidence concerns itraconazole,[1–4] the Infectious Diseases Society of America guidelines recommend measurement of itraconazole trough levels in patients requiring prolonged oral therapy.[5] Targeting peak serum flucytosine concentrations was suggested to prevent emergence of resistant strains and toxicity.[6]

Voriconazole is a triazole antifungal agent used in the treatment of *Aspergillus* infections. It is metabolized by the liver cytochrome P450 system and displays nonlinear pharmacokinetics. The period after hematopoietic stem cell transplantation (HSCT) is characterized by the use of multiple drugs that can affect the cytochrome P450 system. In addition, the CP450 isoenzyme 2C19, which plays a

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TABLE 1
Patient Characteristics

No. of patients	87
No. of voriconazole specimens	201
No. of levels per patient, median (range)	2 (1–7)
Absolute dose in mg (median, range)	400 (200–800)
Dose based on weight in mg/kg, median (range)	5.4 (2.0–16.3)
Indication for voriconazole	
Prophylaxis	67 (77%)
Therapy	20 (23%)
Type of transplant	
Allograft	78 (90%)
Conventional intensity	−27 (35%)
Submyeloablative	−51 (65%)
Autograft	9 (10%)

TABLE 2
Voriconazole Levels by Absolute Daily Voriconazole Dose

Daily Total Dose, mg	No.	Voriconazole level, median (range)	Undetectable	<0.5 μg/mL	<2.0 μg/mL
200	4	2.16 (0–3.07)	1 (25%)	1 (25%)	2 (50%)
400	151	1.09 (0–11.11)*	22 (15%)	43 (28%)	97 (64%)
500	20	1.67 (0–5.99)	2 (10%)	4 (20%)	11 (55%)
600	18	1.57 (0–6.75)	3 (17%)	4 (22%)	11 (61%)
800	8	1.65 (0–12.50)*	2 (25%)	3 (38%)	4 (50%)
Overall	201	1.22 (0–12.50)	30 (15%)	55 (27%)	125 (62%)
P			.84	.86	.83

* $P = .034$.

major role in voriconazole metabolism, exhibits significant genetic polymorphism. Homozygous extensive metabolizers (normal) have significantly lower exposure than heterozygous extensive metabolizers or poor metabolizers.[7] In a preliminary study, we showed significant differences in voriconazole plasma levels in 25 HSCT recipients receiving similar doses of voriconazole.[8]

There is an association between higher plasma voriconazole levels and ocular toxicity.[9,10] An association between successful therapeutic outcome in *Aspergillus* infections and higher plasma voriconazole concentrations has been reported recently.[11] Analysis of data for 249 patients from 6 Phase III clinical trials of voriconazole has also shown a correlation between drug levels and outcome.[12] We recently found a relation between lower voriconazole levels and breakthrough infections with organisms susceptible to voriconazole in a dose-dependent fashion.[13]

However, because of a lack of prospective data the need for therapeutic voriconazole monitoring remains to be established. In this study we review our experience with voriconazole levels in HSCT recipients. The report includes some data that have been published previously.[8]

MATERIALS AND METHODS

Pharmacy records were reviewed to identify all HSCT recipients who had received voriconazole for at least 7 days and had trough plasma voriconazole concentrations measured using high-performance liquid chromatography[14] between January 2003 and May 2006. Steady-state trough blood levels of voriconazole were measured at least 5 days after the drug was initiated. This retrospective review was approved by Northwestern University's Institutional Review Board as part of a project evaluating outcome of allogeneic HSCT.

Our standard antifungal prophylaxis for allograft recipients is itraconazole. We switch to voriconazole when patients receive corticosteroids for graft-versus-host disease (GVHD) or have had a mold infection in the past. Voriconazole was given at the dose of 200 mg twice daily orally in such patients. In patients suspected to have aspergillosis, voriconazole was initiated at the dose of 6 mg/kg twice daily for a day, and then was continued at the dose of 4 mg/kg twice daily. Immunosuppression comprised cyclosporine (matched sibling donors) or tacrolimus (unrelated or mismatched donors). Additionally, recipients of conventional-intensity allografts received methotrexate on Days 1, 3, 6, and 11 posttransplant, whereas recipients of reduced-intensity transplants received mycophenolate mofetil 1000 mg twice daily.

RESULTS

All patients had hematologic malignancies. Table 1 shows patient characteristics. Most patients had undergone allogeneic HSCT, and three-quarters were receiving the drug prophylactically. The absolute daily drug dose was 400 mg in 75%.

As Table 2 shows, the drug was undetectable in 15% of the samples. The levels were <0.5 μg/mL in 27% of all samples and <2.0 μg/mL in 62% of all samples. The absolute voriconazole dose did not affect the categoric distribution of levels significantly, as shown by the *P* values (χ^2 test) in the table. Despite the seemingly different median drug levels (Table 2, column 3), none of the continuous comparisons (analysis of variance [ANOVA]) of levels between different absolute daily doses was significant ($P = .42-.94$) except the 1 between 400 mg and 800 mg ($P = .034$).

As Figure 1 shows, the correlation between voriconazole level and the daily dose was poor ($r = 0.14$; $P = .051$). However, as Table 3 shows, the daily mg/kg dose was significantly higher when the drug level was >5.0 μg/mL. Figure 2 shows levels in the 15

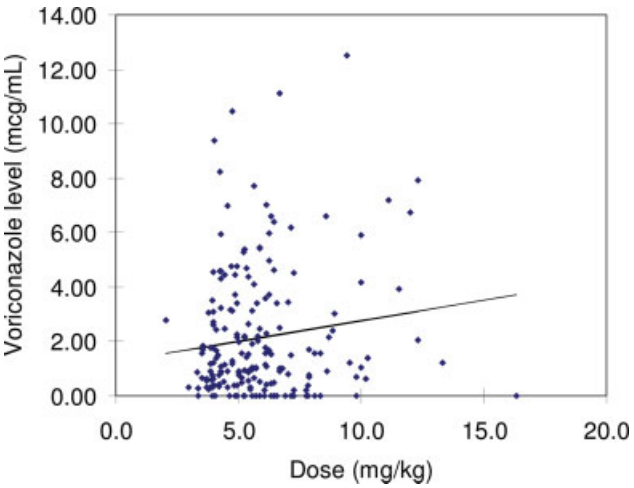

FIGURE 1. Correlation between voriconazole dose and drug level ($r = 0.14$; $P = .051$).

TABLE 3
Voriconazole Levels by Daily mg/kg Voriconazole Dose

Voriconazole level (μg/dL)	No.	Daily total dose in mg, median (range)	Daily dose in mg/kg, median (range)	*P* (for the daily mg/kg dose; compared with voriconazole level >5.00)
Undetectable	30 (15%)	400 (200–800)	5.6 (3.5–11.5)	.008
0.20–0.50	25 (12%)	400 (400–800)	6.2 (3.8–10.2)	.18
0.51–2.00	70 (35%)	400 (400–800)	5.2 (3.7–13.3)	.062
2.01–5.00	53 (26%)	400 (400–800)	4.9 (2.0–9.8)	.0008
>5.00	23 (11%)	400 (400–800)	6.9 (3.4–16.3)	
Overall	201	400 (200–800)	5.4 (2.0–16.3)	

patients with ≥4 drug level values—showing considerable intrapatient variability.

DISCUSSION

Our data show that in adult patients getting standard doses of voriconazole orally, the drug levels are highly variable. Based on the data on file at the Food and Drugs Administration (FDA),[12] 27% of these levels would be associated with a lower likelihood of response. Based on the data of Smith et al,[11] 65% of these levels would be associated with a higher likelihood of failure in patients with confirmed fungal infections. Our own data, in a relatively small number of patients, suggest a relation between lower voriconazole levels and breakthrough infections with organisms susceptible to the drug in a dose-dependent fashion.[13] The retrospective nature of all the evidence limits the conclusions that can be drawn from each individual study. However, when all available data are considered in aggregate, there seems to be a

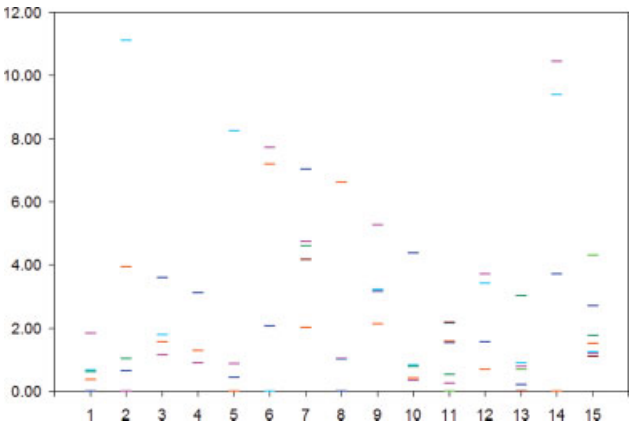

FIGURE 2. Voriconazole levels in 15 patients in whom ≥4 values were available illustrating variability.

suggestion that voriconazole levels are variable, and that there may be a relation between levels and likelihood of therapeutic success.

Voriconazole is primarily metabolized by the liver and displays nonlinear saturation kinetics. Small changes in dose can result in disproportionate changes in plasma concentrations. Changes sometimes occur spontaneously—possibly related to concomitant medications or gastrointestinal problems (eg, malabsorption related to GVHD). Figure 2 and our previous study[8] show this. In addition, differences in metabolism may occur because of genetic polymorphism in the cytochrome P450 enzyme 2C19,resulting in higher and more prolonged exposure to voriconazole for patients who are heterozygous or homozygous poor metabolizers. Over 90% of levels reported in this study were obtained when patients were in the hospital—and usually had been for a few days. Thus, each dose was verified as being given via the medication administration record, thereby eliminating compliance as a possible explanation for the variable results.

Although the evidence suggesting a relation between voriconazole concentrations and efficacy is increasing, there are no data on the magnitude of the problem of potentially subtherapeutic levels. If the proportion of patients with potentially subtherapeutic levels was small, there would be limited reason to monitor levels even if the consequences of subtherapeutic levels were potentially severe. One could simply check levels in patients failing to respond to therapy as expected and increase the dose if needed. However, our study suggests that the proportion of levels that are potentially subtherapeutic is high enough to warrant prospective work. A possible criticism of our study is that the patient population is relatively heterogeneous and the condi-

tions under which the drug was used are not uniform. In fact, this could be considered a strength of the study because it reflects real-life use of the drug.

Additional evidence supporting therapeutic drug monitoring comes from pharmacodynamic data. In vitro pharmacodynamic studies have shown that voriconazole, as with other triazoles, exhibits killing activity that is independent of peak concentrations, with maximum fungicidal activity around 2–3 times the minimum inhibitory concentration (MIC).[15,16] An in vivo murine *Candidiasis* study similarly reported concentration-independent fungicidal activity, with the area under the concentration-time curve (AUC)/MIC ratio being strongly predictive of treatment success.[17] This suggests that maintaining drug levels over the entire treatment interval (rather than peak effect) is important.

The Antifungal Susceptibility Subcommittee of the Clinical and Laboratory Standards Institute has recently proposed interpretive breakpoints for voriconazole and *Candida* species based on a review of laboratory and clinical data.[18] The overall MIC_{90} was 0.25 μg/mL and 99% of the isolates were inhibited at $\leq$1 μg/mL of voriconazole. The MIC breakpoints proposed for voriconazole and *Candida* species are as follows: susceptible, $\leq$1 μg/mL; susceptible dose-dependent, 2 μg/mL; and resistant $\geq$4 μg/mL.

Implicit in the formulation of the recommendations is the suggestion that voriconazole concentrations should be maintained >1 μg/mL over the entire dosing interval (trough level). In our study, maintaining the trough concentration above clinical breakpoints was not consistently achieved because 89 levels (44%) were $\leq$1 μg/mL. Also, potentially subtherapeutic concentrations could not be predicted from the absolute or mg/kg drug dose each patient received.

Although this does not necessarily mean that routine voriconazole therapeutic drug monitoring should be started, we suggest that future studies of voriconazole and other newer agents such as posaconazole should incorporate prospective therapeutic drug monitoring.

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