MAJOR ARTICLE

Voriconazole Therapeutic Drug Monitoring in Patients with Invasive Mycoses Improves Efficacy and Safety Outcomes

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(See the editorial commentary by Lewis on pages 212–4)

Background. Voriconazole is the therapy of choice for aspergillosis and a new treatment option for candidiasis. Liver disease, age, genetic polymorphism of the cytochrome CYP2C19, and comedications influence voriconazole metabolism. Large variations in voriconazole pharmacokinetics may be associated with decreased efficacy or with toxicity.

Methods. This study was conducted to assess the utility of measuring voriconazole blood levels with individualized dose adjustments.

Results. A total of 181 measurements with high-pressure liquid chromatography were performed during 2388 treatment days in 52 patients. A large variability in voriconazole trough blood levels was observed, ranging from ⩽1 mg/L (the minimum inhibitory concentration at which, for most fungal pathogens, 90% of isolates are susceptible) in 25% of cases to >5.5 mg/L (a level possibly associated with toxicity) in 31% of cases. Lack of response to therapy was more frequent in patients with voriconazole levels ⩽1 mg/L (6 [46%] of 13 patients, including 5 patients with aspergillosis, 4 of whom were treated orally with a median dosage of 6 mg/kg per day) than in those with voriconazole levels >1 mg/L (15 [12%] of 39 patients; $P = .02$). Blood levels >1 mg/L were reached after increasing the voriconazole dosage, with complete resolution of infection in all 6 cases. Among 16 patients with voriconazole trough blood levels >5.5 mg/L, 5 patients (31%) presented with an encephalopathy, including 4 patients who were treated intravenously with a median voriconazole dosage of 8 mg/kg per day, whereas none of the patients with levels ⩽5.5 mg/L presented with neurological toxicity ($P = .002$). Comedication with omeprazole possibly contributed to voriconazole accumulation in 4 patients. In all cases, discontinuation of therapy resulted in prompt and complete neurological recovery.

Conclusions. Voriconazole therapeutic drug monitoring improves the efficacy and safety of therapy in severely ill patients with invasive mycoses.

Voriconazole is the first choice therapy for invasive aspergillosis and is a new treatment option for candidiasis, other emerging invasive fungal infections (IFI), such as fusariosis, and refractory IFI [1–5]. Status of the host immunity, localization and extension of infection, early start of antifungal therapy, lack of response to previous therapy, surgical management, and in vitro antifungal susceptibility of the pathogen are key determinants for a successful response [6–9]. The role of antifungal drug blood concentrations with respect to efficacy and safety is unclear. Liver metabolism plays a key role in the disposition of voriconazole, which acts simultaneously as a substrate and inhibitor of multiple enzymes of the cytochrome P450 system [7]. Multiple factors have been found to be associated with a large variability in voriconazole exposure following standard dose administration, such as nonlinear saturable pharmacokinetics, drug-drug interactions, liver disease, patient age (in particular, with respect to children), and genetic polymorphism of the cyto-

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chrome CYP2C19 [3, 7, 10, 11]. In experimental candidiasis, the ratio of voriconazole peak concentration and the 24-h area under the curve over the MIC have been identified as the best pharmacodynamic predictors of treatment success [12]. In contrast, no experimental data are available regarding the pharmacodynamics of voriconazole for the treatment of aspergillosis or other mycoses. Some recent clinical observations have suggested that under- and over-dosing of voriconazole may influence the efficacy and safety of therapy, respectively [1, 13–16]. Recently, experts have suggested that voriconazole trough blood levels should be measured after 1 week of therapy for dose adjustment to target values of 2–6 mg/L [7]. However, the utility of such measurements remains debatable, given that multiple confounding factors may influence the outcome of infection and the assessment of tolerance in severely ill patients [17–19]. This uncertainty highlights the need for additional drug exposure–related efficacy and safety data in patients treated with voriconazole. The objective of the present observational study was to assess the utility of voriconazole therapeutic drug monitoring (TDM).

PATIENTS AND METHODS

Patients. All consecutive adult patients treated with voriconazole at a single university hospital during the period 2004–2006 were identified from the pharmacy records. Patients who received voriconazole with TDM were studied prospectively, and those who received voriconazole without TDM were analyzed retrospectively. Treating physicians based the choice of voriconazole route and dose on the recommendations of the package insert, published guidelines, and the literature [1, 2, 4, 20–22]. IFIs were classified as either proven, probable, or possible according to definitions of the Invasive Fungal Infection Group of the European Organization for Research and Treatment of Cancer and Mycoses Study Group of the National Institute of Allergy and Infectious Diseases [23]. Empirical antifungal therapy was given to patients with persistent febrile neutropenia despite >96 h of broad-spectrum antibacterial therapy. Demographic data, clinical characteristics, diagnosis of IFI, and response to or experience of adverse events associated with voriconazole therapy were recorded.

Response of infection to antifungal therapy. The assessment of response to voriconazole therapy as partial or complete was based on clinical (fever, signs and symptoms of infection, and inflammatory markers) and radiological (CT or MRI findings) improvement or resolution and on proven or presumed eradication of the fungal pathogen [6]. Lack of response to voriconazole therapy was defined by persistent IFI after >14 days of treatment or by progressing IFI (clinical and radiological progression, persistently positive culture results, or death due to IFI) after >7 days of treatment.

Safety of antifungal therapy. The type and severity of severe adverse events and their causal relationship with voriconazole therapy were defined according to the criteria of the National Cancer Institute [24].

Measurement of voriconazole blood levels. Voriconazole trough blood levels were studied in citrated plasma by validated high-pressure liquid chromatography (analytical range, 0.125–25 mg/L) [25, 26]. Voriconazole trough levels were measured because of the lack of clinical data on other pharmacodynamic parameters that might better predict the efficacy and safety of therapy and because routine blood sampling just preceding the next voriconazole dose is practical and reliable for intrapatient and interpatient comparisons. The therapeutic interval for voriconazole troughs was 1–5.5 mg/L [1, 8, 13, 15, 27]. The choice of the 1-mg/L cutoff value had been based on in vitro susceptibility data (MIC_{90}, 0.5–1 mg/L for the majority of fungal pathogens), considering that only the free-circulating fraction of voriconazole (i.e., 40%–50%) is microbiologically active and available for penetration in infected organs [3, 8, 28, 29]. The upper cutoff value was based on data reported for patients who experienced adverse events [1, 13, 14, 30]. The following voriconazole therapy modifications were proposed: (1) a 50% increase in daily dose in patients with trough levels ⩽1 mg/L and lack of response to therapy, as recommended in the package insert, and (2) discontinuation of therapy in patients with trough levels >5.5 mg/L plus/minus adverse events probably related to overdosing.

Statistical analysis. Proportions were compared by the χ^2 test or Fisher's exact test, as appropriate. Continuous variables were compared by the nonparametric Mann-Whitney *U* test or Kruskal-Wallis test, as appropriate. Statistical significance was defined by a 2-sided *P* value <.05. The Spearman method was used to study the correlation of 2 variables. A logistic regression analysis (Stata software, version 8.2; Stata) was performed to assess whether the log-transformed voriconazole trough concentration is a significant predictor of response to therapy (coded as success or lack of response) or safety (coded as absence or presence of severe toxicity).

RESULTS

Patients. Among 96 adult patients treated with voriconazole during the study period, 52 had TDM. All patients with TDM were white; 51 (98%) of 52 were inpatients. The most frequent underlying condition was acute myeloid leukemia with neutropenia following myeloablative chemotherapy. Patients demographic data and clinical characteristics are summarized in table 1.

Data were analyzed retrospectively for 39 (89%) of 44 patients without voriconazole TDM; of these patients, 13 (33%) were neutropenic, 21 (54%) had another type of immunosuppression, and 5 (13%) had no underlying condition.

Voriconazole therapy. A total of 2388 days of voriconazole

Table 1. Demographic and clinical characteristics, invasive fungal infections, and voriconazole therapy in 52 patients with therapeutic drug monitoring.

Variable	Patients with measured voriconazole blood levels (n = 52)
Demographic data	
Age, median years (range)	58.5 (23–78)
Sex, male:female	38 (73):14 (27)
Underlying condition	
Hematological malignancy, neutropenia <0.5 g/L	32 (61)
Solid-organ transplantation	3 (6)
Abdominal surgery	3 (6)
Chronic liver disease	3 (6)
Other condition[a]	7 (13)
None	4 (8)
Fungal infection	
Proven or probable invasive aspergillosis[b]	26 (50)
Lung	19 (36)
Sinus[c]	3 (6)
Disseminated[d]	3 (6)
Intra-abdominal	1 (2)
Proven or probable invasive candidiasis[e]	8 (15)
Bloodstream	3 (6)
Hepatosplenic	4 (7)
Bone	1 (2)
Other proven invasive fungal infection (*Pseudallescheria boydii* and *Paecilomyces* species): bone	2 (4)
Possible invasive fungal infection: lung	11 (21)
Persistent fever during neutropenia	5 (10)
Voriconazole therapy	
First line	33 (64)
Second line	19 (36)
Failure of first-line therapy	1 (2)
Intolerance to first-line therapy	9 (17)
Switch from intravenous to oral therapy	9 (17)
Route of administration	
Intravenous	40 (77)
Switch from intravenous to oral therapy	17 (33)
Oral	12 (23)
Voriconazole daily dose, median mg/kg/day (range)	
Loading dose (oral or intravenous)	12
Maintenance dose	
Intravenous	8 (6–11)
Oral	6.5 (2–11)[f]
Duration of therapy, median days (range)	
Overall	50 (4–1130)
Intravenous	6.5 (4–30)
Oral	55 (5–1130)

NOTE. Data are no. (%) of patients, unless otherwise indicated.

[a] Chronic lung disease (2 patients), diabetes mellitus (2 patients), HIV infection (2 patients), and open knee fracture (1 patient).

[b] Proven aspergillosis (19 patients) and probable aspergillosis (7 patients).

[c] With intracerebral extension (1 patient).

[d] Involvement of lung (3 patients), sinus (2 patients), liver (2 patients), and skin (1 patient).

[e] Proven candidiasis (4 patients) and probable candidiasis (4 patients).

[f] Intravenous vs. oral maintenance daily dose (P = .07).

therapy in 52 patients with TDM were studied. Types and sites of IFI and data on therapy are summarized in table 1.

Among 39 patients without voriconazole TDM, 31 (79%) were treated for aspergillosis (6 proven cases, 16 probable cases, and 9 possible cases), 2 (5%) were treated for proven candidiasis, and 6 (16%) were treated for persistent febrile neutropenia. Patients received voriconazole intravenously in 9 (23%) of the cases, intravenously followed by orally in 12 (31%), and orally in 18 (46%). The voriconazole loading dosage was 12 mg/kg per day, and the median maintenance dosage was 6.5 mg/kg per day (range, 5–8 mg/kg per day). The median duration of therapy was 30 days (range, 7–365 days).

Measurements of voriconazole trough blood levels. A total of 181 voriconazole trough levels were measured (median number per patient, 4.5; range, 1–9). The median time interval between dose administration and measurement of trough levels was 12 h (range, 11–13 h). The first trough levels were measured at a median of 5 days (range, 3–46 days) after starting therapy. The median time elapsed between consecutive blood level measurements was 7 days (range, 1–62 days). Figure 1 shows the trough levels in patients receiving different voriconazole daily doses. A large intradose variability in voriconazole levels was observed. No significant difference was found among trough levels at different daily doses, nor was any correlation between daily doses and trough levels observed ($r^2 = 0.07$). During therapy with identical daily doses in 13 patients, the intraindividual variability of trough levels was substantial. In 5 patients, levels increased (median increase, 61%; range, 22%–125%; 1 patient had an increase >100%); in 8 patients, levels decreased (median decrease, 52%; range, 42%–84%; 4 patients had a decrease >50%).

Response of infection to voriconazole therapy. At the time of clinical assessment, voriconazole trough levels were ⩽1 mg/L in 13 cases (25%) and >1 mg/L in 39 cases (75%). A significantly higher proportion of patients with levels ⩽1 mg/L received oral voriconazole. Lack of response to therapy was more frequently observed in patients with levels ⩽1 mg/L (46%) than in those with levels >1 mg/L (12%; $P = .02$) (table 2). Among patients with levels ⩽1 mg/L, the characteristics of those with lack of response (6 patients) and those responding to therapy (7 patients) were compared. Immunosuppression was present in 5 (83%) of 6 and 5 (71%) of 8 patients, respectively. Aspergillosis was diagnosed in 5 patients (83%; 3 patients received a diagnosis of extrapulmonary aspergillosis) and 4 patients (57%; no patients received a diagnosis of extrapulmonary aspergillosis), respectively. The clinical course of 6 patients with persistence or progression of IFI and voriconazole levels ⩽1 mg/L is shown in table 3. In all 6 patients, IFI responded after an increase in voriconazole doses (no antifungal agent was added to the treatment regimen). Neutropenia resolved in 2 patients (after clinical response of IFI in 1 patient); immunosuppression persisted in 3 patients (in 1 patient receiving azathioprine and/or corticosteroids, 1 patient with AIDS, and 1 patient with liver cirrhosis), and 1 patient was not immunocompromised.

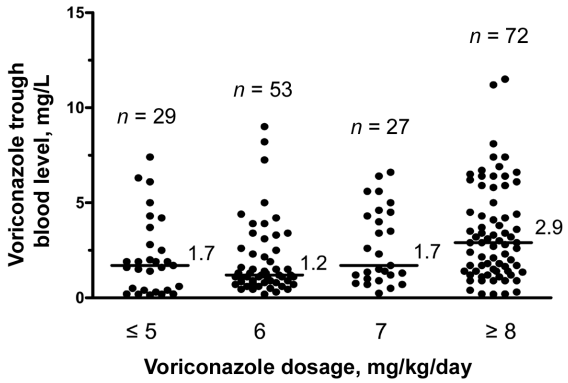

Figure 1. Relationship between voriconazole dosage and voriconazole trough blood level. Each point represents a single blood level measurement. Numbers of measurements for each daily dose are reported. Horizontal bars represent median values (the numerical values are reported on the right of the horizontal bar for each group). Voriconazole dosages have been rounded to the nearest unit.

Among the 5 patients with voriconazole levels >1 mg/L (median voriconazole level, 4.1 mg/L; range, 2.4–9 mg/L) and lack of response to therapy, 1 had probable invasive candidiasis, 1 had probable invasive aspergillosis, 2 had possible IFI, and 1 had breakthrough PCR-proven zygomycosis. In 4 cases, treatment was switched to a salvage regimen (1 patient received caspofungin, 2 received liposomal amphotericin B, and 1 received a combination of both agents) after a median of 9 days of voriconazole therapy (range, 4–21 days). Three patients had complete resolution of IFI (median duration of follow-up, 60 days; range, 45–60 days), and 2 patients died due to IFI (after 5 and 7 days, respectively).

The logistic regression analysis indicated that the log-transformed voriconazole trough level is a significant predictor of response to therapy: a 2-fold increase in blood level is associated with an OR for success of 1.8 (95% CI, 1.1–3.1; $P = .03$). The logistic regression model indicates a 70% probability of response at a voriconazole trough concentration of 1 mg/L (figure 2*A*).

Among the 39 patients without voriconazole TDM, 9 patients (1 with proven, 5 with probable, and 3 with possible IFI) did not respond to therapy (no MIC data were available). For 3 patients, voriconazole doses were increased (2 patients responded, and there was no follow-up in 1 patient); in 2 patients, therapy was switched to a salvage regimen (1 patient responded,

Table 2. Voriconazole trough blood levels and clinical response to antifungal therapy.

Variable	Voriconazole trough blood level		*P*
	⩽1 mg/L (*n* = 13)	>1 mg/L (*n* = 39)	
Route of voriconazole administration			.05
Intravenous	4 (31)	24 (61)	
Oral	9 (69)	15 (39)	
Voriconazole dosage, median mg/kg/day (range)			
Overall	7 (2.5–9)	8 (2–11)	NS
Intravenous	7.5 (7–8)	8 (6–11)	NS
Oral	6 (2.5–9)	7 (2–11)	NS
Response to antifungal therapy			
Interval between start of voriconazle therapy and assessment, median days (range)	21 (10–120)	17.5 (10–180)	NS
Treatment success			
Overall	7 (54)[a]	34 (88)	.02
Complete response	5	27	
Partial response	2	7	
Lack of response	6 (46)	5 (12)	
Persistence	3 (23)	0 (0)	
Progression	3 (23)	4 (10)	
Breakthrough IFI	0 (0)	1 (2)	

NOTE. Data are no. (%) of patients, unless otherwise indicated. NS, not significant.

[a] In 1 patient, comedication with rifampin resulted in low voriconazole blood levels.

and 1 patient died of refractory IFI); and in 4 patients, therapy remained unchanged (all 4 patients died of refractory IFI).

Safety of voriconazole therapy. Voriconazole trough levels were ⩽5.5 mg/L in 36 patients (69%) and >5.5 mg/L in 16 patients (31%) (table 4). The majority of patients with voriconazole levels >5.5 mg/L received voriconazole intravenously, and a significant proportion of these patients received omeprazole comedication. Five serious neurological adverse events (National Cancer Institute grade 3) were observed in patients with voriconazole levels >5.5 mg/L (31%), compared with none among patients with levels ⩽5.5 mg/L (0%; $P = .002$). The clinical characteristics and the course of adverse events in these patients are summarized in table 5. When patients with trough levels >5.5 mg/L with and without toxicity were compared, voriconazole daily doses, route of administration, and blood levels were similar (data not shown). Absence of other causes and prompt and complete neurological recovery after therapy discontinuation suggest the probable relationship between these encephalopathies and voriconazole overdosing. The logistic regression analysis confirmed a significant association between voriconazole trough concentrations and neurotoxicity: the OR for severe toxicity after a 2-fold increase of voriconazole levels in blood was 284 (95% CI, 0.96–84,407; $P = .05$). The estimated probability of neurotoxicity at voriconazole trough levels of 5.5 mg/L and 8 mg/L was 15% and 90%, respectively (figure 2*B*).

A severe cholestasic hepatopathy (defined as 10 times the baseline or 3 times the baseline, if the baseline was >3 times the upper limit of normal) occurred in 6 patients (2 with pre-existing hepatopathy). These events were observed in 8% of patients with voriconazole levels ⩽5.5 mg/L and in 19% of those with levels >5.5 mg/L (the difference was not statistically significant). Although this toxicity was possibly or probably related to voriconazole, no correlation was found between voriconazole trough levels and alkaline phosphatase ($r^2 = 0.01$) or γ-glutamyl transpeptidase ($r^2 = 0.01$). Voriconazole dose was reduced by 50% in 4 cases: cholestatic parameters remained >10 times the upper limit of normal in 2 patients and decreased to 5 times the upper limit of normal in 2 patients. After discontinuation of voriconazole, cholestasis decreased to 3–5 times the upper limit of normal in all patients within a median of 20 days (range, 10–30 days). In 2 patients who had long-term follow-up (10 and 12 months), the liver parameters remained elevated despite the absence of a pre-existing hepatopathy. The logistic regression analysis failed to demonstrate a significant association between voriconazole levels and hepatotoxicity; the OR for hepatotoxicity of a 2-fold increase in voriconazole levels was 1.4 (95% CI, 0.7–3).

Among 39 patients without voriconazole TDM, 7 (18%) experienced serious adverse events possibly related to therapy (2 of which were neurological and 5 of which were hepatic).

Table 3. Characteristics and clinical course of patients with voriconazole (Vor) trough blood levels ⩽1 mg/L and lack of response to antifungal therapy.

Patient	Sex	Age, years	Weight, kg	Underlying disease/ immunosuppression	Invasive fungal infection	Vor daily dose, route	Duration of therapy at time of assessment of response, days	Vor trough blood level, mg/L	Assessment of response to Vor therapy	Modification Vor daily dose, route	Time to first control Vor blood level, days	Vor trough blood levels in follow-up, mg/L	Final assessment of response, days of follow-up
1	M	58	77	Acute leukemia/ neutropenia	Probable pulmonary aspergillosis	5 mg/kg/day (2 × 200 mg), oral	24	<0.2	POI: persistent fever and inflammatory syndrome, RP of initial focus, and new contralateral lesion (on CT)	Increase to 8 mg/kg/ day (2 × 300 mg), oral	10	1.1, 2.1, 1.7	Complete response, 75
2	F	65	56	Crohn disease, surgery for toxic megacolon/corticosteroids and azathioprine	Proven peritoneal aspergillosis:*Aspergillus fumigatus;* MIC of Vor, 0.25 mg/L	7 mg/kg/day (2 × 200 mg), oral salvage therapy after failure of fluconazole therapy	20	0.7	PI after surgery: persistent fever and inflammatory syndrome, persistence of *Aspergillus* species in peritoneal fluid	Increase to 11 mg/kg/ day (2 × 300 mg), oral	5	2, 2.4	Complete response, 60
3	M	68	45.5	HIV infection with AIDS	Proven pulmonary aspergillosis: *A. fumigatus;* MIC of Vor, 0.5 mg/L	9 mg/kg/day (2 × 200 mg), oral (concomitant lopinavir and ritonavir therapy)	14	0.9	POI: persistent fever, cough and inflammatory syndrome, RP of initial focus (on CT)	Increase to 13 mg/kg/ day (2 × 300 mg), oral	7	2.9, 2.9, 3.5	Complete response, 90
4	M	64	62	Hodgkin lymphoma/ neutropenia	Probable hepatosplenic candidiasis	6.5 mg/kg/day (2 × 200 mg), intravenous	34	0.7	PI: persistent fever and inflammatory syndrome, no radiological change (on CT)	Increase to 10 mg/kg/ day (2 × 300 mg), intravenous	7	2.3, 2.0, 2.1	Complete response, 65
5	M	70	81	Alcoholic liver cirrhosis	Proven sinus aspergillosis with cerebral extension: *Aspergillus flavus;* MIC of Vor, 0.25 mg/L	2.5 mg/kg/day (2 × 100 mg), oral	13	1	PI after surgery: persistent fever and symptoms (nasal congestion, facial pain), no radiological change (on MRI)	Increase to 3.5 mg/ kg/day (2 × 150 mg), oral	5	2.8, 1.6, 2.3	Complete response, 50
6	F	61	63	None	Proven sinus aspergillosis: *A. fumigatus;* MIC of Vor, 0.25 mg/L	6.5 mg/kg/day (2 × 200 mg), intravenous	22	<0.2	POI after surgery: RP, ethmoidal focus with extension to skull basis (on MRI)	Increase to 9 mg/kg/ day (2 × 300 mg), intravenous	7	2.7, 3.1, 2.8, 3	Complete response, 180

NOTE. PI, persistent infection; POI, progression of infection; RP, radiological progression.

Table 4. Voriconazole (Vor) trough blood levels and safety of antifungal therapy.

Variable	Vor trough blood level		P
	⩽5.5 mg/L (*n* = 36)	>5.5 mg/L (*n* = 16)	
Vor route			.07
Intravenous	15 (42)	13 (81)	
Oral	21 (58)	3 (19)	
Vor dosage, median mg/kg/day (range)			
Overall	7 (2–11)	8 (6–11)	.13
Intravenous	7.5 (6–10)	8 (6–11)	NS
Oral	6 (2–11)	7 (6–8)	NS
Serious adverse event			
Encephalopathy			
Incidence	0	5 (31)	.002
Interval after start of Vor, days (range)	NA	9 (5–30)[a]	
Cholestatic hepatopathy			
Incidence	3 (8)	3 (19)	NS
Interval after start of Vor, days (range)	50 (5–150)	13 (6–20)	NS
Concomitant therapy			
Omeprazole	6 (17)	7 (44)	.04
Tacrolimus	0	1 (6)	NS

NOTE. Data are no. (%) of patients, unless otherwise indicated.

[a] The time interval elapsed between start of Vor therapy and documentation of Vor blood levels >5.5 mg/L in patients without encephalopathy was a median of 5 days (range, 2–7 days); $P = .04$, vs. time interval in patients with encephalopathy.

The 2 patients with neurological symptoms completely recovered after discontinuation of voriconazole.

DISCUSSION

We report the experience with voriconazole TDM during 2388 treatment-days in 52 white adult patients. A large variability in voriconazole trough levels was observed: voriconazole trough levels were ⩽1 mg/L in 13 (25%) of the patients (the majority of whom were receiving oral therapy) and >5.5 mg/L in 16 (31%) (the majority of whom were receiving intravenous therapy). This observation is consistent with previous reports [16, 27, 31]. Intravenous daily doses were higher than oral daily doses. Confounding factors—such as drug-drug interactions, liver disease, and polymorphism of cytochrome CYP2C19—may have influenced voriconazole metabolism in some individuals. Among white individuals, 26% of heterozygous extensive metabolizers (who experienced 2-fold voriconazole exposure, compared with homozygous extensive metabolizers) and 2% of homozygous poor metabolizers (who experienced 4-fold exposure) have been described [10, 27]. CYP2C19 genotype was not determined in the present study.

Persistence or progression of IFI was observed in a significantly higher proportion of patients with voriconazole trough concentrations ⩽1 mg/L, compared with patients with trough concentrations >1 mg/L. The association between trough levels and response to antifungal therapy was confirmed in a logistic regression model. No fungal in vitro resistance was documented as a cause of treatment failure. No difference in immunosuppressive conditions was found. In all cases involving a lack of response at low voriconazole levels, an increase in voriconazole doses resulting in levels >1 mg/L was successful. The choice of the 1-mg/L cutoff value for voriconazole trough concentrations had been based on (1) in vitro susceptibility data (MIC_{90}, 0.5–1 mg/L for the majority of pathogenic fungi), (2) the fact that only the free-circulating fraction of voriconazole (40%–50%) is microbiologically active and penetrates infected tissues, (3) the fact that blood sampling just preceding the next voriconazole dose is practical and reliable for intrapatient and interpatient comparisons, and (4) the lack of clinical data on other pharmacodynamic parameters that might better predict efficacy and safety [3, 8, 28, 29]. Patients with voriconazole levels ⩽1 mg/L received oral treatment more frequently than did those with levels >1 mg/L. Variability in oral bioavailability associated with meals and hepatic first-pass effect might have contributed to lower exposure [1, 13, 27]. Degradation of oral voriconazole by intestinal cytochrome enzymes may contribute to impaired drug absorption: the reversing effect on this phenomenon of grapefruit juice has been associated with improved bioavailability in mice [32]. No drug-drug interaction could be identified in patients with voriconazole underexposure. In 2 patients, the recommended oral dosage not adjusted for body weight (200 mg twice per day) was lower than the intravenous dosage (4

Table 5. Characteristics of and clinical course in patients with voriconazole (Vor) trough blood levels >5.5 mg/L and serious neurological adverse events.

Patient	Sex	Age, years	Weight, kg	Underlying disease/invasive fungal infection	Vor daily dose, route	Concomitant therapy	Duration of therapy at time of occurrence of adverse event, days	Vor trough blood level, mg/L	Assessment of serious adverse events; causality of Vor; National Cancer Institute grade	Modification to Vor therapy	Time to follow-up Vor blood level after stopping Vor, days	Vor trough blood level during follow-up, mg/L	Final clinical assessment (days of follow-up)
1	F	35	54	Lung transplantation/ probable pulmonary aspergillosis	7.5 mg/kg/day (2 × 200 mg), oral	Tacrolimus	16	6.9	Confusion, agitation, myoclonies, EEG pattern of toxic encephalopathy (normal CT findings); probable; grade 3 (concomitant severe cholestasis)	Discontinuation	NA	NA	Complete resolution (5 days after discontinuation of Vor), prolongation of hospital stay
2	M	61	100	Acute leukemia/probable pulmonary aspergillosis	8 mg/kg/day (2 × 400 mg), intravenous	Omeprazole	30	11.2	Confusion, extrapyramidal signs, myoclonies, EEG pattern of toxic encephalopathy (normal CT findings); probable; grade 3	Decrease dosage to 6 mg/kg/day (2 × 300 mg), then 3 (2 × 150 mg), then discontinuation	5	4.3	Complete resolution (5 days after discontinuation of Vor), prolongation of hospital stay
3	M	59	80	Acute leukemia/ proven pulmonary aspergillosis	8 mg/kg/day (2 × 320 mg), intravenous	Omeprazole	9	5.9	Confusion, worsening hallucinations; probable; grade 3	Discontinuation	5	1.6	Complete resolution (3 days after discontinuation of Vor); rechallenge with a lower dose of Vor was well tolerated
4	M	66	57	Acute leukemia/ proven pulmonary aspergillosis	7 mg/kg/day (2 × 200 mg), intravenous	Omeprazole	6	5.6	Persistent visual and auditive hallucinations; probable; grade 3 (concomitant hepatic serious adverse event)	Decrease dosage to 5 mg/kg/day (2 × 150 mg), then discontinuation	3	1	Complete resolution (4 days after discontinuation of Vor)
5	M	31	74	Acute leukemia/possible pulmonary invasive fungal infection	8 mg/kg/day (2 × 300 mg), intravenous	None	3	9	Confusion, persistent visual hallucinations; probable; grade 3	Discontinuation	NA	NA	Complete resolution (2 days after discontinuation of Vor)

NOTE. NA, not available.

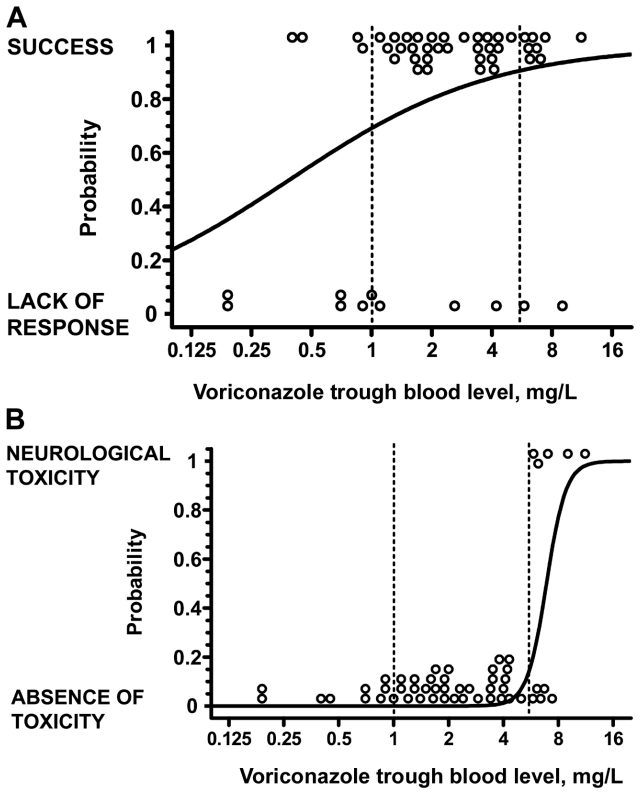

Figure 2. Voriconazole trough blood levels and logistic regression model for response to antifungal therapy *(A)* and for neurotoxicity *(B)*. The symbols represent the voriconazole levels observed in each individual patient with treatment success *(top)* or lack of response to therapy *(bottom)* and with *(top)* or without *(bottom)* signs of neurological toxicity. The continuous line represents the logistic regression model predicting the probability of response to antifungal therapy *(A)* or neurotoxicity *(B)* as a function of the voriconazole trough blood concentration. The vertical dotted lines indicate the proposed 1–5.5-mg/L therapeutic interval of voriconazole.

mg/kg twice per day). Our data confirm and extend previous observations that low voriconazole levels may impair the response of IFI to therapy. The US Food and Drug Administration's voriconazole briefing document reports a pharmacokinetic/pharmacodynamic analysis involving 280 cases of proven or probable IFI that suggests a trend to higher success rates in patients with mean voriconazole levels >0.5 mg/L (136 [56%] of 245 patients), compared with patients with levels <0.5 mg/L (16 [46%] of 35 patients; OR, 1.5; 95% CI, 0.6–3.4) [27]. In an open-label, multicenter trial of voriconazole for first-line or salvage therapy in 116 patients with aspergillosis, 6 treatment failures among 11 patients with mean voriconazole levels <0.5 mg/L were observed [1]. A relationship between voriconazole levels randomly measured during the dosing interval and treatment success was described in 28 patients with IFI: there was a 100% treatment response rate in patients with voriconazole levels >2 mg/L and a 56% response rate in patients with voriconazole levels <2 mg/L [15]. Among a group of 8 critically ill patients who received voriconazole via a nasogastric tube, 2 treatment failures that were possibly associated with low blood levels of voriconazole were observed [33]. Six breakthrough IFIs occurred during voriconazole prophylaxis in a group of 43 allogeneic hematopoietic stem cell transplant recipients with voriconazole trough concentrations <2 mg/L, and none occurred in a group of 24 such patients with voriconazole trough concentrations >2 mg/L [34]. These data are consistent with the exposure-response relationship recently described for posaconazole, another new-generation triazole [35].

Safety issues were also found to be associated with the variability of voriconazole blood levels. We observed a toxic encephalopathy in one-third of patients with trough levels >5.5 mg/L after >1 week of therapy. The association between overdosing and neurotoxicity was confirmed in a logistic regression model. These persistent or worsening neurological manifestations, which differed from transient and spontaneously resolving disturbances of light perception reported in 20%–25% of patients, promptly resolved after discontinuation of therapy. Moreover, in patients with high levels of voriconazole and no neurological symptoms or signs, prompt dose reduction or discontinuation of voriconazole might have prevented toxicity by limiting the duration of overexposure. The majority of patients with blood levels >5.5 mg/L were treated intravenously, with a trend towards higher daily doses. Drug-drug interactions, in particular with omeprazole, may have played a role in voriconazole overdosing [27, 36, 37]. The severe cholestasis that developed during therapy might also have contributed to voriconazole accumulation. Two studies have described visual hallucinations in 4% of cases and encephalopathy in 1% of cases during voriconazole therapy. However, no data on voriconazole levels were reported [2, 22]. Another trial reported voriconazole trough levels >10 mg/L in 6 (5%) of 116 patients, all of whom required discontinuation of therapy: in 3 (50%) of 6 patients, toxicity possibly related to overdosing was described [1, 13, 17]. Other investigators reported a significant association between visual adverse events and voriconazole levels; the rate of such events was 18% among patients with trough concentrations <1 mg/L and 31% among those with trough concentrations >9 mg/L [38]. Six neurological adverse events were described among a group of 28 patients; the hazard ratio was 2.3 (95% CI, 1.4–3.6) per 0.1 mg/L increase in voriconazole trough level [14]. A patient with liver cirrhosis treated with voriconazole (4 mg/kg per day) and pantoprazole developed coma while the voriconazole trough level was 13.9 mg/L and then rapidly recovered when the voriconazole level decreased to <10 mg/L after therapy discontinuation [30].

Abnormal liver function test results have been reported in 1%–10% of patients receiving voriconazole [22, 27, 39]. In our study, severe hepatic toxicity occurred independently of vori-

conazole levels. This finding confirms other observations, which reported only a weak correlation, if any, between voriconazole exposure and severity of hepatotoxicity [14, 16, 18, 27, 31, 38].

The lack of a prospective study design with systematic voriconazole TDM at fixed time points is a limitation of the present study. However, similar clinical observations in patients without TDM suggest that the reported experiences are representative of individuals receiving voriconazole. No IFI with a voriconazole MIC of 1–4 mg/L was documented. In patients with such infections, individualized dose adjustments targeting voriconazole trough levels exceeding these values may be required [3].

In conclusion, the present study shows the importance of voriconazole TDM in severely ill patients with invasive mycoses [7, 17]. Multiple intrinsic and extrinsic factors may unpredictably influence voriconazole pharmacokinetics. Because it is difficult to clinically identify individuals with inappropriate exposure, dose adjustment after documentation of low or high voriconazole levels is critical if infection is not responding to treatment or if toxicity is suspected. Moreover, detection of voriconazole trough levels outside the therapeutic interval of 1–5.5 mg/L during the first week of therapy may prevent treatment failures and neurological toxicity. Prospective trials including voriconazole TDM are needed.

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