Challenging Recommended Oral and Intravenous Voriconazole Doses for Improved Efficacy and Safety: Population Pharmacokinetics–Based Analysis of Adult Patients With Invasive Fungal Infections

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(See the Editorial Commentary by Andes and Lepak, on pages 391–3.)

Background. Recommended oral voriconazole (VRC) doses are lower than intravenous doses. Because plasma concentrations impact efficacy and safety of therapy, optimizing individual drug exposure may improve these outcomes.

Methods. A population pharmacokinetic analysis (NONMEM) was performed on 505 plasma concentration measurements involving 55 patients with invasive mycoses who received recommended VRC doses.

Results. A 1-compartment model with first-order absorption and elimination best fitted the data. VRC clearance was 5.2 L/h, the volume of distribution was 92 L, the absorption rate constant was 1.1 hour^{-1}, and oral bioavailability was 0.63. Severe cholestasis decreased VRC elimination by 52%. A large interpatient variability was observed on clearance (coefficient of variation [CV], 40%) and bioavailability (CV 84%), and an interoccasion variability was observed on bioavailability (CV, 93%). Lack of response to therapy occurred in 12 of 55 patients (22%), and grade 3 neurotoxicity occurred in 5 of 55 patients (9%). A logistic multivariate regression analysis revealed an independent association between VRC trough concentrations and probability of response or neurotoxicity by identifying a therapeutic range of 1.5 mg/L (>85% probability of response) to 4.5 mg/L (<15% probability of neurotoxicity). Population-based simulations with the recommended 200 mg oral or 300 mg intravenous twice-daily regimens predicted probabilities of 49% and 87%, respectively, for achievement of 1.5 mg/L and of 8% and 37%, respectively, for achievement of 4.5 mg/L. With 300–400 mg twice-daily oral doses and 200–300 mg twice-daily intravenous doses, the predicted probabilities of achieving the lower target concentration were 68%–78% for the oral regimen and 70%–87% for the intravenous regimen, and the predicted probabilities of achieving the upper target concentration were 19%–29% for the oral regimen and 18%–37% for the intravenous regimen.

Conclusions. Higher oral than intravenous VRC doses, followed by individualized adjustments based on measured plasma concentrations, improve achievement of the therapeutic target that maximizes the probability of therapeutic response and minimizes the probability of neurotoxicity. These findings challenge dose recommendations for VRC.

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Voriconazole (VRC) is a new-generation azole with broad-spectrum antifungal activity [1]. Wide intraindividual/interindividual variability in VRC plasma concentrations was reported in healthy subjects [2]. Genetic polymorphism of the CYP2C19 enzyme [3, 4] and nongenetic factors (age, liver disease, and drug-drug interactions) contributed to this variability [5]. VRC plasma concentrations ranging from nonmeasurable values to

15 mg/L were observed in patients with invasive fungal infections (IFIs) treated according to recommended dosing schedules [5–10]. There is an increasing evidence of the association between VRC exposure and response of infection or occurrence of neurological and hepatic toxicity. These observations suggest that therapeutic drug monitoring (TDM) may improve efficacy and safety of therapy in patients with life-threatening IFI. The range of therapeutic concentrations and the doses required for achieving this target need further investigations. Population studies are a standard approach for characterizing the determinants of drug pharmacokinetics/pharmacodynamics. We conducted a population pharmacokinetic analysis in adult patients receiving VRC for IFI (1) to describe factors influencing the pharmacokinetic variability, (2) to assess associations between plasma concentrations and efficacy or neurotoxicity/hepatotoxicity, and (3) to define intravenous and oral doses required for achieving drug exposure with the most appropriate efficacy-toxicity profile.

PATIENTS AND METHODS

Patients

All consecutive hospitalized patients receiving VRC therapy on the advice of infectious diseases specialists over a 30-month period underwent TDM and were prospectively enrolled after providing written informed consent. VRC loading/maintenance doses were based on package insert recommendations and total body weight. The doses were adjusted (50% increase/decrease) in case of nonresponse of IFI and toxicity with trough plasma concentrations ≤1 and ≥5.5 mg/L, respectively [5]. IFIs were classified according to definitions of the European Organization for Research and Treatment of Cancer and Mycoses Study Group (EORTC-MSG) [11]. The institutional ethics committee approved the study.

VRC Plasma Concentrations

Days with measured VRC plasma concentrations were defined as study occasions, numbered from 1 to n (number of occasions in each patient), with higher numbers reflecting later time points during the study.

In 35 patients, measurements were performed 5 minutes before and 2, 4, 6, and 12 hours after drug administration and in 20 patients at the end of the dosing interval (C_{min}). Three-milliliter blood samples were collected in sodium-citrate tubes, centrifuged within 2 hours, and frozen at −80°C. VRC plasma concentrations were quantified by high-performance liquid chromatography–ultraviolet (analytical range, 0.125–25 mg/L; mean intrarun/interrun accuracy [± standard deviation {SD}], 93.7% ± 5.0%/96.5% ± 2.4%; and mean intrarun/interrun precision [± SD], 5.2% ± 1.5%/5.4% ± 0.9%) [12]. The method was validated in an international quality control program [13].

Efficacy and Safety of VRC Therapy

On each study occasion, data on VRC dose, route, comedications interacting with VRC metabolism, response of IFI, and adverse events associated with VRC were collected. The response of IFI was assessed by clinical, radiological, and microbiological EORTC-MSG criteria [14]. National Cancer Institute (NCI) criteria defined type and severity of neurological/hepatic adverse events and causal relationships with VRC [15].

Population Pharmacokinetics Analysis

This analysis was performed by NONMEM [16], using mixed-effects regression to estimate population means/variances of pharmacokinetic parameters and to identify factors influencing them.

Structural Model

Search for the best model was performed by comparing 1- and 2-compartment models with first-order oral absorption and linear/saturable elimination after intravenous/oral administration. After estimation of VRC clearance (CL), volume of distribution (V) and oral absorption rate constant (ka), the absolute bioavailability (F) was estimated on the basis of simultaneous fit of intravenous and oral concentrations. Absorption half-life, $t½_a$, was calculated as ln(2)/ka, and elimination half-life, $t½_z$, was derived from ln(2)/(CL/V).

Statistical Model

Interindividual variations in VRC pharmacokinetics were described using exponential error models with a mean of zero and a variance of ω^2. To account for fluctuations in VRC plasma concentrations at study occasions (ie, study days), interoccasion variability (IOV) was tested on CL and F. A proportional error model described residual variability with a mean of zero and a variance of σ^2.

Covariate Model

Influence and shape of the relationship between demographic covariates and pharmacokinetic parameters were assessed by visual inspection of plots of individual Bayesian estimates. Influential covariates were sequentially tested using forward selection followed by backward deletion steps: pharmacokinetic parameters θ were modeled to depend linearly on the covariates (eg, body weight centered on 70 kg; categorical covariates coded as 0/1). Baseline covariates evaluated for model building were sex, age, body weight, concomitant medications interacting with VRC metabolism, and NCI grade 3 cholestasis (ie, alkaline phosphatase [ALKP] and/or gamma glutamyl transferase [γ-GT] levels >20 times the upper limit of normal).

Parameter Estimation and Model Selection

Data were fitted by a first-order conditional method (FOCE INTERACTION). Goodness-of-fit statistics and graphical

displays guided assessment of model choice and adequacy by comparison of objective function values (approximate −2 max log likelihood and χ^2 distribution). A 5.9-point decrease in objective function for an additional parameter (2-sided $P < .01$) determined a significant difference between 2 models.

Model Validation

The bootstrap method with replacement was used to assess the stability of the final model (PsN-Toolkit, version 2.3.1) [17]. Two hundred data sets were reconstructed by resampling from original data. Mean values and 95% confidence intervals (CIs) of bootstrap parameters were compared with estimates from original data. In addition, a simulation based on final pharmacokinetic estimates was performed with NONMEM in 1000 individuals to calculate 95% prediction intervals at each time point.

VRC Plasma Concentration-Effect Relationships

Individual Bayesian estimates of log-transformed VRC peak (C_{max}), 12 hour-trough (C_{min}), and area under the curve (AUC_{0-12}) were derived from the final model. These variables, VRC dose, route, and total body weight were explored for relationship with response and neurotoxicity/hepatotoxicity at each study occasion. The occasion factor reflected a later time point during the study and a longer duration of therapy. The association of the above variables with response and neurotoxicity/hepatotoxicity was analyzed by logistic regression for deriving the VRC plasma concentration range predicting the most appropriate clinical efficacy and safety profile. Cholestasis was coded either as dichotomous variable (cutoff of >20 times the upper limit of normal ALKP and/or γ-GT levels [NCI grade 3]) or by cutoffs >3 times (NCI grade 1), >5 times (grade 2) and >20 times (grade 3) the upper limit of normal. Statistical significance was assigned at 2-sided P values of .05 (Stata V10.0-2004, StataCorp, College Station, TX).

Model-Based Simulations for Optimizing VRC Doses

Concentration-time profiles at steady state in 1000 individuals receiving oral and intravenous VRC doses of 200, 300, or 400 mg twice daily and 200 mg 3 times daily were simulated by the final model including interpatient variability of CL, ka, and F. These simulations aimed at predicting achievement of the therapeutic VRC concentration target.

RESULTS

Patient Demographic and Dose Characteristics

Fifty-five white patients were studied (Table 1). According to-package insert recommendations, the median initial maintenance VRC dose was 295 mg (range, 200–400 mg) twice-daily intravenously and 234 mg (range, 150–400 mg) twice-daily

Table 1. Demographic and Clinical Characteristics of the Study Population

Demographic	
Age, years	58 (23–78)
Sex	
Male	39 (71)
Female	16 (29)
Total body weight, median kg (range)	68 (42–125)
Underlying condition	
Hematological malignancy, neutropenia <0.5 G/L	35 (64)
Other[a]	16 (29)
None	7 (4)
IFI	
Aspergillosis[b,c]	27 (49)
Candidiasis[d]	8 (14)
Other[e]	2 (4)
Possible pulmonary	12 (22)
Suspected (persistent neutropenic fever)	6 (11)
IFI response to antifungal therapy	
Time to clinical assessment after starting VRC, days, median (range)	11 (9–14)
Success	43 (78)
Complete response	33 (60)
Partial response	10 (18)
Lack of response[f,g]	12 (22)
Persistence	3 (5)
Progression	9 (16)
Adverse events probably associated with VRC therapy	
Time to clinical assessment after staring VRC, days, median (range)	12 (4–30)
Neurotoxicity (encephalopathy/hallucinations), grade 3	5 (9)
Hepatic toxicity (cholestatic hepatopathy), grade 3[h]	7 (13)

Data are no. (%) of patients or median value (range).

Abbreviations: IFI, invasive fungal infection; VRC, voriconazole.

[a] Solid organ transplantation (n = 3), abdominal surgery (n = 3), chronic liver disease (n = 3), chronic lung disease (n = 2), diabetes mellitus (n = 2), human immunodeficiency virus infection (n = 2), and open knee fracture (n = 1).

[b] Proven aspergillosis (n = 19) and probable aspergillosis (n = 8).

[c] Pulmonary (n = 19), extrapulmonary (n = 8), sinusitis (n = 4: 1 with intracerebral extension), disseminated infection (n = 3: 3 with involvement of lung, 2 of sinus, 2 of liver, and 1 of skin), and intraabdominal infection (n = 1).

[d] Proven candidiasis (n = 4: 3 with fungemia, and 1 with osteomyelitis) and probable candidiasis (n = 4, all hepatosplenic candidiasis).

[e] Proven osteomyelitis (1 due to *Pseudallescheria boydii*, 1 due to *Paecilomyces* species).

[f] Proven sinus aspergillosis in 2 patients (1 with cerebral extension), proven pulmonary aspergillosis in 1 patient, probable pulmonary aspergillosis in 3 patients, proven peritoneal aspergillosis in 1 patient, probable hepatosplenic candidiasis in 2 patients, proven pulmonary zygomycosis in 1 patient, and possible pulmonary IFI in 2 patients.

[g] In only 1 patient, the immune status and/or the underlying condition evolved (ie, recovery from neutropenia) before response to VRC therapy could be achieved, while in the remaining 11 cases no change occurred before clinical response to antifungal therapy was observed (ie, 6 remained neutropenic, 2 continued to receive corticosteroids [with or without azathioprine], 1 had AIDS, 1 had liver cirrhosis, and 1 had no underlying condition).

[h] Only grade 1 hepatic cytolysis was observed. Therefore, no specific analysis of the association between VRC exposure and cytolytic toxicity was performed (data not shown).

orally; the median adjusted maintenance dose was 251 mg (range, 150–450 mg) twice-daily intravenously and 235 mg (range, 100–450 mg) twice-daily orally. Supplementary Figures 1 and 2 show distributions of VRC doses and correlations with plasma concentrations.

Pharmacokinetic Analysis

The pharmacokinetic analysis was based on 505 VRC plasma concentration measurements (median, 8 per patient [range, 1–47]) on 197 study occasions (40 involving intravenous VRC and 157 involving oral VRC; median, 3 occasions per patient [range, 1–9 occasions]). The first study occasion occurred at a median of 5 days (range, 2–46 days) after the start of VRC therapy; the median time between 2 consecutive occasions was 7 days (range, 2–62 days) and from the first to last occasion was 28 days (range, 1–195 days; median, 7 days (range, 1–26 days) for intravenous VRC and 21 days [range, 1–189 days] for oral VRC). Sixteen patients received omeprazole comedication.

Intravenous and oral VRC pharmacokinetics were best characterized using a 1-compartment model on log-transformed data with first-order absorption; a 2-compartment model could not be adapted. A nonlinear Michaelis-Menten elimination model did not describe data better than the linear model ($\Delta OF = 0.0$); the maximum metabolism rate (V_{max}) and the Michaelis-Menten constant (K_m) were very large compared to VRC concentrations, suggesting a linear increase of VRC concentrations over the dosing range. Visual inspection of individual plots of CL estimates and doses did not reveal any trend toward decreased VRC elimination at higher doses. VRC absolute bioavailability was estimated to be 63%; the assignment of interindividual variability significantly improved the fit ($\Delta OF = -63$), whereas no variability on V and ka was observed, probably owing to poor characterization of the absorption phase. Because of variations of VRC concentrations, interoccasion variability was tested on CL and F. The best fit was obtained when F was allowed to vary, suggesting significant interdose variability in VRC oral bioavailability ($\Delta OF = -137$). Among covariates showing a potential influence on VRC pharmacokinetics, a significant decrease in CL (−52%) was observed in patients with grade 3 cholestasis ($\Delta OF = -45$). Omeprazole inhibited VRC CL by 20% but did not reach statistical significance ($\Delta OF = -2.6$), and no influence on ka was observed ($\Delta OF = -0.3$). The impact of sex, body weight, or age was nonsignificant ($\Delta OF < -1.1$). Parameter estimates for the final models with and without interoccasion variability on F are summarized in Table 2. The average VRC absorption half-life ($t½_a$) was 0.63 hours, and the average elimination half-life ($t½_z$) was 12 hours, which doubled in grade 3 cholestasis. Concentration-time profiles for oral and intravenous VRC with average population prediction and 90% intervals are presented in Figure 1, and goodness of fit plots are presented in Supplementary Figure 3.

Model Validation

Median values and 95% CIs of parameter bootstrap estimates are presented in Table 2. Pharmacokinetic parameters of the final population models from original data (with and without interoccasion variability of F) were close to median bootstrap values and all were included in their 2.5–97.5 percentiles, indicating that the final models are accurate.

Plasma Concentration-Effect Relationships

Infection did not responding to VRC therapy in 12 patients (Table 1) on 16 study occasions: 4 during intravenous therapy (2 on the first occasion, 1 on the second, and 1 on the seventh) and 12 during oral therapy (11 on the first and second occasions and 1 on the fourth occasion). NCI grade 3 neurotoxicity (encephalopathy with agitation, confusion, hallucinations, and myoclonies) probably caused by VRC occurred in 5 patients (Table 1) on 12 study occasions (8 during intravenous therapy and 4 during oral therapy [5 on the first occasion, 4 on the second, and 3 on or beyond the third]). Seven patients (Table 1) presented grade 3 cholestasis on 18 occasions during oral VRC (2 on the first occasion, 5 on the second, and 11 on or beyond the third). Nine patients without baseline cholestasis developed grade 1 (n = 6), grade 2 (n = 2), or grade 3 (n = 1) cholestasis during VRC therapy; worsening of baseline cholestasis occurred in 7 of 23 patients with grade 1 (6 progressed to grade 2, and 1 progressed to grade 3) and in 2 of 10 patients with grade 2 (both progressed to grade 3); in 2, baseline grade 3 remained unchanged.

No independent association of VRC dose, intravenous/oral route, or body weight with efficacy and safety was found in the logistic multivariate regression model (data not shown). The results of the logistic multivariate regression analysis of VRC exposure and response or neurotoxicity are summarized in Supplementary Table 1. A significant association between log-transformed C_{max}, C_{min}, or AUC_{0-12} and response was observed for oral ($P < .001$), while no association for intravenous VRC was found. The time factor (study occasion), reflecting duration of therapy, added to VRC exposure improved this association ($P < .005$).

Grade 3 neurotoxicity was significantly associated with C_{max}, C_{min}, or AUC_{0-12} for both oral and intravenous VRC ($P < .01$), without additional influence of the time factor (study occasion).

No association was observed between C_{max}, C_{min}, or AUC_{0-12} and grade 3 cholestasis ($P = .3$). An ordered logistic regression suggested a possible association between C_{min} and any cholestasis (grade 1–3; $P = .01$), which was not improved by the occasion factor.

Table 2. Population Pharmacokinetic Estimates of Voriconazole

	Population Mean[a]		Bootstrap Evaluation[b]	
Parameter	Estimate	95% CI[c]	Mean	95% CI[c]
A. Final model assuming no interoccasion variability on F				
Structural model				
CL (L/h)	5.5	3.8–7.1	5.7	4.2–7.5
V (L)	101	61–141	95	47–140
ka (h^{-1})	1.1	.7–1.4	0.8	0.2–1.4
F	0.63	.22–.91	0.68	.45–.95
$\theta^{d}_{rifampicin}$	3.1	2.3–3.8	3.1	2.2–3.7
$\theta^{e}_{cholestasis}$	−0.55	−.36 – −.75	−0.55	−.18 – −.69
Statistical model[f]		CV[g]		CV[g]
ω_{CL} (%)	42	53	42	51
ω_{F} (%)	95[h]	78	116	67
σ (%)	70	33	71	25
B. Final model integrating the interoccasion variability on F		95% CI[c]		95% CI[c]
Structural model				
CL (L/h)	5.2	4.0–6.3	5.3	4.0–6.4
V (L)	92	63–120	83.6	43–116
ka (h^{-1})	1.1	.6–1.6	0.8	.1–1.6
F	0.63	.30–.87	0.65	.48–.82
$\theta^{d}_{rifampicin}$	3.0	2.4–3.6	3.0	1.9–3.7
$\theta^{e}_{cholestasis}$	−0.52	−.42 – −.62	−0.51	−.22 – −.65
Statistical model[f]		CV[g]		CV[g]
ω_{CL} (%)	40	50	41	51
ω_{F} (%)	84[h]	68	98	77
IOV on F (%)	93[g]	52	84	63
σ (%)	59	34	64	41

Abbreviations: CI, confidence interval; CL, clearance; F, oral bioavailability; IOV, interoccasion variability; ka, absorption rate constant; V, volume of distribution.

[a] Estimate from the original data set.

[b] Statistics by 200 bootstrap analyses.

[c] Data are around the mean estimate. For F, the antilogit of the 95% CI derived from the logit function is reported.

[d] Relative increase in CL in presence of rifampicin coadministration.

[e] Relative decrease in CL in case of severe hepatic cholestasis.

[f] ω is an estimate of interindividual variability, and σ is an estimate of residual variability in the plasma concentrations, expressed as coefficient of variation.

[g] Coefficient of variation (CV), calculated as $\sqrt{\text{standard error}_{\text{estimate}}/\text{estimate}}$ expressed as a percentage.

[h] Estimates of variability on F within the logit function.

VRC trough (C_{min}) plasma concentration, a parameter easily measurable in routine clinical practice, was selected for logistic regression models predicting probabilities of response of IFI and grade 3 neurotoxicity over the measured concentrations range (Figure 2*A* and 2*B*). VRC troughs of 1.5 and 4.5 mg/L were associated with an 85% probability of response and a 15% probability of grade 3 neurotoxicity, respectively.

Model-Based Simulations for Optimizing VRC Doses

Model-based simulations of concentrations profiles after intravenous and oral VRC were derived while assigning interpatient variability to oral CL and F and pooling interoccasion and intrapatient variability. Table 3 reports predicted steady-state trough concentrations for 200, 300, or 400 mg twice-daily and 200 mg 3 times daily intravenous or oral VRC. Predicted percentages of patients with VRC concentrations <1.5 mg/L (<85% probability of response) and >4.5 mg/L (>15% probability of neurotoxicity) with different intravenous and oral regimens are shown. Figure 3*A*–*D* simulates steady-state VRC concentrations profiles for intravenous and oral regimens best achieving predicted therapeutic targets.

DISCUSSION

This analysis characterized the VRC population pharmacokinetics during prolonged therapy with recommended

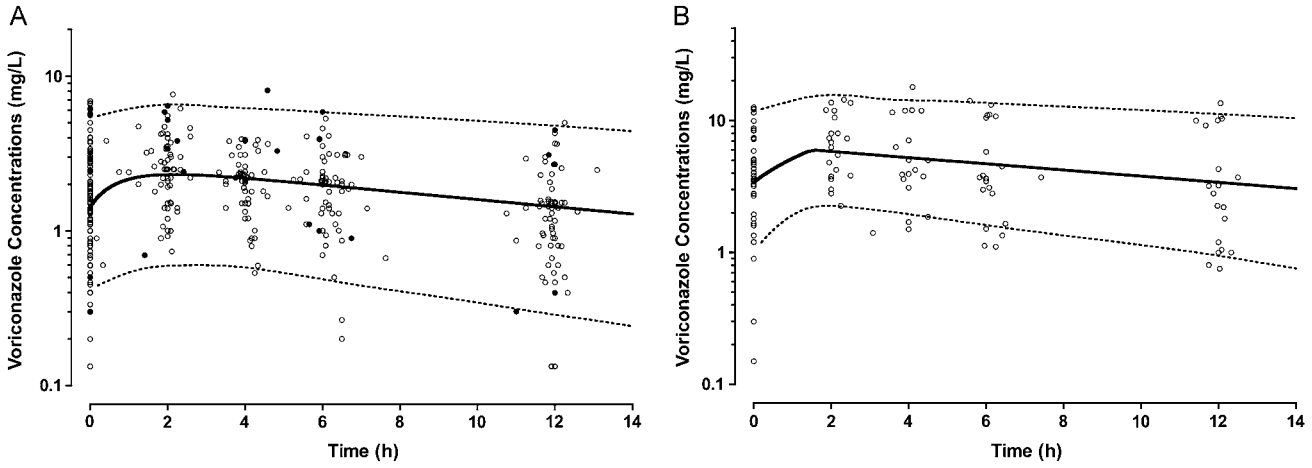
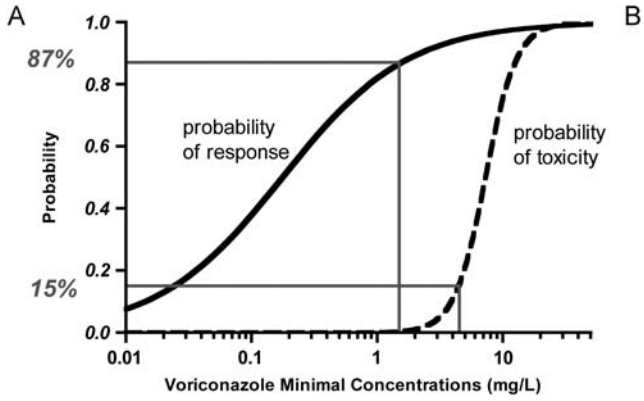


Figure 1. *A*, Voriconazole steady-state plasma concentrations normalized for a 200-mg oral dose (open circles; n = 173) and after a 400-mg oral loading dose (black circles; n = 23). *B*, Voriconazole steady-state plasma concentrations (open circles; n = 126) normalized for a 200-mg intravenous dose (1.5-hour infusion). The solid line represents the population prediction, and the dashed lines the 90% prediction interval.

intravenous and oral doses in adult patients with IFI. A validation by bootstrap estimates confirmed the accuracy and stability of a 1-compartment model with first-order absorption and linear elimination. Oral bioavailability and severe cholestatic hepatopathy were major determinants of variability of VRC plasma concentrations, whereas VRC dosing, body weight, and demographic characteristics had no significant effect. The logistic regression analysis revealed a significant association between VRC exposure and probability of response to therapy or severe neurotoxicity. The VRC trough plasma concentration range of 1.5 to 4.5 mg/L was identified as the therapeutic target with a clinically appropriate efficacy-safety profile (>85% probability of response and <15% probability of neurotoxicity), close to that recently reported by Troke et al [18]. Reassessment of oral and intravenous doses by model-based simulations challenged the package insert recommendations by identifying revised regimens best predicting achievement of the therapeutic target.

Age, sex, and body weight were not found to affect significantly VRC pharmacokinetics. Some parameters of this VRC population pharmacokinetic analysis in patients with IFI differed from those in previous reports [2, 19]. The estimated VRC oral bioavailability was lower (60%) than previously observed (80%–95%) [20, 21]. As vomiting, mucositis, and



B

VRC trough plasma concentration (mg/L)	Probability of response of IFI to VRC therapy	Probability of grade 3 neurotoxicity associated with VRC
0.5	72%	0%
1.0	82%	0%
1.5	**87%**	0.3%
2.0	89%	1%
4.0	93%	11%
4.5	94%	**15%**
5.0	95%	21%
5.5	95%	27%

Figure 2. *A*, Logistic regression model predicting the probability of response to voriconazole (VRC) therapy (solid line) and of grade 3 neurotoxicity probably associated with VRC therapy (dashed line) as a function of the VRC trough plasma concentration. The vertical dotted lines indicate the identified 1.5–4.5 mg/L therapeutic range. *B*, VRC trough plasma concentrations and probabilities predicted by the logistic regression models for (1) response of infection to VRC therapy and (2) grade 3 neurotoxicity associated with VRC. The VRC trough plasma concentration range associated with a >85% probability of response to therapy and a <15% probability of neurotoxicity related to therapy is highlighted in gray and bold.

Table 3. Probability of Achieving Different Voriconazole Trough Plasma Concentrations Targets With 200, 300, and 400 mg Twice-Daily Oral and Intravenous Dosing Regimens

	Probability, by Dosing Regimen and Route of Administration					
	200 mg Twice Daily		300 mg Twice Daily		400 mg Twice Daily	
VRC Trough Concentration Target (mg/L)	Oral (%)	Intravenous (%)	Oral (%)	Intravenous (%)	Oral (%)	Intravenous (%)
1	60	86	78	95	95	97
1.5[a]	49	**70**	**68**	**87**	**78**	92
2	35	56	55	77	67	86
4	11	22	22	43	35	56
4.5[a]	8	**18**	**19**	**37**	**29**	50
5	4.5	15	16	26	26	44

The percentages represent the probabilities of obtaining trough concentrations above the reported targets. The dosing regimens with the most appropriate predicted probabilities of reaching the therapeutic concentration range (ie maximizing efficacy by minimizing neurotoxicity) are reported in bold and underlined.

Similar probability of treatment outcome can be obtained with the 200 mg 3-times daily oral and intravenous regimens (69% and 86% of patients would reach the 1.5 mg/L lower concentration target and 20% and 37% of patients would have concentrations exceeding the 4.5 mg/L upper target, after oral and intravenous administration, respectively). These results are very close to those reported in the table with the 300 mg twice-daily oral and intravenous dosing regimens.

Abbreviation: VRC, voriconazole.

[a] The therapeutic target concentrations for efficacy (ie >85% probability of response) and safety (ie <15% probability of grade 3 neurotoxicity).

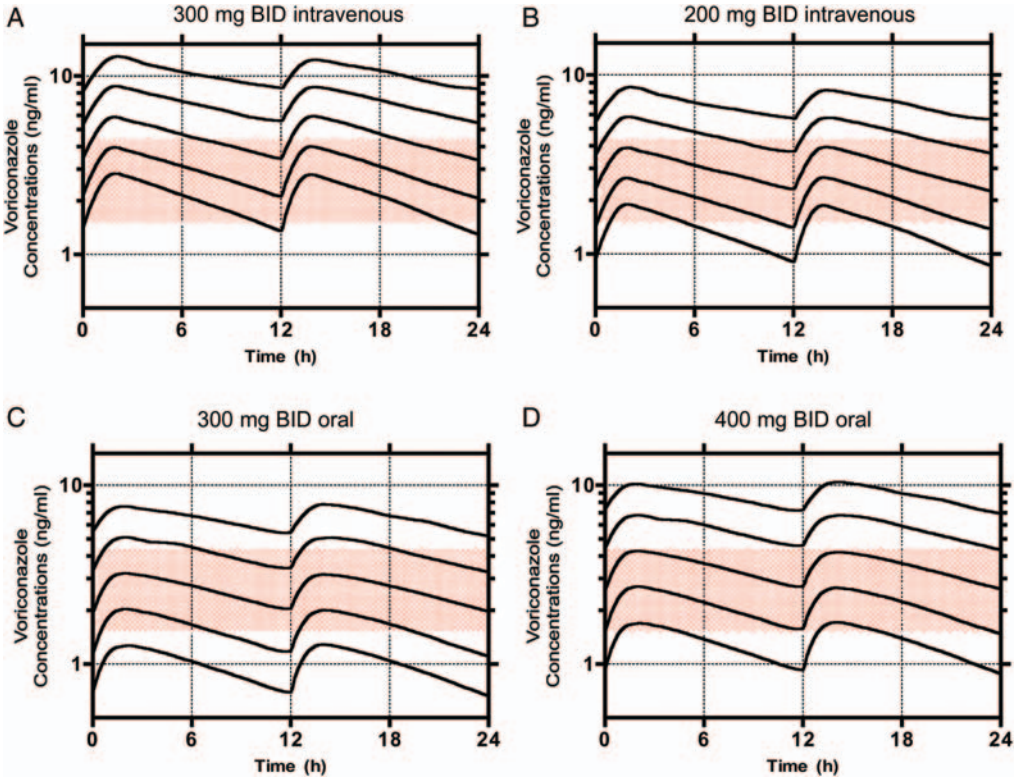


Figure 3. Model-based simulations of voriconazole (VRC) steady-state pharmacokinetic profiles (with 10, 25, 50, 75, and 90 percentiles) after the following VRC dosing regimens: 300 mg twice-daily intravenously (*A*), 200 mg twice-daily intravenously (*B*), 300 mg twice-daily orally (*C*), 400 mg twice-daily orally (*D*). The shaded zones represent the proposed therapeutic interval for VRC trough plasma concentrations of 1.5–4.5 mg/L.

diarrhea are frequent in hemato-oncological patients, gastrointestinal function may have influenced VRC absorption. This may explain the large interindividual and interoccasion variability in oral bioavailability, as reported in allogeneic hematopoietic stem cell transplantation [22]. Aspects influencing drug absorption were, however, not systematically investigated in the present study.

The estimated VRC 12-hour half-life is consistent with reports over the dosing range 200–400 mg, while the expected dose-dependent saturable elimination was not observed. Conflicting results have been reported on nonlinearity of the relationship between VRC dosing and elimination in children and adults [2, 23–25]. The linearity in the present study may result from the limited and unbalanced numbers of measurements across doses, with lacking quantification of the biexponential disposition and nonlinear components. The large interoccasion variability in oral VRC bioavailability with low concentrations in few patients receiving high doses might have precluded the estimation of a saturable elimination process.

The lack of effect of body weight on VRC clearance does not support body weight–adjusted dosing. As in previous investigations [26], severe cholestasis markedly decreased VRC clearance, which requires initial dose adjustment followed by close monitoring of liver parameters and plasma concentrations. As VRC is metabolized by CYP2C9, CYP2C19, and CYP3A4, drug interactions are expected with inhibitors or inducers of these enzymes. Omeprazole induced a nonsignificant 20% decrease in VRC clearance, which is lower than the 40% decrease reported by Wood et al [27]. The smaller than expected effect might be due to substantially larger influences of other factors on variability of exposure. CYP2C19 genetic polymorphism [4, 28, 29] may have contributed to interpatient variability. However, no genotyping data were available, a limitation of the present study.

This population analysis revealed a significant association between VRC trough concentrations >1.5 mg/L and therapeutic effect (>85% probability of response). This threshold was consistent with recently reported minimum inhibitory concentration required to inhibit the growth of 90% of organisms and epidemiological cutoffs of most VRC-susceptible fungal species, as well as clinical reports [18, 30–33]. This association was not observed for intravenous VRC, suggesting that, beyond the small number of events during short intravenous courses, intraindividual/interindividual variability in oral VRC bioavailability is a major determinant of infratherapeutic concentrations resulting in nonresponse. The association of response with the time factor is consistent with adjustment of VRC doses in nonresponding patients and with duration of therapy. The limited data set does not allow the assessment of other factors that may contribute to clinical improvement over time, such as recovery of the immune status or evolving underlying conditions. No information on whether VRC concentrations need to be adjusted according to the site of infection is available.

On the side of toxicity, an association between VRC trough concentrations >4.5 mg/L and severe neurological adverse events (>15% probability) was found, while the time factor had no impact as these occurred early during therapy. A possible association of VRC concentrations with cholestasis was observed. Gorski et al reported the occurrence of cholestasis according to VRC dose and duration of therapy [34]. The present data suggest that cholestasis may reflect both a cause and consequence of increased VRC exposure; a possible vicious circle between cholestasis and VRC accumulation deserves confirmation in independent samples. No clinically significant hepatic cytolysis occurred during VRC therapy.

Model-based simulations involving patients with normal hepatic function predicted that recommended VRC doses of 300 mg intravenously and 200 mg orally twice daily would achieve the 1.5 mg/L threshold with probabilities of 87% and 49%, respectively, and the 4.5 mg/L threshold with probabilities of 37% and 8%, respectively. A narrower concentrations target of 2–4 mg/L with a marginal outcome improvement (>85%–90% probability of response and < 10%–15% probability of neurotoxicity) would significantly increase the trough outliers. Recommended doses are challenged by neurotoxicity for intravenous therapy and nonresponse for oral therapy. In acute infection, efficacy has the priority: 300 mg intravenously and 400 mg orally twice daily rapidly achieve VRC concentrations >1.5 mg/L, while being associated with a higher risk of neurotoxicity. In responding infection or prophylaxis, safety prevails on rapid achievement of therapeutic concentrations: 200 mg intravenously and 300 mg orally twice daily are associated with a lower risk of neurotoxicity. The 60% oral bioavailability observed in this population may explain the differences in the required intravenous/oral VRC doses.

In both scenarios, despite adjusted initial doses, achievement of therapeutic concentration targets remains suboptimal because of important intrapatient/interpatient variability. Individualized adjustments based on VRC trough concentrations during the first week of therapy may avoid prolonged infratherapeutic or supratherapeutic VRC exposure by minimizing risks of decreased efficacy or neurotoxicity. Further monitoring of plasma concentrations may be necessary after a change of dose or route, lack of response, or suspected neurotoxicity. VRC therapy guided by monitoring trough concentrations is recommended by many experts as a component of optimal patient care [5, 22, 35–38]. A Bayesian feedback strategy would be ideally suited for extrapolation of troughs from concentrations measured at any time during the dosing interval [39]. As real-time CYP2C19 genotyping is not routinely available, the

clinical role of this research tool for optimizing VRC exposure remains to be defined.

In conclusion, this analysis involving adult patients with IFI challenges recommended VRC doses. Initial 300–400 mg oral and 200–300 mg intravenous twice-daily doses are best suited to achieve the therapeutic concentration of 1.5–4.5 mg/L. Given the multiple factors contributing to variable VRC absorption, disposition, and clearance, TDM is needed for rapidly identifying inappropriate exposure and optimizing efficacy and safety on an individual basis.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

References

1. Johnson LB, Kauffman CA. Voriconazole: a new triazole antifungal agent. Clin Infect Dis **2003**; 36:630–7.
2. Lazarus HM, Blumer JL, Yanovich S, Schlamm H, Romero A. Safety and pharmacokinetics of oral voriconazole in patients at risk of fungal infection: a dose escalation study. J Clin Pharmacol **2002**; 42:395–402.
3. Hyland R, Jones BC, Smith DA. Identification of the cytochrome P450 enzymes involved in the N-oxidation of voriconazole. Drug Metab Dispos **2003**; 31:540–7.
4. Ikeda Y, Umemura K, Kondo K, Sekiguchi K, Miyoshi S, Nakashima M. Pharmacokinetics of voriconazole and cytochrome P450 2C19 genetic status. Clin Pharmacol Ther **2004**; 75:587–8.
5. Pascual A, Calandra T, Bolay S, Buclin T, Bille J, Marchetti O. Voriconazole therapeutic drug monitoring in patients with invasive mycoses improves efficacy and safety outcomes. Clin Infect Dis **2008**; 46:201–11.
6. Boyd AE, Modi S, Howard SJ, Moore CB, Keevil BG, Denning DW. Adverse reactions to voriconazole. Clin Infect Dis **2004**; 39:1241–4.
7. den Hollander JG, van AC, Rijnders BJ, Lugtenburg PJ, de MS, Levin MD. Incidence of voriconazole hepatotoxicity during intravenous and oral treatment for invasive fungal infections. J Antimicrob Chemother **2006**; 57:1248–50.
8. Pasqualotto AC, Shah M, Wynn R, Denning DW. Voriconazole plasma monitoring. Arch Dis Child **2008**; 93:578–81.
9. Smith J, Safdar N, Knasinski V, et al. Voriconazole therapeutic drug monitoring. Antimicrob Agents Chemother **2006**; 50:1570–2.
10. Zonios DI, Gea-Banacloche J, Childs R, Bennett JE. Hallucinations during voriconazole therapy. Clin Infect Dis **2008**; 47:e7–10.
11. de Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis **2008**; 46:1813–21.
12. Pascual A, Nieth V, Calandra T, et al. Variability of voriconazole plasma levels measured by new high-performance liquid chromatography and bioassay methods. Antimicrob Agents Chemother **2007**; 51:137–43.
13. Bruggemann RJ, Touw DJ, Aarnoutse RE, Verweij PE, Burger DM. International interlaboratory proficiency testing program for measurement of azole antifungal plasma concentrations. Antimicrob Agents Chemother **2009**; 53:303–5.
14. Segal BH, Herbrecht R, Stevens DA, et al. Defining responses to therapy and study outcomes in clinical trials of invasive fungal diseases: Mycoses Study Group and European Organization for Research and Treatment of Cancer consensus criteria. Clin Infect Dis **2008**; 47:674–83.
15. Serious adverse events definitions. National Cancer Institute online guidelines, **2010**. Available at: http://ctep.cancer.gov/reporting/ctc.html.
16. Beal SL, Sheiner LB, Boeckmann A, Bauer RJ. NONMEM user's guide. Ellicott City, MD: Icon Development Solutions, **2006**.
17. Lindbom L, Pihlgren P, Jonsson EN. PsN-Toolkit—a collection of computer intensive statistical methods for non-linear mixed effect modeling using NONMEM. Comput Methods Programs Biomed **2005**; 79:241–57.
18. Troke PF, Hockey HP, Hope WW. Observational study of the clinical efficacy of voriconazole and its relationship to plasma concentrations in patients. Antimicrob Agents Chemother **2011**; 55:4782–8.
19. Nomura K, Fujimoto Y, Kanbayashi Y, Ikawa K, Taniwaki M. Pharmacokinetic-pharmacodynamic analysis of voriconazole in Japanese patients with hematological malignancies. Eur J Clin Microbiol Infect Dis **2008**; 27:1141–3.
20. Leveque D, Nivoix Y, Jehl F, Herbrecht R. Clinical pharmacokinetics of voriconazole. Int J Antimicrob Agents **2006**; 27:274–84.
21. Purkins L, Wood N, Ghahramani P, Greenhalgh K, Allen MJ, Kleinermans D. Pharmacokinetics and safety of voriconazole following intravenous- to oral-dose escalation regimens. Antimicrob Agents Chemother **2002**; 46:2546–53.
22. Trifilio SM, Yarnold PR, Scheetz MH, Pi J, Pennick G, Mehta J. Serial plasma voriconazole concentrations after allogeneic hematopoietic stem cell transplantation. Antimicrob Agents Chemother **2009**; 53:1793–6.
23. Han K, Bies R, Johnson H, Capitano B, Venkataramanan R. Population pharmacokinetic evaluation with external validation and Bayesian estimator of voriconazole in liver transplant recipients. Clin Pharmacokinet **2011**; 50:201–14.
24. Hope WW. Population pharmacokinetics of voriconazole in adults. Antimicrob Agents Chemother **2012**; 56:526–31.
25. Neely M, Rushing T, Kovacs A, Jelliffe R, Hoffman J. Voriconazole pharmacokinetics and pharmacodynamics in children. Clin Infect Dis **2010**; 50:27–36.
26. Tan K, Brayshaw N, Tomaszewski K, Troke P, Wood N. Investigation of the potential relationships between plasma voriconazole concentrations and visual adverse events or liver function test abnormalities. J Clin Pharmacol **2006**; 46:235–43.
27. Wood N, Tan K, Purkins L, et al. Effect of omeprazole on the steady-state pharmacokinetics of voriconazole. Br J Clin Pharmacol **2003**; 56(Suppl 1):56–61.
28. Wang G, Lei HP, Li Z, et al. The CYP2C19 ultra-rapid metabolizer genotype influences the pharmacokinetics of voriconazole in healthy male volunteers. Eur J Clin Pharmacol **2008**.
29. Wang G, Lei HP, Li Z, et al. The CYP2C19 ultra-rapid metabolizer genotype influences the pharmacokinetics of voriconazole in healthy male volunteers. Eur J Clin Pharmacol **2009**; 65:281–5.
30. Arendrup MC, Bruun B, Christensen JJ, et al. National surveillance of fungemia in Denmark (2004 to 2009). J Clin Microbiol **2011**; 49:325–34.

31. Lass-Florl C, Mayr A, Perkhofer S, et al. Activities of antifungal agents against yeasts and filamentous fungi: assessment according to the methodology of the European Committee on Antimicrobial Susceptibility Testing. Antimicrob Agents Chemother **2008**; 52:3637–41.
32. Lockhart SR, Wagner D, Iqbal N, et al. Comparison of in vitro susceptibility characteristics of *Candida* species from cases of invasive candidiasis in solid organ and stem cell transplant recipients: Transplant-Associated Infections Surveillance Network (TRANSNET), 2001 to 2006. J Clin Microbiol **2011**; 49:2404–10.
33. Pfaller M, Boyken L, Hollis R, et al. Use of epidemiological cutoff values to examine 9-year trends in susceptibility of *Aspergillus* species to the triazoles. J Clin Microbiol **2011**; 49:586–90.
34. Gorski E, Esterly JS, Postelnick M, Trifilio S, Fotis M, Scheetz MH. Evaluation of hepatotoxicity with off-label oral-treatment doses of voriconazole for invasive fungal infections. Antimicrob Agents Chemother **2011**; 55:184–9.
35. Andes D, Pascual A, Marchetti O. Antifungal therapeutic drug monitoring: established and emerging indications. Antimicrob Agents Chemother **2009**; 53:24–34.
36. Bruggemann RJ, Donnelly JP, Aarnoutse RE, et al. Therapeutic drug monitoring of voriconazole. Ther Drug Monit **2008**; 30:403–11.
37. Hope WW, Billaud EM, Lestner J, Denning DW. Therapeutic drug monitoring for triazoles. Curr Opin Infect Dis **2008**; 21:580–6.
38. Walsh TJ, Anaissie EJ, Denning DW, et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis **2008**; 46:327–60.
39. Sheiner LB, Beal S, Rosenberg B, Marathe VV. Forecasting individual pharmacokinetics. Clin Pharmacol Ther **1979**; 26:294–305.