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Population Pharmacokinetic Analysis of Voriconazole and Anidulafungin in Adult Patients with Invasive Aspergillosis

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To assess the pharmacokinetics (PK) of voriconazole and anidulafungin in patients with invasive aspergillosis (IA) in comparison with other populations, sparse PK data were obtained for 305 adults from a prospective phase 3 study comparing voriconazole and anidulafungin in combination versus voriconazole monotherapy (voriconazole, 6 mg/kg intravenously [IV] every 12 h [q12h] for 24 h followed by 4 mg/kg IV q12h, switched to 300 mg orally q12h as appropriate; with placebo or anidulafungin IV, a 200-mg loading dose followed by 100 mg q24h). Voriconazole PK was described by a two-compartment model with first-order absorption and mixed linear and time-dependent nonlinear (Michaelis-Menten) elimination; anidulafungin PK was described by a two-compartment model with first-order elimination. For voriconazole, the normal inverse Wishart prior approach was implemented to stabilize the model. Compared to previous models, no new covariates were identified for voriconazole or anidulafungin. PK parameter estimates of voriconazole and anidulafungin are in agreement with those reported previously except for voriconazole clearance (the nonlinear clearance component became minimal). At a 4-mg/kg IV dose, voriconazole exposure tended to increase slightly as age, weight, or body mass index increased, but the difference was not considered clinically relevant. Estimated voriconazole exposures in IA patients at 4 mg/kg IV were higher than those reported for healthy adults (e.g., the average area under the curve over a 12-hour dosing interval [AUC_{0-12}] at steady state was 46% higher); while it is not definitive, age and concomitant medications may impact this difference. Estimated anidulafungin exposures in IA patients were comparable to those reported for the general patient population. This study was approved by the appropriate institutional review boards or ethics committees and registered on ClinicalTrials.gov (NCT00531479).

Invasive aspergillosis (IA) is an important cause of morbidity and mortality in patients with hematological malignancies, as well as those who have undergone allogeneic hematopoietic stem cell transplantation (HSCT) or solid organ transplantation. Antifungal combination therapy with voriconazole (an azole; both intravenous [IV] and oral formulations are available) and anidulafungin (an echinocandin; IV only) is an intriguing possibility for the treatment of IA, due to their different mechanisms of action and lack of pharmacokinetic (PK) drug-drug interaction (1–3). Voriconazole inhibits fungal cytochrome P450 (CYP)-dependent 14-α-sterol demethylase, an essential enzyme in the synthesis of ergosterol (a component of the fungal cell membrane). Anidulafungin is a 1,3-β-D-glucan synthase inhibitor which interferes with fungal cell wall synthesis. A number of *in vitro* studies and animal models have demonstrated additive or synergistic activities of voriconazole and echinocandins against *Aspergillus* species (4–7), indicating that two mechanisms of action may provide an additional benefit over one mechanism alone. Hence, a prospective phase 3 study was conducted to evaluate the efficacy, safety, and tolerability of this combination therapy versus voriconazole monotherapy in HSCT recipients and patients with hematological malignancies with IA (8).

Although much information exists on voriconazole and anidulafungin exposures in healthy subjects and in a range of patients, there are few reported data on voriconazole and anidulafungin exposures in HSCT recipients and other patient populations at high risk of developing IA. In order to better characterize the PK of voriconazole and anidulafungin in this population, sparse PK samples were collected in a subset of study subjects. The PK-pharmacodynamic analysis of the data from this study is reported in the accompanying paper (9).

It is known that anidulafungin exhibits linear and predictable PK (2). Anidulafungin undergoes slow chemical degradation and has negligible renal clearance (<1%). Anidulafungin is not a clinically relevant substrate, inducer, or inhibitor of CYP enzymes. Voriconazole is extensively metabolized by and is also an inhibitor of CYP2C19 (major), CYP2C9 and CYP3A4, which results in extensive drug interactions with concomitant medications (1). Voriconazole exhibits nonlinear PK due to saturation of its own metabolism, and interindividual variability in voriconazole exposure is high. It has been demonstrated that in healthy adults, CYP2C19 genotype, sex, and age are key factors which help explain this variability (1). Approximately 3 to 5% of Caucasians and African Americans and up to 20% of Asians are poor metabolizers (PMs) due to the polymorphism of CYP2C19. An exploratory analysis of the effects of CYP2C19 genotyping status on voriconazole plasma concentration was performed on data collected from this study.

The objectives of these analyses were to (i) describe the PK of voriconazole and anidulafungin in the target patient population, respectively; (ii) identify and characterize patient factors which influence the variability in the PK of voriconazole and anidulafungin; and (iii) estimate individual exposure parameters (e.g., area under the curve over a dosing interval [$AUC_{0-\tau}$] and trough con-

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centration [C_{min}]) based on the final PK parameter estimates and compare them with historical data for healthy adults or the general patient population.

MATERIALS AND METHODS

Study design. This was a prospective, randomized, double-blind, phase 3 study comparing the efficacy, safety, and tolerability of voriconazole and anidulafungin in combination with those of voriconazole monotherapy in patients with proven or probable IA (8). This study was to test the hypothesis of the superiority of the combination therapy. Written informed consent was obtained prior to the patients' entering the study. Patients with possible IA could be enrolled but were required to be upgraded to proven or probable cases within 7 days of enrollment. The modified intent-to-treat (mITT) population was defined as those who received at least one dose of study drug and had independent Data Review Committee-confirmed diagnosis of probable or proven IA. Pretreatment with antifungal agents, including voriconazole and anidulafungin, was allowed up to 4 days per protocol. CYP2C19 genotype samples were collected on day 1.

A total of 454 patients were randomized in a 1:1 ratio to one of two treatment arms for 6-week antifungal therapy: voriconazole and anidulafungin placebo or voriconazole and active anidulafungin. After 2 weeks, the investigator could continue this treatment regimen or switch the patient to voriconazole monotherapy. For the final 2 weeks of treatment, all patients received voriconazole monotherapy. The anidulafungin IV dosing regimen was standard: a 200-mg loading dose followed by 100 mg every 24 h (q24h). The initially recommended voriconazole dosing regimen was a 6-mg/kg IV loading dose every 12 h (q12h) for 24 h followed by 4 mg/kg IV q12h, switching to 300 mg (150 mg for patients <40 kg) orally q12h as appropriate. The use of a 300-mg oral dose would allow investigators to switch to oral therapy early (i.e., after 7 days of IV treatment), since it was expected to provide voriconazole exposure comparable to the 4-mg/kg IV dose based on the data from healthy subjects (10). If patients were on voriconazole or anidulafungin treatment prior to randomization, the loading dose was skipped. In this study, dose adjustment for voriconazole was allowed based on a patient's clinical response, drug tolerability (adverse events), or voriconazole concentrations. The IV doses of voriconazole and anidulafungin/placebo were administered sequentially.

In a subset of IA patients (n = 305 [67%]), two 3-ml blood samples were collected for anidulafungin and voriconazole measurement on up to 4 occasions, which tended to include the time around the peak concentration, the trough concentration, and a concentration in the middle (between peak and trough). Specifically, a day 2 predose sample (just prior to the infusion of voriconazole), a day 3 postdose sample (ideally 0 to 3 h following the end of infusion of voriconazole), a day 7 delayed postdose sample (ideally 6 to 10 h following the end of infusion of voriconazole), and a day 14 predose sample (just prior to the infusion of anidulafungin) were taken. The sampling dates and times could be changed to fit the study site feasibility. PPD Development (Richmond, VA) (following good laboratory practice [GLP] standards) analyzed all the plasma samples using previously validated liquid chromatography coupled with tandem-mass spectrometry (LC-MS/MS) methods (11, 12). Any interaction between the two drugs in the sample analysis was ruled out.

In addition, the investigators could obtain voriconazole concentration data around the peak time in a fast-turnaround fashion to facilitate the potential dose adjustment, by collecting additional plasma samples and sending to designated non-GLP assay laboratories for measurement. It is noted that these concentration data (from 245 patients) were excluded from this analysis to avoid mixing the data from non-GLP laboratories with those from the GLP laboratory.

Population PK analysis. All the PK modeling and simulation were performed with NONMEM (version 7.1.2; Icon Development Solutions, Ellicott City, MD). The ADVAN13 subroutine was used for both compounds. The graphic processing of the NONMEM output was performed with R (version 2.12.2). The previously developed population PK models for anidulafungin and voriconazole were adapted to fit the current data separately (13, 14).

Anidulafungin. In the previous model, data were described using a two-compartment model with first-order elimination, interindividual variability was estimated for clearance using exponential random effects, and residual error was modeled with a proportional error (13). The first-order conditional estimation (FOCE) with interaction method was used.

In the present study, since pretreatment was allowed per protocol, 4 patients in the data set had pre-existing anidulafungin concentrations. To accommodate this, the previous model was augmented by assuming that respective concentrations were at steady state prior to the study drug's being given in these patients. The prestudy concentrations were modeled by a zero-order rate parameter reflecting a continuous infusion into the central compartment, which was allowed to vary between patients. Additionally, the study effect parameters used previously were not utilized in the present evaluation, as this analysis used data from a single study. The forms of the equation for the anidulafungin PK model parameters from our analysis are presented below

$$\begin{aligned} \mathrm{CL} &= \theta_{\mathrm{CL}} + \theta_{\mathrm{WT}} \cdot (\mathrm{WT} - \mathrm{MWT}) + \theta_{\mathrm{SEX}} \cdot \mathrm{SEX} \\ V_1 &= \theta_{V1} \cdot \mathrm{WT} \\ V_2 &= \theta_{V2} \\ Q &= \theta_{Q} \\ \mathrm{Rate} &= \theta_{\mathrm{rate}} \end{aligned} \quad (1)$$

where CL is linear clearance, MWT is mean body weight (60 kg), V_1 is central volume of distribution, V_2 is peripheral volume of distribution, Q is intercompartmental clearance, and θ is the estimate of fixed effect in NONMEM.

Voriconazole. In the previous model, data from healthy adults were described using a two-compartment model with first-order absorption and mixed linear and time-dependent nonlinear (Michaelis-Menten) elimination (14). Only one parameter, maximum fraction of inhibition on maximum elimination rate ($V_{max,inh}$), in healthy adults was impacted by CYP2C19 status, where heterozygous extensive metabolizers (HEMs) and PMs were predicted to have full inhibition ($V_{max,inh}$ = 100%, maximum elimination rate [V_{max}] = 0) of the nonlinear pathway at maintenance dosing. The FOCE method on log-transformed concentrations was used. Interindividual variability was estimated using exponential random effects, additive random effects on a logit scale, or Manly transformed random effects, as appropriate. Residual error was modeled as study-dependent additive errors on the log-transformed concentrations.

In the present study, over 30% of the patients had pre-existing voriconazole concentrations. The same approach was used as that for the anidulafungin model: the prestudy concentrations were modeled by a zero-order rate parameter. Similarly, the study effect parameters used previously were not utilized in the present evaluation, as this analysis used data from a single study. In addition, the previously estimated voriconazole PK parameters were used as an informative prior to stabilize the model (normal inverse Wishart prior approach). The forms of the equation for the voriconazole PK model parameters from our analysis are presented below

$$V_{\max} = V_{\max,1} \cdot \left(1 - V_{\max,\,\mathrm{inh}} \cdot \frac{(T - 1)}{(T - 1) + (T_{50} - 1)}\right); \quad \text{time-dependent } V_{\max} \quad (2)$$

where V_{max} was allowed to reduce from an initial value with time (T). To increase the model stability as well as interpretability of model parameters, the V_{max} function was parameterized so that V_{max} at 1 h ($V_{max,1}$) was the parameter estimated, since there were no PK samples providing information on V_{max} at time zero. The reduction in V_{max} over time was best described by an inhibitory function with a maximum fraction of the inhibition ($V_{max,inh}$). T_{50} describes the time in hours after initiation of dosing where half of the maximum inhibition occurred.

$$
\begin{aligned}
K_m &= \theta_{Km} \\
V_{\max,1} &= \theta_{V\max,1} \cdot (\mathrm{WT}/70)^{0.75} \\
\mathrm{logit}\,(V_{\max,\mathrm{inh}})^{*} &= \theta_{V\max,\mathrm{inh}} \\
T_{50} &= \theta_{T50} \\
\mathrm{CL} &= \theta_{\mathrm{CL}} \cdot (\mathrm{WT}/70)^{0.75} \\
V_2 &= \theta_{V2} \cdot \mathrm{WT}/70 \\
V_3 &= \theta_{V3} \cdot \mathrm{WT}/70 \\
Q &= \theta_{Q} \cdot (\mathrm{WT}/70)^{0.75} \\
\mathrm{logit}(F_1) &= \theta_{F1} \\
k_a &= \theta_{ka} \\
A_{\mathrm{lag}} &= \theta_{\mathrm{Alag}} \\
\mathrm{Rate} &= \theta_{\mathrm{rate}}
\end{aligned}
\tag{3}
$$

K_m is the Michaelis-Menten constant, CL is linear clearance, V_2 is the central volume of distribution, V_3 is the peripheral volume of distribution, Q is intercompartmental clearance, F_1 is oral bioavailability, k_a is the first-order absorption rate constant, A_{lag} is absorption lag time, and θ is the estimate of fixed effect in NONMEM. The asterisk indicates that $V_{\max,\mathrm{inh}}$ is 100% if an adult is a CYP2C19 HEM or PM.

Covariate selection. Attempts were made to determine if any new covariates (e.g., CYP2C19 genotype, body mass index [BMI], age, sex, and race) besides the ones already identified in previous evaluations could be identified. Anidulafungin was also evaluated as a potential covariate during the voriconazole model development for completeness, although the lack of PK interaction between voriconazole and anidulafungin in healthy subjects is known (3). To be included in the final model, a covariate needed to produce a reduction in the objective function value of at least 7.88 (corresponding to a P value of 0.005 with one degree of freedom; the difference of log likelihoods from nested models is approximately asymptotically χ^2 distributed). Patients with missing covariate information were evaluated as a separate category for graphical evaluation and were assigned the median or most common classification for model-based evaluations. For instance, patients with unknown CYP2C19 status were treated as homozygous extensive metabolizers (EMs), since the EM group comprised 67% (153/227) of the patients with known CYP2C19 status.

Model evaluation. Model selection was based on goodness-of-fit criteria, which included basic diagnostic plots, precision of parameter estimates, and the objective function value. The basic diagnostic plots included observations versus population predictions (PRED) and individual predictions (IPRED), conditional weighted residuals (CWRES) versus IPRED and time, and the normalized prediction distribution error (NPDE). In addition, visual predictive check (VPC) was utilized to assess the predictive performance of the models (with 500 simulations) (15).

Model stability was tested through the evaluation of the condition number. A condition number of less than 20 suggests that the degree of colinearity of the parameter estimates is acceptable. A condition number that is in excess of 40 indicates that the model may be unstable due to high colinearity (16).

Shrinkage occurs when there is insufficient information to provide an individual parameter estimate. This is a common problem when sparse or trough data are evaluated using a modeling approach. When the individual parameter estimates exhibit substantial shrinkage, they no longer reflect the individual PK behavior, which can affect derived parameter estimates, such as the total exposure (AUC). Therefore, the extent of shrinkage on eta (η, empirical Bayes prediction of the interindividual random effect) was assessed (17).

Estimation of exposure parameters. For anidulafungin, the steady-state total exposure ($\mathrm{AUC}_{0-24,\mathrm{SS}}$) was determined as dose/CL_i, where CL_i is the individual estimate of clearance. The steady-state trough concentration ($C_{\min,\mathrm{SS}}$) was estimated at 24 h postdose using individual estimated PK parameters.

TABLE 1 Summary of concentration data and patient demographics

Characteristic	Median (range) or value	
	Anidulafungin	Voriconazole
No. of patients (no. of concns)	140 (453)	IV, 305 (899); oral, 61 (66)
Baseline wt (kg)	68.3 (36.9–116.8)	68.0 (35.0–121)
Baseline BMI (kg/m^2)	23.9 (12.9–41.0)	23.8 (12.9–44.9)
Age (yrs)	54.5 (18–83)	54 (17–83)
Sex (no. of males/no. of female)	83/57	181/124
Race (no. white/black/Asian/other)	111/4/25/0	237/8/55/5
CYP2C19 genotype (EM/HEM/PM/unknown[a])		153/65/9/78

[a] The genotyping status for patients who did not provide a sample or whose sample had insufficient volume for analysis was defined as unknown.

In order to estimate voriconazole exposures at the recommended dosing regimens, a simulation data set for patients who received the recommended maintenance doses (e.g., 4 mg/kg IV q12h and 300 mg orally q12h or 150 mg for patients <40 kg) was created using dense sampling time points, with individual estimated PK parameters incorporated. Then the concentrations were estimated and $\mathrm{AUC}_{0-12,\mathrm{SS}}$ values were computed in NONMEM; the $C_{\min,\mathrm{SS}}$ was estimated at 12 h postdose at steady state.

The effects of body size (i.e., weight and BMI) on anidulafungin and voriconazole exposure parameters (AUC and $C_{\min}$) and the effect of age, genotype, race, and selected concomitant medications (i.e., omeprazole, esomeprazole, and fluconazole) on voriconazole exposure parameters were assessed graphically.

RESULTS

Data for analysis. Table 1 summarizes the concentration data and baseline demographics.

Anidulafungin PK model. The previous PK model adequately described the current data with one modification as noted above (a rate parameter to accommodate patients with measurable prestudy drug concentrations). The sex effect was not significant at the $\alpha = 0.05$ level in the current evaluation but was retained in the model to facilitate comparison with previous work. Overall, the parameter estimates are in agreement with those reported previously (Table 2). The condition number was 12.6, suggesting no notable colinearity. The eta (on clearance) shrinkage was low (14.6%). The basic diagnostic plots for anidulafungin showed generally symmetrical distribution of the data points across the line of unity or line of identity although many data points appeared to be widely spread (see Fig. S1 in the supplemental material). This is not unexpected, given the sparse data from a phase 3 study. The NPDE had symmetrical distribution around zero (see Fig. S3 in the supplemental material). The VPC of concentration data versus time is presented in Fig. 1 (left), which showed that the model adequately described the anidulafungin concentration data. Based on the totality of the model performance metrics, the model performance is considered acceptable.

As expected, body weight was identified as the most influential covariate of anidulafungin PK. Anidulafungin exposure (AUC_{0-24}) tended to decrease as the body size (weight and BMI) increased (Fig. 2a; the BMI plot is not shown). The magnitude of the changes in anidulafungin exposure associated with body size was not considered clinically significant, since there was a substantial overlap of the exposure distributions across the weight or BMI span due to interindividual variability.

TABLE 2 Comparison of anidulafungin parameter estimates from population PK model for the current study and the original data (13)[a]

Parameter	Typical value (%RSE)		Interindividual variability, %CV (%RSE)	
	Original data (n = 225)	Current data (n = 140)	Original data	Current data
CL (liters/h)[b]			28 (17.6)	30 (20.4)
θ_{CL}	0.768 (3.80)	0.997 (4.64)		
θ_{WT}	0.00417 (26.9)	0.0083 (24.2)		
θ_{SEX}	0.166 (25.4)	0.101 (69.8)		
θ_{STUDY}	0.278 (20.8)			
V_1 (liters)				
θ_{V1}	0.215 (20.3)	0.127 (117)	NS	NE
Q (liters/h)				
θ_{Q}	20.3 (16.7)	15.5 (21.0)	NS	NE
V_2 (liters)				
θ_{V2}	19.6 (15.1)	34.1 (26.3)	NS	NE
Rate (mg/h)				
θ_{rate}		2.81 (14.7)		NE
Residual error				
σ^2_{1prop} (%)	24.0 (9.69)	29.1 (5.88)		

[a] n, number of patients; CL, clearance; V_1, central volume of distribution; Q, intercompartmental clearance; V_2, peripheral volume of distribution; σ^2_{1prop}, proportional component of the residual error model; NE, not estimated; NS, not supported in model; WT, weight (kg); MWT, 60 kg; SEX, 1 for males and 0 for females; STUDY, study effect; %RSE, percent relative standard error of the estimate, calculated as SE/parameter estimate × 100 (for variability terms, this is the %RSE of the variance estimate); %CV, percent coefficient of variation, calculated as the square root of variance estimate.

[b] The formula for the original PK model is as follows: $CL = \theta_{CL} + (WT - MWT) \times \theta_{WT} + SEX \times \theta_{SEX} + STUDY \times \theta_{STUDY}$.

Anidulafungin exposure parameters. The estimated steady-state anidulafungin exposure parameters in 140 patients from the PK data set in comparison with historical data are summarized in Table 3. The estimated average anidulafungin AUC_{0-24} and C_{min} values for IA patients in this study were comparable to those reported for the general patient population (18).

Anidulafungin concentration data were available for 89 mITT patients, and their corresponding estimated anidulafungin exposure parameters were similar to those estimated for all the patients in the PK data set.

Voriconazole PK model. The previous PK model adequately described the current data with few modifications as noted above (using a rate parameter and normal inverse Wishart prior approach). In general, the parameter estimates from the current model are in agreement with those reported previously, except for clearance (Table 4). In IA patients, the linear component of voriconazole clearance was slightly lower than the value reported previously for healthy adults (i.e., 5.30 versus 6.16 liters/h in a 70-kg subject), and the nonlinear component of clearance ($V_{max,1}$) was minimal (1,000-fold lower than that from the original model). This low $V_{max,1}$ is not unexpected, due to a lack of sufficient concentration data from the first dose, which is critical for describing the rapid decay of the nonlinear component of voriconazole clearance.

In both models, the difference in $V_{max,inh}$ between CYP2C19 HEMs/PMs and EMs was the same: 100% versus 82%. This indicated that the nonlinear clearance in CYP2C19 HEMs/PMs was fully blocked ($V_{max,inh}$ = 100%, V_{max} = 0) and the total clearance was linear in both IA patients and healthy adults with CYP2C19 HEM and PM status. Only in CYP2C19 EM healthy adults did nonlinear clearance pathway play a role, which accounted for approximately 1/3 of total clearance at maintenance dosing (e.g., at a concentration of 5 μg/ml). Overall, voriconazole total clearances at maintenance dosing in IA patients and healthy adults were not substantially different.

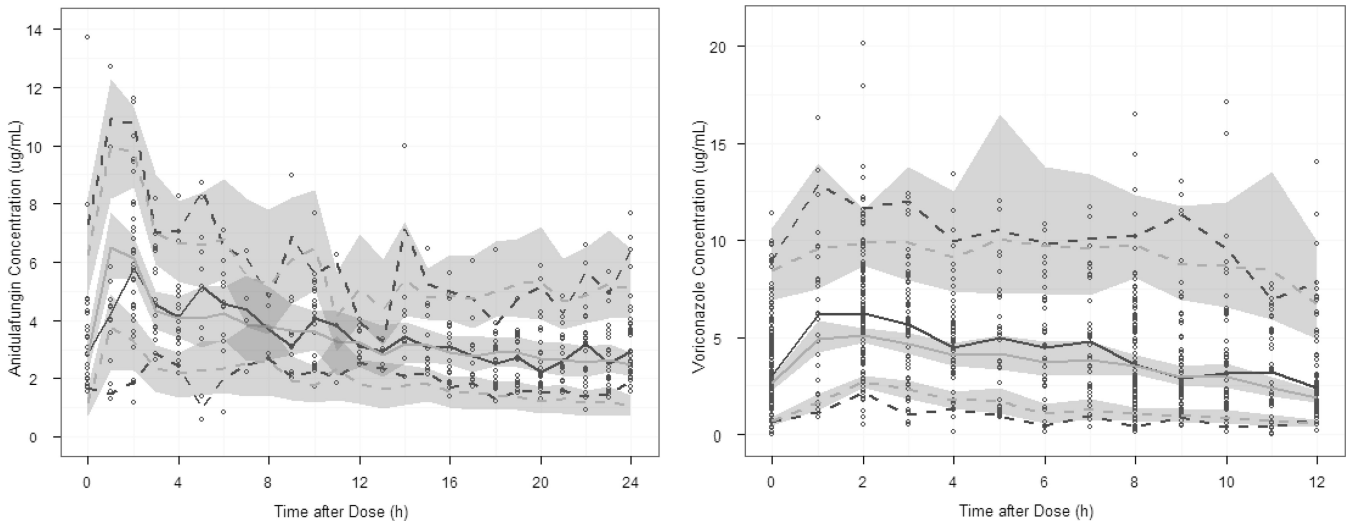

FIG 1 Visual predictive check showing observed and simulated median, 5th-percentile, and 95th-percentile concentrations and 90% prediction intervals for anidulafungin (left) and voriconazole (right). Open symbols represent observed data. Black solid and dashed lines represent the median, 5th percentile, and 95th percentile of the observed concentrations, and gray solid and dashed lines represent the median, 5th percentile, and 95th percentile of the simulated concentrations. The band around the simulated percentiles represents the 90% confidence intervals. Five hundred replicates were simulated. To facilitate the simulation presentation, the time after dose was rounded up in 1-h increments and the observed concentration data were binned to the closest time point. Observed data obtained after 12 h (for voriconazole) or 24 h (for anidulafungin) postdose were not included for simulation.

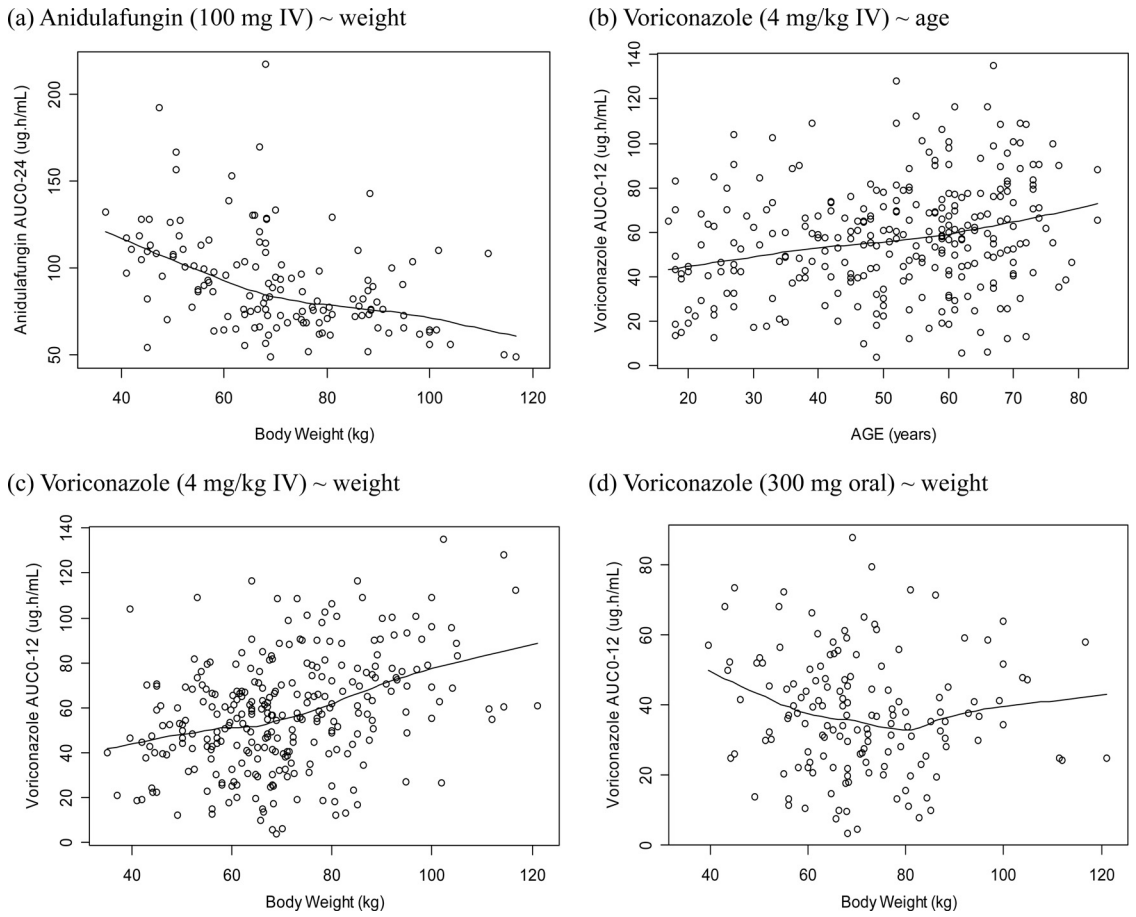

FIG 2 Individual estimated anidulafungin $AUC_{0-24,SS}$ or voriconazole $AUC_{0-12,SS}$ versus body size and age. Open symbols represent individual AUC values; the solid line is the loess smooth.

Voriconazole PK parameters were estimated with generally good precision. The condition number was 32.3, suggesting no notable colinearity. It is noted that the estimated values of eta shrinkage were high (>50% in five PK parameters [50.6% to 89%] [data on file]), as would be expected for a complex model with sparse data to inform the parameters. Nonetheless, the eta shrinkage on linear clearance was low (16.5%). Given the low shrinkage on clearance, this model was deemed acceptable to provide individual estimates for exposure parameters.

Basic diagnostic plots showed that the observed voriconazole

TABLE 3 Estimated voriconazole and anidulafungin exposure parameters based on the final PK models[a]

Drug and parameter	$AUC_{0-\tau,SS}$ (μg · h/ml)		$C_{min,SS}$ (μg/ml)	
Anidulafungin[b]	100 mg IV		100 mg IV	
n	140		140	
Reference arithmetic mean (CV, %)[c]	110.3 (33)		3.3 (42)	
Arithmetic mean (CV, %)	91.8 (31)		2.86 (36)	
5th, 95th percentile	55.7, 139		1.51, 4.59	
Median (range)	86.7 (48.8, 218)		2.67 (1.22, 6.83)	
Voriconazole[b]	4 mg/kg IV	300 mg PO	4 mg/kg IV	300 mg PO
n	283	149	283	149
Reference geometric mean (CV, %)[d]	34.9 (53)	34.0 (53)	1.78 (72)	1.51 (74)
Geometric mean (CV, %)	51.0 (43)	32.9 (45)	3.10 (52)	2.04 (54)
5th, 95th percentile	18.3, 101	10.6, 67.3	0.75, 7.44	0.44, 4.85
Median (range)	57.3 (3.90, 135)	36.7 (3.21, 87.8)	3.78 (0.02, 10.0)	2.46 (0.03, 6.71)

[a] $AUC_{0-\tau,SS}$, area under the curve over the dosing interval at steady state; $C_{min;SS,}$ minimum (trough) concentration at steady state; *n*, number of patients; CV, coefficient of variation.
[b] Dosing frequencies for voriconazole and anidulafungin were q12h and q24h, respectively.
[c] Historical anidulafungin data from patients (mostly with *Candida* infections) ($n = 262$) (18).
[d] Historical voriconazole data from healthy adults ($n = 33$ for the IV dose, $n = 16$ for the oral dose) based on the noncompartmental method (23).

TABLE 4 Comparison of voriconazole parameter estimates from population PK model for the current study and the original data (14)[a]

Parameter	Typical value (%RSE[b])		Interindividual variability[d]	SD[c] (%RSE[b])	
	Original data ($n = 35$)	Current data ($n = 305$)		Original data	Current data
K_m (μg/ml)			$K_m,i = K_m \cdot \exp(\eta_{K_m\text{-}V_{max,1}})$		
θ_{Km}	1.15 (28)	1.15 (10)	$\omega_{K_m\text{-}V_{max,1}}$	1.36 (21)	1.91 (28)
$V_{max,1}$ (μg/h/70 kg[e])			$V_{max,1},i = V_{max,1} \cdot \exp(\eta_{K_m\text{-}V_{max,1}} \cdot \theta_{V_{max,scale}})$		
$\theta V_{max,1}$	114000 (16)	113 (10)	$\omega_{K_m\text{-}V_{max,1}}$	1.36 (21)	1.91 (28)
			$\theta_{V_{max,scale}}$	0.584 (10)	0.583 (10)
$V_{max,inh}$[f]					
$\theta_{Vmax,inh}$	1.50 (9.3)	1.50 (9.3)		NS	NS
T_{50} (h)					
θ_{T50}	2.41 (6.6)	2.42 (5.7)		NS	NS
CL (liters/h/70 kg[e])					
θ_{CL}	6.16 (13)	5.30 (4.2)	ω_{CL}	0.435 (18)	0.634 (11)
V_2 (liters/70 kg)					
θ_{V2}	79.0 (3.1)	77.6 (2.9)	ω_{V2}	0.136 (21)	0.139 (25)
V_3 (liters/70 kg)					
θ_{V3}	103 (6.0)	89.5 (5.4)	ω_{V3}	0.769 (15)	0.831 (26)
Q (liters/h/70 kg[e])					
θ_Q	15.5 (6.8)	15.9 (5.7)	ω_Q	0.424 (22)	0.459 (27)
F_1			$\text{logit}(F_1,i) = \text{logit}(F_1) + \text{ETATR},i$ $\text{ETATR},i = [\exp(\eta F_1 \cdot \theta_{BC-F}) - 1]/\theta_{BC-F}$		
θ_{F1}	0.585 (13)	0.595 (13)	ω_{F1}	0.686 (18)	0.713 (24)
			θ_{BC-F}	0.367 (42)	0.411 (34)
K_a (h^{-1})	100 (FIX)	1.2 (FIX)			
A_{lag} (h)					
θ_{Alag}	0.949 (0.4)	1 (0.52)		NS	NS
Rate (mg/h)					
θ_{rate}		12.8 (9.1)	ω_{R2}		0.910 (20)
Residual error	Original data		Current data		
	$W = \text{SQRT}(\theta_{IV}^2 + \theta_{oral}^2)$				
	θ_{IV}	0.0912 (3.6)	σ_{IV}^2 (%)	53 (6.7)	
	θ_{oral}	0.132 (15)	σ_{oral}^2 (%)	61 (28)	

[a] SD, standard deviation; n, number of patients; K_m, Michaelis-Menten constant; $V_{max;1,}$ maximum elimination rate at 1 h after start of dosing; $V_{max,inh}$, maximum fraction of V_{max} inhibition; T_{50}, time (in hours) at which half of the maximum inhibition occurs; CL, linear clearance; V_2, central volume of distribution; V_3, peripheral volume of distribution; Q, inter-compartmental clearance; $K_{a,}$ first order absorption rate constant; F_1, oral bioavailability {calculation: F_1, $1/[1 + \exp(-\theta F_1)]$; A_{lag}, absorption lag time; W, SD of residual error (on log scale); NS, not supported in the model; WT, weight (kg); ETATR, transformed eta; SQRT, square root.

[b] %RSE: percent relative standard error of the estimate, calculated as SE/parameter estimate × 100. SE in the original model was computed based on a limited nonparametric bootstrap ($n = 10$), and SE in the current study was obtained from $COVARIANCE reported by NONMEM.

[c] Standard deviation of random effects (ω).

[d] The interindividual variability was estimated using exponential random effects unless otherwise specified [e.g., $\text{CL},i = \text{CL} \cdot \exp(\eta_{CL})$].

[e] A power function of 0.75 was applied for clearance terms; i.e., the relationship to weight is not linear.

[f] $V_{max,inh}$ is 100% if an adult is a CYP2C19 HEM or PM.

concentration data with high values (e.g., >12 μg/ml) tended to be slightly underestimated (see Fig. S2 [top right] in the supplemental material). Since only sparse data were collected, it is not feasible to develop a more complex model to incorporate factors, such as deterioration of body function and concomitant medication effect during the therapy course, to help describe the high concentration values. The NPDE had symmetrical distribution around zero (see Fig. S3 in the supplemental material). The VPC of concentration data versus time is presented in Fig. 1 (right), which showed that the model adequately described the voriconazole concentration data. Based on the totality of the model performance metrics, the model performance is considered acceptable.

Attempts to identify new covariates (e.g., CYP2C19 genotype, BMI, age, sex, race, and anidulafungin) on other voriconazole PK parameters were not successful, possibly due to the high shrinkage noted above.

In this analysis, 22% of patients were elderly (>65 years). Although age was not identified as a covariate of voriconazole PK, there was a trend that voriconazole exposure tended to increase slightly as the age increased (Fig. 2b).

Voriconazole IV dose was given based on the actual body weight in this study. At the 4-mg/kg IV dose, voriconazole exposure (AUC_{0-12}) tended to increase slightly as the body size (body weight and BMI) increased (Fig. 2c; the BMI plot is not shown). Nonetheless, the magnitude of the changes in exposure associated with body size was not considered clinically significant, since there was a substantial overlap of the exposure distributions across the weight or BMI span due to large interindividual variability. No obvious trend was observed between voriconazole exposure at a 300-mg oral dose and body weight (Fig. 2d).

Among 103 out of 305 IA patients, one patient was on fluconazole, two patients were on both fluconazole and omeprazole, and

all other patients were on either omeprazole or esomeprazole (the *S* enantiomer of omeprazole) when the PK samples were collected. It is known that omeprazole and fluconazole (CYP2C19 inhibitors) can increase voriconazole exposure (19, 20), i.e., an approximately 41% increase in voriconazole AUC_{0-12} by 40 mg once daily omeprazole and an approximately 79% increase in voriconazole AUC_{0-12} by 200 mg once daily fluconazole in healthy subjects. Voriconazole exposures in the absence or presence of these concomitant medications were compared, but no visual trend was observed in these IA patients (see Fig. S4 in the supplemental material). This preliminary assessment could be confounded by other factors also contributing to the interindividual variability in voriconazole exposure. Thus, no further exploration of concomitant medications as potential covariates was performed during PK model development.

Voriconazole exposure parameters. Among the 305 patients who provided measurable voriconazole concentration data, 283 patients received the 4-mg/kg IV maintenance dose and 149 patients received the 300-mg oral maintenance dose during the treatment period. The estimated steady-state voriconazole exposure parameters in IA patients at 4 mg/kg IV or 300 mg orally q12h in comparison with historical data are also summarized in Table 3.

Based on the estimation, approximately 80% of IA patients would have voriconazole trough concentrations ranging from 1 to 6 μg/ml at 4 mg/kg IV q12h, and approximately 85% of patients would have trough concentrations within this range at 300 mg orally q12h. A good correlation between voriconazole AUC_{0-12} and trough concentration at steady state was identified in adults and children in earlier studies (21, 22). The correlation between estimated voriconazole AUC_{0-12} and C_{min} in this study is expressed as follows (also, see Fig. S5 in the supplemental material): $AUC_{0-12} = 7.011 + (12.687 \cdot C_{min})$ ($R^2 = 0.99$).

Voriconazole concentrations were available in 204 mITT patients, and 141 of them received the oral dosing regimen. The estimated voriconazole exposure parameters in mITT patients were not substantially different from those estimated for all the patients from the PK data set. In addition, there were no marked differences in voriconazole exposures in mITT patients between the two treatment groups (combination therapy versus voriconazole monotherapy).

Additionally, voriconazole exposures were simulated in these IA patients if they were receiving lower dosing regimens. For instance, at 3 mg/kg IV q12h, geometric mean values (coefficients of variation [CV])of AUC_{0-12} and C_{min} were 38.5 μg · h/ml (43%) and 2.33 μg/ml (53%), respectively; at 200 mg orally q12h, geometric mean values (CV) of AUC_{0-12} and C_{min} were 22.0 μg · h/ml (46%) and 1.37 μg/ml (54%), respectively.

Voriconazole dose adjustment in mITT population. There were a total of 277 mITT patients in this study. All the mITT patients received the IV dosing regimen, and 192 of them also received the oral dosing regimen. Overall, voriconazole dose was reduced in 20% (55/277) of mITT patients, and 3% (8/277) of patients had dose escalation. There were no marked differences in frequency of dose adjustment between the two treatment groups (Table 5). Specifically, voriconazole concentration results led to dose modification in only 5% (13/277) of mITT patients: 9 had dose reduction due to elevated plasma concentrations (i.e., peak concentration exceeded 9 μg/ml), while 4 had dose escalation due to low plasma concentrations (including one subject with concomitant use of phenytoin). Voriconazole dose was reduced in 17% (46/277) of mITT patients due to adverse events (mainly hepatic adverse events) and was increased in 1% (4/277) of patients due to insufficient response.

TABLE 5 Summary of voriconazole dose adjustment in mITT patients

Group[a]	No. of patients (%) with:					
	Dose reduction			Dose escalation		
	Total	IV	Oral[b]	Total	IV	Oral[b]
Combination therapy ($n = 135$)	32 (24)	18 (13)	20 (22)	4 (3)	2 (1)	2 (2)
Monotherapy ($n = 142$)	23 (16)	9 (6)	16 (16)	4 (3)	1 (0.7)	3 (3)

[a] Criteria for dose reduction: IV dose ≤ 3.5 mg/kg; oral dose < 300 mg; criteria for dose escalation: IV dose > 4.5 mg/kg; oral dose > 300 mg.
[b] A total of 92 mITT patients in the combination group and 100 in the monotherapy group received the oral dosing regimen. For percentage calculation, the total number of patients during IV or oral period in each group was used as the denominator.

DISCUSSION

Anidulafungin. As expected, body size had a slight effect on anidulafungin exposure, since weight was identified as a covariate on anidulafungin clearance. Although anidulafungin exposure at the 100-mg IV dose tended to decrease slightly as weight or BMI increased, the difference was not considered clinically significant. The exposures in patients with high body weight or BMI were still within the range observed in those with low body weight or BMI. This indicates that the weight effect is nominal and does not warrant a dose adjustment based on body size. This is consistent with the previous findings (13, 18). Of note, the highest body weight and BMI included in this analysis were 117 kg and 41 kg/m^2, respectively. Obese IA patients above this range were not evaluated here.

Voriconazole. The estimated voriconazole exposures in IA patients at the 4-mg/kg IV dose in this study were higher than those reported for healthy adults in the reference study (geometric mean AUC_{0-12}, 51.0 versus 34.9 μg · h/ml, i.e., 46% higher) (Table 3) (23). This may be partially explained by the following. In this analysis, 22% of patients were elderly (>65 years old), and the median age was 54 years. Although the PK model did not detect an age effect, the estimated exposures showed numeric difference between nonelderly and elderly patients (geometric mean AUC_{0-12} values, 48.9 versus 59.3 μg · h/ml). It is known that hepatic enzymatic capacity tends to decrease in the elderly. In addition, there was a concomitant use of omeprazole or esomeprazole in 29% of patients who were included in this analysis. Although no trends were identified in the preliminary assessment, the effect of these concomitant medications on voriconazole exposure is known (20). In contrast, all the healthy subjects from the reference study were under 55 years old, with a median age of 34 years and a BMI of <31.5 kg/m^2, and were prohibited from receiving any concomitant medications with the potential to inhibit or induce CYP enzymes (23). Of note, 13% of IA patients (41/305) at the study entry had abnormal liver function tests (i.e., aspartate aminotransferase ≥3 times the upper limit of normal [ULN], alanine aminotransferase ≥3 times the ULN, and/or total bilirubin ≥1.5 times the ULN). The impact of abnormal

liver function tests on the metabolism rate of voriconazole is unknown.

The estimated average oral bioavailability of voriconazole was 64% in IA patients. The estimated voriconazole exposures in IA patients taking the 300-mg oral q12h dose were comparable to those reported for healthy adults (geometric mean AUC_{0-12}, 32.9 versus 34.0 μg · h/ml) (Table 3) (23).

In healthy subjects (from phase 1 studies in a well-controlled setting), on average, CYP2C19 PMs have 4-fold and 2-fold higher voriconazole concentrations than their EM and HEM counterparts, respectively (1). Nonetheless, the exposures of voriconazole vary widely within each genotype and overlap considerably across CYP2C19 genotypes. These differences were not of a clinically relevant magnitude, and no dose adjustment based on CYP2C19 genotyping status was warranted in the product label (1). Our analysis is consistent with the previous findings that CYP2C19 genotyping status did not have a clinically relevant effect on voriconazole exposure in IA patients (see Table S1 in the supplemental material).

Voriconazole IV dosing is instructed to be administered based on actual body weight. It has been speculated that voriconazole is not distributed extensively in human adipose tissue (24, 25). To assess if this recommendation is appropriate for obese patients, voriconazole exposures in IA patients were evaluated by body size (weight and BMI). A trend was observed at the 4-mg/kg IV dose: voriconazole exposure tended to increase slightly as the body size increased (Fig. 2c). Nonetheless, the estimated exposures in patients with high body weight (e.g., >100 kg) or BMI (e.g., >30 kg/m^2) were still within the range observed in patients with low body weight or BMI. Hence, it is deemed that the current IV dosing recommendation based on actual body weight is acceptable in obese patients. Of note, the highest body weight and BMI included in this analysis were 121 kg and 45 kg/m^2, respectively. Obese IA patients above this range have not been evaluated here.

Among the 277 mITT patients, 55 (20%) patients had dose reduction (most of them to a 3.5- or 3-mg/kg IV dose or a 250- or 200-mg oral dose), and 8 (3%) patients had dose escalation. The most common reason for dose reduction was hepatic adverse events. Only 13 patients had dose adjustments (9 reductions and 4 escalations) based on the fast-turnaround voriconazole concentrations. This confirmed that the currently recommended dosing regimen is suitable for the majority of IA patients and voriconazole dose adjustment could be managed by monitoring patients' adverse events and clinical response. Monitoring voriconazole levels is an additional option to facilitate dose adjustment, but not a necessity.

In summary, a two-compartment PK model with first-order elimination adequately described the anidulafungin IV data from IA patients. A two-compartment PK model with first-order absorption and mixed linear and nonlinear (Michaelis-Menten and time-dependent V_{max}) elimination adequately described the voriconazole IV and oral data from IA patients, where the nonlinear component of clearance was minimal.

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