AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

PHARMACOLOGY

Pharmacokinetics of Anidulafungin in Obese and Normal-Weight Adults

Roeland E. Wasmann,[a,b] Rob ter Heine,[a] Eric P. van Dongen,[c] David M. Burger,[a] Vincent J. Lempers,[a] Catherijne A. Knibbe,[d,e] Roger J. Brüggemann[a,b]

[a]Department of Pharmacy, Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, The Netherlands

[b]Center of Expertise in Mycology, Radboudumc/CWZ, Nijmegen, The Netherlands

[c]Department of Anesthesiology, Intensive Care and Pain Management, St. Antonius Hospital, Nieuwegein, The Netherlands

[d]Department of Clinical Pharmacy, St. Antonius Hospital, Nieuwegein, The Netherlands

[e]Division of Pharmacology, Leiden Academic Centre for Drug Research, Leiden University, Leiden, The Netherlands

ABSTRACT In 2025, approximately one out of five adults will be obese. Physiological changes associated with obesity have been shown to influence the pharmacokinetics of drugs. Anidulafungin is frequently used in critically ill patients, and to achieve optimal efficacy, it is essential that its dose is appropriate for each patient's characteristics. We combined data from obese subjects with data from normal-weight subjects and determined an optimal dosing regimen for obese patients by population pharmacokinetic modeling. Twenty adults, 12 of which were normal-weight healthy subjects (median weight, 67.7 kg; range, 61.5 to 93.6 kg) and 8 of which were morbidly obese subjects (median weight, 149.7 kg; range, 124.1 to 166.5 kg) were included in the analysis. Subjects received a single dose of 100 mg anidulafungin intravenously over 90 min, upon which blood samples were obtained. Monte Carlo simulations were performed to optimize dosing in obesity. A three-compartment model and equal volumes of distribution described the data best. Total body weight was identified as a descriptor for both clearance and the volume of distribution, but the effect of weight on these parameters was limited. Simulations showed that with the licensed 100-mg dose, more than 97% of subjects with a weight above 140 kg will have an area under the concentration-time curve from 0 to 24 h of less than 99 mg · h/liter (the reference value for normal-weight individuals). We found that in obese and normal-weight subjects, weight influenced both of the anidulafungin pharmacokinetic parameters clearance and volume of distribution, implying a lower exposure to anidulafungin in (morbidly) obese individuals. Consequently, a 25% increase in the loading and maintenance doses could be considered in patients weighing more than 140 kg.

KEYWORDS anidulafungin, antifungal therapy, echinocandin, modeling, obese

The worldwide prevalence of obesity, which is a body mass index (BMI) above 30 kg/m², has tripled over the past 40 years, and morbid obesity is starting to appear worldwide. The prevalence of obesity increased from 3.2% in 1975 to 10.8% in 2014 for men and from 6.4% to 14.9% for women. Morbid obesity was virtually nonexistent in 1975, with an estimated prevalence of 0.0 to 0.5%, which increased to 0.8% for men and 1.8% for women in 2014. If this rate of increase persists, by 2025, approximately one in every five individuals will be obese (1). Because obese patients are more susceptible to nosocomial infections and are more prone to develop complications due to common infections, an increase in the number of hospitalized obese patients with serious infections can be expected (2). It is well established that obesity results in physiological

Received 10 January 2018 **Returned for modification** 14 March 2018 **Accepted** 20 April 2018

Accepted manuscript posted online 30 April 2018

Citation Wasmann RE, ter Heine R, van Dongen EP, Burger DM, Lempers VJ, Knibbe CA, Brüggemann RJ. 2018. Pharmacokinetics of anidulafungin in obese and normal-weight adults. Antimicrob Agents Chemother 62:e00063-18. https://doi.org/10.1128/AAC.00063-18.

Address correspondence to Roeland E. Wasmann, roeland.wasmann@radboudumc.nl, or Roger J. Brüggemann, roger.bruggemann@radboudumc.nl.

TABLE 1 Summary of subject demographics

Baseline characteristic	Values for: Normal-wt subjects (n = 12)	Obese subjects (n = 8)
No. (%) of subjects by sex		
Male	10 (83.3)	3 (37.5)
Female	2 (16.7)	5 (62.5)
Median (range) values for:		
Age (yr)	24.5 (21–30)	43 (29–66)
Total body wt (kg)	67.7 (60.5–93.6)	149.7 (124.1–166.5)
Ht (cm)	177 (164–188)	170.5 (159–190)
Body mass index (kg/m^2)	22.4 (20.3–27.3)	49.1 (40.0–57.6)
Lean body wt (kg)[a]	55.7 (39.3–70.0)	66.4 (55.4–91.0)

[a]According to the formula of Janmahasatian et al. (10).

changes that have a clinically relevant impact on the pharmacokinetics (PK) of many drugs, including antimicrobial agents, such as micafungin and cefazolin (3–5). It is therefore important to understand the impact of obesity on the PK of antimicrobial agents.

Anidulafungin is one of the three available echinocandin antifungal agents and is licensed for use as an intravenous (i.v.) treatment for invasive candidiasis in adult patients at an initial 200-mg loading dose followed by 100 mg daily. Its efficacy is putatively driven by the ratio of the area under the concentration-time curve (AUC) over the MIC (6). With the emergence of echinocandin resistance, it is essential to adequately dose patients (with any given weight) for optimal efficacy (7).

Contrary to the recommendations for caspofungin, no dose increase based on a higher total body weight (TBW) is recommended by the manufacturer (8). Recently, we described the anidulafungin PK in eight morbidly obese subjects with weights ranging from 124 to 167 kg, determined using a noncompartmental approach, and we found that exposure was, on average, 32.5% lower in those subjects than the reported exposures in the general population (9). In the current study, we combined data from this study in obese subjects (9) with data from two phase I PK studies in normal-weight subjects and analyzed the data using nonlinear mixed-effects modeling. The aim of this study was to determine whether and to what extent the pharmacokinetics of anidulafungin are influenced by obesity (10) and to propose an optimal dosing regimen for overweight, obese, and morbidly obese individuals.

RESULTS

Data for analysis. A total of 283 anidulafungin plasma concentrations were obtained from 20 study participants (195 observations in 12 normal-weight subjects and 88 observations in 8 obese subjects). Patient characteristics are summarized in Table 1. The mean TBW was 67.7 kg (range, 60.5 to 93.6 kg) and 149.7 kg (range, 124.1 to 166.5 kg) for the normal-weight and obese subjects, respectively. None of the plasma samples had values below the limit of quantification, and two samples were removed from the data before model building because of a possible sampling error.

Population pharmacokinetic model. A three-compartment model with first-order elimination from the central compartment and an additive error model on the log scale fitted the data best. As the volumes of distribution (V) of the three compartments were similar (i.e., volume of distribution of the central compartment [V_1], 19.5 liters; volumes of distribution of peripheral compartments [V_2 and V_3], 25.8 liters for V_2 and 17.2 liters for V_3) but were estimated with a relative high imprecision (relative standard error of the estimate, >50%). We therefore simplified the model by equalizing V_1, V_2, and V_3. This model resulted in a similar model fit and goodness-of-fit (GOF) plots. Interindividual variability (IIV) was estimated for clearance and all three volumes of distribution. The use of a residual error for each separate study rather than one residual error resulted in a 46-point decrease in the objective function value (OFV) ($P < 0.0001$). Parameter estimates of the structural model are provided in Table 2.

TABLE 2 Pharmacokinetic parameter estimates of the structural and final models[b]

Parameter	Structural model		Final model	
	Value (% RSE)	95% CI	Value (% RSE)	95% CI
Typical value				
CL (liters/h)	1.08 (3.9)	0.99–1.16		
$CL_{70\ kg} \times (TBW/70)^{\theta_1}$ (liters/h)				
$CL_{70\ kg}$			0.996 (4.2)	0.91–1.09
θ_1			0.322 (22.6)	0.169–0.496
V_1 (liters)	18.9 (4.7)	17.2–20.6		
$V_{1,\ 70\ kg} \times (TBW/70)^{\theta_2}$ (liters)				
$V_{1,\ 70\ kg}$			16.6 (2.8)	15.6–17.6
θ_2			0.631 (15.6)	0.386–0.834
$V_2 = V_3$ (liters)	Equal to V_1		Equal to $V_{1,\ 70\ kg}$	
Q_1 (liters/h)	0.153 (6.2)	0.133–0.173	0.153 (6.4)	0.13–0.18
Q_2 (liters/h)	15.7 (6.1)	13.7–17.7	14.1 (7.0)	12.2–16.0
Interindividual variability[a] (%)				
CL	15.4 (34.7)	8.4–20.2	12.5 (50.3)	4.5–17.7
V	21.1 (28.6)	14.2–26.4	10.0 (39)	5.5–14.2
Residual error (%)				
σ_{add} study 1	12.6 (20.8)	9.4–15.1	11.0 (16.5)	9.0–13.1
σ_{add} study 2	4.4 (18.4)	3.3–5.3	4.4 (19.3)	3.2–5.5
σ_{add} study 3	8.4 (10.3)	7.4–9.3	8.7 (14)	7.1–10.0
OFV	−931		−975	

[a] Calculated by $\sqrt{(e^{\omega^2}-1)}$, where ω^2 represents the variance.

[b] The eta and epsilon shrinkages of the interindividual variability for CL and V, and all three residual errors were all below 10%. Abbreviations: CL, clearance; $CL_{70\ kg}$, CL standardized to that for a typical 70-kg individual; V_1, volume of distribution of the central compartment; V_2 and V_3, volumes of distribution of peripheral compartments; $V_{1,\ 70\ kg}$, volume of distribution of the central compartment standardized to that for a typical 70-kg individual; Q_1, intercompartmental clearance between V_1 and V_2; Q_2, intercompartmental clearance between V_1 and V_3; σ_{add}, additive error on log scale; RSE, relative standard error based on the covariance step in NONMEM; 95% CI, 95% confidence interval obtained from nonparametric bootstrap analysis (n = 1,000); OFV, objective function value.

Covariate model. Exploration using scatter plots of empirical Bayesian estimates for clearance and volume of distribution versus TBW indicated a relation for both clearance and the volume of distribution of the central compartment (Fig. 1). Inclusion of TBW as a covariate on clearance lowered the IIV by 20%, from 15.4% (95% confidence interval [CI,], 8.4 to 20.2%) to 12.5% (95% CI, 4.5 to 17.7%), and lowered the IIV on the volume of distribution by almost 50%, from 21.1% (95% CI, 14.2 to 26.4%) to 10.0% (95% CI, 5.5 to 14.2%). Both clearance and V_1 were found to change with TBW using a power function with an estimated exponent of 0.322 (95% CI, 0.17 to 0.50) and 0.631 (95% CI,

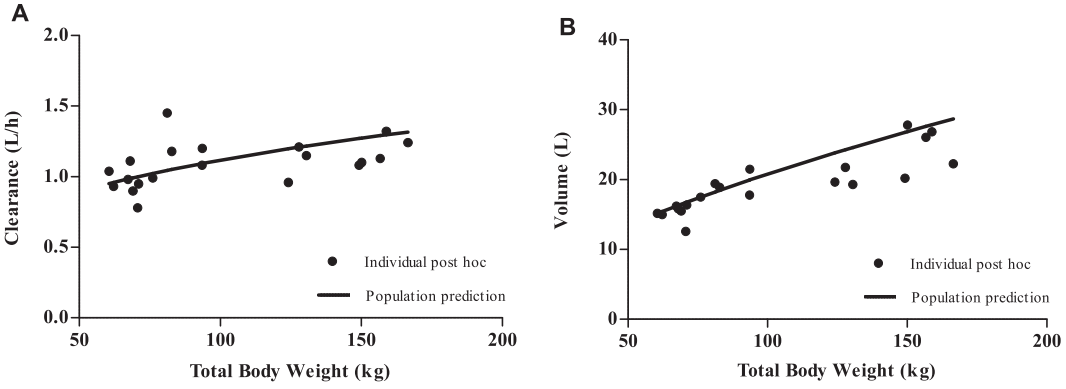

FIG 1 Individual empirical Bayes estimates for clearance (A) and volume of distribution (B) versus total body weight from the structural model (dots) and final model-predicted relationship (line).

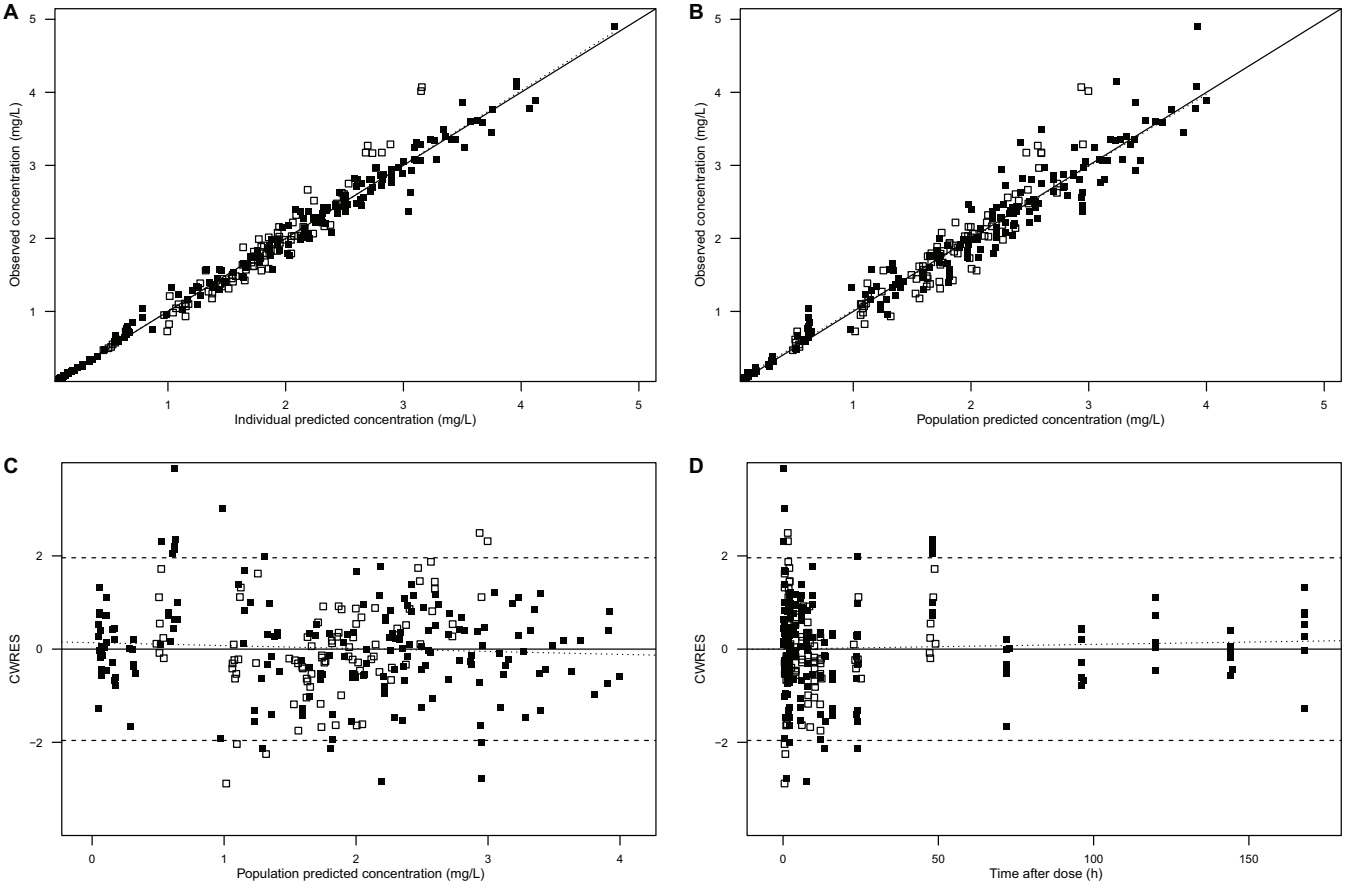

FIG 2 Goodness-of-fit diagnostics of the final population pharmacokinetic model of anidulafungin in normal-weight (filled squares) and morbidly obese (open squares) adult subjects. (A) Individual predicted concentration versus observed concentration; (B) population predicted concentration versus observed concentration; (C) conditional weighted residuals (CWRES) versus population predicted concentration; (D) conditional weighted residuals versus time after dose. Broken lines, a locally weighted least-squares regression; solid lines, the line of identity.

0.39 to 0.83), respectively. The GOF plots of the final model can be found in Fig. 2 and show no major deviations.

The results from nonparametric bootstrap analysis, listed in Table 2, show the precision of the parameters in our population. The prediction-corrected visual predictive check (pcVPC), shown in Fig. 3, demonstrates the validity of the final model. The 95% CIs of the simulations are consistent with the median and 5th and 95th percentiles of the observed concentrations. The width of the 95% CI seems to describe the variation in observed concentrations adequately.

Monte Carlo simulation. Figure 4 shows the distribution of the median (interquartile range [IQR]) AUC from 0 to 24 h (AUC_{0-24}) on day 14 after administration of the licensed 200-mg loading dose and daily 100-mg maintenance dose with increasing weight from a 60-kg to a 170-kg TBW. The median AUC_{0-24} for typical normal-weight subjects with weights between 60 and 80 kg was 99 mg · h/liter (IQR, 91 to 108 mg · h/liter) (Fig. 4). Figure 4 illustrates that virtually all subjects with a weight above 160 kg had an AUC_{0-24} below the median for normal-weight subjects. Furthermore, the median AUC_{0-24} for the subject group with weights between 140 and 150 kg fell below the 80% AUC_{0-24} for the normal-weight reference group. In addition, more than 97% of these subjects had an AUC_{0-24} below the 99-mg · h/liter median. Figure 5 shows the change in AUC_{0-24} when subjects with a total body weight above 140 kg received a 25% dose increase. This augmented dose gave a level of exposure to anidulafungin in subjects weighing up to 170 kg similar to the exposure typically observed in subjects weighing 60 to 80 kg.

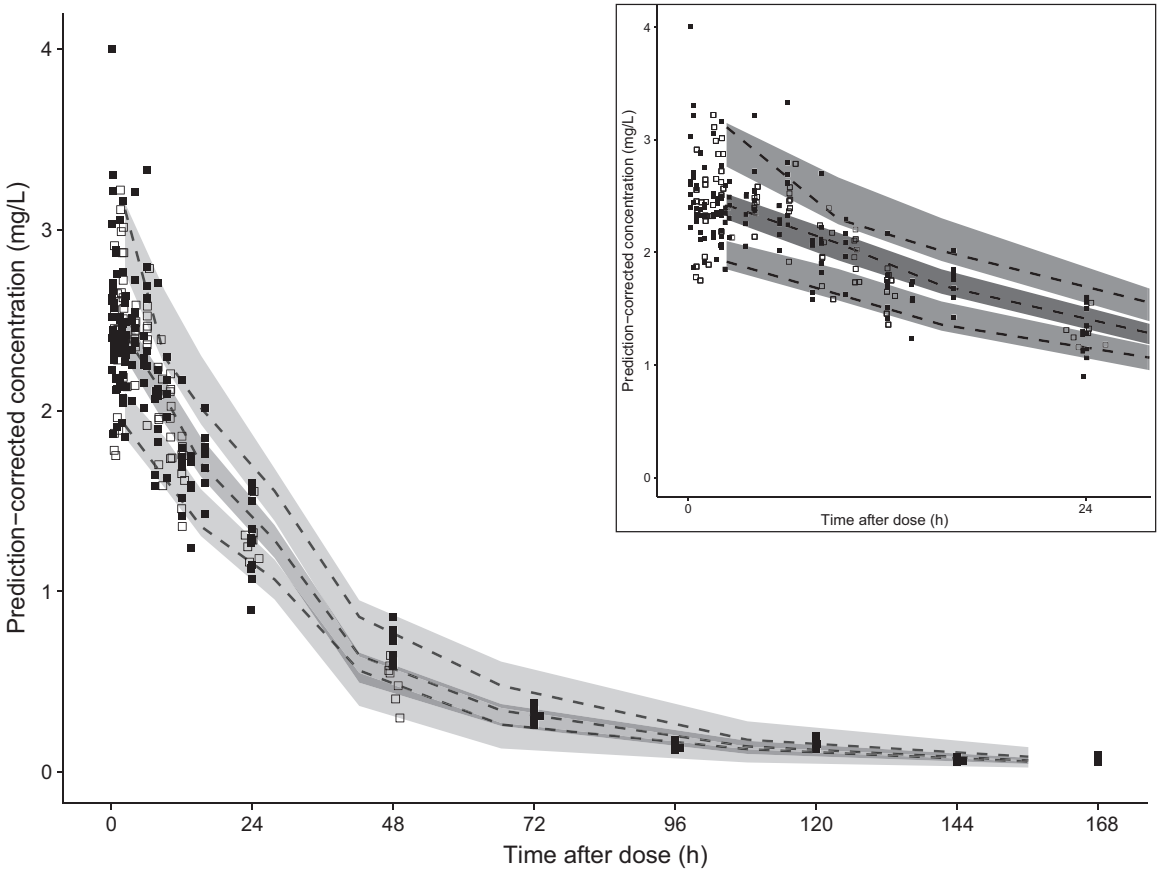

FIG 3 Prediction-corrected visual predictive check for the final pharmacokinetic model of anidulafungin, based on 1,000 simulations. Prediction-corrected simulated (shaded areas) and observed (squares and dashed lines) anidulafungin concentrations versus time after dosing in normal-weight (filled squares) and morbidly obese (open squares) adult subjects. The middle dashed line connects the median values per bin. The outer dashed lines connect the 5th and 95th percentiles of the observations. The shaded areas are the 95% confidence intervals for the 5th and 95th percentiles and the median. (Inset) Expanded view of data from 0 to 24 h.

DISCUSSION

We report here the first population pharmacokinetic model to describe the behavior of anidulafungin in subjects with a wide weight range (60.5 to 166.5 kg). Previous investigations in obese subjects lacked data for normal-weight subjects and were able to make a direct comparison only of average PK parameters. In doing so we improved the analysis of the effects of weight on, especially, clearance and, as a consequence, were able to provide a better suggestion for optimal dosing in (morbidly) obese patients.

The relationship between clearance and body size was best described using a power function on TBW with an exponent of 0.322. The relatively small exponent on TBW indicates only a minor effect of weight on clearance, as visualized in Fig. 1A. In addition, TBW explained approximately 20% of the interindividual variability in our population. These results may be explained by the fact that anidulafungin is mainly cleared from the plasma by slow spontaneous chemical degradation and that only a minor fraction (10%) is cleared by excretion of unchanged drug in the feces (11). As a consequence, it can be anticipated that changes in body composition are only of minor influence in the degradation process. The impact of body weight on the unchanged fraction of anidulafungin excreted in the feces could offer an explanation, but the effect size is unknown and has not been reported.

Previous studies also found a significant increase in clearance and, consequently, a lower AUC at increasing weight (12, 13). Although these studies had sample sizes much larger than the sample size in the present study, we are of the opinion that these

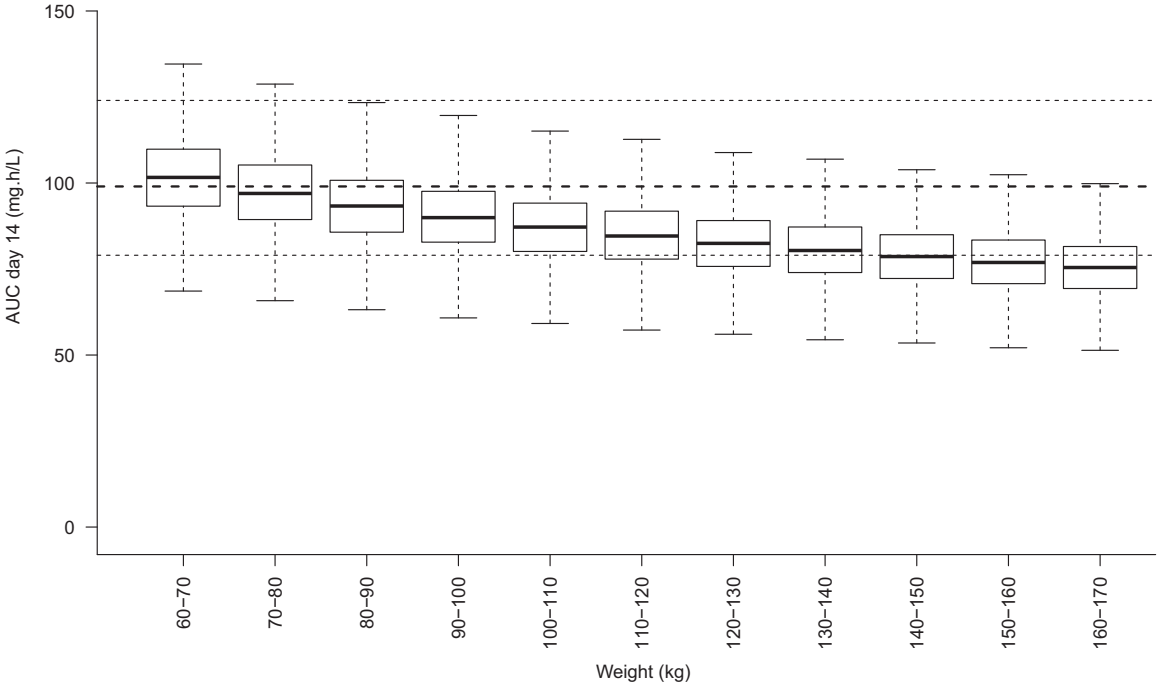

FIG 4 Area under the concentration-time curve (AUC) of anidulafungin at steady state on day 14 achieved with the licensed dose (i.e., a 200-mg loading dose on day 1 followed by 100 mg daily) based on simulations in 55,000 subjects. The horizontal dashed lines represent the exposure of 99 mg · h/liter, typically found in subjects weighing between 60 and 80 kg, and the 80% to 125% range of this median value. The boxes represent the 25th, 50th (median), and 75th percentiles, and whiskers represent the highest and lowest values within 1.5 times the interquartile range.

studies are inconclusive with regard to the impact of body weight, as both median body weight and the body weight range were low (median weights in the studies described in references 12 and 13, 60 and 68 kg, respectively). In addition, the results might be obscured, as an increased clearance can also be attributed to an underlying illness, as reported previously in critically ill patients (14–16).

An increased clearance and a larger volume of distribution were also reported in critically ill patients with suspected or proven fungal infection in three studies, with the AUC_{0-24} values being 69.8 mg · h/liter (14), 82.7 mg · h/liter (15), and 92.7 mg · h/liter (16). The combination of critical illness and obesity further predisposes an individual to suboptimal exposure. This was exemplified by an investigation by Liu et al., who reported a single case of a 240-kg patient receiving 150 mg anidulafungin daily with an AUC of 55.3 mg · h/liter (16). A dose increase of 50% was suggested for patients weighing more than 200 kg or patients with a BMI of $\geq$80 kg/m^2 (16). However, this begs the question whether this minor increase in dose is enough when treating critically ill obese patients, given that it is known that anidulafungin has relatively few side effects (8). This becomes more relevant in fungal infections with less susceptible perpetrators (7, 14–16).

While no threshold value for exposure has been determined for anidulafungin, in a population pharmacokinetic-pharmacodynamic analysis by Liu, a trend of a positive association between exposure and efficacy was found for anidulafungin (17). Due to the relatively small sample size, a target AUC could not be estimated (17). In the absence of well-defined targets, we chose another approach to safeguard identical exposure. This is a pragmatic bioequivalence-like approach and aimed for a dosing regimen that ensures an appropriate AUC of approximately 99 mg · h/liter, comparable to that in normal-weight subjects. Using this approach, our investigation showed that a 25% dose increase in patients with weights above 140 kg and up to 170 kg both at the start and during maintenance should lead to an exposure comparable to that in the general normal-weight patient population. This dose adjustment could be implemented by

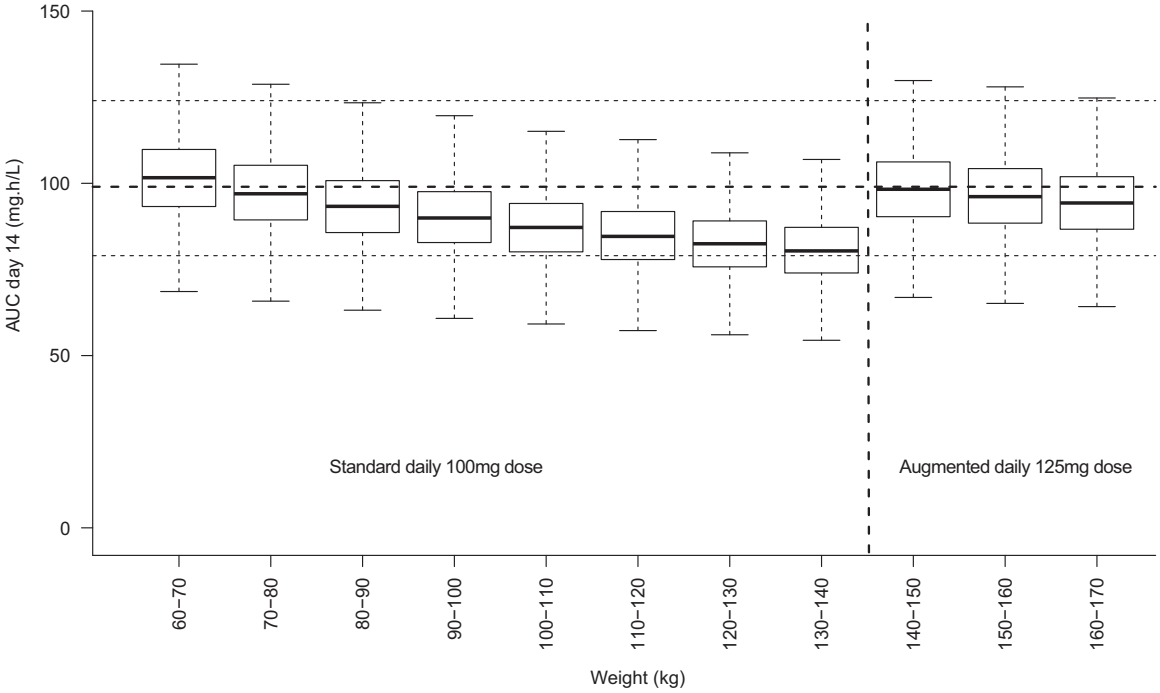

FIG 5 Area under the concentration-time curve (AUC) of anidulafungin at steady state on day 14 based on simulations in 55,000 subjects. Subjects weighing up to 140 kg received the standard 200-mg loading dose on day 1 followed by 100 mg daily. Subjects weighing more than 140 kg received a 25% dose increase to a 250-mg loading dose on day 1 followed by 125 mg daily. The horizontal dashed lines represents the exposure of 99 mg · h/liter, typically found in subjects weighing between 60 and 80 kg, and the 80% to 125% range of this median value. The vertical dashed line shows the cutoff for the 25% dose increase. The boxes represent the 25th, 50th (median), and 75th percentiles, and whiskers represent the highest and lowest values within 1.5 times the interquartile range.

increasing the daily dose. However, the costs of anidulafungin are not to be ignored. To reduce the costs associated with the discarding of half-empty vials, alternate strategies of repetitive cycles of 200 mg followed by three doses of 100 mg might provide a suitable alternative (18), thereby achieving an equivalent cumulative exposure over 4 days.

This study has a few limitations. We investigated a relatively small group of 8 obese subjects and 12 normal-weight subjects, with the latter mainly consisting of males (83%) between 21 and 30 years old. The observed increase in both clearance and volume of distribution was estimated using a power function with an estimated exponent instead of the frequently used fixed allometric exponent of 0.75 on clearance and 1 on volume of distribution. Although our study lacks external validation to confirm these exponents, we did find values for clearance that corresponded to those presented in previous reports of studies in both 60- and 150-kg adults (17). Because of a lack of external validation, we report values for exposure only up to a weight of 170 kg, the maximum weight in our population. For individuals with weights above 170 kg, the relationship will hold but the uncertainty will increase. Furthermore, the allometric exponent of 1 on the volume of distribution for (morbidly) obese individuals can be debated, as these individuals are not simply bigger but have a different body composition with a different ratio of muscle, water content, and adipose tissue (19).

In summary, in our internally validated PK model for obese and normal-weight subjects, weight was found to influence both clearance and volume of distribution. This leads to lower exposure to anidulafungin in (morbidly) obese individuals. As a consequence, a 25% increase in both the loading and maintenance doses could be considered in patients weighing more than 140 kg.

MATERIALS AND METHODS

Subjects and patients. Data from three studies, one study in obese patients (the ADOPT study) and two studies in healthy controls (the VER002-1 and XBAE studies) (Pfizer, Inc., data on file), were combined

TABLE 3 Anidulafungin studies and design included for analysis

Study	Design and objective	Phase	Anidulafungin dose	No. of subjects	Population	No. of samples	PK sampling times (h)
ADOPT	Single-dose, open-label study evaluating PK	IV	100 mg i.v. over 90 min	8	Healthy Caucasian obese males and females	88	0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, 24, 48
VER002-1	Multiple-dose, open-label study evaluating PK	I	100 mg i.v. over 90 min	5	Healthy Caucasian normal-wt males and females	55	Predose,1.75, 2, 2.25, 2.5, 3.5, 5.5, 7.5, 9.5, 13.5, 23.75
XBAE	Single-dose, open-label study evaluating PK	I	100 mg i.v. over 90 min	7	Healthy Caucasian normal-wt males	140	Predose, 0.17, 0.33, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 12, 16, 24, 48, 72, 96, 120, 144, 168

for our current analysis. In the ADOPT study, obese Caucasian subjects (BMI $\geq$ 40 kg/m^2) were given 100 mg anidulafungin i.v. over 90 min several hours prior to bariatric surgery and were sampled until 48 h postinfusion (9). The two healthy volunteer studies in normal-weight Caucasian subjects also involved a 100-mg i.v. dose administered over 90 min (20). The VER002-1 study was a multiple-dose study, from which we used the 24-h sampling PK data measured after administration of the initial 100-mg dose. The XBAE study was a single-ascending-dose study. We used the data measured after administration of the 100-mg dose with sampling up to 168 h. The data that were used for modeling are summarized in Table 3. All studies were conducted in accordance with the Declaration of Helsinki. All study participants provided written informed consent before inclusion, ethical approval was provided for each of the original studies, and all data were analyzed anonymously.

Analytical assay. Anidulafungin plasma concentrations were quantified using validated assays. In the ADOPT study, samples were analyzed by ultraperformance liquid chromatography with fluorescence detection as described before (9). The samples in the VER002-1 study were measured by high-performance liquid chromatography (HPLC) with UV detection at 300 nm. The assay was validated over a concentration range of 0.02 to 51.20 mg/liter and had an interday accuracy of between 95.5 and 101%, precision of between 1.33 and 11.6%, and recovery of between 80.3 and 82.3%. The samples in the XBAE study were analyzed by a validated HPLC with fluorescence detection (excitation wavelength, 310 nm; emission wavelength, 450 nm) assay with a concentration range of 0.005 to 10.00 mg/liter. Interday accuracy, obtained during a 3-day validation, was 98.5 to 109.8%, while precision was 3.3 to 12.2% with a 59 to 64% recovery.

Structural pharmacokinetic model. All data were analyzed using the nonlinear mixed-effects software package NONMEM (version 7.3.0; Icon Development Solutions, Ellicott City, MD) and PsN software (version 4.4.8) with PiranaJS (version 1.01) as an interface (21). R (version 3.2.4) was used for graphical processing of the data and the NONMEM output. In NONMEM, the ADVAN 5 option and the first-order conditional estimation method were used for all model runs. Models with one, two, and three compartments were explored and evaluated by visual inspection of the data. All random effects were assumed to be lognormally distributed. Concentration data were log transformed, and we used an additive error model in the log domain to describe the residual variability. Model selection was based on the following goodness-of-fit (GOF) criteria: (i) successful minimization and a successful covariance step, (ii) visual inspection of diagnostic plots (observed versus individual and population predicted concentrations and conditional weighted residuals versus time and population predicted concentrations), (iii) the precision of the parameter estimates, and (iv) a decrease of the objective function value (OFV) of at least 3.84 (chi-squared, 1 degree of freedom, $P < 0.05$). Candidate models were further evaluated by use of a prediction-corrected visual predictive check (pcVPC) based on 1,000 Monte Carlo simulations.

Pharmacokinetic model with covariates. After developing the structural and statistical model, a covariate analysis was performed using weight-derived parameters. The relationship between individual empirical Bayes estimates for clearance and volume of distribution versus TBW and other commonly investigated weight-derived parameters, such as BMI, lean body weight (LBW) (10), and body surface area (BSA) (22), was examined in scatter plots. Linear and power functions with fixed (allometric) or estimated exponents were investigated and standardized to a typical 70-kg male with a height of 1.8 m. Stepwise covariate modeling was performed by the use of forward inclusion and backward elimination steps. For inclusion of the covariate in the model, covariates were included one at a time, using a *P* value cutoff of $<$0.005 (OFV decrease, at least 7.9), together with GOF scatter plots and evaluation of plots of *post hoc* estimates of individual clearance and volume of distribution versus covariates compared to those for the structural model. For backward elimination, a *P* value cutoff of $<$0.001 (OFV increase, 10.8) was used. Finally, we evaluated whether the model was physiologically plausible and contained clinically relevant covariates.

The performance of the final model was assessed by internal validation with a pcVPC based on 1,000 Monte Carlo simulations. Parameter precision was evaluated by nonparametric bootstrap analysis, using 1,000 data set replicates.

Monte Carlo simulation. Changes in exposure with increasing weight were visualized by performing Monte Carlo simulations. The final model was used to simulate different loading/maintenance anidulafungin regimens chosen at the discretion of the investigators, i.e., (i) the licensed 200-mg loading dose and a 100-mg maintenance dose daily, (ii) a 25% increased dose consisting of a 250-mg loading dose and

a 125-mg maintenance dose daily, and (iii) a 50% increased dose consisting of a 300-loading dose and a 150-mg maintenance dose daily. A data set with a weight range from 60 to 170 kg was built with 5,000 subjects per 10-kg weight band, making a total of 55,000 virtual subjects. The AUC_{0-24} at steady state on day 14 was calculated for each virtual subject.

No human pharmacodynamic target has been reported for anidulafungin. Therefore, we used the pragmatic but arbitrary bioequivalence approach to determine the dose that obese patients should receive to attain a median exposure within the criterion of a level of exposure of 80 to 125% of that for normal-weight subjects (weight, between 60 and 80 kg) (23, 24).

ACKNOWLEDGMENTS

We acknowledge Arthur Pistorius for providing technical support and Stein Schalkwijk for his efforts in data interpretation. Finally, we thank Pfizer, Inc., for sponsoring the clinical trial in obese subjects (the ADOPT study) and providing the data for normal-weight subjects (from the VER002-1 and XBAE studies).

There is no funding to declare for this analysis.

Pfizer, Inc., was not involved in the analysis, interpretation, or manuscript preparation.

R.J.B. has served as a consultant to Astellas Pharma, Inc., F2G, Gilead Sciences, Merck Sharp & Dohme Corp., and Pfizer, Inc., and has received unrestricted and research grants from Astellas Pharma, Inc., Gilead Sciences, Merck Sharp & Dohme Corp., and Pfizer, Inc. All contracts were through Radboudumc, and all payments were invoiced by Radboudumc. None of the other authors has a conflict to declare.

R.E.W. and R.T.H. participated in analysis of the data and writing of the article. V.J.L. and E.P.V.D. participated in study design and writing of the article. D.M.B. participated in writing of the article. R.J.B. and C.A.K. participated in study design, analysis of the data, and writing of the article.

REFERENCES

1. NCD Risk Factor Collaboration. 2016. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. Lancet 387:1377–1396. https://doi.org/10.1016/S0140-6736(16)30054-X.
2. Falagas ME, Kompoti M. 2006. Obesity and infection. Lancet Infect Dis 6:438–446. https://doi.org/10.1016/S1473-3099(06)70523-0.
3. Knibbe CA, Brill MJ, van Rongen A, Diepstraten J, van der Graaf PH, Danhof M. 2015. Drug disposition in obesity: toward evidence-based dosing. Annu Rev Pharmacol Toxicol 55:149–167. https://doi.org/10.1146/annurev-pharmtox-010814-124354.
4. Hall RG, Swancutt MA, Gumbo T. 2011. Fractal geometry and the pharmacometrics of micafungin in overweight, obese, and extremely obese people. Antimicrob Agents Chemother 55:5107–5112. https://doi.org/10.1128/AAC.05193-11.
5. Brill MJ, Houwink AP, Schmidt S, Van Dongen EP, Hazebroek EJ, van Ramshorst B, Deneer VH, Mouton JW, Knibbe CA. 2014. Reduced subcutaneous tissue distribution of cefazolin in morbidly obese versus non-obese patients determined using clinical microdialysis. J Antimicrob Chemother 69:715–723. https://doi.org/10.1093/jac/dkt444.
6. Andes D, Diekema DJ, Pfaller MA, Bohrmuller J, Marchillo K, Lepak A. 2010. In vivo comparison of the pharmacodynamic targets for echinocandin drugs against Candida species. Antimicrob Agents Chemother 54:2497–2506. https://doi.org/10.1128/AAC.01584-09.
7. Wiederhold NP. 2016. Echinocandin resistance in Candida species: a review of recent developments. Curr Infect Dis Rep 18:42. https://doi.org/10.1007/s11908-016-0549-2.
8. European Medicines Agency. 2016. Summary of product characteristics: Ecalta. European Medicines Agency, London, United Kingdom. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000788/WC500020673.pdf.
9. Lempers VJ, van Rongen A, van Dongen EP, van Ramshorst B, Burger DM, Aarnoutse RE, Knibbe CA, Bruggemann RJ. 2016. Does weight impact anidulafungin pharmacokinetics? Clin Pharmacokinet 55:1289–1294. https://doi.org/10.1007/s40262-016-0401-8.
10. Janmahasatian S, Duffull SB, Ash S, Ward LC, Byrne NM, Green B. 2005. Quantification of lean bodyweight. Clin Pharmacokinet 44:1051–1065. https://doi.org/10.2165/00003088-200544100-00004.
11. Damle BD, Dowell JA, Walsky RL, Weber GL, Stogniew M, Inskeep PB. 2009. In vitro and in vivo studies to characterize the clearance mechanism and potential cytochrome P450 interactions of anidulafungin. Antimicrob Agents Chemother 53:1149–1156. https://doi.org/10.1128/AAC.01279-08.
12. Liu P, Mould DR. 2014. Population pharmacokinetic analysis of voriconazole and anidulafungin in adult patients with invasive aspergillosis. Antimicrob Agents Chemother 58:4718–4726. https://doi.org/10.1128/AAC.02808-13.
13. Dowell JA, Knebel W, Ludden T, Stogniew M, Krause D, Henkel T. 2004. Population pharmacokinetic analysis of anidulafungin, an echinocandin antifungal. J Clin Pharmacol 44:590–598. https://doi.org/10.1177/0091270004265644.
14. van Wanrooy MJ, Rodgers MG, Uges DR, Arends JP, Zijlstra JG, van der Werf TS, Kosterink JG, Alffenaar JW. 2014. Low but sufficient anidulafungin exposure in critically ill patients. Antimicrob Agents Chemother 58:304–308. https://doi.org/10.1128/AAC.01607-13.
15. Bruggemann RJ, Middel-Baars V, de Lange DW, Colbers A, Girbes AR, Pickkers P, Swart EL. 2017. Pharmacokinetics of anidulafungin in critically ill intensive care unit patients with suspected or proven invasive fungal infections. Antimicrob Agents Chemother 61:e01894-16. https://doi.org/10.1128/AAC.01894-16.
16. Liu P, Ruhnke M, Meersseman W, Paiva JA, Kantecki M, Damle B. 2013. Pharmacokinetics of anidulafungin in critically ill patients with candidemia/invasive candidiasis. Antimicrob Agents Chemother 57:1672–1676. https://doi.org/10.1128/AAC.02139-12.
17. Liu P. 2013. Population pharmacokinetic-pharmacodynamic analysis of anidulafungin in adult patients with fungal infections. Antimicrob Agents Chemother 57:466–474. https://doi.org/10.1128/AAC.01473-12.
18. Bruggemann RJ, Van Der Velden WJ, Knibbe CA, Colbers A, Hol S, Burger DM, Donnelly JP, Blijlevens NM. 2015. A rationale for reduced-frequency dosing of anidulafungin for antifungal prophylaxis in immunocompromised patients. J Antimicrob Chemother 70:1166–1174. https://doi.org/10.1093/jac/dku477.
19. Eleveld DJ, Proost JH, Absalom AR, Struys MM. 2011. Obesity and allometric scaling of pharmacokinetics. Clin Pharmacokinet 50:751–753. https://doi.org/10.2165/11594080-000000000-00000.

20. Food and Drug Administration. 2012. Clinical pharmacology and biopharmaceutics review: Eraxis. Food and Drug Administration, Silver Spring, MD.
21. Keizer RJ, Karlsson MO, Hooker A. 2013. Modeling and simulation workbench for NONMEM: tutorial on Pirana, PsN, and Xpose. CPT Pharmacometrics Syst Pharmacol 2:e50. https://doi.org/10.1038/psp.2013.24.
22. Du Bois D, Du Bois EF. 1989. A formula to estimate the approximate surface area if height and weight be known. 1916. Nutrition 5:303–311.
23. Food and Drug Administration. 2001. Guidance for industry: statistical approaches to establishing bioequivalence. Food and Drug Administration, Silver Spring, MD. http://www.fda.gov/downloads/Drugs/./Guidances/ucm070244.pdf.
24. European Medicines Agency. 2010. Guideline on the investigation of bioequivalence. European Medicines Agency, London, United Kingdom. http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf.