TITLE: POPULATION PHARMACOKINETICS OF ANIDULAFUNGIN IN CRITICALLY ILL PATIENTS

RUNNING TITLE: POPULATION PHARMACOKINETICS OF ANIDULAFUNGIN

AUTHORS

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CONFLICTS OF INTEREST:

William Hope (WH) holds or has recently held research grants with F2G, AiCuris, Astellas Pharma, Spero Therapeutics, Matinas Biosciences, Antabio, Amplyx, Allecra, Bugworks, NAEJA-RGM, AMR Centre, and Pfizer. He holds awards from the National Institutes of Health, Medical Research Council, National Institute of Health Research, FDA and the European Commission (FP7 and IMI). WH has received personal fees in his capacity as a consultant for F2G, Amplyx, Ausperix, Spero Therapeutics and BLC/TAZ. WH is an Ordinary Council Member for the British Society of Antimicrobial Chemotherapy. Santiago Grau (SG) has received personal fees from Merck Sharp & Dohme, Angelini Pharma and Pfizer. Juan Pablo Horcajada (JPH) has received personal fees Pfizer, Merck Sharp & Dohme and Astellas Pharma and he has held research grants with Merck Sharp & Dohme. Other authors have nothing to declare.

ABSTRACT

A two-compartment pharmacokinetic population model of anidulafungin was fitted to PK data from 23 critically-ill patients (age 65 (range 28-81 years), total body weight (TBW): 75 (range 54-168) kg). TBW was associated with clearance and was incorporated into a final population PK model. Simulations suggested patients with higher TBW had less extensive MIC coverage. Dosage escalation may be warranted in patients with high TBW to ensure optimal drug exposures for treatment of both *C. albicans* and *C. glabrata*.

The 2009 Infectious Diseases Society of America treatment guidelines for candidemia recommend the use of an echinocandin as initial therapy for critically ill patients (1). Anidulafungin is commonly used for the treatment of diseases caused by *Candida* spp. in critically ill patients. However, there are relatively limited population pharmacokinetic data for this patient population (1-3). A deep understanding of PK/PD relationships underpins the design of safe and effective regimens and highlights those circumstances where a standard fixed regimen may fail. Herein, we describe the population PK of anidulafungin in critically ill patients and evaluate the probability of achieving target $AUC_{0\text{-}24h}$/MIC values at steady state against *C. albicans* and *C. glabrata* with the currently licensed regimen.

A total of 23 critically ill patients with proven or suspected invasive fungal infection (from Hospital del Mar, Barcelona, Spain) receiving anidulafungin were recruited. The study was approved by the Ethics Committee of Parc de Salut Mar (2016/6987/I) in Barcelona, Spain and written informed consent was obtained from patients or their legal representative before enrollment.

All patients received a loading dose of 200 mg of anidulafungin (Ecalta ®) followed by a maintenance dosage of 100 mg/24h infused over 1 hour. Sampling occurred after the 3rd day of treatment and blood was collected pre-infusion and 1, 3, 5, 8, 18 and 24 h post administration in the majority of the patients. Anidulafungin concentrations were measured using a previously described validated HPLC method (3) .

Population pharmacokinetic modelling was performed using Pmetrics (4, 5). One and two-compartment models were fitted to the data. The elimination from the central compartment and intercompartmental distribution were modeled as first-order processes. Age, gender, TBW, APACHE score and liver cirrhosis were evaluated as covariates using stepwise linear regression. Potential covariates were separately entered into the model and retained if their inclusion resulted

in a statistically significant improvement in the log likelihood value and/or improvements in the observed-predicted plots.

The fit of each model to the data was assessed using a linear regression of observed-predicted values both before and after the Bayesian step. The mean prediction error and the mean bias-adjusted squared prediction error were used to assess bias and imprecision, respectively. Models were compared by calculating twice the difference in log likelihood values, which was then assessed against a Chi-square distribution using the appropriate degrees of freedom (i.e. difference in number of parameters for each model). To further assess the predictive accuracy of the final model, a visual predictive check (VPC) was performed.

Monte Carlo simulations (n=1000) of plasma concentrations were employed to calculate the $AUC_{0\text{-}24}$/MIC at steady state (i.e. from 144-168 hours post treatment initiation). From the 1000 simulated concentration–time profiles, a probability of target attainment (PTA) against *C. albicans* and *C. glabrata* was calculated using a free $AUC_{0\text{-}24}$/MIC target of 20 and 7, respectively. These targets have been associated with the stasis endpoint using a preclinical model of disseminated candidiasis using CLSI methodology (6). A range of MIC values (0.002-16 mg/L) and a range of TBWs (70 and 150 kg) were examined. Human protein binding of 99% was used to estimate free drug concentrations (7).

The demographics of the study population were as follows: a total of 10 patients (43.5%) were male; the median (range) age was 65 (28-81) years; the total body weight (range) was 75 (54-168) kg and the median APACHE severity score (range) was 21 (10-48). Nine patients (39.1%) had liver cirrhosis with a Child Pugh score of A (n=1), B (n=3) and C (n=5). The median (range) of the estimated $AUC_{0\text{-}24h}$ were 102.19 (51.22-185.64) mg*h/L. The concentration–time profiles of anidulafungin in patients are shown in Figure 1.

Estimates for central tendency, dispersion and 95% credibility limits for the population PK parameters are shown in Table 1. Total body weight (TBW) was the only covariate that explained

any portion of the observed variance. In the final model, the clearance (CL) of anidulafungin was described using a power function (CL=CL1* (TBW/70)**0.75). Figure 2 shows the observed-predicted values before and after the Bayesian step. After maximum a posteriori probability (MAP)-Bayesian estimation, the observed-versus-predicted plot had an intercept and slope of 0.099 and 0.934, respectively and an $r^2 = 0.734$. The bias and imprecision were both acceptable (bias = 0.0729 mg/liter and imprecision, 0.982 mg/liter). The predictive value of the model was further confirmed using a VPC plot (Figure 3).

Patients with larger TBW receiving a standard dosage of anidulafungin developed less drug exposure than smaller patients. The difference in predicted MIC coverage between patients weighing 70 and 150 kg was a single MIC dilution. For *C. albicans* a PTA ≥ 90% was achieved for patients with TBW ≤ 70 kg for *C. albicans* isolates with MIC values ≤ 0.032 mg/L. For heavier patients the coverage of *C. albicans* MIC was not as extensive and high PTAs were only achieved for isolates with MIC values ≤ 0.016 mg/L. This difference was mitigated by an increase in maintenance dosage to 150 mg/day in heavier patients (data not shown). For *C. glabrata* a PTA ≥ 90% could be achieved for MIC values ≤ 0.064 mg/L for patients with a TBW up to 150 kg receiving the standard anidulafungin dosage (Figure 4). When the same dosage increase was simulated, a PTA ≥ 90% could be achieved for MIC values ≤ 0.125 mg/L and ≤ 0.064 mg/L for patients with a TBW of 70 kg and 150 kg, respectively (data not shown).

The finding that total body weight had an influence on anidulafungin clearance is consistent with a significant body of evidence supporting this observation for the echinocandin class in general (1, 9-11). Both linear and exponential relationships have been used to describe the effect of weight on clearance (10). Regardless of the function that is ultimately used, heavier patients require progressively higher absolute dosages to achieve comparable drug exposures to those observed in smaller patients. For both *C. albicans* and *C. glabrata*, a TBW of 150 kg resulted in the loss of an MIC dilution that can be covered using the current licensed regimen compared with

70 kg patients. Critically ill patients with high TBW may require higher dosages of anidulafungin for the treatment of *C. albicans* or *C. glabrata* infections to avoid potential clinical failures. Further prospectively conducted studies are warranted.

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Table 1. Population pharmacokinetic parameters of anidulafungin

Parameter [a] (Units)	Median	Mean	95% Credibility limits	Standard Deviation
CL1 (L/h/70kg)	0.936	0.852	0.862-0.987	0.199
V (L)	16.275	18.413	9.735-27.223	10.199
Kcp (h^{-1})	0.702	2.0417	0.222-2.179	3.028
Kpc (h^{-1})	0.394	0.951	0.083-0.905	1.142

[a]CL1: Clearance per 70kg so that CL=CL1* (Total Body Weight/70)**0.75); V: volume of the central compartment; Kcp and Kpc are the first-order intercompartmental rate constants.

Figure 1

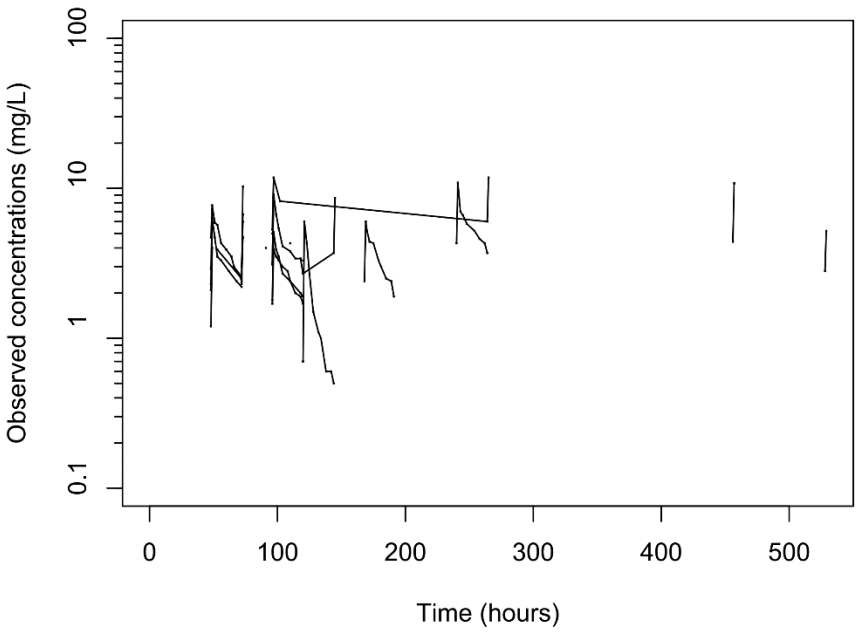

FIG 1. Anidulafungin concentration-time profile of patients receiving a loading dose of 200 mg i.v followed by a mantenaince dose of 100 mg q24h i.v. Intensive sampling was performed after the third day of treatment.

Figure 2.

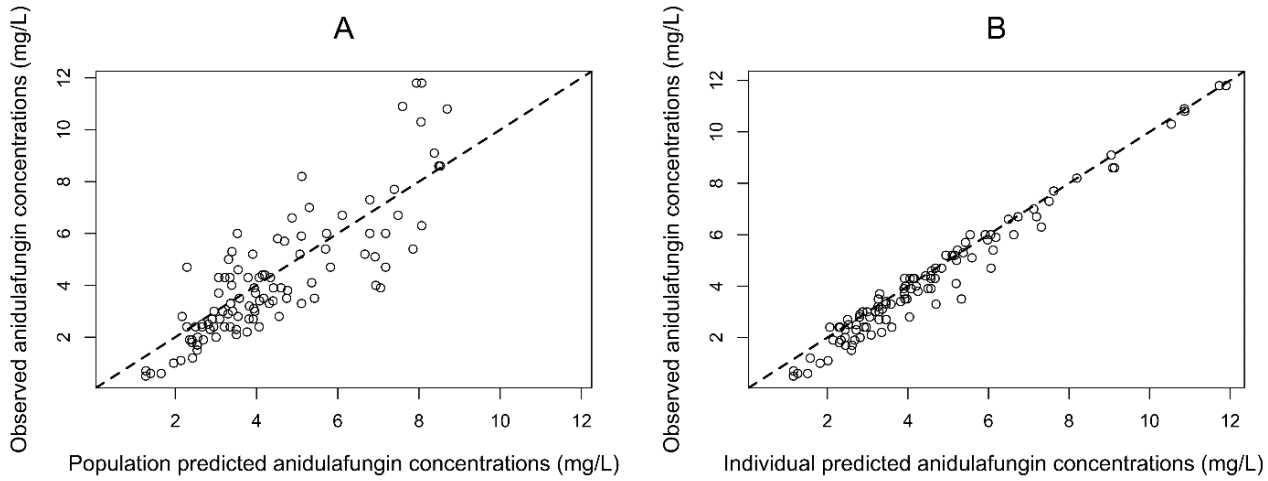

FIG 2. Population (A) and individual (B) predicted minocycline concentrations vs. observed concentrations of minocycline. The broken line is the line of identity (observed = predicted concentrations).

Figure 3.

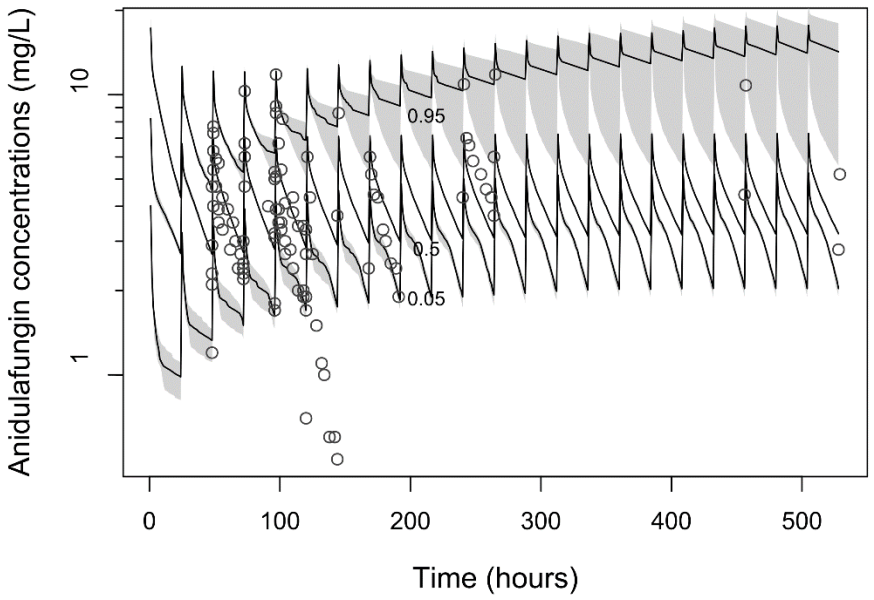

FIG 3. Visual predictive check of anidulafungin plasma concentrations versus time for the final model. Gray shading shows the confidence bound around each simulated centile. Open circles are the observed concentrations of anidulafungin.

Figure 4.

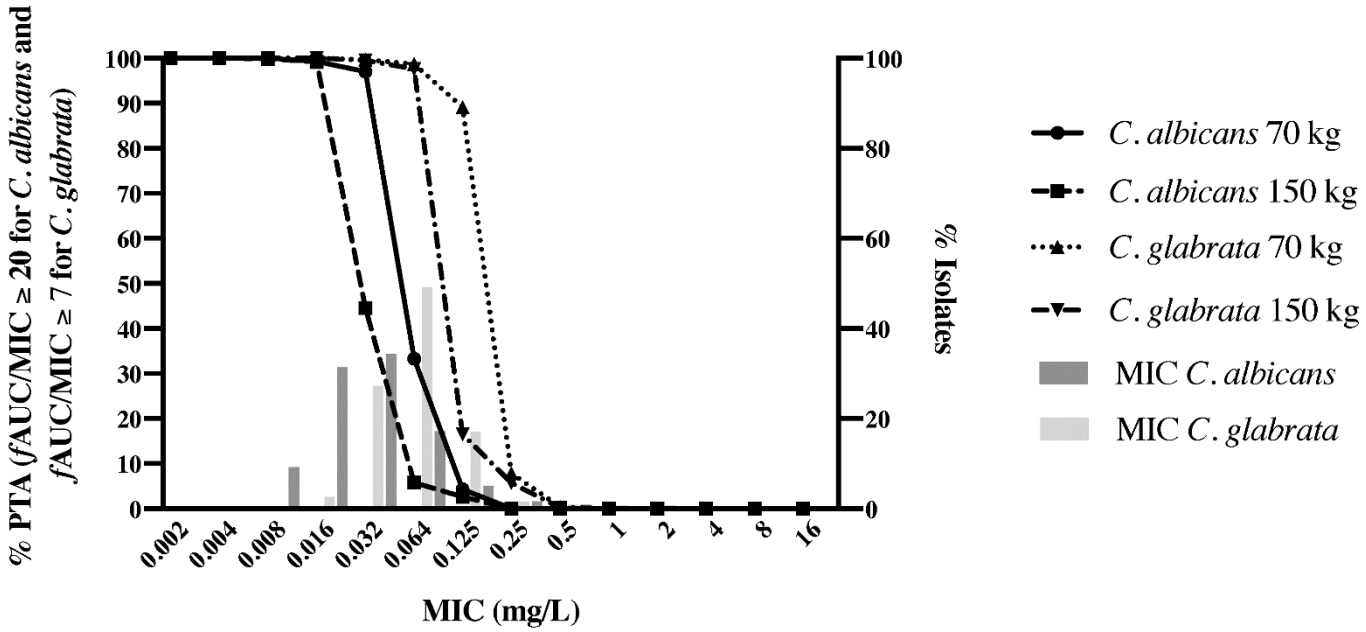

FIG 4. PTA of anidulafungin for patients with different total body weights (70 and 150 kg) against *C. albicans* and *C. glabrata* and MIC distributions according to CLSI methodology (11)

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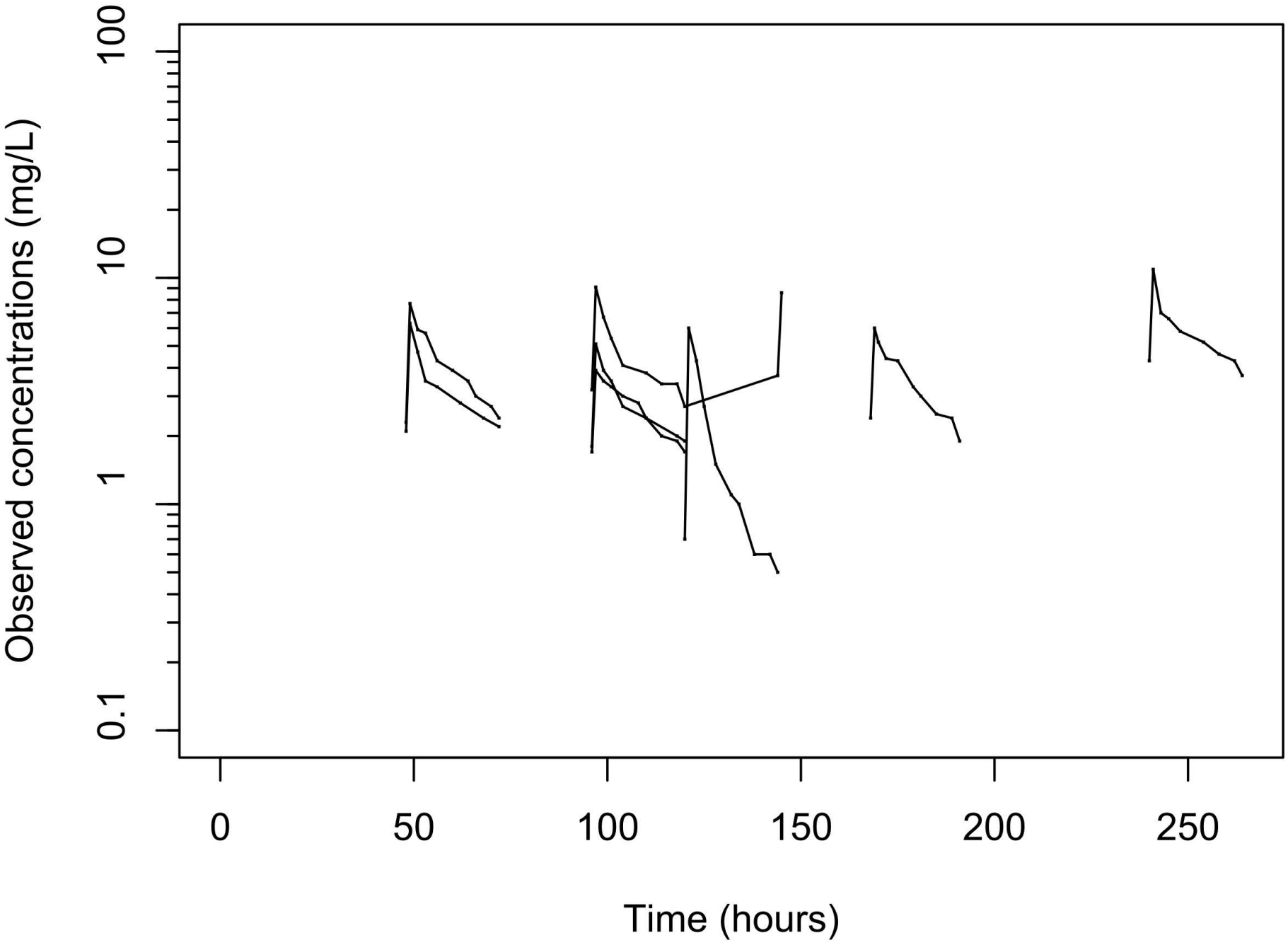
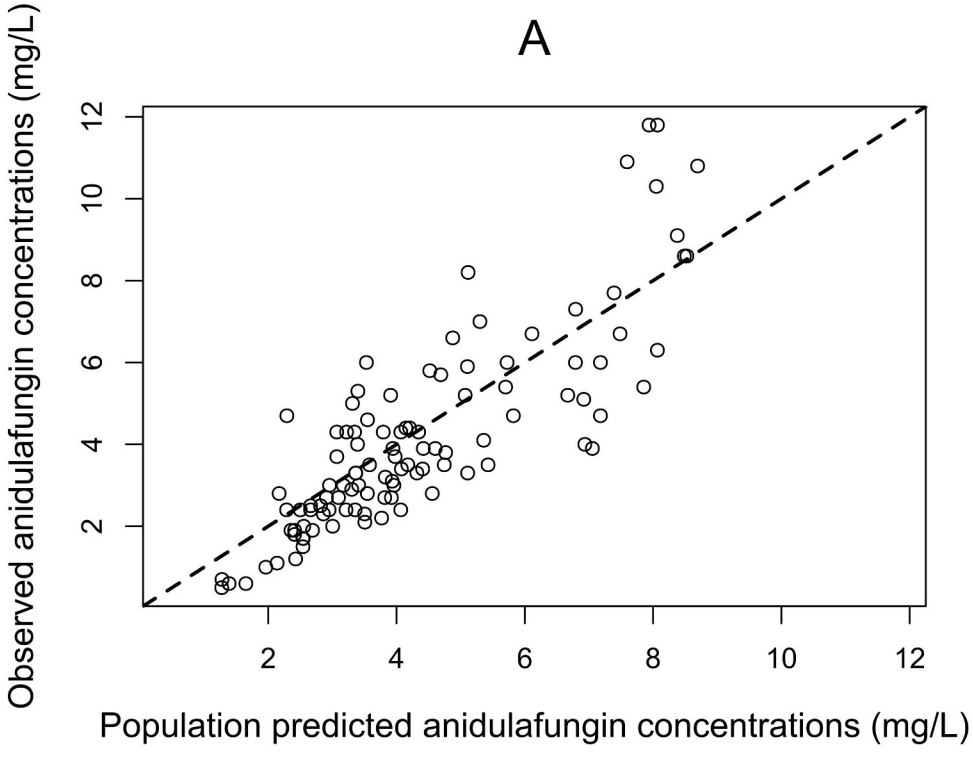
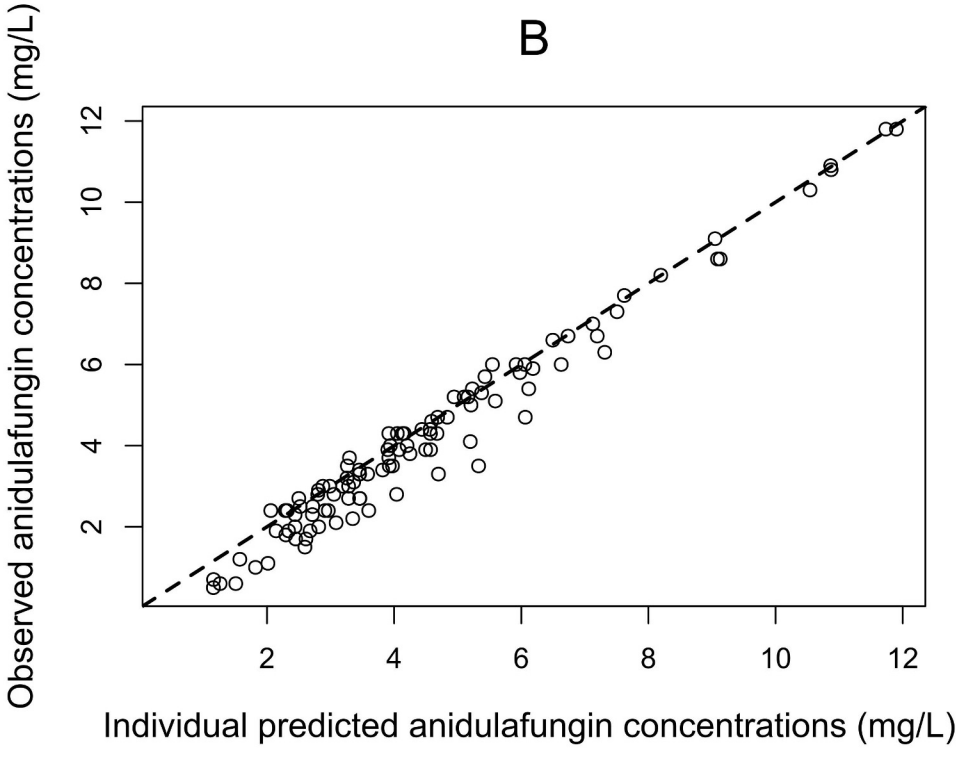
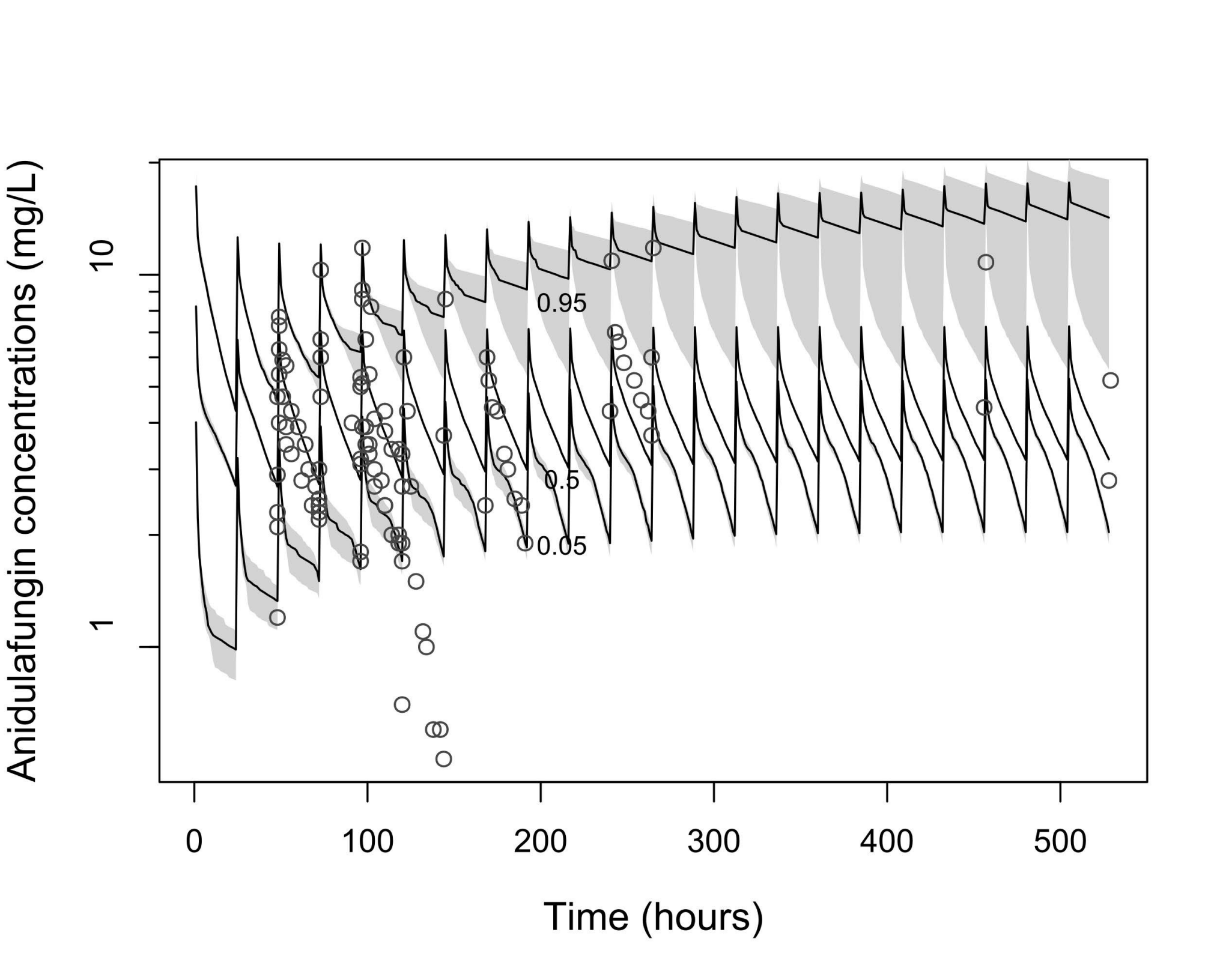
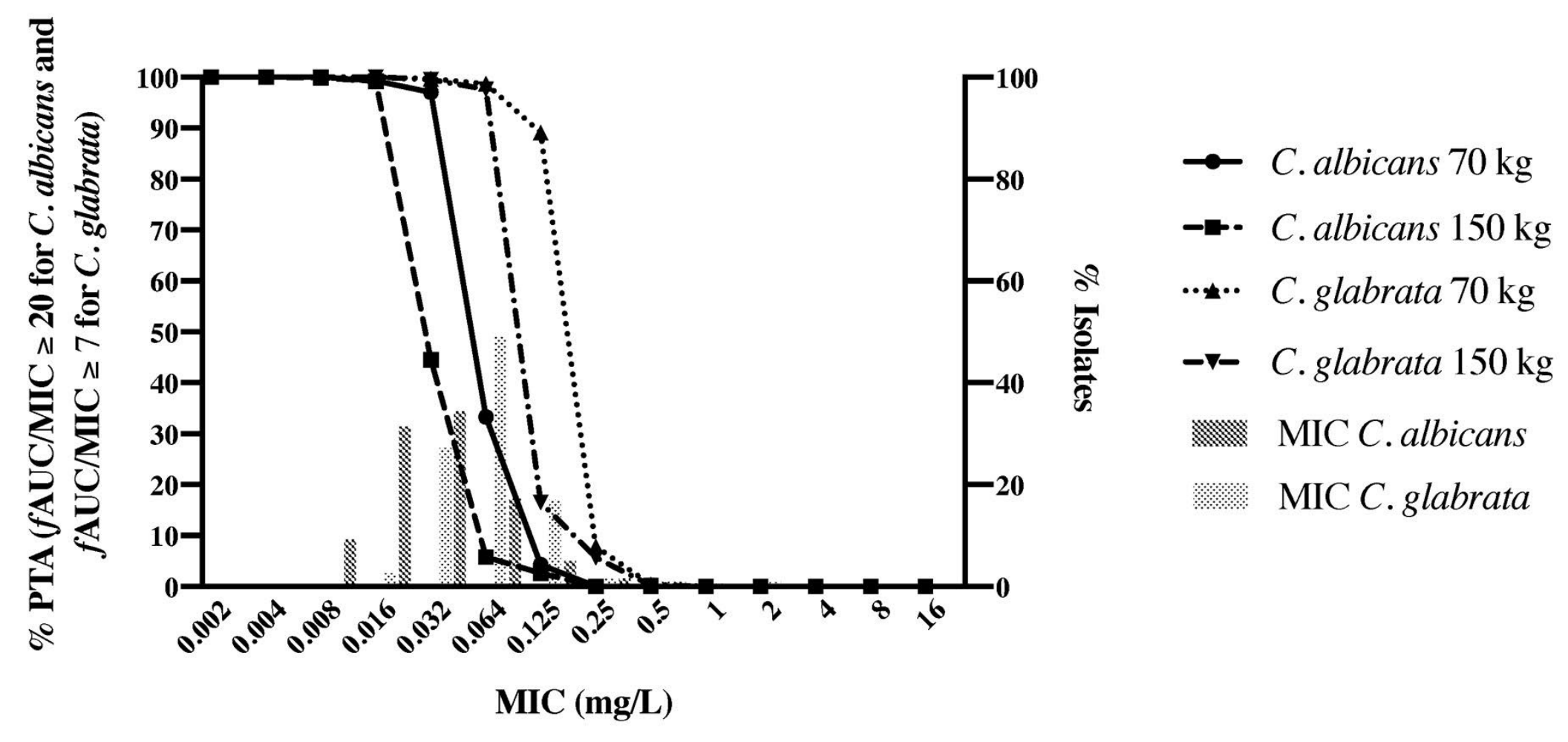

Observed concentrations (mg/L)
100
10
1
0.1
0
50
100
150
200
250
Time (hours)


A
Observed anidulafungin concentrations (mg/L)
Population predicted anidulafungin concentrations (mg/L)
2
4
6
8
10
12


B
Observed anidulafungin concentrations (mg/L)
Individual predicted anidulafungin concentrations (mg/L)
2
4
6
8
10
12


Anidulafungin concentrations (mg/L)
10
1
0.95
0.5
0.05
0
100
200
300
400
500
Time (hours)


% PTA (fAUC/MIC ≥ 20 for C. albicans and fAUC/MIC ≥ 7 for C. glabrata)
100
90
80
70
60
50
40
30
20
10
0
0.002
0.004
0.008
0.016
0.032
0.064
0.125
0.25
0.5
1
2
4
8
16
MIC (mg/L)
% Isolates
C. albicans 70 kg
C. albicans 150 kg
C. glabrata 70 kg
C. glabrata 150 kg
MIC C. albicans
MIC C. glabrata