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Population pharmacokinetics of micafungin in ICU patients with sepsis and mechanical ventilation

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Objectives: To identify the factors associated with the interindividual pharmacokinetic (PK) variability of micafungin and to evaluate the probability of reaching the previously determined PK/pharmacodynamic efficacy thresholds (AUC/MIC >5000 for non-*parapsilosis* *Candida* sp. and ≥ 285 for *Candida parapsilosis*) with the recommended 100 mg daily dose in ICU patients with sepsis and mechanical ventilation.

Methods: One hundred patients were included and 436 concentrations were available for PK analysis performed with NONMEM software. PTA was determined by Monte Carlo simulations.

Results: Micafungin obeyed a two-compartment model with first-order elimination from the central compartment. Mean parameter estimates (percentage interindividual variability) were 1.34 L/h (34%) for clearance (CL), 11.80 L (38%) and 7.68 L (39%) for central (Vc) and peripheral (Vp) distribution volumes, respectively, and 4.67 L/h (37%) for distribution clearance. CL, Vc and Vp increased by 14% when the albumin level was ≤ 25 g/L and CL decreased by 25% when SOFA score was ≥ 10 . Body weight was related to CL, Vc and Vp by allometric models. PTA was $\geq 90\%$ in *Candida albicans* and *Candida glabrata* infections, except when the MIC was ≥ 0.015 mg/L, and ranged between 0% and 40% for *C. parapsilosis* infections with MIC ≥ 0.5 mg/L.

Conclusions: A possible increase in the dose should be evaluated for infections due to *C. parapsilosis* and for infections due to *C. albicans* and *C. glabrata* with MICs ≥ 0.015 mg/L.

Introduction

Micafungin is an antifungal agent belonging to the echinocandin class. It inhibits the synthesis of β -D-glucan, a major compound of the fungal cell wall, and is primarily used at the recommended 100 mg daily dose for the treatment of candidaemia or invasive candidiasis.¹ The pharmacokinetics (PK) of micafungin in non-critically ill patients has been characterized in many studies. Micafungin is known to display linear PK and to have a distribution volume of 0.2 L/kg, which corresponds to the extracellular water, and an elimination half-life of 11–15 h.^{1–6} The PK of micafungin in ICU patients is less well characterized. A recent study found that micafungin exposure was significantly reduced in ICU compared with non-critically ill subjects.⁷ Several hypotheses were raised to explain this modified PK [decrease in albumin level, change in metabolic status, impact of disease severity and higher body weight (BW)], but could not be investigated because of the insufficient number of patients. A population PK study conducted on a high number of patients could therefore be interesting in order to identify the determinants of micafungin PK in ICU patients. Such elements could be useful in order to evaluate the possible interest of an adaptation of the dose in this population. Indeed, the efficacy of micafungin is related to its AUC/MIC ratio and efficacy thresholds of 285 for *Candida parapsilosis* and 5000 for non-*parapsilosis* *Candida* sp. were identified in patients with invasive candidiasis.^{8,9}

We therefore conducted a prospective population PK analysis within a large population of ICU patients in order to identify the factors associated with the interindividual variability of PK parameters and to determine the probability of reaching those AUC/MIC efficacy thresholds with the recommended 100 mg daily dose.

Patients and methods

Patients and treatment

The PK study was part of a clinical trial (EMPIRICUS), the main objective of which was to evaluate the benefit of micafungin in patients with suspected but not proven candidiasis. Main inclusion criteria were age >18 years, ICU stay >5 days and mechanical ventilation >4 days before randomization, presence of a systemic inflammatory response syndrome, at least one extradiagnostic site of *Candida* sp. colonization and use of broad-spectrum antibacterial agents >4 days during the last 7 days. Patients with evidence of bacterial infections explaining the symptoms, with proven invasive fungal infection, with neutrophil count <500/mm³, who received an antifungal treatment in the week preceding inclusion were excluded.

Patients were randomized in a 1:1 scheme to receive either micafungin (100 mg daily dose administered as a 1 h infusion for 14 days) or placebo. More details on the trial design, objectives, inclusion and exclusion criteria can be found elsewhere.¹⁰

Ethics

Patients included in the EMPIRICUS clinical trial (registration number NCT01773876) were also included in the ancillary PK study. The study involved 19 ICUs in France and was approved by an authorized ethics committee (Comité de Protection des Personnes CPP Sud Est V) on 7 December 2011 and the French Health Authorities (AFSSAPS) on 2 December 2011. Written informed consent was obtained from all participants or their proxies in case of impaired decision-making capacity at the time of enrolment.

PK sampling and micafungin assay

Five blood samples (5 mL per sample) were drawn per patient in heparinized tubes. The samples were all drawn after the first administration of micafungin: at the end of the infusion; between 30 min and 1 h after the infusion; between 2 and 4 h after the infusion; between 8 and 16 h after the infusion; and just before the second infusion. Based on our stability study, blood samples had to be centrifuged within 1 h at +4°C and the plasma had to be immediately put at +4°C or –20°C, but for no longer than overnight, before being stored at –80°C. Samples were then sent in dry ice to the laboratory every 3 months to be analysed. Micafungin plasma concentration was measured by an HPLC method with fluorometric detection. Briefly, 50 μ L of the internal standard working solution (i.e. 20 mg/L buprenorphine in ethanol:water, 50:50) was added to 100 μ L of plasma samples. Protein precipitation was performed by adding 400 μ L of acetonitrile. After 30 s of mixing, the tubes were centrifuged for 5 min at 20000 g. Fifty microlitres of water was added to 150 μ L of the supernatant and the resulting mixture was transferred to autosampler vials and 20 μ L was injected into the chromatographic system. The chromatographic column was a Cluzeau Satisfaction C8 Plus (100 \times 3 mm, 3 μ m; Sainte-Foy-la-Grande, France). The mobile phase consisted of a mixture of two solvents, A and B. Solvent A was water containing trifluoroacetic and formic acid (1:0.001:0.0001 v:v:v) and triethylamine to adjust the pH value to 3 whereas solvent B was acetonitrile containing 5% (v:v) of water. Initially, the column was equilibrated at 0.80 mL/min with a mobile phase consisting of 65% A and 35% B. One minute after injection, the proportion of B was linearly increased to 80% within 7 min and remained at that proportion for an additional 2 min. After this step, the composition of the mobile phase was set to initial conditions (65% A and 35% B) and the column was equilibrated for 5 min prior to the next injection. Excitation and emission wavelengths were 273 and 464 nm for micafungin and 285 and 350 nm for buprenorphine, respectively. The overall intra- and interday precision and inaccuracy were <13% over the calibration range of the method (0.2–20 mg/L), with 0.2 mg/L being the limit of quantification (LOQ) of the method.

Population PK modelling

Concentration–time data were analysed by use of the first-order conditional estimation with interaction method of the non-linear mixed-effects modelling program NONMEM (version 7.3). Several structural PK models were investigated. Classical one- and two-compartment models with several error models (i.e. proportional, exponential and additive random effects) were investigated as means of describing interpatient and residual variabilities. Interindividual variability was described by assuming that individual parameters arise from a multivariate lognormal distribution with mean vector and variance-covariance matrix to be estimated. Covariates to be tested were chosen *a priori*, based (i) on previous results, like BW, (ii) on theoretical knowledge about micafungin PK: total protein, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic oxaloacetate transaminase (SGPT), alkaline phosphatase (ALP), bilirubin, prothrombin time as surrogate markers of hepatic metabolism, albumin for protein binding, and (iii) on particularities in ICU patients: SOFA score, extracorporeal membrane oxygenation (ECMO), haemodialysis. Age and gender were also investigated. All covariate values were obtained on the PK day. Systematic testing for the influence of continuous covariates on the PK parameters was done by use of a generalized model, according to the following equations:

$$CL = TV(CL) \times \left(\frac{COV}{\text{median COV}} \right)^{\theta_{cov}} \quad (1)$$

where $TV(CL)$ was the typical value of the apparent clearance for a patient with the median covariate (COV) value and θ_{cov} was the corresponding influential factor. When BW was considered as a covariate, θ_{cov} was

estimated and not fixed to a theoretical value because simple allometric scaling with BW is known to perform better in adult patients.¹¹

$$CL = TV(CL) \times \theta_{COV} \quad (2)$$

where θ_{COV} was estimated when the covariate value was above a given cut-off value. θ_{COV} was otherwise fixed to 1. The value associated with the most important decrease in the objective function was chosen as the optimal cut-off. This second equation was also used for categorical covariates (haemodialysis, ECMO and gender). When a covariate was supposed to be related simultaneously to several PK parameters (e.g. albumin on clearance and distribution volumes), the same influential factor was estimated on all tested parameters. In case the value of a given covariate was not known in every patient, the covariate analysis was first performed on the subset of patients whose covariate value was known and secondly on the entire population, the corresponding PK parameter being set to the mean value for patients whose covariate value was unknown. At this step, the influence of the covariate still had to be significant in order to be kept in the model.

A covariate was retained in the model if it produced a minimum decrease in the objective function of 3.84 U ($P=0.05$, 1 degree of freedom) and if its effect was biologically plausible. An intermediate multivariate model that included the significant covariates was then obtained. A covariate was retained in the final multivariate model if its deletion from the intermediate model led to a 6.63 point increase in the objective function ($P=0.01$, 1 degree of freedom). At each step, the goodness of fit was evaluated by use of a graph of the weighted residuals versus time after administration of the dose (time) or by use of a graph of the weighted residuals versus the predicted concentration. Hyperparameterization was investigated by inspecting the correlation matrix. Individual Bayesian estimates of clearance were used to calculate the individual $AUC_{0-\infty}$ after the first dose.

The accuracy and robustness of the final population model were assessed by a visual predictive check (VPC) based on 500 simulations of the original dataset using the final model and by a bootstrap based on 1000 resamplings of the original dataset.^{12,13} Lack of bias was also evaluated by inspection of the normalized prediction errors with respect to time after dose and population predictions.¹⁴ Goodness of fit was also visualized on the graphs displaying the population predictions or individual predictions versus observed concentrations.

Dose evaluation

The final model was used to evaluate the probability of reaching the AUC/MIC efficacy thresholds that were previously determined for *Candida albicans* (threshold=5000), *Candida glabrata* (threshold=5000) and *C. parapsilosis* (threshold=285) according to the dose, SOFA score, BW, albumin and MIC.⁸ Five different doses (100, 150, 200, 250 and 300 mg), SOFA < and ≥ 10 , albumin \leq or > 25 g/L, and eight different BW (50, 60, 70, 80, 90, 100, 110 and 120 kg) were investigated. EUCAST MIC clinical breakpoints were used (valid from 16 November 2015; available at http://www.eucast.org/clinical_breakpoints/). For each *Candida* sp., the highest investigated MIC corresponded to either its respective susceptible/intermediate (S/I) or intermediate/resistant (I/R) micafungin breakpoint. S/I and I/R breakpoints have the same values for *C. albicans* (0.016 mg/L) and *C. glabrata* (0.03 mg/L), but are very different for *C. parapsilosis* (0.002 and 2 mg/L, respectively). Since all MICs of micafungin for *C. parapsilosis* are above the S/I breakpoint, the I/R breakpoint was used as the highest MIC. One thousand theoretical patients were simulated for each SOFA score/dose/BW/albumin/MIC combination.

Results

Patients

One hundred patients were recruited in the micafungin arm. One patient had to be excluded because the sampling times were not

recorded. The demographic characteristics of the remaining 99 patients are displayed in Table 1. Nineteen patients were on intermittent haemodialysis (IHD) and 11 patients were on ECMO during the PK day.

Micafungin assay

Four hundred and thirty six samples were available for analysis. The measured concentrations ranged between 0.31 and 17.8 mg/L. No concentration below the LOQ of the method was observed.

PK modelling

The final model was a two-compartment model with linear elimination from the central compartment. Interindividual variability could be estimated for all the PK parameters: clearance (CL), central distribution volume (V_c), peripheral distribution volume (V_p), distribution clearance (Q), but no covariance between Etas could be estimated. Among the investigated covariates (BW, age, sex, SGOT, SGPT, prothrombin time, ALP, total bilirubin, total protein, albumin and SOFA score), BW, albumin and SOFA score were found to significantly influence the interindividual variability of CL, V_c and V_p .

The final covariate model was then:

$$CL(L/h) = 1.34 \times \left(\frac{BW}{84}\right)^{0.59} \times 1.14 \text{ (if albumin } \leq 25 \text{ g/L)} \times 0.75 \text{ (if SOFA } \geq 10)$$

$$V_c(L) = 11.8 \times \left(\frac{BW}{84}\right)^{0.61} \times 1.14 \text{ (if albumin } \leq 25 \text{ g/L)}$$

$$V_p(L) = 7.68 \times \left(\frac{BW}{84}\right)^{0.67} \times 1.14 \text{ (if albumin } \leq 25 \text{ g/L)}$$

$$Q(L/h) = 4.67$$

A proportional residual variability was found to best describe the data. All parameter values of the final model and bootstrap results are given Table 2. Eta shrinkage was equal to 4.0%, 6.5%, 30.0% and 58.4% for CL, V_c , V_p and Q, respectively.

Table 1. Characteristics of the patients (66 males, 33 females)

	N	Median	Range
Age (years)	99	61.4	29.9–92.7
Body weight (kg)	99	84.5	48–141
SOFA score	99	7	0–19
Total bilirubin (μ mol/L)	85	11.6	2.3–6.48
SGOT (IU/L)	88	48	11–3304
SGPT (IU/L)	89	39	9–758
ALP (IU/L)	85	136	54–706
PT (%)	90	72	23–100
Total protein (g/L)	89	57	32–79
Albumin (g/L)	76	21	9–66

N, number of available values; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; ALP, alkaline phosphatase; PT, prothrombin time.

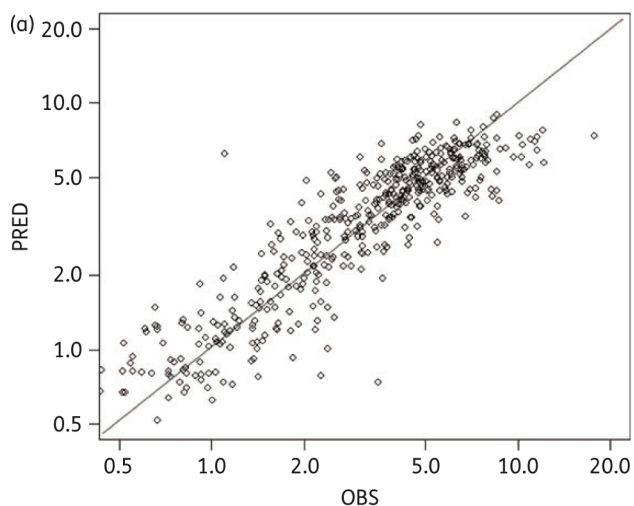
Epsilon shrinkage was equal to 28.9%. The highest correlation observed between two different parameters was 0.79.

No bias was observed on the graphs displaying the population predictions or individual predictions with respect to observed concentrations (Figure 1), the normalized prediction errors with respect to population predictions or time after dose (Figure 2) or

Table 2. Mean parameter estimates and relative standard deviations for the final model

Parameter	Original dataset		Bootstrap	
	mean estimate	RSD %	mean	RSD %
CL (L/h)	1.34	7.5	1.34	7.9
Vc (L)	11.8	8.8	11.6	9.5
Vp (L)	7.68	8.9	7.75	9.2
Q (L/h)	4.67	11.8	4.82	13.3
$\theta_{BW,CL}$	0.59	22.0	0.58	30.6
$\theta_{BW,Vc}$	0.61	29.5	0.59	37.8
$\theta_{BW,Vp}$	0.67	37.3	0.69	40.4
$\theta_{ALB,CL,Vc,Vp}$	1.14	7.0	1.14	7.7
$\theta_{SOFA,CL}$	0.75	8.0	0.75	7.89
ω_{CL}	0.114	22.8	0.109	11.9
ω_{Vc}	0.143	25.9	0.149	15.9
ω_{Vp}	0.150	32.0	0.134	23.6
ω_Q	0.139	84.1	0.093	66.6
σ	0.0144	43.7	0.0133	22.8

CL, clearance; Vc, central distribution volume; Vp, peripheral distribution volume; Q, distribution clearance; $\theta_{BW,CL}$, influential factor of BW on CL; $\theta_{BW,Vc}$, influential factor of BW on Vc; $\theta_{BW,Vp}$, influential factor of BW on Vp; $\theta_{ALB,CL,Vc,Vp}$, influential factor of albumin on CL, Vc and Vp when albumin ≤ 25 g/L; $\theta_{SOFA,CL}$, influential factor of SOFA on CL when SOFA score ≥ 10 ; ω_{CL} , interindividual variability of CL; ω_{Vc} , interindividual variability of Vc; ω_{Vp} , interindividual variability of Vp; ω_Q , interindividual variability of Q; σ , proportional residual variability; RSD, relative standard deviation.



the VPCs (Figure 3). The non-parametric 95% CI built with the VPC included 93% of the observed data.

Dose evaluation

PTAs were first calculated in case of albumin >25 g/L.

C. albicans and *C. glabrata*

The PTA was always $\geq 90\%$ for MICs inferior to 0.004 mg/L (*C. albicans*) and 0.0075 mg/L (*C. glabrata*), whatever BW and SOFA values. For MICs ≥ 0.015 –0.016 mg/L, high PTA necessitated doses between 150 and 300 mg, depending on MIC, BW and SOFA score (Figures 4 and 5).

C. parapsilosis

For an MIC equal to the I/R breakpoint (2 mg/L), the PTA was 0% in all cases for the recommended 100 mg dose and increased to at best 15% for a 300 mg dose combined with a BW of 50 kg and SOFA score ≥ 10 . Depending on BW and SOFA score, doses between 150 and 300 mg were necessary to reach PTA $>90\%$ for MIC = 0.25–0.5 mg/L, whereas such a probability could not be obtained, even with a 300 mg dose, for MIC = 1 mg/L. PTA always $>94\%$ with the 100 mg dose could be obtained only for MICs ≤ 0.125 mg/L. These results are displayed in Figure 6.

Lower PTAs were obtained in case of albumin ≤ 25 g/L. These results are available in Figures S1 to S3 (available as Supplementary data at JAC Online).

Discussion

This is the first population PK model for micafungin in ventilated ICU patients with sepsis. The model accurately described the data and the results are very consistent with the PK parameters that were recently reported in 20 ICU patients.⁷ Indeed, the mean of the individual values for CL and total distribution volume (Vc + Vp) in the present study are similar to the values described in

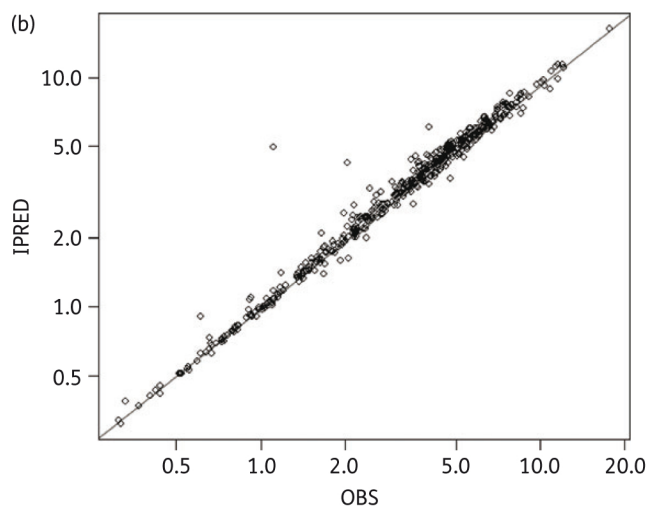


Figure 1. Goodness-of-fit curves representing (a) the population predictions (PRED) versus observed concentrations (OBS) and (b) the individual predictions (IPRED) versus OBS. Solid diagonal line shows $x=y$.

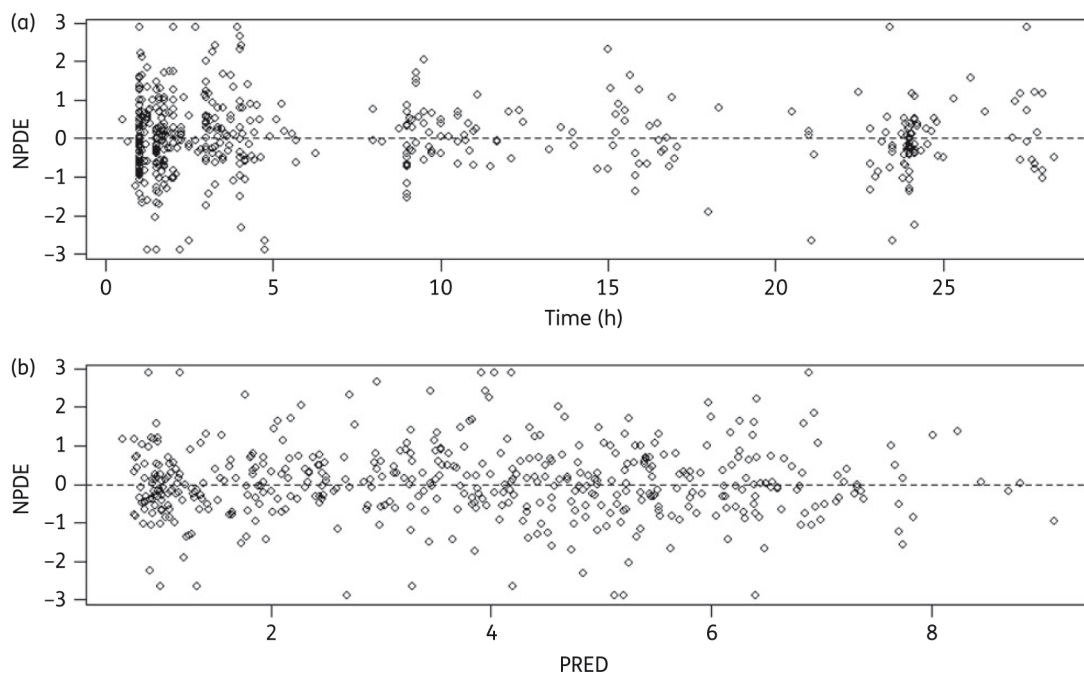


Figure 2. Lack of bias in the final model evidenced by the normalized prediction errors (NPDE) with respect to (a) time after dose (Time) and (b) population predictions (PRED).

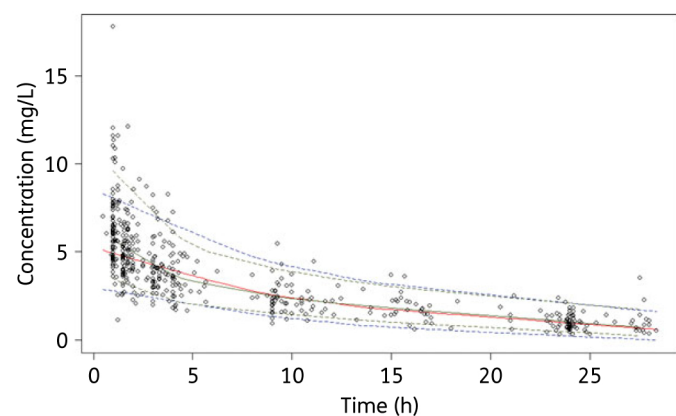


Figure 3. Visual predictive checks with the final model. Circles are the observed concentrations. The upper dotted blue, solid red and lower dotted blue lines represent the 97.5th, 50th and 2.5th percentiles obtained from the simulated concentrations. The upper dotted green line, solid green line and lower dotted green line represent the 97.5th, 50th and 2.5th percentiles obtained from the observed concentrations. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

the paper by Lempers *et al.*⁷ (1.47 versus 1.5 L/h for CL and 22.4 versus 25.6 L for total distribution volume). Because our parameters were calculated after the first dose, this similarity with the steady-state parameters obtained in the Lempers *et al.* study supports the linear PK profile of micafungin, which allows the prediction of steady-state exposures using the PK parameters obtained after the first dose. Our results confirm that ICU patients have lower exposure compared with healthy subjects or even

non-ICU patients (Table 3). Since ICU patients are often characterized by hypoalbuminaemia and micafungin is very highly bound (99.85%) to albumin,¹ a possible explanation for this lower exposure was a decrease in protein binding, as such a decrease should be associated with an increase in total clearance.¹⁵ Such a phenomenon was first observed for micafungin in patients with severe hepatic dysfunction.⁶ Our results support this hypothesis as an albumin level ≤ 25 g/L was associated with an increase in micafungin clearance. Interestingly, this 25 g/L value is roughly the same cut-off (i.e. 23.6 g/L) as was found to be associated with a change in the concentration of caspofungin, another echinocandin highly bound to albumin.¹⁶ Theoretically, an increase in total clearance secondary to a decrease in protein binding has no impact on free clearance, so the free concentration remains constant and no consequence on efficacy is expected.¹⁵ Since free micafungin concentration was not measured in the present study, the lack of relationship between the albumin level and free clearance of micafungin could not be investigated and should be further confirmed. However, because the influence of protein binding on efficacy is not fully understood, albumin levels ≤ 25 and >25 g/L were considered for the simulations. Two other factors were found to explain the interindividual variability of micafungin PK parameters: BW and SOFA score. Although the influence of BW has already been shown in several studies,¹⁷⁻¹⁹ this is to our knowledge the first time the influence of SOFA score is reported. SOFA is a hybrid score, ranging between 0 and 24, that takes into account renal, hepatic, cardiac, respiratory, CNS and coagulating functions, which consequently reflects the general status of the organs and is predictive of outcome in critically ill patients. Indeed, a SOFA score ≥ 11 was found to be associated with an increase in the mortality rate.²⁰ Interestingly, this cut-off value of 11 is similar to the value of 10 that we found to be

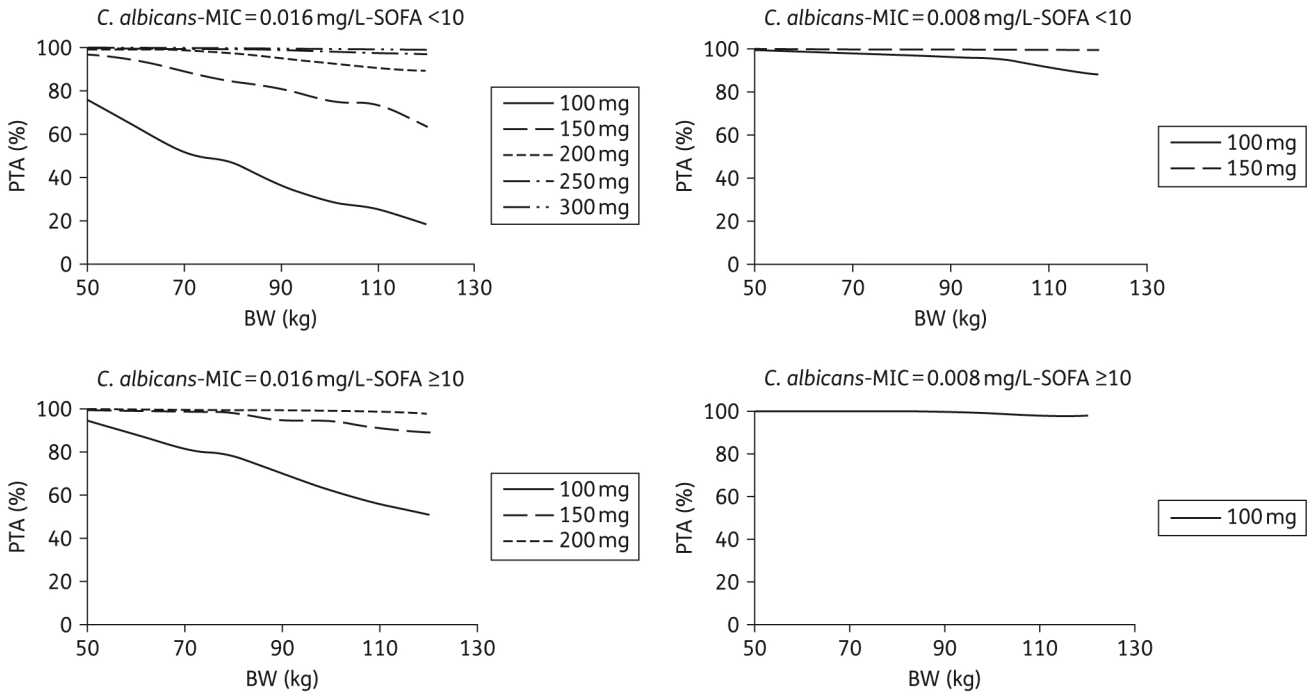


Figure 4. PTA for *C. albicans* with an MIC equal to 0.016 mg/L (the EUCAST clinical breakpoint) or 0.008 mg/L, according to dose, body weight and SOFA score in ICU patients with albumin >25 g/L.

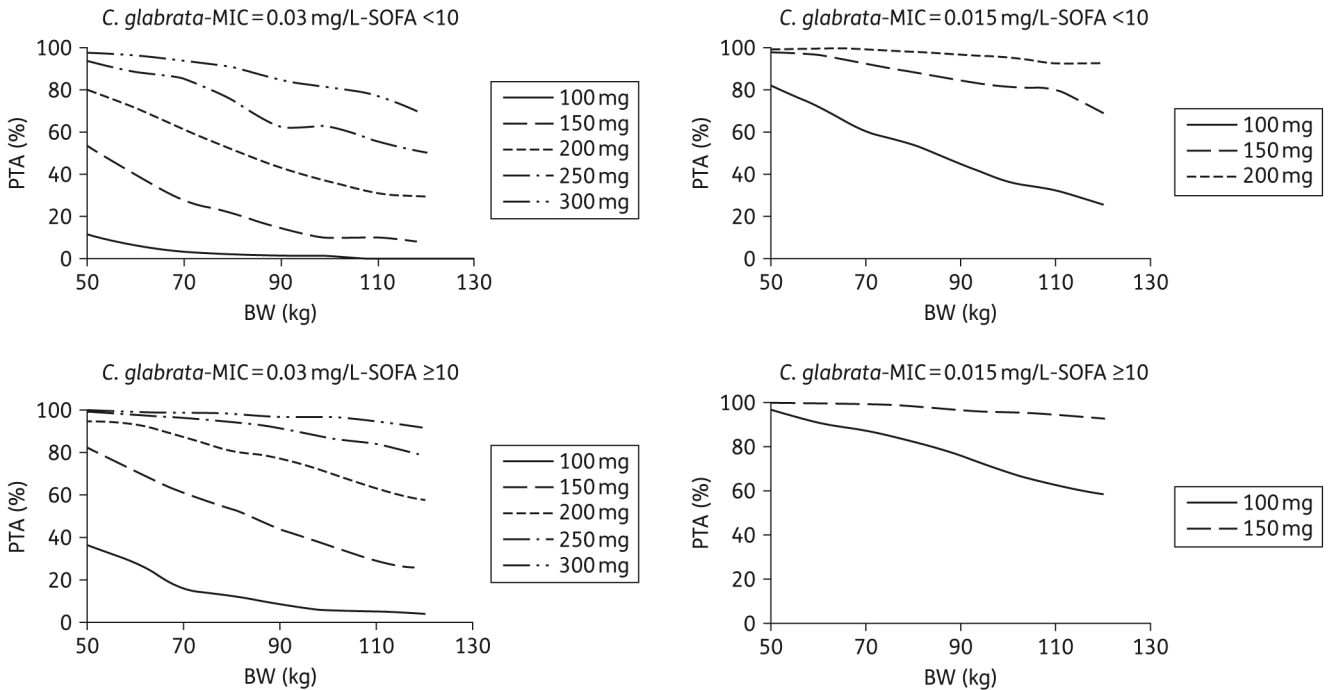


Figure 5. PTA for *C. glabrata* with an MIC equal to 0.03 mg/L (the EUCAST clinical breakpoint) or 0.015 mg/L, according to dose, body weight and SOFA score in ICU patients with albumin >25 g/L.

associated with a mean 25% decrease in micafungin clearance. Micafungin is partially metabolized at the hepatic level by several enzymatic pathways (arylsulfatase, catechol-*O*-methyltransferase and cytochromes P450) and is also eliminated

unchanged via biliary excretion.^{1,2} It is therefore possible that a given degree of organ failure, reflected by the SOFA score, is responsible for an alteration of micafungin metabolism or biliary excretion. Of note, bilirubin, which is integrated into the SOFA

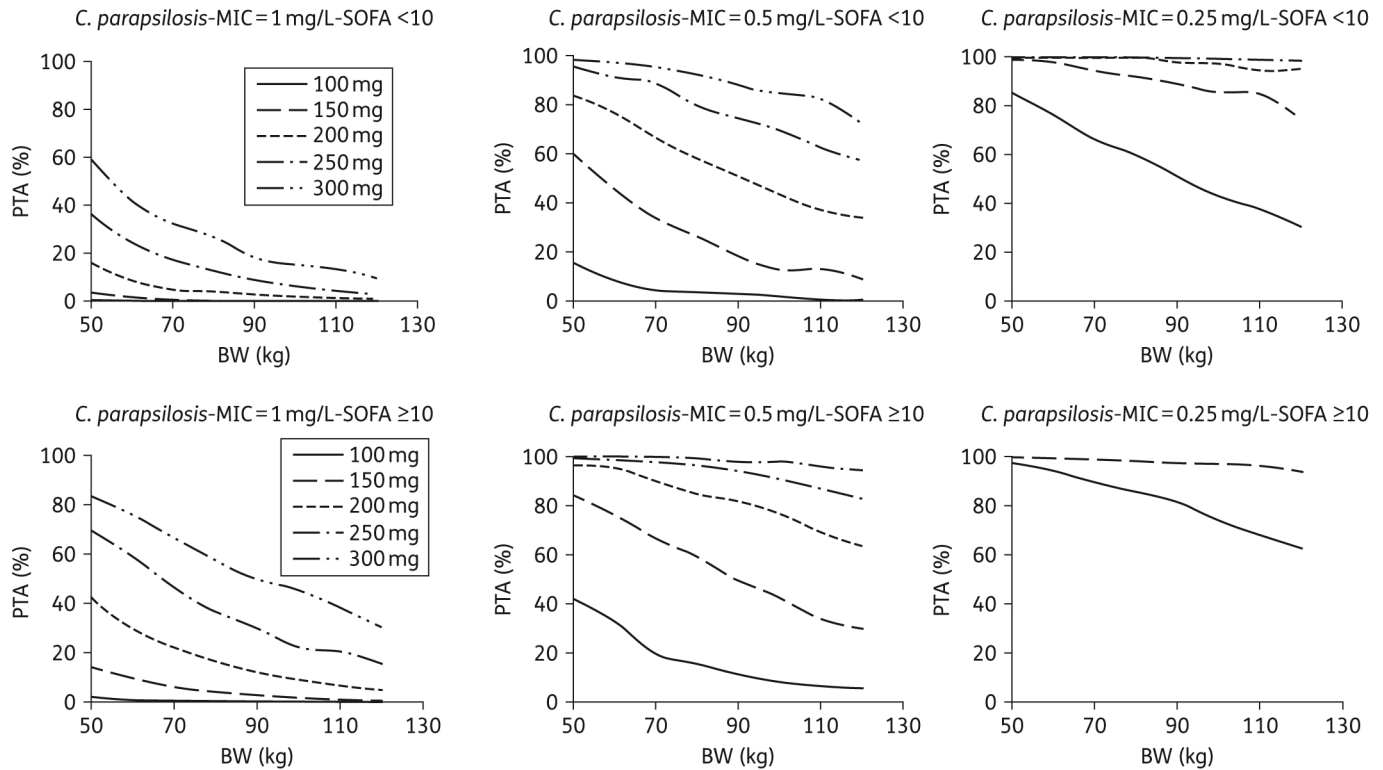


Figure 6. PTA for *C. parapsilosis* with an MIC equal to 1 mg/L (half the EUCAST clinical breakpoint), 0.5 mg/L or 0.25 mg/L, according to dose, body weight and SOFA score in ICU patients with albumin >25 g/L.

Table 3. Mean micafungin AUC (mg·h/L) with respect to albumin and SOFA score for a typical patient of 84 kg and comparison with literature data (either AUC_{0-∞} after the first dose or AUC₀₋₂₄ at steady-state)

SOFA score	Present study		ICU patients	Non-ICU patients	Healthy subjects
	albumin ≤25 g/L	albumin >25 g/L			
≥10	87.3	99.5	78 ^a	100 ^b	134.5 ^c
<10	65.5	74.6			

^aValue described in reference.⁷

^bMean of published values in references.⁴⁻⁶

^cMean of published values in references.^{4,6,25,26} AUC_{0-∞} after the first dose (references⁴⁻⁶), AUC₀₋₂₄ at days 3-7 (references^{3,7,25,26}).

score, was individually not found to influence micafungin clearance, as was also the case for the other covariates supposed to reflect hepatic status (SGOT, SGPT, ALP and prothrombin time). The likely reason is that these covariates do not precisely reflect the elimination pathways of micafungin, so their clearance rates may not parallel micafungin clearance. Other covariates that were found not to influence micafungin PK were IHD and ECMO. The lack of influence of IHD can be explained by the high protein binding of the drug and was already evidenced in patients under haemodialysis filtration.^{21,22} To our knowledge, this is the first report on micafungin PK during ECMO. However, lack of influence

of ECMO on caspofungin was previously reported.²³ The octanol/water (logP) partition coefficient is thought to be related to the ability of a drug to be sequestered or not by the ECMO circuit.²³ Like caspofungin, micafungin displays a low logP (-1.5), evidencing that micafungin is freely soluble in water and is consequently not expected to interact with the organic material of the ECMO circuit.

Monte Carlo simulations showed that the current 100 mg dose would provide a high probability of reaching the target AUC/MIC in patients with infections due to *Candida albicans* or *C. glabrata*, provided the MIC is <0.016 mg/L for *C. albicans* and <0.015 mg/L for *C. glabrata* (Figures 4 and 5). However, not attaining the target AUC/MIC does not mean the treatment will be inefficient. Indeed, in the study that evidenced these AUC/MIC thresholds, the success rate was 86.7% in patients with AUC/MIC ≤5000. Besides, the same study also found that reaching too high AUC/MIC ratios (i.e. >12 000) was associated with a decrease in the success rate that reached approximately the same value as the one observed for AUC/MIC ≤5000.⁸ Because of this, a systematic increase in the dose cannot be proposed without a prospective evaluation of its effect in terms of efficacy/safety. Such studies could nevertheless be interesting in patients for whom the 100 mg dose is associated with a very low PTA: patients with infection due to *C. glabrata* with MIC ≥0.015 mg/L and patients with infection due to *C. albicans* with MIC=0.016 mg/L. Such cases could be quite frequent since, according to the MIC distributions displayed by EUCAST: (i) 27% of the *C. albicans* strains that are considered susceptible to micafungin have an MIC of 0.016 mg/L; and (ii) 33% of the *C. glabrata* strains susceptible to micafungin have

an MIC ≥ 0.015 mg/L. The situation is clearer for *C. parapsilosis* as <1% of its strains have an MIC ≤ 0.125 mg/L. Consequently, the current 100 mg dose provides a very low PTA in the great majority of the patients, a result that was also found in a recent study.²⁴ This strongly supports the use of higher doses, despite an efficacy rate of 86% was nevertheless observed in patients not attaining the AUC/MIC efficacy threshold for *C. parapsilosis* (versus 100% for the patients attaining this threshold).⁸

In conclusion, the present study reported the first population PK model for micafungin in ICU patients with sepsis and mechanical ventilation. Micafungin PK was found to be related to BW, to an albumin level greater or inferior to 25 g/L and to a SOFA score greater or inferior to 10. The recommended 100 mg dose is associated with a very low probability of attaining the target AUC/MIC value in the case of infection due to *C. albicans* or *C. glabrata* with MIC ≥ 0.015 mg/L as well as in almost all cases of infection due to *C. parapsilosis*. The possibility of higher micafungin doses in these patients should be evaluated.

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References

- 1 Theuretzbacher U. Pharmacokinetics/pharmacodynamics of echinocandins. *Eur J Clin Microbiol Infect Dis* 2004; **23**: 805–12.
- 2 Wagner C, Graninger W, Presterl E *et al*. The echinocandins: comparison of their pharmacokinetics, pharmacodynamics and clinical applications. *Pharmacology* 2006; **78**: 161–77.
- 3 Hiemenz J, Cagnoni P, Simpson D *et al*. Pharmacokinetic and maximum tolerated dose study of micafungin in combination with fluconazole versus fluconazole alone for prophylaxis of fungal infections in adult patients undergoing a bone marrow or peripheral stem cell transplant. *Antimicrob Agents Chemother* 2005; **49**: 1331–6.
- 4 Hebert MF, Smith HE, Marbury TC *et al*. Pharmacokinetics of micafungin in healthy volunteers, volunteers with moderate liver disease, and volunteers with renal dysfunction. *J Clin Pharmacol* 2005; **45**: 1145–52.
- 5 Undre N, Stevenson P, Baraldi E. Pharmacokinetics of micafungin in HIV positive patients with confirmed esophageal candidiasis. *Eur J Drug Metab Pharmacokinet* 2012; **37**: 31–8.
- 6 Undre N, Pretorius B, Stevenson P. Pharmacokinetics of micafungin in subjects with severe hepatic dysfunction. *Eur J Drug Metab Pharmacokinet* 2014; **40**: 285–93.

- 7** Lempers VJ, Schouten JA, Hunfeld NG *et al.* Altered micafungin pharmacokinetics in intensive care unit patients. *Antimicrob Agents Chemother* 2015; **59**: 4403–9.
- 8** Andes D, Ambrose PG, Hammel JP *et al.* Use of pharmacokinetic-pharmacodynamic analyses to optimize therapy with the systemic antifungal micafungin for invasive candidiasis or candidemia. *Antimicrob Agents Chemother* 2011; **55**: 2113–21.
- 9** Pound MW, Townsend ML, Drew RH. Echinocandin pharmacodynamics: review and clinical implications. *J Antimicrob Chemother* 2010; **65**: 1108–18.
- 10** Timsit JF, Azoulay E, Cornet M *et al.* EMPIRICUS micafungin versus placebo during nosocomial sepsis in *Candida* multi-colonized ICU patients with multiple organ failures: study protocol for a randomized controlled trial. *Trials* 2013; **14**: 399.
- 11** Mahmood I. Prediction of clearance and volume of distribution in the obese from normal weight subjects: an allometric approach. *Clin Pharmacokinet* 2012; **51**: 527–42.
- 12** Post TM, Freijer JI, Ploeger BA *et al.* Extensions to the visual predictive check to facilitate model performance evaluation. *J Pharmacokinet Pharmacodyn* 2008; **35**: 185–202.
- 13** Parke J, Holford NH, Charles BG. A procedure for generating bootstrap samples for the validation of nonlinear mixed-effects population models. *Comput Methods Programs Biomed* 1999; **59**: 19–29.
- 14** Brendel K, Comets E, Laffont C *et al.* Evaluation of different tests based on observations for external model evaluation of population analyses. *J Pharmacokinet Pharmacodyn* 2010; **37**: 49–65.
- 15** Benet LZ, Hoener BA. Changes in plasma protein binding have little clinical relevance. *Clin Pharmacol Ther* 2002; **71**: 115–21.
- 16** Nguyen TH, Hoppe-Tichy T, Geiss HK *et al.* Factors influencing caspofungin plasma concentrations in patients of a surgical intensive care unit. *J Antimicrob Chemother* 2007; **60**: 100–6.
- 17** Grau S, Luque S, Campillo N *et al.* Plasma and peritoneal fluid population pharmacokinetics of micafungin in post-surgical patients with severe peritonitis. *J Antimicrob Chemother* 2015; **70**: 2854–61.
- 18** Gumbo T, Hiemenz J, Ma L *et al.* Population pharmacokinetics of micafungin in adult patients. *Diagn Microbiol Infect Dis* 2008; **60**: 329–31.
- 19** Nakagawa Y, Ichii Y, Saeki Y *et al.* Plasma concentration of micafungin in patients with hematologic malignancies. *J Infect Chemother* 2007; **13**: 39–45.
- 20** Ferreira FL, Bota DP, Bross A *et al.* Serial evaluation of the SOFA score to predict outcome in critically ill patients. *JAMA* 2001; **286**: 1754–8.
- 21** Pea F, Viale P, Pavan F *et al.* Pharmacokinetic considerations for antimicrobial therapy in patients receiving renal replacement therapy. *Clin Pharmacokinet* 2007; **46**: 997–1038.
- 22** Hirata K, Aoyama T, Matsumoto Y *et al.* Pharmacokinetics of antifungal agent micafungin in critically ill patients receiving continuous hemodialysis filtration. *Yakugaku Zasshi* 2007; **127**: 897–901.
- 23** Spriet I, Annaert P, Meersseman P *et al.* Pharmacokinetics of caspofungin and voriconazole in critically ill patients during extracorporeal membrane oxygenation. *J Antimicrob Chemother* 2009; **63**: 767–70.
- 24** Yang Q, Wang T, Xie J *et al.* Pharmacokinetic/pharmacodynamic adequacy of echinocandins against *Candida* spp. in intensive care unit patients and general patient populations. *Int J Antimicrob Agents* 2016; **47**: 397–402.
- 25** Hebert MF, Blough DK, Townsend RW *et al.* Concomitant tacrolimus and micafungin pharmacokinetics in healthy volunteers. *J Clin Pharmacol* 2005; **45**: 1018–24.
- 26** Hebert MF, Townsend RW, Austin S *et al.* Concomitant cyclosporine and micafungin pharmacokinetics in healthy volunteers. *J Clin Pharmacol* 2005; **45**: 954–60.