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Altered Micafungin Pharmacokinetics in Intensive Care Unit Patients

Vincent J. Lempers,[a,b] Jeroen A. Schouten,[c] Nicole G. Hunfeld,[d] Angela Colbers,[a,b] Henk J. van Leeuwen,[e] David M. Burger,[a,b] Paul E. Verweij,[b,f] Peter Pickkers,[g] Roger J. Brüggemann[a,b]

Radboud University Medical Center, Department of Pharmacy, Nijmegen, The Netherlands[a]; Radboud Institute for Health Sciences, Nijmegen, The Netherlands[b]; Canisius Wilhelmina Hospital, Department of Intensive Care, Nijmegen, The Netherlands[c]; Erasmus Medical Center, Department of Intensive Care, Rotterdam, The Netherlands[d]; Rijnstate Hospital, Department of Intensive Care, Arnhem, The Netherlands[e]; Radboud University Medical Center, Department of Medical Microbiology, Nijmegen, The Netherlands[f]; Radboud University Medical Center, Department of Intensive Care, Nijmegen, The Netherlands[g]

Micafungin is considered an important agent for the treatment of invasive fungal infections in the intensive care unit (ICU). Little is known on the pharmacokinetics of micafungin. We investigated micafungin pharmacokinetics (PK) in ICU patients and set out to explore the parameters that influence micafungin plasma concentrations. ICU patients receiving 100 mg of intravenous micafungin once daily for suspected or proven fungal infection or as prophylaxis were eligible. Daily trough concentrations and PK curves (days 3 and 7) were collected. Pharmacokinetic analysis was performed using a standard two-stage approach. Twenty patients from the ICUs of four hospitals were evaluated. On day 3 ($n = 20$), the median (interquartile range [IQR]) area under the concentration-time curve from 0 to 24 h (AUC_{0-24}) was 78.6 (65.3 to 94.1) mg · h/liter, the maximum concentration of drug in serum (C_{max}) was 7.2 (5.4 to 9.2) mg/liter, the concentration 24 h after dosing (C_{24}) was 1.55 (1.4 to 3.1) mg/liter, the volume of distribution (V) was 25.6 (21.3 to 29.1) liters, the clearance (CL) was 1.3 (1.1 to 1.5) liters/h, and the elimination half-life ($t_{1/2}$) was 13.7 (12.2 to 15.5) h. The pharmacokinetic parameters on day 7 ($n = 12$) were not significantly different from those on day 3. Daily trough concentrations (day 3 to the end of therapy) showed moderate interindividual (57.9%) and limited intraindividual variability (12.9%). No covariates of the influence on micafungin exposure were identified. Micafungin was considered safe and well tolerated. We performed the first PK study with very intensive sampling on multiple occasions in ICU patients, which aided in resolving micafungin PK. Strikingly, micafungin exposure in our cohort of ICU patients was lower than that in healthy volunteers but not significantly different from that of other reference populations. The clinical consequence of these findings must be investigated in a pharmacokinetic-pharmacodynamic (PK-PD) study incorporating outcome in a larger cohort. (This study is registered at ClinicalTrials.gov under registration no. NCT01783379.)

The incidence of fungal infections continues to pose a serious threat in the intensive care unit (ICU) and is associated with a high mortality rate and prolonged duration of ICU and hospital stay (1–4). Almost 20% of all isolated pathogens in ICU patients are determined to be fungi, with *Candida* species accounting for the majority of fungal infections (1).

Echinocandins are currently considered the primary treatment for patients with invasive candidiasis or candidemia (5, 6). Micafungin is an intravenous antifungal agent of the echinocandin class that exerts potent *in vitro* and *in vivo* activity against both *Candida* and *Aspergillus* species (7–10). In the clinical setting, micafungin has demonstrated efficacy in treating invasive candidiasis and candidemia (11, 12).

ICU patients may be subject to severely altered pharmacokinetic (PK) characteristics compared to those of non-critically ill patients. In this population, physiological changes, such as organ failure (hepatic and/or renal dysfunction), with the consequence of an altered drug volume of distribution (V) and/or clearance (CL), the use of organ support (i.e., renal replacement therapy and/or extracorporeal membrane oxygen [ECMO]), and interacting comedications may result in highly varied pharmacokinetics of drugs, including antimicrobial agents (13, 14). In addition, V and CL may be subject to increased inter- and intrasubject variability due to altered plasma protein binding (15). Also, it has been hypothesized that disease severity might result in altered drug PK behavior (16).

The PK of micafungin is very well defined in non-critically ill patients. Micafungin exhibits linear PK over a wide dosage range in adults, with steady state being reached by day 4, without the need for a loading dose (17). Specifically, dose adaptations are not required in patients with renal or hepatic impairment and renal replacement therapy (18–22). Nevertheless, there are very limited data available on micafungin PK in ICU patients; thus, it remains unclear whether the PK is altered in this population of critical ill patients due to the above-mentioned aspects.

We set up this study to describe the PK of micafungin in ICU patients and explore the parameters of influence on interindividual variability in micafungin plasma concentrations. This study aids in obtaining more knowledge on drug behavior in a group of highly vulnerable patients.

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Address correspondence to Roger J. Brüggemann, roger.bruggemann@radboudumc.nl.

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MATERIALS AND METHODS

Study design. We performed an open-label, multiple-dose, and multicenter observational PK study of micafungin in adult ICU patients (registered at ClinicalTrials.gov under registration no. NCT01783379). Our study was conducted in accordance with the Declaration of Helsinki and good clinical practice regulations. The study was carried out in The Netherlands in accordance with applicable rules concerning the review of research ethics committees and informed consent. The study was conducted from January until December 2013 in the ICUs of the Radboud University Medical Center (Nijmegen), Canisius Wilhelmina Hospital (Nijmegen), Rijnstate Hospital (Arnhem), and Erasmus Medical Center (Rotterdam), The Netherlands.

Study population. Patients admitted to the ICU to receive micafungin for suspected or proven fungal infection were eligible if they met the following inclusion criteria: ≥18 years of age on the day of the first micafungin dose, not receiving micafungin treatment for >2 days before enrollment, and having a central venous or arterial catheter. Patients were excluded who had history of hypersensitivity to echinocandins or excipients similar to those found in the micafungin preparation, HIV or hepatitis B/C infection, or abuse of alcohol or drugs. An empirical sample size of 20 evaluable patients was selected to adequately define micafungin PK (23).

Treatment. All patients received 100 mg of micafungin once daily by intravenous infusion over 1 h (18). Micafungin therapy continued as long as was considered clinically relevant by the treating physician. Yet, for the purpose of this study, PK sampling was limited to a maximum of 14 days, with an additional 3 days after cessation of therapy.

Baseline parameters. At screening (day 0 of study), the following parameters were registered: age, gender, race, weight, height, body mass index (BMI), fat free mass (FFM) (as calculated according to Janmahasatian et al. [24]), relevant comedication(s), medical history, indication for admission to the ICU, indication for micafungin use, relevant abnormalities (e.g., type of renal replacement therapy, mechanical ventilation, excess body fluid), or acute physiology and chronic health evaluation II (APACHE II), sequential organ failure assessment (SOFA), and Child-Pugh score. During the study, patient comedications, clinical characteristics, and relevant abnormalities were recorded on all study days. In addition, on days on which PK was measured (i.e., days 3 and 7), weight, BMI, FFM, SOFA score, and Child-Pugh score were documented. Microbiological data were obtained throughout the study as part of routine patient care.

Vital signs were monitored immediately before and after micafungin infusion and hourly for the first 4 h afterwards on days on which PK was measured.

Laboratory data. Blood was sampled three times a week and on days on which PK was measured for the determination of biochemical and hematological parameters, including serum electrolytes, total protein, albumin, blood urea nitrogen (BUN), aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), gamma-glutamyl transferase (GGT), alkaline phosphatase (AP), total bilirubin, C-reactive protein (CRP), lactate dehydrogenase (LDH), triglycerides, creatinine kinase, creatinine, hemoglobin, hematocrit, white blood cell differential, and platelet count.

Pharmacokinetic sampling. At day 3 (±1 day) of treatment, a PK curve of 10 samples was drawn with sampling times (t) of 0 (predose), 0.5, 1 (end of infusion), 2, 4, 6, 8, 12, 18, and 24 h postinfusion. A second PK curve of six samples was drawn on day 7 with sampling t of 0 (predose), 1, 4, 8, 12, and 24 h postinfusion. On all study days up until day 14, trough concentrations 24 h after dosing (C_{24}) were drawn until 3 days after cessation of therapy. Patients were considered evaluable if at least the first PK curve on day 3 was completed. Blood samples (±2 ml) were collected from an indwelling arterial catheter in lithium-heparin-containing tubes (nongel) and stored immediately at 4°C. Within 48 h after collection, samples were centrifuged at 1,900 × g for 5 min. Plasma was aspirated, directly transferred to polypropylene tubes, and stored at −80°C.

Safety. In addition to clinical observations, adverse events were reported on all study days. Local researchers and physicians determined a potentially causal relationship with micafungin administration.

Analytical assay for micafungin. After pretreatment with a protein precipitation solution (50% acetonitrile, 50% methanol, and 0.1% formic acid), analysis was performed with a validated ultraperformance liquid chromatography (UPLC) method, using a fluorescence detector (dynamic range for micafungin, 0.01 to 32.40 mg/liter; concentration-dependent accuracy range [n = 15], 97.61% to 101.64%). Intraday precision ranged between 1.41% and 5.14% (n = 5). In addition, interday precision varied between 0.69% and 2.20% (n = 15). A stability analysis of micafungin in whole blood confirmed that micafungin was stable for a minimum of 7 days at 4°C (mean concentration ± standard deviation [SD], 98.56% ± 1.91%, n = 4).

Micafungin PK data analysis. Pharmacokinetic parameters (area under the concentration-time curve from 0 to 24 h [AUC_{0-24}], maximum concentration of drug in serum [C_{max}], C_{24}, half-life [$t_{1/2}$], volume of distribution [V], clearance [CL], and terminal elimination rate constant [k_{el}]) were calculated using noncompartmental analysis (Phoenix version 6.3). The AUC_{0-24} was calculated using the linear up-log down trapezoidal rule. In addition, C_{max} and C_{24} were directly observed from the data. Half-life was calculated by $\ln 2/k_{el}$, in which k_{el} was determined by linear regression of the terminal points of the log-linear plasma concentration-time curve. V was calculated using the formula dose/AUC · k_{el}, and CL was calculated as dose/AUC_{0-24}.

A paired t test was performed on the log-transformed pharmacokinetic parameters of days 3 and 7 in order to detect statistically significant differences over time. Geometric mean ratios (GMRs) with a 90% confidence interval (CI) falling entirely within the range of 0.80 to 1.25 were considered to indicate no significant differences in pharmacokinetic parameters. Linear regression was performed to determine the relationships between the log-transformed pharmacokinetic parameters AUC_{0-24}, CL, and V and covariates (i.e., gender, age, weight, [plus related parameters BMI and FFM]), renal replacement therapy, APACHE II score, SOFA score, Child-Pugh score, liver enzyme levels (ALAT, ASAT, AP, bilirubin, GGT, and LDH), and other laboratory parameters (albumin, BUN, creatinine, and CRP levels). Statistical analyses were performed using SPSS version 20.0 (SPSS, Inc., Chicago, IL, USA). A P value of <0.05 was considered statistically significant.

RESULTS

Patients. Twenty-eight patients were included from the ICUs of three Dutch hospitals. The fourth hospital did not achieve inclusion of evaluable patients. Twenty patients completed the first PK curve on day 3 and were evaluable for analysis. The remaining 8 patients were withdrawn from the study before day 3 due to the removal of a central venous catheter (n = 3), switch to fluconazole (n = 1), and death (n = 4). Baseline demographics (n = 20) are available in Table S1 in the supplemental material. Micafungin was administered as treatment for suspected or proven fungal infections (n = 19) or prophylaxis against fungal infections (n = 1) caused by *Candida* spp., *Aspergillus* spp., or both. Three patients received micafungin therapy for longer than the initial study duration of 14 days. In the remaining 17 patients, study participation was discontinued due to clinical response before day 14 (n = 4), removal of central venous catheter (n = 4), switch to fluconazole (n = 2), discharge to another ward (n = 2), or death (n = 5).

Micafungin pharmacokinetics. Subjects received a median of 7 micafungin doses once daily (range, 3 to 14), resulting in a total of 20 PK curves on day 3 and 12 PK curves on day 7 (see Table S1 in the supplemental material). A total of 371 samples for PK analysis were drawn. One aberrant concentration was observed in a single patient (18.9 mg/liter at t of 19.98 h). Using Grubbs' test for

TABLE 1 Micafungin pharmacokinetics on day 3 and day 7

Parameter	PK curve on day (median [IQR]):	
	3 ($n = 20$)	7 ($n = 12$)
AUC_{0-24} (mg · h/liter)	78.6 (65.3–94.1)	65.7 (55.9–88.7)
C_{max} (mg/liter)	7.2 (5.4–9.2)	6.2 (5.1–9.2)
C_{24} (mg/liter)	1.6 (1.4–3.1)	1.6 (1.3–2.4)
$t_{1/2}$ (h)	13.7 (12.2–15.5)	14.4 (12.8–16.3)
V (liters)	25.6 (21.3–29.1)	28.7 (16.8–32.1)
CL (liters/h)	1.3 (1.1–1.5)	1.5 (1.2–1.8)
k_{el} (1/h)	0.05 (0.04–0.06)	0.05 (0.04–0.05)

outliers, this single data point was excluded for further analysis (Z, 3.93; critical Z, 2.68; $n = 19$).

The median and interquartile range (IQR) (25 to 75%) AUC_{0-24} on days 3 and 7 were 78.6 (65.3 to 94.1) mg · h/liter and 65.7 (55.9 to 88.7) mg · h/liter, respectively. The median (IQR) C_{max} was 7.2 (5.4 to 9.2) mg/liter on day 3 and 6.2 (5.1 to 9.2) mg/liter on day 7. The median (IQR) C_{24} was 1.6 (1.4 to 3.1) mg/liter on day 3 and 1.6 (1.3 to 2.4) mg/liter on day 7. An overview of all pharmacokinetic parameters of micafungin on days 3 and 7 is shown in Table 1 and Fig. 1, 2, and 3. Daily trough concentrations over time are shown in Fig. 4. At the start of therapy, the median C_{24} at t of 24 h differed significantly from that at t of 48 h ($P = 0.009$), whereas the median C_{24} at t of 48 h did not differ significantly from that at t of 72 h. No significant difference in C_{24} at later time points was seen.

The GMR for AUC_{day7}/AUC_{day3} was 0.97 (90% CI, 0.85 to 1.11). In addition, the GMRs for C_{max} and C_{24} were 0.94 (90% CI, 0.81 to 1.10) and 0.87 (90% CI, 0.59 to 1.28; Table 1), respectively. The median interindividual coefficient of variation (CV) of micafungin trough concentrations (day 3 to the end of therapy) amounted to 57.9% (95% CI, 57.7 to 58.2; 92 samples) and the median intraindividual CV to 12.9% (95% CI, 12.7 to 13.2; $n = 16$) over the same period. The micafungin C_{24} correlated well with AUC on day 3 ($r^2 = 0.919$, $P < 0.01$) and day 7 ($r^2 = 0.983$, $P < 0.01$) (see Fig. S1 in the supplemental material).

Covariates. The micafungin PK parameters AUC_{0-24}, CL, and V on days 3 and 7 were not significantly influenced by specific covariates (gender, age, weight [including BMI and FFM], renal replacement therapy, APACHE II score, SOFA score, Child-Pugh score, liver function enzyme levels [ALAT, ASAT, AP, bilirubin, GGT, and LDH]) and other laboratory parameters (albumin, BUN, creatinine, and CRP levels). No interacting comedication was identified throughout the course of treatment.

Safety. After the start of micafungin dosing, 18/20 subjects (90%) experienced a total of 65 new or aggravated clinical adverse events (AEs) during follow-up. Five serious AEs were reported (persistent infections due to anastomotic leak, renal failure, metabolic acidosis, thrombosis, and the need for vasoactive drugs), leading to the death of these five subjects. It was concluded that these serious AEs were not related to the administration of micafungin. Of the reported 65 AEs, four were categorized as possibly related to micafungin therapy (elevated liver function enzymes, reported as an increase of >3 times the upper limit of normal). None of these AEs resulted in modifications or discontinuation of micafungin therapy.

DISCUSSION

To our knowledge, this cohort of ICU patients is unique in size and sampling intensity with PK curves on multiple occasions and daily trough concentrations over the complete course of treatment. It reflects a real-life situation with a population being treated for fungal infections. This aided us in describing the PK of micafungin in a cohort that is frequently subject to altered PK.

Strikingly, we found much lower exposure in this cohort of ICU patients than the exposure described in the literature. Using an unpaired t test (on mean exposure ± standard deviation [SD] and number of patients), the exposure in this cohort appeared to be significantly lower than that in healthy volunteers (20, 25–27). A statistical comparison with other patient populations did not yield a significant different AUC (19, 20, 22, 27, 28) (see Table S2 in the supplemental material). This might suggest a negative impact of disease on the exposure of micafungin. We found 57.9% interindividual variability in micafungin C_{24}. To our knowledge, interindividual variability in micafungin C_{24} in ICU patients has not been reported prior to this study. In comparison, caspofungin interindividual variability in ICU patients was reported to be 45.6% ($n = 21$) in a study from our group and 57% ($n = 6$) in the

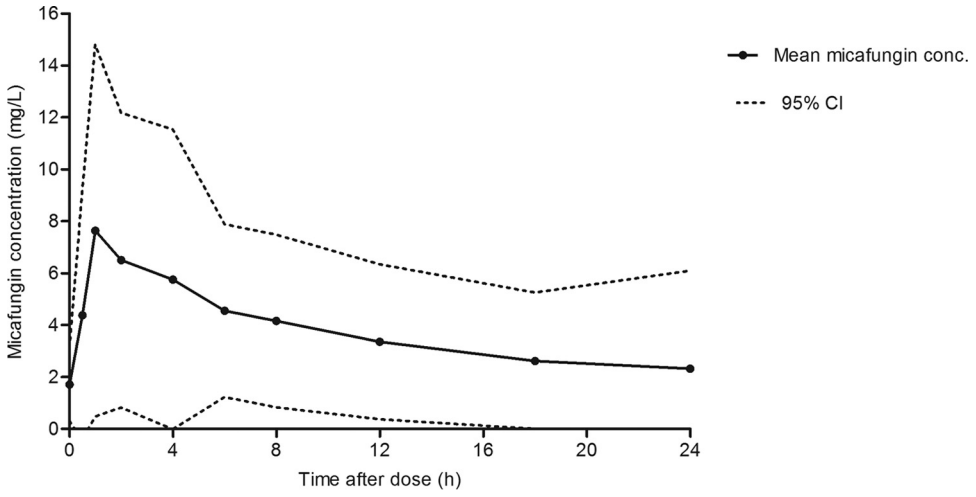


FIG 1 Mean plasma concentration (conc.)–time curve of micafungin (100 mg/day) on day 3.

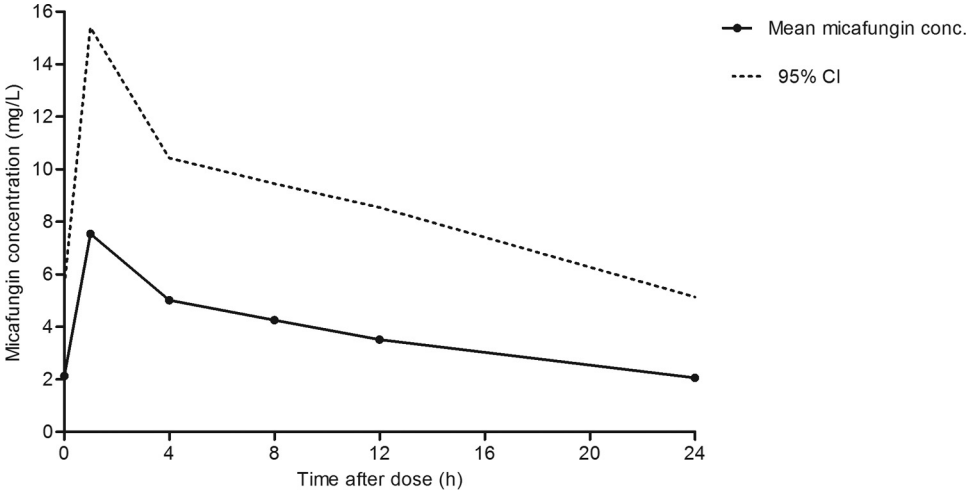


FIG 2 Mean plasma concentration-time curve of micafungin (100 mg/day) on day 7.

Defining Antibiotic Levels in Intensive Care Unit Patients (DALI) study (14, 29).

We can think of four possible explanations for the lower exposure of micafungin: (i) altered protein binding, (ii) changes in metabolic route, (iii) impact of disease severity, and (iv) a higher average body weight in this cohort than in reference populations. These are discussed below.

(i) As a general rule, an increased free fraction due to protein displacement will lead to a lower total drug exposure (30). Micafungin is highly protein bound (>99%). Hence, a lower exposure due to lower protein binding (a higher free fraction) is possible. This would also match previous findings in subjects with severe hepatic dysfunction and findings with caspofungin (27, 31). Due to the limited variability in albumin status (all were hypoalbuminemic), we could not make a distinction between micafungin exposure in patients with normal albuminemia versus hypoalbuminemia. Unfortunately, no unbound micafungin plasma concentrations were analyzed; thus, protein displacement cannot be confirmed or rejected as a possible cause for the lower exposure.

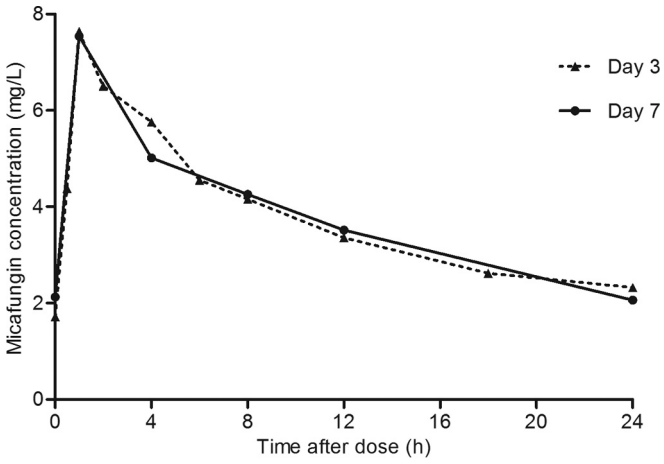


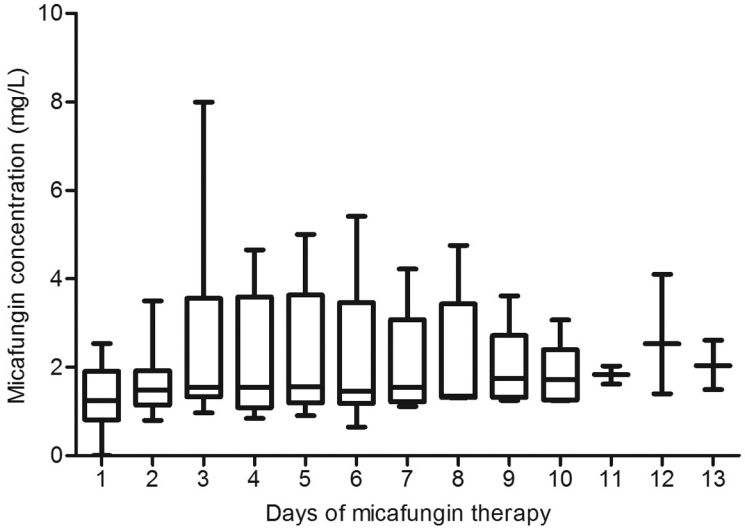
FIG 3 Mean plasma concentration-time curve of micafungin (100 mg/day) on days 3 and 7.

(ii) In patients with severe hepatic dysfunction, lower exposure of micafungin parent compound and higher and more variable plasma concentrations of the M-5 metabolite were reported (27). This has also been confirmed in younger patients (32). The authors suggested this was due to either a higher rate of formation or lower CL of the M-5 metabolite. Decreased clearance of the M-5 metabolite seems the most plausible explanation, but increased formation of the M-5 metabolite is a possible explanation for lower micafungin exposure. We did not measure the exposure of micafungin metabolites and therefore were unable to confirm this as a possible explanation.

(iii) This ICU population was heterogeneous in terms of APACHE II and SOFA scores. For anidulafungin, it has been hypothesized that exposure is lower for patients with a higher disease severity score, although this correlation did not reach statistical significance (16). For caspofungin, an identical study by our group demonstrated that disease severity did not impact exposure (29). For micafungin, disease severity (both APACHE II and SOFA scores) did not reveal a correlation with exposure and therefore can be ruled out as a possible cause for the low exposure.

(iv) Last, Gumbo et al. (33) demonstrated that micafungin systemic clearance in bone marrow transplant patients increased as a function of body weight of >66.3 kg. Recently, a formula has been proposed to individualize micafungin doses for overweight and obese patients (34). Body weight and other weight-derived parameters, BMI and FFM, were not identified as covariates in this study, possibly a result of the average weight in this study being close to the ideal body weight. Also, the weight distribution in the current study was comparable to that in other studies, thereby ruling out a relatively high body weight as a possible cause for the low exposure.

In addition to the above findings, these data suggest that steady-state concentrations of micafungin are reached by day 3 at the latest, which is consistent with previous reports (18, 35). At the initiation of micafungin therapy, the C_{24} at 24 h was significantly lower than that at 48 h (but not comparing t of 48 h to t of 72 h). Despite the fact that micafungin demonstrated clinical efficacy in pivotal trials at current regimens, the use of a loading dose of



Study day	1	2	3	4	5	6	7	8	9	10	11	12	13
Median conc (mg/L)	1.25	1.48	1.55	1.54	1.56	1.46	1.55	1.35	1.75	1.72	1.83	2.53	2.03
Ratio*	-	0.84	0.96	1.00	0.99	1.07	0.94	1.15	0.77	1.02	0.94	0.72	1.24
Subjects (n)	17	19	18	16	16	12	6	5	5	5	3	3	3

* Previous day / current day

FIG 4 Micafungin (100 mg/day) trough concentrations on days 1 to 13 of therapy. The box plots show the median and IQR (5th to 95th percentile) values.

micafungin in ICU patients should be evaluated to increase exposure on the first day of therapy.

We did not observe altered micafungin PK in a small subcohort of patients with renal dysfunction (modification of diet in renal disease [MDRD], 10 to 30 ml/min/1.73 m^2) or in those receiving renal replacement therapy (see Table S1 in the supplemental material), which confirms previous findings in the literature (20–22, 36, 37).

The clinical consequence of the lower exposure in this cohort is subject to debate, as in the setting of lower exposure, efficacy might be compromised (38, 39). Recently, Andes et al. (40) demonstrated by analysis of two micafungin phase III trials that the probability of mycological cure in adult patients with invasive candidiasis or candidemia receiving micafungin therapy (55% were admitted to the ICU) was higher if the patient attained an AUC/MIC ratio between 3,000 and 12,000 compared to a ratio of <3,000 (98.0% versus 85.1%, respectively). The authors concluded that if the MIC was <0.06 mg/liter, the vast majority of the patients would attain the lower target of 3,000 (11, 12, 40). A subgroup analysis of the 55% ICU patients in this cohort is lacking in this paper. Unfortunately, no hypothesis can be generated from this paper on the efficacy of micafungin in the selected group of patients in the ICU.

In our population with median AUC_{0-24}s of 78.6 mg · h/liter and 65.7 mg · h/liter on days 3 and 7, respectively, setting a target AUC/MIC ratio of 3,000 and a clinical breakpoint (CBP) of 0.03 mg/liter would result in 75% of our population not being able to attain the target value (AUC_{0-24}, ≥90 mg · h/liter) on both days on which PK was measured for micafungin. Obviously, using higher CBPs would result in even larger proportions of patients not achieving this PK-PD target. The success of therapy in our cohort might be driven by pathogens with low MICs (<0.03 mg/liter), which would result in 100% target attainment. However, data on susceptibility are lacking in this research, and conclusions on the exposure response in relation to the susceptibility of the pathogen as drawn by Andes et al. (40) cannot be substantiated.

Unfortunately, in daily practice, we are confronted with a critical delay in obtaining MICs from cultured species. In the absence of these susceptibility data/MICs, the population average exposure of healthy volunteers might serve as a reference value, as these average concentrations represent the best-case scenario (for the standard dose). An individual who achieves this exposure is less likely to demonstrate a suboptimal clinical response. Further inducing the likeliness of achieving mycological cure, higher standard doses of micafungin in this patient population could be considered, as it has been confirmed that micafungin has a favorable tolerability profile and displays dose-proportional linear pharmacokinetics (19, 20, 41). Last, to avoid concentration-dependent therapeutic failure, therapeutic drug monitoring of micafungin (TDM) could be a valuable tool in this especially vulnerable patient population.

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R. J. Brüggemann designed the study. V. J. Lempers conducted the study. J. A. Schouten, N. G. Hunfeld, H. J. van Leeuwen, and P. Pickkers

recruited patients for this study. A. Colbers was responsible for data management. V. J. Lempers, A. Colbers, D. M. Burger, and R. J. Brüggemann analyzed the data. P. E. Verweij supervised the microbiology results. All authors read and improved the manuscript for publication.

This study was performed at Radboud University Medical Centers, Canisius Wilhelmina Hospital, Rijnstate Hospital, and Erasmus Medical Center.

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