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Low Caspofungin Exposure in Patients in Intensive Care Units

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ABSTRACT In critically ill patients, drug exposure may be influenced by altered drug distribution and clearance. Earlier studies showed that the variability in caspofungin exposure was high in intensive care unit (ICU) patients. The primary objective of this study was to determine if the standard dose of caspofungin resulted in adequate exposure in critically ill patients. A multicenter prospective study in ICU patients with (suspected) invasive candidiasis was conducted in the Netherlands from November 2013 to October 2015. Patients received standard caspofungin treatment, and the exposure was determined on day 3 of treatment. An area under the concentration-time curve from 0 to 24 h (AUC_{0-24}) of 98 mg · h/liter was considered adequate exposure. In case of low exposure (i.e., <79 mg · h/liter, a $\geq 20\%$ lower AUC_{0-24}), the caspofungin dose was increased and the exposure reevaluated. Twenty patients were included in the study, of whom 5 had a positive blood culture. The median caspofungin AUC_{0-24} at day 3 was 78 mg · h/liter (interquartile range [IQR], 69 to 97 mg · h/liter). A low AUC_{0-24} (<79 mg · h/liter) was seen in 10 patients. The AUC_{0-24} was significantly and positively correlated with the caspofungin dose in mg/kg/day ($P = 0.011$). The median AUC_{0-24} with a caspofungin dose of 1 mg/kg was estimated using a pharmacokinetic model and was 114.9 mg · h/liter (IQR, 103.2 to 143.5 mg · h/liter). In conclusion, the caspofungin exposure in ICU patients in this study was low compared with that in healthy volunteers and other (non)critically ill patients, most likely due to a larger volume of distribution. A weight-based dose regimen is probably more suitable for patients with substantially altered drug distribution. (This study has been registered at ClinicalTrials.gov under registration no. NCT01994096.)

KEYWORDS antifungal therapy, intensive care, pharmacokinetics, therapeutic drug monitoring

Invasive candidiasis is an important cause of morbidity and mortality in immunocompromised and critically ill patients. Patients in intensive care units (ICUs) are especially at risk for invasive candidiasis due to the presence of risk factors such as the use of a central venous catheter, parenteral nutrition, renal replacement therapy, mechanical ventilation, previous broad-spectrum antibiotic therapy, immunosuppression, neutropenia, or recent major surgery (1, 2). Candidemia is the fourth most common cause of health care-associated bloodstream infections in ICU patients, and *Candida* species are the most commonly isolated health care-associated bloodstream pathogens (3). A

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mortality of 40% has been reported in patients with invasive candidiasis. Moreover, invasive candidiasis is associated with a prolonged hospital stay and increased costs (4–9).

Prompt initiation of effective antifungal therapy in the appropriate dosage is required to improve the outcome in patients with invasive candidiasis (10, 11). The Infectious Diseases Society of America (IDSA) and the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the management of candidiasis recommend the use of an echinocandin, such as caspofungin, as primary therapy for (suspected) invasive candidiasis in critically ill patients (12, 13). In healthy volunteers receiving the standard dose of caspofungin, the mean area under the concentration-time curve from 0 to 24 h (AUC_{0-24}) was 98 mg · h/liter (14–16).

In critically ill patients, drug exposure may be influenced by altered drug distribution and clearance (17–21), and this may require drug concentration-guided dosing (22). For ICU patients the inter- and intraindividual variabilities in caspofungin trough concentrations appeared to be high (23). Factors that were associated with low caspofungin plasma concentrations were body weight above 75 kg and hypoalbuminemia, which is present in up to 60% of ICU patients (23, 24). Capillary permeability, third spacing, and multiorgan failure may also influence the caspofungin concentration in ICU patients (23). Furthermore, caspofungin exposure might be influenced by disease severity (10, 11).

The primary objective of this study was to determine if the standard dose of caspofungin resulted in adequate exposure in critically ill patients. In addition, the exposure was reevaluated after a dose escalation in patients with low drug exposure. Finally, we used a population pharmacokinetic model to estimate at which dose the target exposure was reached.

RESULTS

Twenty patients were included in the study, and their medical records were reviewed. The median age of the patients was 56 years (range, 25 to 83 years), and 16 patients (80.0%) were Caucasian. The patients' characteristics are shown in Table 1. Patients had suspected invasive candidiasis based on culture results (Table 1) and clinical symptoms. Five patients had a positive blood culture. The median *Candida* score was 3.5 out of 5 (interquartile range [IQR], 2.0 to 4.0). Patients received caspofungin for a median period of 7 days (range, 3 to 25 days). Treatment with caspofungin was continued in 8 patients (40.0%), and antifungal treatment was switched to fluconazole in 6 patients (30.0%) with a *Candida albicans* strain that was susceptible to fluconazole. Treatment was switched to liposomal amphotericin B in 2 patients (10.0%) (in 1 patient because of lack of efficacy and in 1 patient because of possible retinal involvement). In total, 4 patients (20.0%) died during treatment with caspofungin, of whom 1 patient had a positive blood culture for *Candida glabrata* (MIC, 0.125 mg/liter). Liver enzymes increased in 3 patients (15.0%) during treatment with caspofungin; all 3 patients received the standard dose of caspofungin. According to the Naranjo adverse drug reaction probability scale (25), there was a possible relationship with the use of caspofungin (score of 2 out of 13 for all 3 patients).

Caspofungin pharmacokinetics and exposure. The population pharmacokinetic parameters of caspofungin are described using a two-compartment model, and the results are shown in Table 2. The median AUC_{0-24} of caspofungin was 78.1 mg · h/liter (range, 61.4 to 129.4 mg · h/liter). The mean plasma concentration-time curve is shown in Fig. 1. The AUC_{0-24} was below 79 mg · h/liter (i.e., $\geq 20\%$ reduction) in 10 patients (50.0%). The caspofungin exposure and dose adjustments for the individual patients are shown in Table 3. The AUC_{0-24} of caspofungin showed no significant correlation with the caspofungin dose (not corrected for the weight of the patient) (correlation coefficient, 0.164; $P = 0.490$). The AUC_{0-24} of caspofungin showed a significant correlation with the caspofungin dose, corrected for the weight of the patient (mg/kg/day) (correlation coefficient, 0.557; $P = 0.011$). In addition, the weight of the patients was significantly correlated with the volume of distribution in the central compartment (V_1)

TABLE 1 Patient characteristics

Characteristic ^a	Value for patients (n = 20)
No. (%) male	11 (55)
Median (range) age, yr	56 (25–83)
Median (range) wt, kg	78 (48–139)
No. (%) with underlying condition:	
Abdominal	8 (40)
Cardiovascular	2 (10)
Renal	1 (5)
Respiratory	4 (20)
Other ^b	5 (25)
No. (%) with reason for ICU admission:	
Sepsis	10 (50)
Abdominal	6 (30)
Renal	2 (10)
Other	2 (10)
Renal insufficiency	2 (10)
Respiratory insufficiency	6 (30)
Postoperative	2 (10)
Median (range) stay in ICU, days	16 (4–45)
No. (%) with CVVH	8 (40)
Median (range) score	
APACHE II	19 (8–34)
APACHE IV	95 (47–169)
SAPS3	59 (31–104)
SOFA	8 (2–20)
No. (%) with <i>Candida</i> species:	
<i>C. albicans</i>	10 (50)
<i>C. glabrata</i>	7 (35)
<i>C. tropicalis</i>	1 (5)
Not specified	2 (10)
No. (%) with culture matrix:	
Blood	5 (25)
Drain fluid ^c	6 (30)
CVC tip	2 (10)
Pus in a closed space ^d	4 (20)
Throat	3 (15)

^aAbbreviations: APACHE, acute physiology and chronic health evaluation; CVC, central venous catheter; CVVH, continuous venovenous hemofiltration; ICU, intensive care unit; SAPS3, simplified acute physiology score; SOFA, sepsis-related organ failure assessment.

^bOne patient each with HIV, lymphoma, Mizuho disease, spondylodiscitis, and pressure ulcers.

^cThree patients with abdominal fluid and three patients with pleural fluid.

^dTwo abdominal, 1 hip, and 1 cardiovascular.

(correlation coefficient, 0.602; $P = 0.005$) and clearance (CL) (correlation coefficient, 0.604; $P = 0.005$) of caspofungin. No significant correlation of the caspofungin AUC_{0-24} with patient age, liver enzymes, albumin concentration, or disease severity scores was found (Table 4). Furthermore, the caspofungin AUC_{0-24} was not significantly different in patients with different gender, race, presence of continuous venovenous hemofiltration (CVVH), presence of sepsis, or interacting comedication (Table 5). Caspofungin trough concentrations were determined in 9 patients when patients were on an adequate dose regimen. The median trough concentration was 2.6 mg/liter (range, 1.0 to 3.4 mg/liter). The individual trough concentrations for each patient are shown in Table 3.

Bayesian adaptive dose selection to reach the target exposure of 98 mg · h/liter resulted in a median weight-based dose regimen of caspofungin of 0.9 mg/kg (IQR, 0.7 to 1.0 mg/kg). Selecting a caspofungin dose of 1 mg/kg resulted in a median AUC_{0-24} of 114.9 mg · h/liter (IQR, 103.2 to 143.5 mg · h/liter). When a fixed-dose regimen of 50 mg for patients with a weight of <70 kg, 70 mg for patients weighing between 70 and

TABLE 2 Population pharmacokinetic parameters of caspofungin ($n = 20$)

Parameter ^a	Median (range)
AUC _{0–24} (mg · h/liter)	78.1 (61.4–129.4)
C _{min} (mg/liter)	1.7 (1.1–3.9)
C _{max} (mg/liter)	7.4 (4.7–14.7)
CL (liters/h)	0.66 (0.37–1.26)
V ₁ (liters)	9.1 (5.5–13.2)
V ₂ (liters)	8.6 (5.2–59.0)
t _{1/2α} (h)	2.5 (2.2–4.0)
t _{1/2β} (h)	19.8 (12.3–66.0)

^aAbbreviations: AUC_{0–24}, area under the concentration-time curve from 0 to 24 h; C_{max}, maximal concentration; C_{min}, minimal concentration; CL, clearance; V₁, volume of distribution in the central compartment; V₂, volume of distribution in the peripheral compartment; t_{1/2α}, half-life at α phase; t_{1/2β}, half-life at β phase.

100 kg, and 100 mg for patients with a weight of ≥ 100 kg was selected, the median AUC_{0–24} was 104.3 mg · h/liter (IQR, 88.6 to 123.6 mg · h/liter).

DISCUSSION

The median AUC_{0–24} of caspofungin was 78 mg · h/liter and the caspofungin exposure was low in 50% of the patients receiving the standard dose of caspofungin. The caspofungin AUC_{0–24} was significantly correlated with the caspofungin dose in mg/kg/day, and the weight of the patients was significantly correlated with the central V₁ and CL of caspofungin. Based on the results of our study, the current dose regimen, of 50 mg for patients weighing ≤ 80 kg and 70 mg for patients weighing > 80 kg, may not be the most suitable dose regimen for ICU patients to reach the target exposure of caspofungin. Based on the population pharmacokinetic model we developed, a weight-based dose regimen of 1 mg/kg once daily would probably be a more appropriate dose regimen for ICU patients. Simulation of this dose in the model resulted in an AUC_{0–24} between 98 mg · h/liter, the limit set for efficacy (14–16), and 210 mg · h/liter, the limit set by the manufacturer of caspofungin for which a dose reduction is recommended (15), in all patients. The association with body weight was in agreement with an earlier study of caspofungin trough concentrations in ICU patients (23) and with a study in overweight and obese people where lower caspofungin AUCs were observed in obese persons than in thinner persons (26). Caspofungin has shown good tolerability at higher doses. The use of caspofungin in a dose of 70 to 200 mg per day was well tolerated, and the incidence of drug-related adverse events was similar for the standard and high-dose regimens (27–31). One clinical trial studied the efficacy of a higher caspofungin dose (150 mg daily). This study showed no clear benefits of this dosing

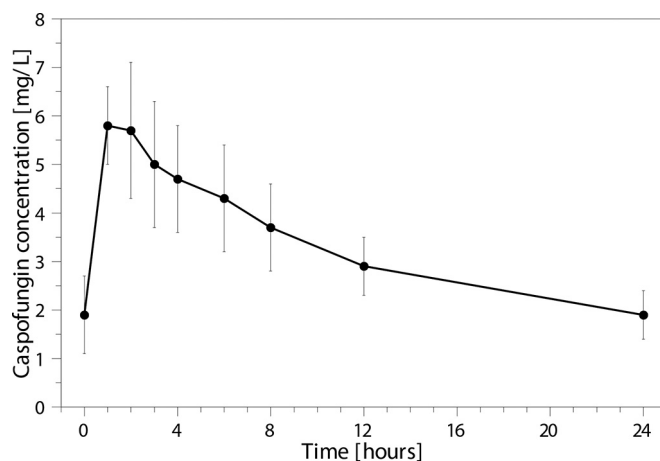


FIG 1 Caspofungin concentration-time curve on day 3 of treatment, showing mean with standard deviation for each time point.

TABLE 3 Caspofungin exposure and dose adjustments for individual patients

Patient	Wt (kg)	Caspofungin dose 1		Caspofungin dose 2		Trough concn (mg/liter) ^b
		Dose (mg)	AUC _{0–24} (mg · h/liter) ^a	Dose (mg)	AUC _{0–24} (mg · h/liter)	
1	60	35 ^c	67.0	50	113.6	
2	100	70	101.9			2.6
3	95	70	81.8			
4	48	50	109.3			3.4
5	79	50	71.6	— ^d		
6	80	50	62.6	—		
7	70	35 ^c	74.2	50	109.3	2.2 (1.0–2.8)
8	94	70	68.0	100	127.8	3.0
9	74	50	82.1			2.2
10	76	50	64.3	—		
11	74	50	73.2	70	91.6	2.0 (1.5–2.7)
12	99	70	128.1			3.4 (3.4–3.4)
13	83	70	82.1			2.8 (2.1–2.8)
14	80	50	98.9			
15	85	70	80.8			
16	52	50	91.0			
17	75	50	73.1	—		
18	139	70	61.4	100	74.8	
19	75	50	129.4			2.2 (1.6–3.1)
20	76	50	75.4	—		

^aAUC_{0–24}, area under the concentration-time curve over 24 h.

^bCaspofungin trough concentration expressed as median with range.

^cReduced caspofungin dose due to severe liver failure/cirrhosis (Child-Pugh score C).

^d—, caspofungin was discontinued.

strategy; however, the study was not performed particularly in ICU patients, and the caspofungin exposure was not measured (28). Since our model was built with data from only 20 patients and most patients had suspected invasive candidiasis, a weight-based dose regimen of 1 mg/kg needs to be confirmed in a larger data set with regard to the efficacy of the treatment.

The median AUC_{0–24} of caspofungin found in this study was 78 mg · h/liter. The AUC_{0–24} was low compared to the AUC_{0–24} of 98 mg · h/liter established in healthy volunteers (14–16), an AUC_{0–24} of 110 to 117 mg · h/liter found in non-critically ill patients (32, 33), and an AUC_{0–24} of 89 to 116 mg · h/liter established in ICU patients (34, 35). The volume of distribution in the peripheral compartment (V₂) was larger than

TABLE 4 Spearman correlations with the caspofungin AUC_{0–24}^a

Characteristic	Correlation coefficient	P value
Age (years)	0.093	0.698
Caspofungin dose (mg/kg/day)	0.057	0.011
Liver enzymes		
ALT (U/liter)	–0.267	0.255
AST (U/liter)	–0.259	0.270
Bilirubin (μmol/liter)	–0.109	0.657
Alkaline phosphatase (U/liter)	–0.085	0.729
γ-Glutamyl transpeptidase (U/liter)	–0.060	0.801
Albumin (g/liter)	0.213	0.367
Disease severity scores		
APACHE II	0.220	0.352
APACHE IV	0.194	0.426
SAPS3	0.341	0.141
SOFA	0.216	0.361

^aAbbreviations: AUC_{0–24}, area under the concentration-time curve from 0 to 24 h; ALT, alanine aminotransaminase; APACHE, acute physiology and chronic health evaluation; AST, aspartate aminotransaminase; SAPS, simplified acute physiology score; SOFA, sepsis-related organ failure assessment.

TABLE 5 Caspofungin AUC_{0–24} in different patient groups^a

Characteristic	Caspofungin AUC _{0–24h} (mg · h/liter) ^b in patients:		P value ^c
	With characteristic	Without characteristic	
Gender (male)	74.2 (64.3–82.1)	91.0 (72.4–105.6)	0.175
Race (Caucasian)	78.6 (72.0–96.9)	74.4 (67.3–96.6)	0.682
CVVH	74.8 (67.3–102.2)	82.0 (72.0–96.9)	0.734
Sepsis	77.5 (70.5–103.8)	78.6 (67.8–84.3)	0.796
Corticosteroid use	81.8 (68.0–101.9)	77.0 (72.0–94.7)	0.600

^aAbbreviations: AUC_{0–24h}, area under the concentration-time curve from 0 to 24 h; CVVH, continuous venovenous hemofiltration.

^bCaspofungin AUC_{0–24h} expressed as median with interquartile range.

^cDetermined by using the Mann-Whitney U test.

that in healthy volunteers and patients in other studies (15, 16, 32–35). The half-life ($t_{1/2}$) was comparable to the $t_{1/2}$ in other ICU patients (34) and was longer than the $t_{1/2}$ in healthy volunteers (15, 16). The low AUC_{0–24} of caspofungin in our study is therefore most likely the result of a larger V . Fluid extravasation as a result of endothelial dysfunction and capillary leak, edema in sepsis, ascites, and other third spaces, fluid resuscitation, and hypoalbuminemia are factors that are frequently present in ICU patients and can all lead to an increased V and a lower drug concentration (18–20). Low AUC values and increased V in ICU patients are also seen with other antifungal drugs, such as fluconazole and anidulafungin (36, 37). Although one study showed a lower response rate among patients with a higher acute physiology and chronic health evaluation II (APACHE II) score (38), the AUC_{0–24} of caspofungin was not associated with disease severity scores, which was in agreement with recent findings (34, 36). Hence, the use of disease severity scores does not seem appropriate to predict pharmacokinetic parameters.

Two patients in our study suffered from severe liver damage or cirrhosis (Child-Pugh score C), and they therefore received a daily caspofungin dose of 35 mg according to the summary of product characteristics of caspofungin. The AUC_{0–24} was low in both patients, and the dose was increased to 50 mg, after which the AUC_{0–24} was adequate and liver enzymes remained stable. These results are in accordance with two case reports where 50 mg and 70 mg were given to patients with moderate hepatic dysfunction and where the exposure was similar to the exposure in healthy volunteers (39, 40). These findings illustrate that liver drug metabolism may be underestimated in the presence of liver test abnormalities or evidence of cirrhosis (41). Furthermore, a recent study in ICU patients with Child-Pugh score B showed that the recommended caspofungin dose of 35 mg resulted in low caspofungin exposure, and a simulation of several dosing regimens showed that adequate exposure was reached with a daily caspofungin dose of 50 to 70 mg (42). Since the Child-Pugh score is highly driven by the albumin level, ICU patients with hypoalbuminemia are often incorrectly classified with a Child-Pugh B score. Based on the results of that study, the authors state that the caspofungin maintenance dose should not be reduced in noncirrhotic ICU patients based on the Child-Pugh score if the classification is driven by hypoalbuminemia, as the decreased maintenance dose results in a significantly lower caspofungin exposure (42). Combined with the case reports and recent study (39, 40, 42), our findings suggest that patients with moderate hepatic dysfunction should perhaps initially receive a higher empirical maintenance dose, with close follow-up with therapeutic drug monitoring (TDM) and monitoring of liver enzymes. Further research in this patient group is needed to provide evidence for the development of new dosing recommendations.

Since caspofungin was used as empirical treatment for suspected invasive candidiasis, the MIC of the *Candida* species was determined in only 4 patients. *In vivo* studies have demonstrated that the AUC/MIC ratio is a good descriptor of the echinocandin exposure-response relationship. In these *in vivo* studies, an AUC_{0–24}/MIC ratio of 865

was established for a 1-log kill of *C. albicans* for caspofungin, an AUC_{0-24}/MIC ratio of 450 for a 1-log kill of *C. glabrata*, and an AUC_{0-24}/MIC ratio of 1,185 for a 1-log kill of *C. parapsilosis* (MIC values determined according to CLSI criteria) (14). Considering an AUC_{0-24} of approximately 100 mg · h/liter, the AUC_{0-24}/MIC ratio target can be reached when *C. albicans* strains have MIC values of <0.125, when *C. glabrata* strains have MIC values of <0.25, and when *C. parapsilosis* strains have MIC values of <0.10. However, *C. parapsilosis* strains often have MIC values of >0.10, and therefore the AUC_{0-24} of approximately 100 mg · h/liter is not sufficient to reach the AUC_{0-24} target ratio (43). The median AUC_{0-24} of the patients in this study was lower; however, in case of an infection with a *Candida* species with a low MIC value, the AUC_{0-24}/MIC ratio can still be sufficient with a lower AUC_{0-24} value. Meanwhile, a large variability in caspofungin MIC values among testing laboratories is seen, and routine *in vitro* susceptibility testing of caspofungin against *Candida* by using the CLSI or EUCAST method is currently not recommended until this reproducibility problem in susceptibility testing is resolved (44). Besides, in case of empirical treatment, the MIC of the *Candida* species is not known at the start of the treatment. Then, the strategy would be to acquire at least adequate exposure to cover susceptible *Candida* species, since a delay in appropriate antifungal therapy affects mortality (10).

In conclusion, the AUC_{0-24} of caspofungin in ICU patients in this study was low compared with that in healthy volunteers and other (non)critically ill patients, most likely due to a larger volume of distribution. A weight-based dose regimen of 1 mg/kg/day for patients with an increased volume of distribution and clearance, and TDM in patients with liver failure, is probably a more suitable approach to achieve optimal exposure of caspofungin, although this approach needs to be confirmed with a larger data set.

MATERIALS AND METHODS

Study design. This multicenter prospective study was conducted at the 46-bed ICU department of the University Medical Center Groningen and the 18-bed ICU department of the Medisch Spectrum Twente, the Netherlands, from November 2013 to October 2015. Patients were eligible for inclusion if the following criteria were met: (1) age ≥ 18 years, (2) admission to the ICU department, (3) (suspected) invasive candidiasis according to the 2008 definition of Invasive Fungal Disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group (45), and (4) treatment with caspofungin. In both centers caspofungin was the standard treatment for (suspected) invasive candidiasis. Patients were excluded if they did not have an arterial line for blood sampling. The local ethics committee of both hospitals approved the study (Institutional Review Board 2012-371), and the study was registered at ClinicalTrials.gov under registration no. NCT01994096. Written informed consent was obtained from the patient or the legal representative of the patient.

Caspofungin was administered once daily by intravenous infusion over 1 h. The recommended dose regimen of caspofungin consists of a loading dose of 70 mg on day one, followed by a daily maintenance dose of 50 mg for patients weighing ≤ 80 kg or a daily maintenance dose of 70 mg for patients weighing > 80 kg. In patients with moderate hepatic insufficiency (Child-Pugh score B), a dose reduction to 35 mg per day is recommended by the manufacturer of caspofungin. The manufacturer has no clinical experience with adult patients with severe hepatic insufficiency (Child-Pugh score C) (46). In this study, patients with severe hepatic insufficiency received a daily dose of 35 mg. As a steady state of caspofungin is reached on the first day after the loading dose (16), blood samples were taken on day 3 (± 1 day) just before administration of caspofungin and 1, 2, 3, 4, 6, 8, 12, and 24 h after the start of the infusion. Caspofungin plasma concentrations were determined within 24 h, using a validated liquid chromatography-tandem mass spectrometry assay (47). An AUC_{0-24} of 98 mg · h/liter or higher was considered adequate exposure. *C. albicans* is the most common species seen in candidemia, and *in vivo* studies showed an AUC_{0-24}/MIC ratio of 865 for a 1-log kill of *C. albicans* for caspofungin. The epidemiological cutoff value for *C. albicans* is 0.125 mg/liter. Therefore, an AUC of approximately 100 mg · h/liter is sufficient for the treatment of susceptible *C. albicans* species. Furthermore, this AUC value is in line with the AUC of 98 mg · h/liter that was seen in healthy volunteers receiving the standard dose of caspofungin (14–16). A reduction of at least 20% relative to the target AUC_{0-24} (i.e., AUC_{0-24} of < 79 mg · h/liter) was considered a clinically relevant reduction (46, 48). In patients with an AUC_{0-24} of < 79 mg · h/liter, the caspofungin dose was increased. In case of a 20 to 40% lower AUC_{0-24} , the dose was increased by 40%, and in case of a $> 40\%$ lower AUC_{0-24} , the caspofungin dose was doubled. If the caspofungin dose was adjusted, the AUC_{0-24} was reevaluated 3 days (± 1 day) after dose adjustment. When target exposure was attained, trough levels were measured every 3 days during treatment on the ICU, with a maximum of 28 days. This enabled the evaluation of potential fluctuations in caspofungin concentration over time. In case of an infection with a fluconazole-susceptible *Candida* strain, antifungal treatment could be switched to fluconazole (step-down therapy), as judged by the attending physician.

In case an echinocandin was indicated, treatment with caspofungin was continued. Mortality was assessed at day 28 after the start of the caspofungin treatment.

Data collection. Patient data were collected through review of the medical records using a standardized case report form. Demographic and clinical data were collected, including age, race, gender, weight, underlying condition, reason for ICU admission, whether or not receiving continuous venovenous hemofiltration (CVVH), *Candida* species and localization, and the *Candida* score (49). Vital signs (temperature, blood pressure, heart rate, respiratory rate, and oxygenation) and laboratory parameters (leukocyte count, C-reactive protein, albumin, bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, γ -glutamyl transpeptidase, serum electrolytes, serum urea, and serum creatinine concentration) were routinely measured on the ICU. These parameters were used to calculate disease severity scores on the day that the first AUC_{0-24} of caspofungin was obtained, including the acute physiology and chronic health evaluation II (APACHE II) (50) and APACHE IV (51) scores, the simplified acute physiology score (SAPS3) (52), and the sepsis-related organ failure assessment (SOFA) (53). Furthermore, data on caspofungin dose adjustments, duration of treatment with caspofungin, and relevant comedication were recorded. The potential causal relationship of adverse events with the use of caspofungin was analyzed by the attending physician and the local investigator using the Naranjo adverse drug reaction probability scale (25).

Pharmacokinetic and statistical analyses. The caspofungin AUC_{0-24} was calculated using the log-linear trapezoidal rule with KINFIT, MWPharm 3.80 (Mediware, the Netherlands) (54). A two-compartment model based on the observed caspofungin concentrations was created in MWPharm using the KINPOP module with an iterative 2-stage Bayesian procedure. As a starting point for the model, pharmacokinetic parameters, including the clearance (CL), volume of distribution in the central compartment (V_1), volume of distribution in the peripheral compartment (V_2), and half-lives ($t_{1/2}$) for distribution and elimination, were derived from those in the literature (46). Based on the initial model and the patient data, a population pharmacokinetic model for our population was parameterized. Subsequently, individual pharmacokinetic parameters were determined for each included patient from fitting the model to the patient data. Interindividual variability of the pharmacokinetic parameters was assumed to be log-normally distributed, and an assay error of 0.1 mg/liter (lower limit of quantification) plus 0.15 times the measured concentration (mg/liter) was taken into account. Individual pharmacokinetic parameters were used to describe the medians and ranges for the pharmacokinetic parameters in this population. Continuous covariates included age, weight, length, and creatinine clearance of the patient and the caspofungin dose. Categorical covariates included the gender of the patient. Finally, we used the individual pharmacokinetic data in combination with the population pharmacokinetic model to derive at which dose the target exposure of ≥ 98 mg · h/liter was reached.

We assessed the correlation of the caspofungin AUC_{0-24} with the caspofungin dose, corrected for the weight of the patient (mg/kg/day, total body weight of the patient at hospital admission), with factors that can influence the pharmacokinetics of caspofungin, such as the patient's age, liver enzymes, albumin concentration, and disease severity score. Furthermore, we compared the caspofungin AUC_{0-24} between patient groups with different gender, different race, whether or not receiving CVVH, the presence of sepsis, and interacting comedication. A Spearman correlation coefficient was calculated to determine correlations between two continuous variables. For comparing two groups, the Mann-Whitney U test was used. All statistical analyses were performed using SPSS Statistics for Windows, version 22.0 (IBM SPSS, Armonk, NY). A *P* value of <0.05 was considered statistically significant.

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