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Pharmacokinetics and optimal exposure of antifungal drugs in critically ill patients

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Chapter 8

The exposure and optimal dose of caspofungin in critically ill patients

Abstract

Background: Echinocandins, such as caspofungin, are recommended as primary therapy for invasive candidiasis (IC) in critically ill patients. The inter- and intra-individual variability in caspofungin trough concentration appears to be high in patients in the Intensive Care Unit (ICU).

Methods: A multicenter prospective intervention study in patients with (suspected) IC was conducted at the ICU departments of 2 hospitals in the Netherlands, from November 2013 to December 2014. Patients received caspofungin according to the Summary of Product Characteristics and the exposure was determined on day 3 of treatment. The area under the concentration-time curve (AUC) over 24 hours was used as a measure of the exposure, where an AUC of 98 mg*h/L was established as an adequate exposure. In case of reduced exposure (i.e. $\geq 20\%$ reduction in AUC), the caspofungin dose was increased and the exposure was re-evaluated.

Results: By the time of this interim analysis, 10 patients were included in the study. The median initial caspofungin AUC was 72.9 mg*h/L (interquartile range, 66.3 to 87.1 mg*h/L). The AUC was $> 20\%$ below 98 mg*h/L in 6 out of 10 patients. Multiple linear regression analysis showed a positive association of the caspofungin AUC with the caspofungin dose (mg/kg/day) ($P = 0.007$) and the albumin concentration ($P = 0.079$).

Conclusions: The AUC of caspofungin in ICU patients in this study was low compared with healthy volunteers and other (non-) critically ill patients. Further research is needed to provide evidence for the development of new dosing recommendations for this patient group.

8.1 Introduction

Invasive candidiasis (IC) is an important cause of morbidity and mortality in immunocompromised and critically ill patients. Patients in intensive care units (ICU) are especially at risk of IC due to the presence of risk factors, such as the use of a central venous catheter, parental nutrition, renal failure, mechanical ventilation, previous broad spectrum antibiotic therapy, immunosuppression, neutropenia, or a

recent major surgery [1,2]. IC occurs in approximately 10% of the ICU patients, representing up to 15% of all nosocomial infections [1]. A crude mortality of 31 to 61% is found in adult patients with IC, and IC is associated with a prolonged hospital stay and increased costs [3–7].

Prompt initiation of effective antifungal therapy in the appropriate dosage is required to improve outcome in patients with IC [8,9]. 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 IC in critically ill patients [10,11]. In healthy volunteers receiving the standard dose of caspofungin, the mean area under the concentration-time curve (AUC) over 24 hours was 98 (88–108) mg*hr/L [12–14]. In critically ill patients, the pharmacokinetics and hence the plasma concentration of a drug may be influenced by altered drug distribution and clearance [15–19]. Inter- and intra-individual variability in caspofungin trough concentration appeared to be high in ICU patients [20]. Factors that were associated with low caspofungin plasma concentrations were body weight > 75 kg and hypoalbuminemia, which is present in up to 60% of the ICU patients [20,21]. Capillary permeability, third spacing, and multi organ failure may also influence the caspofungin concentration in ICU patients [10]. Furthermore, plasma concentrations of caspofungin might be influenced by disease severity [8,9].

The primary objective of this study was to determine the optimal dose of caspofungin in relation to adequate exposure in critically ill patients. Secondary objectives were to establish the pharmacokinetic parameters of caspofungin in critically ill patients and to assess the relation between the plasma concentration of caspofungin and disease severity.

8.2 Methods

8.2.1 Study design

This multicenter prospective intervention 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 December 2014. Patients were eligible for inclusion if the following criteria were met: (1) age \geq 18 years, (2) admission to the ICU department, (3) (suspected) invasive candidiasis, and (4) treatment with caspofungin. Patients were excluded if they did not have a central venous line for blood sampling. The local ethics committee approved the study (Institutional Review Board protocol no. 2012-371) and the study was registered at ClinicalTrials.gov (NCT 01994096). Written informed con-

sent was obtained from the patient or the legal representative of the patient before any study-related procedures were performed.

Caspofungin was administered once daily by intravenous infusion over 1 hour according to the Summary of Product Characteristics (SPC) of caspofungin [22]. The recommended dose regimen of caspofungin consists of an intravenous loading dose of 70 mg on day 1, followed by a daily maintenance dose of 50 mg for patients ≤ 80 kg and 70 mg for patients > 80 kg. In patients with impaired hepatic clearance, a dose reduction to 35 mg per day is recommended [22]. Steady state of caspofungin is reached on the first day after the loading dose [14]. On day 3 (± 1 day), blood samples were taken just before administration of caspofungin and 1, 2, 3, 4, 6, 8, 12, and 24 hours after the start of the infusion, to determine the AUC over 24 hours in steady state and other pharmacokinetic parameters of caspofungin. The AUC was used as a measure for the exposure, where an AUC of 98 mg*h/L was established as an adequate exposure [12–14]. An AUC value below 79 mg*h/L (i.e. $\geq 20\%$ reduction) was considered as a clinically relevant reduced exposure [22, 23] and in this case the caspofungin dose was increased. In case of a decline in AUC of 20 to 40% the dose was increased with 40%, and in case of a decline in AUC $> 40\%$, the caspofungin dose was doubled. If the caspofungin dose was adjusted, the AUC was determined on day 3 (± 1 day) after dose adjustment. When the patient was on an adequate dose regimen, trough levels were followed every 3 days during treatment on the ICU, with a maximum of 28 days, to evaluate potential fluctuations in caspofungin concentration over time. Mortality was assessed at day 28 after the start of the caspofungin treatment.

8.2.2 Data collection

Caspofungin plasma concentrations were determined within 24 hours, using a validated liquid chromatography-tandem mass spectrometry assay [24]. Non compartmental analysis (KINFIT, MWPharm 3.60, Medeware, the Netherlands [25]) was used to calculate the pharmacokinetic parameters, including the clearance (CL), volume of distribution (V_d), half life ($t_{1/2}$), and the AUC over 24 hours, which was calculated using the log-linear trapezoidal rule. 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, sex, weight, underlying condition, reason for ICU admission, presence of renal replacement therapy, *Candida* species, site of infection, and the *Candida* score [26]. Vital signs (temperature, blood pressure, heart rate, respiratory rate, oxygenation) and laboratory parameters (leukocyte count, C-reactive protein, albumin, bilirubin, alkaline phosphatase, aspartate aminotransaminase (ASAT), alanine aminotransaminase (ALAT), γ -glutamyl transpeptidase, serum electrolytes, serum urea, and serum creatinine

concentration) were routinely measured on the ICU. Disease severity scores were calculated on the day the first AUC of caspofungin was obtained, including the acute physiology and chronic health evaluation (APACHE II [27] and APACHE IV [28]), the simplified acute physiology score (SAPS 3 [29]), and the sepsis-related organ failure assessment (SOFA [30]). Medical data were recorded on caspofungin dose adjustments, duration of treatment with caspofungin, and comedication. Suspected adverse events were reported, in accordance with Good Clinical Practice, and a potential causal relationship with the use of caspofungin was established by the physician of the patient and the local investigator using the Naranjo adverse drug reaction probability scale [31].

8.2.3 Statistical analysis

For the univariate analysis, a Spearman correlation coefficient was calculated to determine correlations between 2 continuous variables. For comparing 2 or more groups, the Mann-Whitney U test and Kruskal-Wallis test were used. We assessed the correlation of the caspofungin AUC with the caspofungin dose (mg/kg/day) and with factors that can influence the pharmacokinetics of caspofungin, such as the patients age, weight, liver test results, albumin concentration, and with disease severity scores. Furthermore, we compared the caspofungin AUC between patient groups with different sex, race, the presence of dialysis, and interacting comedication. To assess the relationship between the caspofungin exposure and several explanatory variables, variables with a P-value of < 0.10 from the univariate analysis and variables that potentially can influence the caspofungin exposure were included in the multiple linear regression analysis. Multiple linear regression analysis, with the AUC of caspofungin as dependent variable, was performed with backward analysis, thereby removing non-significant variables, starting with the one with the highest P value. All statistical analyses were performed using SPSS for Windows, version 22.0 (IBM SPSS, Chicago, Illinois). A P value < 0.05 was considered statistically significant.

8.3 Results

By the time of this interim analysis, 10 patients were included in the study and their medical records were reviewed. The mean age of the patients was 53 years (range, 25 - 83 years), 6 patients were male and 7 patients were Caucasian. The patients' characteristics are shown in Table 8.1. The mean stay on the ICU was 18.1 days (range 4 - 42 days), and 5 patients received continuous veno-venous hemofiltration (CVVH). The mean APACHE II was 19 (range, 9 - 32), the mean APACHE IV was 102.4 (range, 62 - 135), the mean SAPS 3 was 58.1 (range, 31 - 74), and the

mean SOFA was 9.1 (range, 3 - 14). Two patients had candidemia and 8 patients had suspected invasive candidiasis based on culture results in abdominal fluid in 2 patients, pus in a closed space in 2 patients, sputum in 2 patients, and in pleural fluid and a central venous catheter tip in 1 patient each. The causative pathogen was *Candida albicans* in 7 patients, followed by *C. glabrata* in 2 patients, and a yeast not specified in 1 patient. The mean candida score was 2.7 (range, 1.8 - 4.0).

The mean duration of treatment with caspofungin was 6.9 days (range, 3 - 15 days). Four patients received hydrocortisone, 2 patients received prednisolone, 1 patient received efavirenz, 1 patient received tacrolimus and mycophenolate, and 1 patient received fluconazole as comedication. Caspofungin was discontinued because empirical treatment was no longer indicated in 4 patients, antifungal treatment was continued with fluconazole due to a cultured *C. albicans* sensitive to fluconazole in 3 patients, switch to amphotericin B in 2 patients (1 patient lack of efficacy, 1 patient possible retinal involvement), and because 1 patient died. At day 28 after the start of the treatment with caspofungin, 1 patient was deceased. Liver enzymes increased in 3 patients during treatment with caspofungin. According to the Naranjo adverse drug reaction probability scale there was a possible relation with the use of caspofungin (score of 2 out of 13 for all 3 patients).

8.3.1 Caspofungin pharmacokinetics and exposure

The pharmacokinetic parameters of caspofungin on day 3 of the treatment are shown in Table 8.2. The initial median AUC over 24 hours of caspofungin was 72.9 mg*h/L (interquartile range [IQR], 66.3 - 87.1 mg*h/L). The mean plasma concentration-time curve is shown in Figure 8.1. The caspofungin AUC showed the best association with the caspofungin concentration 8 hours after the start of the infusion (correlation coefficient 0.954; $P < 0.001$) and 12 hours after the start of the infusion (correlation coefficient 0.953; $P < 0.001$). The correlation coefficient of the AUC with the trough concentration (24 hours after the start of the infusion) was 0.839; $P < 0.001$. When patients were on an adequate dose regimen, caspofungin trough concentrations were determined (in 5 patients) and were stable over time.

The AUC was $> 20\%$ below 98 mg*h/L in 6 patients (Table 8.1). Two of these patients received a caspofungin dose of 35 mg per day due to severe liver failure or liver cirrhosis. In 3 of the 6 patients, the caspofungin dose was increased with 40% where after the exposure was adequate. In the other 3 patients, caspofungin was discontinued before the second AUC could be determined. The AUC of caspofungin showed no significant correlation with the patients' age, weight, liver test results, albumin concentration, caspofungin dose, and disease severity scores. Furthermore, the caspofungin AUC was not significantly different in patients with different sex, race, the presence of dialysis, or interacting comedication. In the multiple

Table 8.1: Patient characteristics and caspofungin exposure. Abbreviations: AUC_{0-24} , area under the concentration-time curve over 24 hours; APACHE, acute physiology and chronic health evaluation; ICU, intensive care unit.

Patient	Gender	Age (yrs)	Weight (kg)	Underlying condition	Reason for ICU admission	APACHE II score	Caspofungin dose (mg)	AUC_{0-24} (mg* h/L)	Caspofungin dose 2 (mg)	AUC_{0-24} 2 (mg* h/L)
1	Female	51	60	Liver cirrhosis, colectomy	Anuria, ascites	22	35	67.0	50	113.6
2	Female	50	100	Kidney stone extraction	Urosepsis	14	70	101.9	-	-
3	Male	70	95	HIV, PCP pneumonia	Respiratory insufficiency	32	70	81.8	-	-
4	Female	39	48	Spina bifida, pressure ulcers	Septic shock	9	50	109.3	-	-
5	Female	50	79	Mycotic aneurysm	Risk for rupture	9	50	71.6	-*	-
6	Male	83	80	Sigmoid carcinoma, resection	Hemodynamic instability, sepsis	24	50	62.6	-*	-
7	Male	25	70	Mizuno disease	Liver and renal failure, urosepsis	18	35	74.2	50	109.3
8	Male	33	94	Asthma with bronchiectasis, lung transplantation	Systemic inflammatory response syndrome	19	70	68.0	100	127.8
9	Male	66	74	Rheumatoid arthritis, tuberculosis	Respiratory insufficiency	24	50	82.1	-	-
10	Male	66	76	Oesophageal carcinoma, resection	Respiratory insufficiency	19	50	64.3	-*	-

* Caspofungin was discontinued.

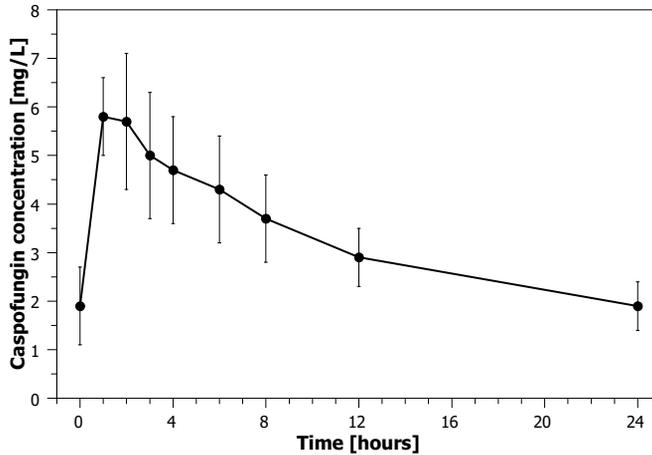


Figure 8.1: Caspofungin concentration-time curve on day 3 of the treatment (mean with standard deviation).

linear regression analysis, variables obtained by the univariate analysis (caspofungin dose (mg/kg/day), ASAT, ALAT) and variables that can theoretically indicate altered pharmacokinetics (albumin concentration [20]) were included. The multiple linear regression analysis showed a significant and positive association of the initial caspofungin AUC with the caspofungin dose (mg/kg/day) (effect 93.533 (95% confidence interval [CI], 35.386 - 151.680), $P = 0.007$) and the albumin concentration (effect 1.729 (95% CI, -0.261 - 3.719); $P = 0.079$).

8.4 Discussion

The median AUC of caspofungin found in this study was 72.9 mg*h/L. The AUC was low compared to the AUC of 98 (88 - 108) mg*hr/L established in healthy volunteers [12-14], an AUC of 110 - 117 mg*hr/L found in non-critically ill patients [32], and an AUC of 88.7 mg*hr/L (IQR, 72.2 - 97.5 mg*h/L) recently established in ICU patients [33]. The V_d was larger and the C_{max} of caspofungin was lower compared to healthy volunteers and patients in other studies [13,14,32,33]. The $t_{1/2}$ was comparable to the $t_{1/2}$ in other ICU patients [33] and was longer than the $t_{1/2}$ in healthy volunteers [13,14]. The low AUC of caspofungin in our study is therefore most likely the result of a larger V_d . Fluid extravasation as a result of endothelial dysfunction and capillary leak, edema in sepsis, ascites, fluid resuscitation, and hypoalbuminemia are factors that are often present in ICU patient and can all lead to an enlarged

Table 8.2: Pharmacokinetic parameters of caspofungin ($n=10$). Abbreviations: AUC_{0-24} , area under the concentration-time curve over 24 hours; C_{max} , the maximal concentration; C_{min} , and minimal concentration; CL, clearance; IQR, interquartile range; V_d , volume of distribution; $t_{1/2}$, half life.

Parameter	Median (IQR)
AUC_{0-24} (mg*h/L)	72.9 (66.3 - 87.1)
C_{min} (mg/L)	1.7 (1.4 - 2.2)
C_{max} (mg/L)	6.4 (6.0 - 7.5)
CL (L/h)	0.45 (0.29 - 0.52)
V_d (L)	10.01 (8.27 - 11.78)
$t_{1/2}$ (h)	17.02 (14.54 - 20.30)

V_d and a lower drug concentration [16–18].

Multiple linear regression analysis showed that the initial caspofungin AUC was significantly associated with the caspofungin dose in mg/kg/day. Furthermore, the 3 patients between 75 and 80 kg who received a dose of 50 mg, according to the SPC of caspofungin, all had AUCs (> 20%) below the AUC of 98 mg*h/L, the established set-point for adequate exposure. If this finding can be confirmed in subsequent study participants, this could indicate that the currently used cut-off value of > 80 kg for a higher maintenance dose of 70 mg may be too high and more patients should receive the higher maintenance dose of 70 mg once daily. 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 between the standard and high-dose regimens [34–38]. Furthermore, a positive correlation of the caspofungin AUC with the albumin concentration was found. Caspofungin is extensively bound to albumin [22] and hypoalbuminemia can lead to an increased drug V_d and an enhanced clearance of the free drug [39]. The association with both weight and albumin concentration was in agreement with an earlier study of caspofungin trough concentrations in ICU patients [20]. Although one study showed a lower response rate among patients with a higher APACHE II [40], the AUC of caspofungin was not associated with disease severity scores, which was in agreement with recent findings [33,41].

Two patients in our study suffered from severe liver damage or cirrhosis and received a daily caspofungin dose of 35 mg according to the SPC of caspofungin. The AUC was low in both patients and the dose was increased to 50 mg, after which liver enzymes remained stable. This finding is in accordance with two case reports

where 50 and 70 mg was given to patients with moderate hepatic dysfunction and where the exposure was similar to the exposure in healthy volunteers [42,43]. These findings illustrate the fact that at the bed site, liver drug metabolism may be underestimated in the presence of liver test abnormalities or evidence of cirrhosis. Combined with the case reports, our findings suggest that these patients should perhaps initially receive an empiric maintenance dose of 50 mg per day instead of 35 mg, 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.

A limitation of this study is the small number of patients. However, the study is ongoing and more patients will be included to obtain a more reliable result. Furthermore, the minimal inhibitory concentration (MIC) of the *Candida* species was only determined in 1 patient. Since most patients had suspected IC based on culture data from non-sterile sites, the MIC of the *Candida* species was not determined in these patients. *In vivo* studies have demonstrated that the AUC/MIC is a good descriptor of the echinocandin exposure-response relationship. For caspofungin an AUC_{0-24h}/MIC of 865 was established for a 1 log kill of *C. albicans* and an AUC_{0-24h}/MIC of 450 for a 1 log kill of *C. glabrata* [12]. Considering the AUC of approximately 100 mg*h/L, the AUC/MIC target can be reached when *C. albicans* species have MIC values ≤ 0.125 and *C. glabrata* have MIC values ≤ 0.25 . The median AUC of the patients in this study was lower, however, in case of low MIC values, the AUC/MIC can still be sufficient with lower AUC values.

Since 60% of the patients had a low caspofungin exposure, TDM can be of added value for the treatment with caspofungin in ICU patients. TDM can help to ensure timely target attainment of caspofungin in these patients. Since the crude mortality is still up to 61% in critically ill patients with IC, we believe that TDM is a powerful tool to optimize the antifungal treatment with caspofungin. A prospective randomized clinical trial should be carried out to determine if therapeutic interventions, to increase the caspofungin exposure, result in an improved treatment outcome.

8.5 Conclusion

In conclusion, the AUC of caspofungin in ICU patients in this study was low compared with healthy volunteers and other (non-) critically ill patients. The caspofungin AUC was significantly associated with the caspofungin dose (mg/kg/day) and with the albumin concentration.

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