Pharmacokinetics of caspofungin in ICU patients


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Objectives: Caspofungin is used for treatment of invasive fungal infections. As the pharmacokinetics (PK) of antimicrobial agents in critically ill patients can be highly variable, we set out to explore caspofungin PK in ICU patients.

Methods: ICU patients receiving caspofungin were eligible. Patients received a loading dose of 70 mg followed by 50 mg daily (70 mg if body weight >80 kg); they were evaluable upon completion of the first PK curve at day 3. Additionally, daily trough samples were taken and a second PK curve was recorded at day 7. PK analysis was performed using a standard two-stage approach.

Results: Twenty-one patients were evaluable. Median (range) age and body weight were 71 (45–80) years and 75 (50–99) kg. PK sampling on day 3 (n=21) resulted in the following median (IQR) parameters: AUC0–2 488.7 (72.2–97.5) mg.h/L; Cmin 2.15 (1.40–2.48) mg/L; Cmax 7.51 (6.05–8.17) mg/L; V 7.72 (6.12–9.01) L; and CL 0.57 (0.54–0.77) L/h. PK sampling on day 7 (n=13) resulted in AUC0–2 4107.2 (90.4–125.3) mg.h/L, Cmin 2.55 (1.82–3.08) mg/L, Cmax 8.65 (7.16–9.34) mg/L, V 7.03 (5.51–7.73) L and CL 0.54 (0.44–0.60) L/h. We did not identify any covariates significantly affecting caspofungin PK in ICU patients (e.g. body weight, albumin, liver function). Caspofungin was well tolerated and no unexpected side effects were observed.

Conclusions: Caspofungin PK in ICU patients showed limited intraindividual and moderate interindividual variability, and caspofungin was well tolerated. A standard two-stage approach did not reveal significant covariates. Our study showed similar caspofungin PK parameters in ICU patients compared with non-critically ill patients.

Keywords: antifungal drugs, PK, echinocandins, intensive care units

Introduction

Fungal infections are the fourth most common cause of nosocomial infections in ICU patients and account for about one in five of all infections in critically ill patients.1 Of these fungal infections, the vast majority are caused by Candida spp. and Aspergillus spp.1 Invasive fungal disease has significant negative impacts on mortality and the durations of ICU and hospital stay.2,3

Caspofungin belongs to the class of echinocandins. These are currently regarded as primary treatments for invasive candidiasis or candidaemia in non-neutropenic and neutropenic patients with moderate to severe illness or recent exposure to azoles.4 Caspofungin can also be used for treatment of invasive aspergillosis when patients are refractory to or intolerant of voriconazole.5 Echinocandins work by inhibiting synthesis of β-(1,3)-D-glucan, an essential component of Candida and Aspergillus cell walls.

The pharmacokinetics (PK) of antimicrobial agents in ICU patients can be highly variable and different from those in other patient populations. Factors associated with alterations in PK include changes in organ function (renal and hepatic dysfunction), V, use of extracorporeal CL techniques and the use of interacting drugs.6 Also, CL may be subject to increased intersubject and intrasubject variability due to changes in protein binding in the setting of hypoalbuminaemia, which has an incidence of ~40%–50% in this patient population.7,8

Previous studies showed that the PK parameters of caspofungin were influenced by hepatic impairment, body weight and hypoalbuminaemia: caspofungin β-phase half-life and AUC0–∞
were increased in patients with hepatic impairment after a single 70 mg dose. PK parameters were comparable when patients with mild hepatic impairment received a reduced daily dose of 35 mg compared with controls receiving a regular daily dose of 50 mg.\footnote{9} Body weight >75 kg in surgical ICU patients was shown to decrease $C_{\text{min}}$, whilst another study showed that increases in body weight led to increases in V and CL and decreases in $C_{\text{max}}$ and AUC.\footnote{10,11} Hypoaalbuminaemia also influenced caspofungin PK in surgical ICU patients; $C_{\text{min}}$ was higher in patients with albumin concentrations $>$23.6 g/L than in patients with lower albumin concentrations.\footnote{10} Renal dysfunction ranging from moderate to end-stage renal disease increased caspofungin exposure by 30%–50% after single-dose administration.\footnote{12} The effect on caspofungin exposure after multiple dosing in a cohort with alterations in the PK behaviour of caspofungin. The objective of this trial was to describe the PK of caspofungin in ICU patients and determine the influence, if any, of previously described covariates (body weight, hypoaalbuminemia and hepatic impairment), as well as yet unknown covariates (such as the disease scores APACHE II and SOFA, renal function and extracorporeal CRRT techniques).

Methods

Study design

This open-label, Phase IV, multiple-dose, multicentre observational trial was conducted in compliance with the Declaration of Helsinki during 2012 and 2013. The study was carried out in the Netherlands in accordance with the applicable rules concerning the review of research ethics committees (the primary review was conducted by the Arnhem–Nijmegen Ethics Committee) and informed consent. All patients admitted to the ICU in two university medical centres and three community hospitals in the Netherlands receiving caspofungin for suspected or proven fungal infection or as prophylaxis were eligible if they were at least 18 years of age at the start of caspofungin therapy, started caspofungin therapy maximally 2 days before inclusion and were managed with a central venous or arterial catheter. Patients were excluded: in case of a known allergy for echinocandins or excipients; if they had HIV, hepatitis B or hepatitis C; if they had a history of drug or alcohol abuse; or if they had previously participated in this study. An empirical size of 20 evaluable patients was chosen to adequately define the PK of caspofungin and to be able to identify at least two covariates.\footnote{13} Patients were treated with caspofungin at a dose according to its product information.\footnote{14} A loading dose of 70 mg on the first day of therapy was given, followed by 50 mg daily or a dose adjusted according to body weight (70 mg daily if body weight $>$80 kg) or hepatic dysfunction (35 mg daily if the Child–Pugh class was B or C). Dose deviations were allowed upon clinical decision. Caspofungin was administered by intravenous infusion over 1 h. Patients were treated with caspofungin for as long as considered clinically relevant by the treating physician. However, for the purpose of PK, the maximum duration of this study was limited to 14 days of caspofungin treatment and 3 days after cessation of therapy.

Baseline parameters

Upon inclusion, the following parameters were registered: gender, age, race, weight, BMI, lean body mass (LBM; formula of Jammahosatian et al.\footnote{15}), indication for ICU admission, caspofungin indication, clinical characteristics, and haematological parameters. In addition, APACHE II score (within 24 h of ICU admission), SOFA score and Child–Pugh class, comedication and (type of) renal replacement therapy were recorded. During the study, body weight, BMI, LBM, SOFA score and Child–Pugh class were recorded on days on which PK curves were drawn. Comedication (dexamethasone, rifampicin, phenytoin, carbamazepine, cyclosporin A and tacrolimus), (change in) clinical characteristics and renal replacement therapy were recorded daily.

Chemistry

Blood samples were obtained three times a week and on days PK curves were drawn for determination of biochemical and haematological parameters, including serum electrolytes, bilirubin, alkaline phosphatase, aspartate aminotransaminase, alanine aminotransaminase, $\gamma$-glutamyl transpeptidase, lactate dehydrogenase, total protein, albumin, glucose, total cholesterol, triglycerides, blood urea nitrogen, creatinine, uric acid and C-reactive protein. Haemoglobin, white blood cell differential counts and platelet counts were also determined.

Vital signs

Vital signs (temperature, blood pressure, pulse rate and arterial O$_2$ saturation) were monitored immediately before and after administration and on days of PK curves every hour for 4 h after the start of infusion.

PK sampling

A PK curve was drawn on day 3 (±1) of treatment at $t=0$ (pre-dose) and 0.5, 1, 2, 4, 6, 8, 12, 16, 20 and 24 h post-infusion. For quantification of intradividual variation a second PK curve was drawn on day 7 (±1) at $t=0$ (pre-dose) and 1, 4, 8, 12 and 24 h post-infusion. Additional trough samples were drawn daily on all other study days up to 14 days of therapy and until 3 days after cessation of caspofungin therapy. Blood samples (2 mL) were collected in lithium–heparin-containing tubes and centrifuged for $\approx$5 min at 1900 g within 48 h of collection. Plasma was aspirated and transferred into plastic tubes and stored at $-80^\circ$C immediately after aspiration until analysis. Patients were eligible if the first PK curve was completed.

Safety

Adverse events were reported in addition to medical observations on all study days. A potential causal relationship with caspofungin was determined by the local investigators.

Analytical method

Caspofungin concentrations were determined by a validated UPLC method. Samples were pretreated with a protein precipitation solution. The dynamic range of the assay for caspofungin was 0.1–20 mg/L, with an accuracy range ($n=15$), which was concentration dependent, of 99.0%–101.8%. Intraday precision varied between 1.1% and 4.2% and interday precision varied between 0% and 1.1%.

PK analysis

A standard two-stage approach was used for analysis of the data. Non-compartmental analysis in Phoenix (version 6.3) was used for calculation of PK parameters (AUC$_{0-24}$, $C_{\text{max}}$, $C_{\text{min}}$, CL, V and $t_{1/2}$). The AUC was determined using the log-linear trapezoidal rule. The elimination
rate constant was determined by linear regression of the terminal points of
the log-linear plasma concentration time curve. Values of C_{\text{max}} were
directly observed from the data.

Table 1. Demographic and other characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Evaluable ICU patients (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>13 (61.9)</td>
</tr>
<tr>
<td>female</td>
<td>8 (38.1)</td>
</tr>
<tr>
<td>Age (years), median (range)</td>
<td>71 (45 – 80)</td>
</tr>
<tr>
<td>Caucasian, n (%)</td>
<td>17 (81.0)</td>
</tr>
<tr>
<td>Weight (kg), median (range)</td>
<td>75 (50–99)</td>
</tr>
<tr>
<td>BMI (kg/m²), median (range)</td>
<td>24.9 (19.0–36.4)</td>
</tr>
<tr>
<td>Elderly (≥65 years), n (%)</td>
<td>21 (100)</td>
</tr>
</tbody>
</table>

Clinical characteristics

| Post-abdominal surgery, n (%) | 8 (38.1) |
| Kidney function/renal replacement therapy, n (%) | 7 (33.3) |
| MDRD >50 mL/min/1.73 m² | 5 (23.8) |
| MDRD 31 – 50 mL/min/1.73 m² | 4 (19.0) |
| CVVH | 4 (19.0) |
| Hepatic dysfunction, Child–Pugh B, n (%) | 1 (4.8) |
| psoalbuminaemia, n (%) | 25 (13 – 47) |
| ≤20, n (%) | 7 (33.3) |
| >20, n (%) | 14 (66.7) |

Microbiological characteristics

| Infection location, n (%) | 16 (76.2) |
| normally sterile location | 4 (19.0) |
| blood | 1 (4.8) |
| Species, n (%) | 18 (90.0) |
| Candida spp. | 7 (38.9) |
| non-albicans | 1 (5.6) |
| mixed | 10 (55.6) |
| albicans | 10 |
| non-albicans (not further determined) | 8 |
| glabrata | 7 |
| tropicalis | 4 |
| parapsilosis | 1 |
| Aspergillus spp. | 1 (5.0) |
| Candida and Aspergillus spp. | 1 (5.0) |

Mortality was 48%. Baseline demographics and clinical character-
istics of the 21 evaluable patients are shown in Table 1.

Results

Patients

Twenty-four patients were included in the ICUs of five Dutch
hospitals. Of these patients, 21 completed the first PK curve on
day 3; three patients died before completion of this PK curve. For
the 21 evaluable patients, mean APACHE II score was 25.7 (95%
CI 21.2 – 30.1), mean SOFA score was 8.7 (95% CI 6.5 – 10.9), aver-
gain length of ICU stay was 29 (95% CI 17 – 41) days and hospital
mortality was 48%. Baseline demographics and clinical character-
istics of the 21 evaluable patients are shown in Table 1.

Patients were treated with caspofungin as prophylaxis (n = 1),
pre-emptive treatment or as treatment for suspected or proven
Candida or Aspergillus infections (n = 19) or for a combined
Candida/Aspergillus infection (n = 1) (Table 1). The median dura-
tion of caspofungin therapy was 9 days (range 4 – 14 days).

Statistical analysis

Linear regression was performed on the log-transformed AUCs of days 3
and 7 independently and other PK parameters (CL and V). Covariates of
potential impact on PK were selected based on visual inspection of the
plot of the covariate versus the PK parameter of interest. Next, the follow-
ing covariates were formally tested: body weight, albumin, liver function,
APACHE II, SOFA and Child–Pugh class. A paired t-test on the log-
transformed AUC for day 7 compared with day 3 was performed in SPSS
20.0 (SPSS Inc., Chicago, IL, USA). A P value <0.05 was considered
significant.

Table 2. Caspofungin PK parameters on days 3 and 7 [median (IQR)]

<table>
<thead>
<tr>
<th>PK curve day 3 (n = 21)</th>
<th>PK curve day 7 (n = 13)</th>
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</thead>
<tbody>
<tr>
<td>AUC_{0–24} (mg-h/L)</td>
<td>88.7 (72.24 – 97.54)</td>
</tr>
<tr>
<td>CL (L/h)</td>
<td>0.57 (0.54 – 0.77)</td>
</tr>
<tr>
<td>V (L)</td>
<td>7.72 (6.12 – 9.01)</td>
</tr>
<tr>
<td>C_{\text{min}} (mg/L)</td>
<td>2.15 (1.40 – 2.48)</td>
</tr>
<tr>
<td>C_{\text{max}} (mg/L)</td>
<td>7.51 (6.05 – 8.17)</td>
</tr>
<tr>
<td>t_{1/2} (h)</td>
<td>15.67 (14.44 – 18.94)</td>
</tr>
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</table>

Caspofungin PK

The PK curve on day 3 was completed in 21 patients; the second
PK curve on day 7 was completed in 13 patients. Table 2 shows the PK parameters for caspofungin on days 3 and 7 of therapy.

The median AUC_{0–24} on day 3 was 88.7 (IQR 72.2 – 97.5) mg-h/L
and the median AUC_{0–24} on day 7 was 107.2 (IQR 90.4 –
125.3) mg-h/L. The mean plasma concentration–time curve for
the two PK curves is shown in Figures 1 – 3 and Figures S1 and
S2 (both available as Supplementary data at JAC Online).

The median interindividual coefficient of variation from day 6
to day 14 was 45.6% (CI 41.3 – 53.0) and the median intraindivi-
dual coefficient of variation over the same period was 14.0%
(n = 13; 95% CI 8.6 – 17.1).

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The AUC_{0–24} for day 7 was significantly higher than that for day 3 for patients who received the same dose over time (n = 11, \( P = 0.032 \)). The geometric mean AUC_{day 7}/AUC_{day 3} ratio was 1.13 (90% CI 1.05–1.21). In addition to this finding, visual inspection of daily trough concentrations showed a slight increase over time, as shown in Figure 4.

Covariates
Caspofungin PK parameters AUC_{0–24}, CL and V were not influenced by covariates (gender, body weight and the related parameters BMI and LBM, APACHE II score, SOFA score, Child–Pugh class, liver function, renal function, renal replacement therapy and serum albumin; n = 21 patients per variable) as analysed with a standard two-stage approach. Of note, four patients with a body weight >80 kg received a caspofungin dose of 70 mg daily, in contrast to three patients weighing >80 kg who received 50 mg daily (body weight 104, 86 and 85 kg, respectively) and two patients who received 70 mg daily while weighing <80 kg (72 and 74 kg, respectively). Furthermore, all patients were in Child–Pugh class B, indicating significant functional compromise, but only one patient received the recommended reduced dose of 35 mg daily for 3 days.

With regard to drug interactions, only one patient received interacting drugs in a time frame of 7 days prior to starting caspofungin until 3 days after cessation of therapy. This patient received a single dose of dexamethasone on the first day of caspofungin therapy.

Safety
A total of 76 adverse events were reported, of which 10 were classified as serious. The reported serious adverse events were re-bleeding (n = 1), cerebrovascular event (n = 2), septic shock (n = 2) and death (n = 5). Only one patient with a serious adverse event survived. According to the local investigators, none of these serious adverse events was related to caspofungin therapy. No actions were taken regarding caspofungin therapy. Of the remaining 66 reported adverse events, 2 were categorized as possibly related to caspofungin therapy (liver function abnormalities), but no action was taken with regard to caspofungin therapy in all patients experiencing an adverse event.

Discussion
We describe the PK of caspofungin in ICU patients and our attempt to define covariates influencing caspofungin PK. Caspofungin PK parameters appear similar in critically ill patients compared with non-critically ill patient populations and healthy subjects.\(^{3,10,16,17}\) In addition, the PK parameters of caspofungin in ICU patients were predictable and showed limited intraindividual and moderate interindividual variation at steady-state.

The PK parameters of caspofungin were not influenced by covariates (e.g. body weight, hypoalbuminaemia and hepatic impairment).

Our findings showed a statistically significantly higher AUC_{0–24} on day 7 compared with day 3, indicating that steady-state had not been reached by day 3. In addition, visual inspection of daily
trough concentrations supported the statistical finding suggesting steady-state was not yet reached on day 3. This is different from the findings of Stone et al., who calculated the geometric mean day 14/day 1 ratio to be 1.03 (90% CI 0.98–1.08). This analysis was done in eight patients and might therefore not have significant power to find a difference in exposure over time. In addition Stone et al. compared day 1 with day 14 but omitted the drop in exposure between day 2 and 6 trough concentrations. Our hypothesis is that, if day 14 was compared with day 3, this would likely result in findings similar to those reported in our study.

Observed median caspofungin PK parameters on day 7 were comparable to mean trough concentrations found in surgical ICU patients (2.55 versus 2.15 mg/L) and also to predicted mean AUC0–24, Cmin, Cmax and CL during steady-state in haematopoietic stem cell transplant patients (107 versus 117 mg h/L, 2.55 versus 3.04 mg/L, 8.65 versus 8.47 mg/L and 0.54 versus 0.45 L/h respectively). The median PK parameters on day 7 were also comparable to geometric mean parameters in healthy subjects on day 14 (AUC0–24 107 versus 100 mg h/L and Cmax 8.65 versus 9.94 mg/L). Of note, our patients received a loading dose of 70 mg followed by 50 mg daily or a dose adjusted according to body weight or hepatic impairment, in contrast to the studies by Nguyen et al. and Stone et al., where all patients received a fixed dose of 50 mg daily after a loading dose of 70 mg on the first day irrespective of body weight.

Contrary to what we expected in a heterogeneous, critically ill patient population where PK parameters are likely to be influenced by sepsis and organ failure, caspofungin PK parameters were not impacted to a clinically relevant degree. Data in the literature suggest this is different for anidulafungin, although the clinical relevance of these observations is debatable. Whereas our patient population was heterogeneous in renal function and APACHE II scores, it was relatively homogeneous in terms of hepatic dysfunction, weight and hypoalbuminaemia. The PK parameters of caspofungin seem predictable in ICU patients, irrespective of underlying disease or organ dysfunction.

Using the standard two-stage approach for PK analysis we were unable to identify any relevant covariates affecting caspofungin PK in this study. This is in contrast to suggestions made in the literature. Nguyen et al. previously reported albumin concentrations >23.6 g/L and body weight <75 kg to be predictive of higher trough concentrations. All patients in the study by Nguyen et al. received a loading dose of caspofungin of 70 mg followed by a daily dose of 50 mg. In our study, hypoalbuminaemia, body weight and other weight-derived parameters such as BMI and LBM did not reveal a significant relation with caspofungin exposure or derived parameters. This may be explained by limited variation in our population as all our patients were hypoalbuminaemic and the range in body weight was 50–99 kg upon inclusion. Another explanation could be that most of our patients weighing >80 kg received 70 mg daily conforming with product specifications; therefore the effect of body weight on AUC in this study will be influenced by the dose adjustment. Since caspofungin is highly protein bound (~96%), unbound plasma concentrations could be of interest in this patient population. Unfortunately, no unbound plasma concentrations could be determined. Therefore, we cannot suggest any implications of variability in protein binding for PK parameters.

Renal dysfunction did not correlate with higher AUC0–24 or other PK parameters in this study, in contrast to what is described in the EMA scientific discussion of caspofungin. The use of extracorporeal CL techniques in our study did not influence PK parameters either, in contrast to previous publications. Moreover, an influence of renal dysfunction would not be expected, considering the metabolic route of caspofungin.

All patients in our study were formally classified as Child–Pugh B, but no change in CL was found in comparison with other patient populations with normal liver function tests. The influence of hepatic dysfunction on the PK of caspofungin has been reported previously by Mistry et al., who showed reduced CL of caspofungin in patients with moderate to severe hepatic dysfunction (classified as Child–Pugh B or C). However, formal classification as Child–Pugh B in our patient population was mainly driven by hypoalbuminaemia and less by abnormal liver function tests associated with a decrease in metabolic capacity, since no patients were actually suffering from hepatic dysfunction. This is the first study, to our knowledge, with extensive PK scheduling on two separate days and daily trough concentrations...
PK of caspofungin in the ICU

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in a heterogeneous ICU population. Caspofungin PK parameters in ICU patients found in this study were predictable and did not appear to be influenced to a relevant extent by covariates. Previous anidulafungin PK studies have shown lower total exposure (AUC) compared with non-critically ill patients and higher intersubject variability in AUC compared with healthy subjects. Although anidulafungin is even more protein bound (>99%) than caspofungin, hypoaalbuminemia did not influence the PK of anidulafungin in ICU patients either. Renal replacement therapy does not appear to influence the PK of any of the echinocandins caspofungin, anidulafungin and micafungin in ICU patients.

In summary, the PK of caspofungin in ICU patients showed limited intra-individual and moderate inter-individual variability and caspofungin was well tolerated in this patient population. Caspofungin PK appeared to be comparable to PK in other, non-critically ill patients and a standard two-stage approach did not reveal any covariate impacting on caspofungin PK. From our research we can conclude that ICU patients do not need higher dosing compared with other reference groups. Furthermore, we strongly recommend debate about whether the Child–Pugh classification should be used to make dose adaptations of caspofungin in this specific cohort of patients, where the classification is highly impacted by albumin.

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Transparency declarations

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Supplementary data

Figures S1 and S2 are available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

References