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Pharmacokinetics of Caspofungin in Critically Ill Patients on Continuous Renal Replacement Therapy

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Caspofungin pharmacokinetics was assessed in 27 critically ill patients, including 7 on continuous venovenous hemofiltration (CVVH), 8 on continuous venovenous hemodialysis (CVVHD), and 13 not requiring continuous renal replacement therapy (CRRT). Caspofungin exposure during CRRT was very similar to that of the control group and comparable to that in healthy volunteers. Caspofungin clearance by CRRT was very low. Therefore, the standard dosage of caspofungin is probably adequate for critically ill patients undergoing CVVH or CVVHD.

Extracorporeal devices can exert hardly predictable effects on drug disposition (1–5). The echinocandin caspofungin (molecular mass, 1,093 Da) is licensed for treatment of invasive candidiasis, for empirical therapy of persistent fever during neutropenia, and for salvage therapy of invasive aspergillosis (6, 7). Caspofungin pharmacokinetics during continuous renal replacement therapy (CRRT), however, has been unknown so far. Therefore, we investigated the influence of continuous venovenous hemofiltration (CVVH) and continuous venovenous hemodialysis (CVVHD) on the pharmacokinetics of caspofungin in critically ill patients in order to assess the appropriateness of standard dosage during CRRT.

The local ethics committee approved the protocol. Written informed consent was granted by competent patients and *post hoc* consent by incompetent patients. We enrolled consecutive adult patients at a medical intensive care unit (ICU) with an indication for caspofungin.

CVVH was performed with an Aquarius system (Edwards Lifesciences, Unterschleissheim, Germany) and a 0.71-m^2 polysulfone hemofilter (Baxter PSHF 700; Minntech Corporation, Minneapolis, MN). Replacement solution (HF-Bic 35-210; Fresenius, Bad Homburg, Germany) was infused in predilution and postdilution modes. Anticoagulation was performed with enoxaparin (8). CVVHD with regional citrate anticoagulation was applied in patients at an enhanced risk of bleeding using the Multifiltrate Ci-Ca device and an Ultraflux AV 1000 S, a 1.8-m^2 polysulfone dialyzer by Fresenius. Regional anticoagulation was performed with 4% trisodium citrate, and neutralization was with 0.5 mol calcium chloride (details are given in Tables 1 and 2).

Sampling was performed on day 1 of caspofungin treatment (single dose) and at steady state on day 4 or later. Blood samples of 2 ml were drawn from an arterial line at 1, 2, 4, 8, 12, and 24 h after the start of caspofungin infusion. For patients on CRRT, ultrafiltrate/dialysate samples were taken simultaneously. In addition, blood samples from the hemofilter/dialyzer inlet and outlet were collected at 1 and 24 h.

Blood samples were centrifuged at 350 × *g* for 10 min. The storage temperature was −80°C. Caspofungin concentrations were quantified by liquid chromatography combined with mass spectrometry after protein precipitation and online purification

TABLE 1 Continuous venovenous hemofiltration[a]

Patient no.	Sampling	HRT (h)	Predilution SuR (ml/h)	Postdilution SuR (ml/h)
1	First	24.5/−17	1,000	2,000
2	First	23/−6.5	1,500	1,000
	Second	20	1,000	1,000
3	First	0	1,000	1,500
4	First	18.5/−17	1,000	1,500
5	First	−0.5	1,500	1,500
	Second	−0.5	1,500	1,000
6	First	20.5	1,500	1,500
7	Second	70/−6/−15.5	1,000	1,000

[a] HRT, hemofilter running time, which is the time from the start of hemofiltration with the respective hemofilter to the start of the study caspofungin infusion. A hemofilter running time of 0 means change of the hemofilter together with the start of caspofungin infusion. A negative hemofilter running time means that the filter was changed during sampling; the negative number depicts the time between the start of the study caspofungin infusion and the start of hemofiltration with the new hemofilter. In patients 1, 2, and 4, the hemofilter was changed once during the study; in patient 7, it was changed twice. The maximum filter running time was 72 h unless there was clotting of the filter. Predilution SuR, flow rate of replacement fluid applied in predilution mode, i.e., before the hemofilter. Postdilution SuR, flow rate of replacement fluid applied in postdilution mode, i.e., behind the hemofilter. The blood flow rate was set to 180 ml/min. Interruptions of continuous renal replacement therapy (CRRT) during sampling occurred because of diagnostic procedures such as CT scan or hemofilter clotting. Patient 7 was first on continuous venovenous hemodialysis (CVVHD) with regional citrate anticoagulation because of severe thrombocytopenia. Twenty-seven days later, on her second study day, she had been switched to continuous venovenous hemofiltration (CVVH) because her thrombocytopenia had markedly improved. For CRRT, a double-lumen dialysis catheter (Quinton Marhurkar or Joline) was inserted into a central vein.

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TABLE 2 Continuous venovenous hemodialysis[a]

Patient no.	Sampling	DRT (h)	Q_D (ml/h, (mean ± SD))
7	First	40.5	1,500 ± 0
8	First	6	2,350 ± 122
9	First	19.5	2,083 ± 41
	Second	18.5	2,000 ± 0
10	First	−1	2,500 ± 0
	Second	39	2,500 ± 0
11	First	69.5/−1.5	2,400 ± 0
	Second	44/−9	2,400 ± 0
12	First	23.5	2,000 ± 0
13	First	23.5	2,000 ± 0
14	First	67/−11	2,500 ± 0

[a] DRT, dialyzer running time, which is the time between start of continuous venovenous hemodialysis with the respective dialyzer and the start of the study caspofungin infusion. A DRT time of 0 means change of the dialyzer together with the start of caspofungin infusion. A negative dialyzer running time means that the dialyzer was changed during sampling. In patients 12 and 14, the dialyzer was changed once during the study. The maximum dialyzer running time was 72 h unless there was clotting of the dialyzer. Q_D, flow rate of dialysate (K2 by Fresenius) during the sampling. The amount of citrate applied for regional anticoagulation and the calcium dose for neutralization were guided by systemic and postfilter free calcium concentrations according to the manufacturer's guidelines. The blood flow rate was set to 80 to 120 ml/min. Interruptions of continuous renal replacement therapy during sampling, occurred because of diagnostic procedures such as CT scan or dialyzer clotting. For CRRT, a double-lumen dialysis catheter (Quinton Marhurkar or Joline) was inserted into a central vein. Patient 7 was first on CVVHD with regional citrate anticoagulation because of severe thrombocytopenia. Twenty-seven days later, on her second study day, she had been switched to CVVH because her thrombocytopenia had markedly improved. For CRRT, a double-lumen dialysis catheter (Quinton Marhurkar or Joline) was inserted into a central vein.

by solid-phase extraction (online SPE-LC-MS/MS) based on an instrumentation setup described previously (9). Quantification was based on external calibration with caspofungin and the use of an internal standard. The assay is free of matrix and drug interferences and is linear from 200 to 15,000 ng/ml, with an interday imprecision of <9.5% and an interday inaccuracy of better than ±9.0%. Pharmacokinetics was calculated by a noncompartmental model using Kinetica-2000 (InnaPhase Corporation, Champs-sur-Marne, France). The area under the concentration-time curve from time zero to 24 h (AUC_{0-24}) was computed using the log linear method whenever the concentration in a trapezoid decreased or with the trapezoidal method when the concentration increased.

The caspofungin clearance via CVVH (CL_{HF}) and CVVHD (CL_{HD}) was estimated by two methods in order to detect an eventual adsorption of caspofungin to hemofilter/dialyzer membranes: first, from the sieving coefficient (S_c) and the saturation coefficient (S_d), respectively, and second, from the difference between caspofungin concentrations in the hemofilter/dialyzer inlet and outlet ($C_{in} - C_{out}$) (Table 3) (10).

The statistical significance of eventual differences in pharmacokinetic parameters between patients on and off CRRT was evaluated by the Mann-Whitney U test with Bonferroni's correction for multiple testing.

Thirty-six plasma sample sets were obtained from 27 patients (Table 4). Assessment under both single-dose and steady-state conditions was possible for only 8 patients. Pharmacokinetic parameters were similar on and off CRRT as well as during CVVH and CVVHD (Table 5). Six sets of ultrafiltrate samples were drawn from patients on CVVH. Ultrafiltrate concentrations amounted

TABLE 3 Estimation of caspofungin clearance achieved by continuous renal replacement therapy[a]

Therapy	Parameter	Calculations
CVVH	CL_{HF} calculated from sieving coefficient S_c[b]	$S_c = C_{UF}/C_{pl}$; $CL_{HF} = S_c \cdot UFR$; $CL_{HF} = CL_{HF\ predilution} + CL_{HF\ postdilution} + FRR \cdot S_c$; $CL_{HF\ predilution} = SuR_{predilution} \cdot BFR/(BFR + SuR_{predilution}) \cdot S_c$; $CL_{HF\ postdilution} = SuR_{postdilution} \cdot S_c$
	CL_{HF} calculated from hemofilter outlet/inlet concn	$CL_{HF} = (C_{in} - C_{out})/C_{in} \cdot BFR$
	Hemofilter outlet concn corrected for postdilution[c]	$C_{out\ corr\ HF} = C_{out\ meas} \cdot (BFR - SuR_{postdilution} - FRR)/BFR$
CVVHD	CL_{HD} calculated from saturation coefficient S_d	$S_d = C_d/C_{pl}$; $CL_{HD} = (Q_D + FRR) \cdot S_d$
	CL_{HD} calculated from dialyzer outlet/inlet concn	$CL_{HD} = (C_{in} - C_{out})/C_{in} \cdot BFR$
	Dialyzer outlet concn corrected for hemo-concn[d]	$C_{out\ corr\ HD} = C_{out\ meas} \cdot (BFR - FRR)/BFR$

[a] The elimination of caspofungin via hemofiltration was estimated from the sieving coefficient and from the difference between the caspofungin plasma concentrations before and after the hemofilter. Caspofungin clearance by CVVHD was calculated from the difference between the caspofungin blood concentrations in the dialyzer inlet and in the outlet. S_c, sieving coefficient of caspofungin; C_{out}, caspofungin concentration in the hemofilter/dialyzer outlet; C_{in}, caspofungin concentration in the hemofilter/dialyzer inlet; C_{UF}, caspofungin concentration in the ultrafiltrate; C_{pl}, caspofungin plasma concentration at the same time; CL_{HF}, hemofilter clearance of caspofungin; UFR, ultrafiltration rate; $CL_{HF\ predilution}$, caspofungin hemofilter clearance achieved by predilution; $CL_{HF\ postdilution}$, caspofungin hemofilter clearance achieved by postdilution; FRR, fluid removal rate achieved by continuous venovenous hemofiltration (CVVH) or continuous venovenous hemodialysis (CVVHD) (ml/h); $SuR_{predilution}$, flow rate of substitution solution applied by predilution mode; BFR, blood flow rate through the hemofilter/dialyzer; $SuR_{postdilution}$, flow rate of substitution solution applied by postdilution mode; $C_{out\ corr\ HF}$, caspofungin concentration in the hemofilter outlet corrected for hemoconcentration; $C_{out\ meas}$, caspofungin concentration measured in the hemofilter/dialyzer outlet; S_d, saturation coefficient; CL_{HD}, caspofungin clearance achieved by CVVHD; C_d, caspofungin concentration in the dialysate; Q_D, dialysate flow rate; $C_{out\ corr\ HD}$, caspofungin concentration in the dialyzer outlet corrected for hemo-concentration.

[b] Since the replacement fluid was applied simultaneously in predilution mode and in postdilution mode, the total caspofungin hemofilter clearance (CL_{HF}) had to be calculated from the caspofungin hemofilter clearance achieved by predilution and the hemofilter clearance achieved by postdilution.

[c] The hemofilter outlet blood samples were drawn immediately after the hemofilter, before the substitution solution was infused in postdilution mode. Therefore, the hemo-concentration in the hemofilter outlet blood samples had to be corrected.

[d] During CVVHD with regional citrate anticoagulation, trisodium citrate was infused behind the port where the inlet samples were taken and calcium chloride was added behind the port for the outlet samples. Therefore, in this setting, only the fluid removal rate had to be taken into account for correction of the dialyzer outlet concentration.

TABLE 4 Demographic and clinical characteristics of the patients[a]

Characteristic[b]	Value[c]					
	CVVH (patients 1–7; $n = 7$)		CVVHD (patients 7–14; $n = 8$)		Control (patients 15–27; $n = 13$)	
	Single dose	Steady state	Single dose	Steady state	Single dose	Steady state
No. of data sets	5	4	4	7	4	12
Sex						
Male	2	2	3	5	2	6
Female	3	2	1	2	2	6
Age (yr)	61.0 (16.0)	58.5 (14.0)	53.5 (37.0)	58.0 (37.0)	56.5 (34.0)	56.0 (59.0)
Wt (kg)	77.5 (53.0)	86.0 (42.0)	82.5 (45.0)	85.0 (57.0)	73.0 (47.0)	72.5 (46.0)
Main diagnosis						
Septic shock	4	3	3	3	4	6
Pneumonia	4	4	3	4	3	8
Hematologic disease	3	4	3	5	2	10
HSCT	1	1	1	4	1	5
SOT	0	0	1	2	0	0
Solid tumor	1	0	2	2	0	0
CAS indication						
Empirical	3	3	4	6	2	10
Invasive candidiasis	2	1	0	1	2	2
Laboratory values						
Creatinine (mg/dl)	1.30 (1.60)	1.37 (1.12)	1.53 (1.07)	1.19 (1.63)	0.45 (1.49)	0.50 (1.75)
Urea (mg/dl)	64.7 (40.7)	76.7 (51.5)	89.2 (17.5)	60.9 (170.0)	49.1 (46.4)	64.6 (107.2)
COP (mm Hg)	17.2 (2.4)	17.2 (5.8)	15.1 (5.5)	17.2 (10.6)	16.4 (2.8)	16.6 (4.80)
Albumin (g/dl)	2.58 (0.98)	3.25 (0.71)	2.12 (1.15)	2.96 (0.90)	3.55 (0.97)	2.69 (2.73)
Bilirubin (mg/dl)	2.41 (5.66)	2.79 (4.40)	0.59 (11.5)	0.79 (15.33)	0.71 (1.49)	2.73 (15.42)
Prothrombin time (%)	72 (58)	82 (73)	73 (34)	79 (69)	88 (25)	78 (70)
Diuresis (ml/day)	0 (1,550)	475 (650)*	0 (950)	0 (1,750)*	3,775 (4,850)	3,250 (5,950)*
CAS treatment						
Daily dose (mg)	70 (0)	70 (20)	70 (0)	70 (20)	70 (0)	50 (20)
Daily dose (mg/kg)	0.90 (0.77)	0.81 (0.16)	0.85 (0.57)	0.78 (0.28)	1.05 (0.68)	0.77 (0.41)
CYA treatment	0	0	1	2	1	2

[a] Twenty-eight patients were enrolled. One patient died during the sampling period and therefore had to be excluded from the study. Thirteen patients were already on caspofungin when admitted to the ICU, and thus, sampling after the first dose was missed. The second sampling was missed for 5 patients. According to the manufacturer's recommendation, the maintenance dose amounted to 50 mg per day in patients with a body weight of ≤80 kg and 70 mg once daily when body weight was >80 kg. A loading dose of 70 mg was applied to all patients. CVVH, patients on continuous venovenous hemofiltration; CVVHD, patients on continuous venovenous hemodialysis with regional citrate anticoagulation; single dose, sampling at the first day of caspofungin treatment; steady state, sampling at steady state of caspofungin treatment on day 4 or later; control, critically ill patients not requiring renal replacement therapy.

[b] HSCT, status after hematopoietic stem cell transplantation; SOT, solid organ transplantation; CAS indication, clinical indication for treatment with caspofungin (CAS); empirical, empirical treatment with caspofungin according to the current guidelines (6, 7); invasive candidiasis, patients 1, 2, 9, 14, 16, and 19 suffered from candidemia and patient 15 had a *Candida* pancreatitis; creatinine, plasma creatinine (normal range, 0.67 to 1.17 mg/dl); urea, plasma urea (normal range, 19.0 to 44.0 mg/dl); COP, colloid osmotic pressure (normal range, 19.0 to 30.0 mm Hg); albumin, plasma albumin concentration (normal range, 4.19 to 5.35 g/dl) (no correlation between plasma albumin and maximum concentration [C_{max}], minimum concentration [C_{min}], or area under the concentration-time curve from 0 to 24 h [AUC_{0-24}] of caspofungin was identified by linear regression). Creatinine, urea, and colloid osmotic pressure were determined on the study day, and the plasma albumin concentration was determined up to 14 days before the study. Bilirubin, total plasma bilirubin (normal range, 0 to 1.28 mg/dl); prothrombin time normal range, 70 to 130%; diuresis, urine output per 24 h (*, diuresis was lower in patients on CVVH or CVVHD than in patients not on CRRT [$P < 0.008$ within the steady-state group]); CAS treatment, treatment with caspofungin (infusion time, 1 h); CYA treatment, immunosuppression with cyclosporine. None of the patients received any other drug with known influence on caspofungin concentrations such as rifampin, efavirenz, nevirapine, phenytoin, dexamethasone, or carbamazepine. Body weight, kidney and liver function tests did not significantly differ between the groups.

[c] Values are number of patients unless otherwise indicated, in which case they are shown as median (range).

to only 0.33% of the respective plasma levels; i.e., the median (range) S_c was 0.0033 (0.0157). The CL_{HF} calculated from S_c was as low as 8.0 (37.8) ml/h (1.8% [9.6%] of total clearance). When estimated from hemofilter outlet and inlet concentrations, the CL_{HF} was higher (61.0 [10,712.2] ml/h).

Dialysate sampling was performed during all 11 sampling periods in patients on CVVHD. The S_d was 0.0027 (0.2470), yielding a CL_{HD} of 5.9 (530.5) ml/h (2.5% [66.5%] of the total caspofungin clearance). The CL_{HD} calculated from $C_{in} - C_{out}$ amounted to 5.5 (1,550.5) ml/h.

Single-dose and steady-state pharmacokinetics of caspofungin were unchanged during CRRT. Limitations of our study are the small size and the heterogeneity of the study population. Ultrafiltrate and dialysate concentrations of caspofungin were very low and close to the limit of quantification of our assay. The differences between hemofilter/dialyzer inlet and outlet caspofungin

TABLE 5 Caspofungin plasma pharmacokinetics during continuous renal replacement[a]

Sampling and patient group	Patient	Day of CAS	C_{max} (μg/ml)	AUC_{0-24} (μg · h/ml)	$t_{1/2}$ (h)	CL (ml/h/kg)	V (ml/kg)
Single dose							
CVVH	1	1	12.4	92	9.8	7.8	113
	2	1	6.7	66	11.7	9.6	164
	3	1	8.4	91	16.1	5.9	138
	4	1	22.0	172	8.0	6.7	79
	5	1	4.8	45	14.1	9.6	199
	Median		8.4	91	11.7	7.8	138
	Range		17.2	127	8.1	3.7	121
CVVDH	8	1	6.1	45	9.2	15.7	210
	9	1	6.2	53	14.5	10.3	220
	10	1	10.2	99	14.9	4.6	102
	11	1	11.9	109	10.3	9.2	139
	Median		8.2	76	12.4	9.8	175
	Range		5.8	64	5.7	11.1	118
Control	15	1	6.0	48	8.7	12.5	157
	16	1	7.6	49	8.6	9.0	113
	17	1	15.9	176	15.4	5.0	111
	18	1	7.0	66	10.3	16.7	252
	Median		7.3	58	9.5	10.8	135
	Range		9.9	128	6.8	11.7	141
Steady state							
CVVH	2	8	10.4	98	12.4	6.1	112
	5	4	11.5	116	13.4	3.9	77
	6	7	7.3	42	7.2	11.6	122
	7	36	13.9	133	12.4	4.5	81
	Median		11.0	107	12.4	5.3	97
	Range		6.6	91	6.2	7.7	45
CVVHD	7	9	8.4	96	15.2	5.7	127
	9	7	11.9	146	19.5	3.1	89
	10	6	13.5	174	19.6	2.2	64
	11	6	10.5	141	13.7	4.5	89
	12	5	11.7	123	11.7	4.2	72
	13	4	10.8	148	21.2	2.8	86
	14	24	9.7	86	10.9	5.6	89
	Median		10.8	141	15.2	4.2	89
	Range		5.1	88	10.3	3.5	63
Control	16	10	11.3	128	12.0	4.2	74
	17	5	15.6	199	18.5	2.9	76
	18	8	8.0	88	11.7	8.6	144
	19	6	11.8	133	14.4	3.9	83
	20	6	9.1	96	12.7	7.8	145
	21	4	9.1	125	20.0	3.7	109
	22	4	6.9	92	15.0	4.8	104
	23	6	12.2	172	17.8	2.5	64
	24	4	6.0	47	8.1	11.7	138
	25	7	7.7	69	9.9	7.2	104
	26	9	8.4	104	12.4	5.1	92
	27	7	7.8	55	7.4	12.5	134
	Median		8.8	100	12.6	4.9	104
	Range		9.6	152	12.6	10.1	81

[a] Single dose, sampling on day 1 of caspofungin treatment; steady state, sampling on day ≥4 of caspofungin treatment; CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; control, critically ill patients not on renal replacement therapy; day of CAS, day of treatment with caspofungin; C_{max}, caspofungin peak plasma concentration; AUC_{0-24}, area under the time-concentration curve over the dosage interval; $t_{1/2}$, caspofungin plasma half-life; CL, total caspofungin body clearance; V, apparent volume of distribution. No statistical differences were found between the groups.

levels were highly variable, mostly very small, and similar to the imprecision of our assay. This precluded a precise calculation of caspofungin clearance by CRRT. Furthermore, we used polysulfone membranes in both CRRT protocols. However, details of extracorporeal procedures, particularly the material of the applied membranes, might have a considerable impact on drug elimination. Thus, striking differences in caspofungin levels were reported in two patients undergoing different modes of extracorporeal membrane oxygenation (4, 5). The different extracorporeal clearances that we obtained by estimation from $C_{in} - C_{out}$ and from S_c suggest some absorption of caspofungin by the hemofilter membrane, which, however, had no detectable effect on caspofungin plasma pharmacokinetics. Altered hydration state, hemodynamics, and perfusion during critical illness can affect pharmacokinetics (11, 12). Low plasma albumin levels were associated with low caspofungin trough concentrations in patients at a surgical ICU (13). In contrast, in our patients, hypoalbuminemia did not correlate with caspofungin exposure (data not shown), which was quite similar to that in healthy volunteers, where the maximum concentration (C_{max}) was ~10 μg/ml, $AUC_{0-24\ h}$ ~100 μg · h/ml, and CL ~10 ml/kg (14, 15).

Micafungin, another echinocandin, displayed unaltered kinetics during CVVHD with a cellulose triacetate dialyzer and during continuous hemodiafiltration using a polymethyl-methacryl membrane (16, 17). Anidulafungin disposition was largely unchanged by CVVH with a polysulfone membrane (18). Thus, the available data suggest predictable and constant pharmacokinetics of echinocandins in critically ill patients requiring CRRT. Echinocandin passage through the membranes seems low because of high protein binding, exceeding 90%. Obviously, relevant membrane adsorption does not occur.

In conclusion, the influence of CRRT on caspofungin elimination appears to be negligible, and the standard dosage is probably appropriate for ICU patients on CRRT. Further studies should address different CRRT techniques and membrane materials.

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