Micafungin Plasma Levels Are Not Affected by Continuous Renal Replacement Therapy: Experience in Critically Ill Patients

M. G. Vossen,^a D. Knafl,^a M. Haidinger,^b R. Lemmerer,^a M. Unger,^c S. Pferschy,^a W. Lamm,^d A. Maier-Salamon,^e W. Jäger,^e F. Thalhammer^a

Clinical Division of Infectious Disease, Department of Medicine I, Medical University of Vienna, Vienna, Austria^a; Internistisches Zentrum Nord, Vienna, Austria^b; Clinical Division of Rheumatology, Department of Medicine III, Medical University of Vienna, Vienna, Austria^c; Department of Internal Medicine I—Intensive Care Unit 13i2, Medical University of Vienna, Vienna, Austria^d; Department of Clinical Pharmacy and Diagnostics, University of Vienna, Vienna, Austria^e

ABSTRACT Critically ill patients often experience acute kidney injury and the need for renal replacement therapy in the course of their treatment in an intensive care unit (ICU). These patients are at an increased risk for candidiasis. Although there have been several reports of micafungin disposition during renal replacement therapy, to this date there are no data describing the elimination of micafungin during high-dose continuous venovenous hemodiafiltration with modified AN69 membranes. The aim of this prospective open-label pharmacokinetic study was to assess whether micafungin plasma levels are affected by continuous hemodiafiltration in critical ill patients using the commonly employed AN69 membrane. A total of 10 critically ill patients with micafungin treatment due to suspected or proven candidemia were included in this trial. Prefilter/postfilter micafungin clearance was measured to be 46.0 ml/min (± 21.7 ml/min; $n = 75$ individual time points), while hemofilter clearance calculated by the sieving coefficient was 0.0038 ml/min (± 0.002 ml/min; $n = 75$ individual time points). Total body clearance was measured to be 14.0 ml/min (± 7.0 ml/min; $n = 12$). The population area under the curve from 0 to 24 h (AUC_{0-24}) was calculated as 158.5 mg $\cdot$ h/liter (± 79.5 mg $\cdot$ h/liter; $n = 13$). In spite of high protein binding, no dose modification is necessary in patients receiving continuous venovenous hemodiafiltration with AN69 membranes. A dose elevation may, however, be justified in certain cases. (This study has been registered at ClinicalTrials.gov under identifier NCT02651038.)

KEYWORDS continuous venovenous hemodiafiltration, micafungin, antifungal agent, continuous renal replacement therapy, pharmacokinetics

About five percent of patients experiencing severe sepsis and septic shock suffer from invasive candidiasis and require management in a critical care unit (1). Fungal sepsis greatly increases morbidity and mortality in critically ill patients (2, 3). A third of all candidemias in the United States are reported in patients residing in an intensive care unit (1).

Critically ill patients often require continuous renal replacement therapy (cRRT) due to kidney failure and hemodynamic instability. Drug administration in these patients is complicated by pharmacokinetics/pharmacodynamics different from those of noncritically ill patients (4). In general, dose finding trials and thus drug dosage recommendations for patients in need of renal replacement therapy are rare.

Micafungin is a broad-spectrum antifungal agent of the echinocandin class. These drugs inhibit the synthesis of 1- β -D-glucan in the fungal cell wall. Micafungin is

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Address correspondence to M. G. Vossen, matthias.vossen@meduniwien.ac.at.

recommended for the initial treatment of *Candida* septicemia in most current guidelines and has been shown to inhibit “budding” of *Aspergillus* spp. (5–12). Due to its extensive metabolism in the liver, there is no need for dose adjustments in patients with reduced renal function (13). Until now, there have been only small trials and case reports describing very limited elimination during continuous venovenous hemofiltration (CVVHF) using polyethersulfone and polysulfone membranes as well as interventional lung assistance (14, 15). There are, however, no data available describing elimination of micafungin during continuous venovenous hemodiafiltration (CVVHDF) nor data available when using the commonly employed AN69 membrane, which is often used in the treatment of critically ill patients in Europe (16). Additionally, critically ill patients often exhibit changes in drug metabolism as well as volume of distribution. All these changes may lead to inappropriate micafungin serum levels, potentially facilitating the development of drug resistance as well as failure of therapy.

Due to the resulting clinical need, we performed a prospective open-label pharmacokinetic trial in 10 critically ill intensive care unit patients receiving micafungin during CVVHDF and CVVHD (continuous venovenous hemodialysis).

RESULTS

Demographic data. Ten patients receiving an antifungal therapy with micafungin and in need of renal replacement therapy due to acute kidney injury were enrolled in this trial. All patients were critically ill, with a mean sequential organ failure assessment (SOFA) score of 16.8 (± 2.9). In two patients, micafungin serum levels could be measured starting with the first dose, and all other patients had already received at least four doses of micafungin; therefore, achievement of steady-state kinetics upon the inclusion of these patients in the trial was assumed. Due to interruptions in the cRRT and other clinical reasons, it was not possible to collect a full set of samples for every patient. As a result, there are 13 distinct area-under-the-curve (AUC) measurements for 10 patients. Data sets from three patients (patients 3, 4, and 10) had to be excluded from the analysis due to completely or extensively missing data points as a result of death or early discontinuation of renal replacement therapy. Available data were added to Table 1 (values in brackets) but were not used to calculate average pharmacokinetic values, with the exception of prefilter/postfilter clearance and clearance by sieving coefficient (Sc). Three female and seven male patients were included. The average age was 56.6 (± 11.4) years; the average body weight was 90.3 (± 18.2) kg. In only one patient was micafungin treatment initiated because of proven candidemia (*Candida glabrata* in multiple blood cultures); most patients received treatment with micafungin due to suspected fungal infection. In six patients, possible fungal pathogens were identified during follow-up (Table 2). Overall survival after screening was low due to the advanced illness of most patients. Only three patients survived more than 2 weeks. One patient had to be excluded from analysis because cRRT was discontinued shortly after inclusion in the trial. Only one patient (patient 4 in Table 2) received a dose larger than 100 mg per day due to his body weight. The average dose was 1.2 mg/kg body weight. Micafungin was tolerated well by all patients; no micafungin-related side effects were observed. Table 2 summarizes the demographics of the trial population. Blood flow ranged from 100 to 180 ml/min, and dialysate flow ranged from 900 to 2,000 ml/h. Table 3 shows the parameters of cRRT used for each patient.

Pharmacokinetic data. The average peak plasma concentrations (C_{pi}) at 1 and 2 h postinfusion were 14.3 mg/dl (± 6.8 mg/dl; $n = 7$) and 10.0 mg/dl (± 4.3 mg/dl; $n = 14$), respectively. The average trough concentration (C_{trough}) was 3.8 mg/dl (± 2.5 mg/dl; $n = 20$) with a terminal half-life ($t_{1/2\beta}$) of 15.9 h (± 4.9 h; $n = 12$) (Fig. 1). Micafungin levels in dialfiltrate and, thus, sieving coefficients were very low. The average corrected prefilter/postfilter difference in measured micafungin concentrations in all patients was 35.2% ($\pm 21.1\%$; $n = 81$), while the elimination rate of the patients treated with CVVHDF/AN69 membranes only was 40.0% ($\pm 19.5\%$; $n = 68$) at any one time. Accounting for altered apparent micafungin concentrations by predilution and substitution, the average clearance (CL) in CVVHDF/AN69 membrane-treated patients calcu-

TABLE 1 Individual pharmacokinetic parameters^a

Patient no.	Dose (mg/kg)	AUC ₀₋₂₄ (mg · h/liter)	CL _{tot} (liters/h)	CL _{pre-post} (ml/min)	Sc	CL _{Sc} (ml/h)	V _D (liters)	V _D (liters/kg)	t _{1/2β} (h)	AUC/MIC with target MIC of 0.016 mg/liter	AUC/MIC with target MIC of 0.032 mg/liter
1	1.25	83.08	1.25	53.3 (±4.5)	0.000078	0.21	17.24	0.22	11.84	5,193	2,596
2	1.11	101.05	0.99	37.5 (±9.9)	0.000115	0.23	16.04	0.18	20.25	6,316	3,158
3	1.11		[1.38]	7 (±3)	0.000057	0.04					
4	1.33										
5	0.85	186.81	0.54	12.8 (±5.4)	0.000043	0.07	7.25	0.06	13.34	11,676	5,838
6	1.02	72.00	1.40	32 (±21.5)	0.000142	0.24	18.17	0.19	12.48	4,500	2,250
7	0.91	173.72	0.58	78.2 (±6.1)	0.000055	0.22	7.89	0.07	13.97	10,858	5,429
8	1.33	226.21	0.44	37 (±12.6)	0.000078	0.35	7.56	0.10	23.31	14,138	7,069
9	1.54	300.75	0.33	61.9 (±3.9)	0.000105	0.32	4.68	0.07	16.83	18,797	9,398
10	1.54		[1.09]	38.6 (±17.2)	0.000085	0.19					
Mean ± SD		158.54 (±79.50)	0.84 (±0.42)	46.0 (±21.7)	0.000089 (±0.000045)	0.23 (±0.12)	11.86 (±5.58)	0.13 (±0.06)	15.95 (±4.92)	10,211 (±4,850)	5,106 (±2,425)

^aMean values were calculated from original per-time-point values and not as a "mean of means." AUC/MIC values are given with respect to the AUC₀₋₂₄ values shown within this table. Values for pharmacokinetic parameters in brackets (for patients 3 and 10) are given as a reference but were excluded from analysis due to the limited data set available for these patients. AUC, area under the curve; CL_{tot}, total body clearance; CL_{pre-post}, clearance calculated from prefilter and postfilter micafungin concentrations; Sc, sieving coefficient; CL_{Sc}, clearance calculated from prefilter and dialysate/dialysate micafungin concentrations; V_D, volume of distribution; t_{1/2β}, terminal half-life time.

TABLE 2 Patient demographics^a

Patient no.	Sex	Age (yr)	Body wt (kg)	BMI	Infection	Pathogen	SOFA (day 1)	Survival (days)	Dose (mg)	Dose (mg/kg)
1	M	56	80	24.69	Sepsis	<i>C. glabrata</i>	20	5	100	1.25
2	M	58	90	27.78	Pancreatitis		19	12	100	1.11
3	F	63	90	30.07	Sepsis	<i>C. albicans</i>	19	1	100	1.11
4	M	65	113	37.32	Endocarditis	<i>C. glabrata</i>	14	6	150	1.33
5	M	27	117	32.41	Pancreatitis, sepsis		17	7	100	0.85
6	M	65	98	32.00	Pneumonia		13	186	100	1.02
7	M	50	110	38.06	Sepsis, COPD	<i>C. albicans</i> , <i>C. tropicalis</i> (BAL)	20	— ^b	100	0.91
8	M	66	75	25.95	Pneumonia, <i>Candida glabrata</i> sepsis	<i>C. glabrata</i>	19	1	100	1.33
9	F	51	65	22.49	Purulent peritonitis	<i>C. albicans</i> , <i>C. tropicalis</i> (BAL)	15	6	100	1.54
10	F	65	65	27.77	Pneumonia		12	62	100	1.54
Mean ± SD		56.6 (± 11.4)	90.3 (± 18.2)	28.9 (± 8.0)			16.8 (± 2.9)			1.20 (± 0.23)

^aBMI, body mass index; BAL, specimen found in bronchoalveolar lavage fluid; COPD, chronic obstructive pulmonary disease; SOFA, sequential organ failure assessment, a severity of illness score for hospital mortality, assessed on day 1 of the trial participation.

^b—, still living.

lated from prefilter and postfilter micafungin serum concentrations was measured to be 50.5 ml/min (±19.0 ml/min; $n = 66$ individual time points). Sieving coefficients were 0.000094 (±0.000044; $n = 67$ individual time points) and 0.000045 (±0.000024; $n = 8$ individual time points) for patients treated with CVVHDF/AN69 membranes and citrate-calcium hemodialysis/polysulfone membranes, respectively. Total body clearance (CL_{tot}) was measured to be 14.0 ml/min (±7.0; $n = 12$). The population AUC from 0 to 24 h (AUC_{0-24}) was calculated as 158.5 mg · h/liter (±79.5 mg · h/liter; $n = 13$). Based on the calculated AUCs, a range of AUC/MIC ratios between 2,596 for a target organism with an MIC of 0.032 mg/liter and 18,797 for a target organism with an MIC of 0.016 mg/liter was observed. The mean AUC/MIC ratios were calculated to be 10,211 (±4,850; $n = 7$) and 5,106 (±2,425; $n = 7$) for target MICs of 0.016 mg/liter and 0.032 mg/liter, respectively. In comparison, patients 1 and 5, who both received the first dose of micafungin on day 1 of their trial participation, achieved AUC/MIC values of 5,139 and 11,676 for an MIC of 0.016 mg/liter and 2,596 and 5,838 for an MIC of 0.032 mg/liter, respectively, after the first dose of micafungin. The individual pharmacokinetic parameters of all patients may be found in Table 1.

DISCUSSION

There have been three trials describing micafungin pharmacokinetics during continuous hemofiltration (total of 14 patients in two trials) and hemodialysis (4 patients); however, there have been no reports of micafungin clearance during hemodiafiltration.

TABLE 3 cRRT parameters^a

Patient no.	cRRT mode	Capillary	Q_b (ml/min)	Q_d (ml/h)	Q_{uf} (ml/h)	Q_{s_pre} (ml/h)	Q_{s_post} (ml/h)	FRR (ml/h)	Hct (%)
1	HDF	ST150	100	900	1,900	1,000	900	0	25.4
2	HDF	ST150	180	1,000	1,000	500	500	0	21.3
3	Citrate HD	AV1000S	120	2,000	0	0	0	0	19.7
4	HDF	ST150	150	1,000	1,300	500	500	300	23.8
5	Citrate HD	AV1000S	120	2,000	0	0	0	0	22.1
6	HDF	ST150	180	1,000	1,100	500	500	100	27.2
7	HDF	ST150	150	1,300	2,850	1,300	1,300	250	25.0
8	HDF	ST150	180	800	800	400	400	0	26.4
9	HDF	ST150	100	900	2,333	1,333	900	100	28.4
10	HDF	ST150	150	1,000	1,250	500	500	250	30.7

^aHDF, hemodiafiltration; HD, hemodialysis; cRRT, continuous renal replacement therapy; Q_b , blood flow; Q_d , dialysate flow; Q_{uf} , ultrafiltrate flow; Q_{s_pre} , predilution rate; Q_{s_post} , postdilution rate; FRR, fluid removal rate; Hct, hematocrit.

FIG 1 Mean prefilter and postfilter micafungin concentrations corrected for pre- and postdilution.

Additionally, all previous trials have been performed with cellulose triacetate, poly-methyl metacrylate, or polysulfone membranes but not with AN69 membranes. Consequently, the present trial was performed in 10 critically ill patients, 8 of which received CVVHDF with a 1.5-m² modified AN69 membrane and two of which were treated with CVVHD using a 1.8-m² polysulfone membrane. Due to early discontinuation of trial participation, the data from three patients were not eligible for further analysis.

With 0.84 liters/h equaling 14.0 ± 7.0 ml/min, our study showed a total body clearance similar to that previously reported for critically ill patients receiving continuous venovenous hemofiltration (Table 4). cRRT clearance measured between the filter inlet and the filter outlet exceeded the total body clearance calculated by dividing the AUC by the administered dose. This may be due to an overestimation of the AUC from 0 to infinity (AUC_{0-∞}), resulting in a reduced total body clearance as well as an overestimation of clearance by our formula. In a comparison of the prefilter/postfilter

TABLE 4 Comparison of previously published micafungin pharmacokinetic parameters

Parameter ^a	Value for drug from indicated reference ^b						
	Anidulafungin (24)	Anidulafungin (25)	Anidulafungin (26)	Caspofungin (23) ^c	Micafungin (27)	Micafungin (28)	Micafungin (14)
V _D (liters)			41.97 ± 22.64	138 (121 ml/kg)		17.5 ± 4.4	
t _{1/2β} (h)			28.78 ± 10.40	11.7 (8.1)			
C _{max, 0-24} (mg/liter)	7.36	6.2 ± 1.7	8.5 ± 3.6	8.4 (17.2)	6.31 ± 1.08	12.7 ± 10.2	9.15 ± 1.95
C _{trough} (mg/liter)	2.02	3.0 ± 0.6	2.9 ± 1.1				2.46 ± 0.75
CL _{tot} (liters/h)			1.08 ± 0.41	7.8 (3.7 ml/h/kg)	0.054 ± 0.04 ml/min/kg	1.4 ± 0.7	0.88 ± 0.27
AUC ₀₋₂₄ (mg · h/liter)	81.33	93.9 ± 9.4	109.9 ± 49.82	91 (127)	50.04 ± 6.48 ^d		119.01 ± 27.20
Dosage (mg)	200 mg LD, 100 mg MD	200 mg LD, 100 mg MD	200 mg LD, 100 mg MD	70 mg	40-50 mg	150-300 mg	100 mg

^aAUC, area under curve; CL_{tot}, total body clearance; C_{max, 0-24}, maximum micafungin concentration during the first 24 h; C_{trough}, micafungin trough concentration; V_D, volume of distribution; t_{1/2β}, terminal half-life time.

^bUnless otherwise indicated, units of measurement are as described for the parameters. LD, loading dose; MD, maintenance dose.

^cRanges for this drug are given in parentheses.

^dThis value is the AUC₀₋₁₂.

clearance to that calculated by the sieving coefficient, which was expectably low (CL_{sc} of $0.23 \text{ ml/h} = 0.0038 \pm 0.002 \text{ ml/min}$), and considering the high molecular weight and very high protein-bound fraction of micafungin, the resulting discrepancy is obvious. This could be a result of adsorption of albumin-bound micafungin to tubing and membrane material. Calculation of the clearances from uncorrected pre- and postfilter concentrations results in a considerably lower clearance of 25.4 ml/min ($\pm 24.1 \text{ ml/min}$; $n = 73$), which, however, still exceeds the calculated total body clearance. Although the median was higher due to the large AUC found for patient 9, considering the large standard deviation, AUC values were within the range of those published previously for patients undergoing continuous renal replacement therapy or those published for healthy subjects (mean, $134.5 \text{ mg} \cdot \text{h/liter}$) (14, 17) (Table 4). AUC/MIC values exceeded the previously described threshold of 3,000 in all patients if a target MIC of 0.016 mg/liter was assumed. However, there is no universal consensus on the optimal value of the lower threshold, with some publications recommending an AUC/MIC value of $>5,000$ (17).

Since the EUCAST breakpoints describe *Candida albicans* as anidulafungin susceptible below 0.03 mg/liter , and anidulafungin is used as a marker substance for echinocandins in most microbiological laboratories, the worst-case scenario would be an MIC target of 0.032 mg/liter . For this target, 2 of 7 patients (29%) in the present trial did not reach the AUC/MIC threshold of 3,000. In a model based on a heterogeneous population, including 11.7% patients undergoing hemodialysis, the target attainment rate for simulated patients suffering from any *Candida* species infection with an MIC of 0.03 mg/liter was 76.7% after administration of 100 mg micafungin once daily (18). We could not, however, identify a discriminator that would explain why patients 1 and 6 showed considerably lower AUCs than the other patients in our trial. Patient 1 did show an accumulation effect on the second dose, and as a result the AUC may have increased further during subsequent doses. On the other hand, especially in cases of candidemia, early sufficient therapy greatly increases survival, so early high AUCs should be targeted as they may improve survival (19). Additionally, this explanation is not valid for patient 6. Consequently, a higher dose of micafungin could be considered in critically ill patients with a suspected or proven *Candida* infection with an MIC above 0.016 mg/liter . Increasing the dosage for all patients, however, might lead to an exposure above an AUC/MIC ratio of 12,000, which resulted in a worse outcome, possibly due to a previously described "eagle effect" inherent to echinocandins, although the clinical relevance of this effect is heavily debated (18, 20).

Our study is limited, like most trials performed in intensive care units, by the short mean observation time of our patients. This results in only a short pharmacokinetic evaluation in each patient. We, however, observed two complete dosing intervals in most patients, resulting in a large number of individual time points suitable for clearance calculation. Additionally, due to the large number of previously published articles describing the pharmacokinetics of micafungin in patients undergoing different modes of renal replacement therapy or none at all, this trial was designed as an open-label pharmacokinetic trial without a control group.

While we focused on critically ill patients, data on the use of micafungin in intermittent renal replacement therapy are still missing. In these patients, antifungal treatment is not common but sometimes necessary. The use of polysulfone membranes should, however, not result in a considerable intradialytic clearance of micafungin.

In conclusion, we report a higher clearance of micafungin in patients undergoing continuous venovenous hemodiafiltration with modified AN69 membranes than in patients undergoing continuous hemodialysis with polysulfone membranes. The maximum concentration of drug in serum (C_{max}) and consequently the AUCs determined in our trial are higher than those published by Maseda et al. for continuous venovenous hemofiltration with 1.2-m^2 polyethersulfone membranes, who calculated a higher total body clearance (14). Based on these results, a modification of the current micafungin dosing recommendations in patients receiving continuous renal replacement therapy is not indicated regardless of the employed modality. We could, however, identify two

patients in our population who did not achieve adequate AUC/MIC ratios for a target MIC of 0.032 mg/liter. A comparison of the AUC data found in our trial to those described in earlier studies shows that even in trials describing comparably high AUCs, at the lower end of the published standard deviation, an AUC/MIC target of 3,000 is not attained for an MIC of 0.032 mg/liter (14, 18). As a result, higher micafungin doses may be warranted in some selected cases but cannot be recommended without further prospective trials. Further study regarding the survival benefit of such an elevated dose is warranted.

MATERIALS AND METHODS

Patients. Ten critically ill patients at the General Hospital of Vienna/Medical University of Vienna were included in this trial after the patients gave oral and written informed consent. The main inclusion criterion was prescription of micafungin due to suspected or proven fungal infection by the treating physician. All patients received extracorporeal renal replacement therapy due to acute kidney injury developed on the basis of the current septic episode and presented with anuria or oliguria as defined by a maximum urinary production of 500 ml/24 h (Table 2). None of the trial participants received albumin substitution during the pharmacokinetic measurements. The trial was approved by the local independent ethics committee of the Medical University of Vienna (vote number 1163/2012) and the competent authorities. It was registered at clinicaltrials.gov (identifier NCT02651038). In 8 of 10 patients, CVVHDF was performed as previously described using a 1.5-m² modified AN69 membrane (ST150 set; Baxter-Gambro, Austria) (21). The other two patients received CVVHD using a 1.8-m² polysulfone membrane (AV1000S; Fresenius Medical, Austria) (Table 3). The membranes were not changed during the conduct of the study. Flow rates were continued as prescribed by the treating physician.

Micafungin (Mycamine, 100 mg; Astellas, Austria) was reconstituted and diluted with normal saline to 1 mg/ml and administered intravenously using a central venous catheter over a period of 30 min (Table 2). Blood samples were collected prefilter and postfilter prior to the infusion and at time points 1, 2, 4, 6, 8, and 24 h on days 1 and 2 of the trial. Ultrafiltrate samples were collected at the same time points from the outlet of the ultrafiltrate compartment of the dialyzer. All samples were immediately centrifuged at $1,000 \times g$ for 10 min, and the supernatant was stored at -80°C until analysis.

HPLC analysis. The concentration of micafungin in plasma and ultrafiltrate was determined by high-performance liquid chromatography (HPLC). Briefly, after the addition of 300 μl of methanol to 100 μl of plasma, the samples were centrifuged ($13,000 \times g$ for 5 min). The clear supernatant was diluted 1:3 with mobile phase A, and 80 μl was injected onto the HPLC column. One hundred microliters of ultrafiltrate was diluted with 500 μl of mobile phase A without any prior precipitation procedure, and again 80 μl was injected onto the column. The determination of micafungin concentration was performed using a Dionex UltiMate 3000 system (Dionex Corp., Sunnyvale, CA) with an UltiMate 3000 fluorescence detector (excitation, 273 nm; emission, 464 nm). Separation of micafungin was carried out at 45°C on a Hypersil BDS-C₁₈ column (5 μm , 250- by 4.6-mm inside diameter [ID]; Thermo Fisher Scientific, Inc., Waltham, MA), preceded by a Hypersil BDS-C₁₈ precolumn (5 μm , 10- by 4.6-mm ID). The mobile phase consisted of a continuous gradient mixed from 10 mM ammonium acetate-acetic acid buffer, pH 4.5 (mobile phase A), and methanol (mobile phase B). The gradient ranged from 10% phase B at 0 min to 90% at 15 min, where it remained constant for 5 min. Subsequently, the percentage of methanol decreased within 2 min to 10% in order to equilibrate the column for 8 min. The mobile phase consisted of 0.1% acetic acid-methanol (90:10, vol/vol) at a flow rate of 1.0 ml/min. Calibration of the chromatogram was accomplished using the external standard method. Linear calibration curves were calculated from the peak areas of micafungin compared to the external standard by spiking drug-free human plasma and ultrafiltrate with standard solutions of micafungin to obtain a concentration range of 0.01 to 10 $\mu\text{g/ml}$ (average correlation coefficients, >0.99). The lower limit of quantification (LLQ) for micafungin in plasma and ultrafiltrate was 0.01 $\mu\text{g/ml}$. Coefficients of accuracy and precision for this compound were $<8.7\%$.

Data analysis. The serum concentration curves of micafungin were analyzed using Graphpad Prism and Microsoft Excel. To account for dilution effects by fluid addition pre- and postfilter, the measured micafungin concentrations were corrected for these factors. The formulae are described below. SOFA scores were calculated for the first day of trial participation for each patient (22).

The following pharmacokinetic parameters were calculated as previously described: area under the curve from 0 to 24 h (AUC_{0-24}), total body clearance (CL_{tot}), hemofilter clearance (CL), volume of distribution (V_D), and elimination half-life ($t_{1/2b}$) (21, 23). Due to the collection of samples directly at the filter inlet and outlet, in patients receiving CVVHDF with the Prismaflex system, all values were corrected either for predilution or for postfilter hemoconcentration based on substitution rates, as described in the formulae below.

Sieving or saturation coefficient-based formulae:

$$\text{CL}_{\text{HF}} = \text{CL}_{\text{HF}_{\text{pre}}} + \text{CL}_{\text{HF}_{\text{post}}} + \text{FRR} \times \text{Sc} \quad (1)$$

$$\text{CL}_{\text{HDF}} = \text{CL}_{\text{HF}_{\text{pre}}} + \text{CL}_{\text{HF}_{\text{post}}} + \text{CL}_{\text{HD}} \quad (2)$$

With

$$\text{CL}_{\text{HD}} = (\text{FRR} + Q_d) \times \text{Sc} \quad (3)$$

$$CL_{HF_pre} = SR_{pre} \times \frac{BFR}{(BFR + SR_{pre})} \times Sc, CL_{HF_post} = SR_{post} \times Sc \text{ and } Sc = \frac{C_{uf}}{C_{pl}} \quad (4)$$

Hemofilter inlet/outlet-based formulae:

$$CL_{pre/post} = \frac{C_{pre_corr} - C_{post_corr}}{C_{pre_corr}} \times BFR \quad (5)$$

With

$$C_{pre_corr} = \frac{BFR + SR_{pre}}{BFR} \text{ and } C_{post_corr_HF} = C_{post} \times \frac{BFR - SR_{post} - FRR}{BFR} \text{ or} \quad (6)$$

$$C_{post_corr_HD} = C_{post} \times \frac{BF - FRR}{BFR} \quad (7)$$

where BFR is the blood flow rate, C is the micafungin concentration, C_{pl} is the micafungin plasma concentration measured at the hemofilter inlet, C_{uf} is the micafungin concentration in ultrafiltrate/dialysate, Sc is the sieving/saturation coefficient, SR is the substitution rate prefilter (pre) or postfilter (post), FRR is the fluid removal rate during renal replacement therapy, Q_d is the dialysate flow, HF is hemofiltration, HDF is hemodiafiltration, HD is hemodialysis, and corr indicates a corrected value as described above.

Since for most patients pharmacokinetic parameters were measured twice during the 49-h study period, average values were calculated as the means of the individual pharmacokinetic values determined for each micafungin administration wherever possible.

To allow for an estimation of attainment of pharmacokinetic targets, the AUC/MIC was calculated for MICs of 0.016 and 0.032 mg/liter. An AUC/MIC target value of >3,000 was deemed sufficient. Patients with an AUC/MIC below this threshold were demonstrated to show a subpar response to micafungin treatment, while the best treatment outcome was recorded for AUC/MIC ratios between 3,000 and 12,000 (18).

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