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Optimal doses of caspofungin during continuous venovenous hemodiafiltration in critically ill patients

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The aim of the present study was to describe the pharmacokinetics of caspofungin in 12 critically ill adult patients with suspected or proven invasive candidiasis who were receiving continuous venovenous hemodiafiltration (CVVHD).

CVVHD was performed using a polysulfone hemofilter (Fresenius, Germany). Caspofungin was administered at usual doses. Pre-filter and post-filter blood, ultradiafiltrate, and urine samples were collected at steady state on day 3 or later, before the dose infusion started, and 0.5, 1, 1.5, 2, 4, 6, 8, and 24 h after the infusion ended.

The drug concentrations were measured by high performance liquid chromatograpy (HPLC) and the following pharmacokinetic parameters were calculated: area under the concentration-time curve ($AUC_{0\text{-}24h}$), elimination $t_{1/2}$, volume of distribution (Vd), clearance, trough concentration (C_{trough}), and maximum concentration (C_{max}).

The results of our study are summarized in Tables 1 and 2 and Fig. 1. Caspofungin was negligible in the ultradiafiltrate and urine samples, confirming the lack of drug elimination through hemofiltration or hemodialysis. Similar findings were previously described by Weiler et al. [1]. Additionally, the mean concentration of caspofungin was slightly higher in the post-filter line than in the pre-filter line (Fig. 1), allowing us to rule out the adsorption to the filter hypothesized in other studies with echinocandins [2, 3].

In four patients (33%), the trough concentration of caspofungin was lower than the MIC_{90}s published for *Candida* and *Aspergillus* spp., including *Candida parapsilosis* (2 mg/L) [4]. On the other hand, among echinocandins, micafungin has been associated with 1 log kill/24 h in a murine model of disseminated candidiasis when an AUC/MIC of 865, 450, or 1185 is achieved for *Candida albicans*, *Candida glabrata*, or *C. parapsilosis*, respectively [5]. Taking into account a MIC of 0.1 mg/L [4], and using the target pharmacokinetics/pharmacodynamics (PK/PD) described for micafungin, we would have reached this concentration in only nine patients (75%, AUC > 86.5 mg h/L) for *C. albicans* and four patients (33%, AUC > 118.5 mg h/L) for *C. parapsilosis* but all patients for *C. glabrata* (AUC > 45 mg h/L) (Table 2). These data suggest that caspofungin dosing could be insufficient in some critically ill patients.

In conclusion, CVVHD appears to have a negligible effect on caspofungin clearance. However, the licensed regimen of caspofungin was not adequate to reach the PK/PD targets in some critically ill patients, regardless of the use of CVVHD. Nevertheless, future studies are needed to confirm these findings.

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Table 1 Individual arterial caspofungin concentrations (mg/L) of the 12 patients studied

Time (h)	1	2	3	4	5	6	7	8	9	10	11	12
Predose	3.09	2.12	2.94	0.90	1.50	3.04	2.10	2.93	2.18	3.16	2.69	2.62
0.5	10.85	6.96	8.50	4.38	4.59	9.86	7.09	8.23	7.81	11.17	10.24	7.02
1	9.34	6.19	8.23	2.80	4.44	9.11	6.10	7.23	6.69	9.91	8.88	5.78
1.5	8.55	5.75	7.05	NA	4.41	8.24	5.27	6.04	6.03	8.42	8.39	5.09
2	7.51	5.47	6.91	2.43	3.85	7.37	4.96	5.88	5.72	7.74	7.92	4.61
4	6.38	4.49	6.13	2.12	3.77	6.54	4.13	5.66	5.32	6.94	6.62	3.94
6	5.63	3.96	5.63	NA	3.04	5.84	3.54	5.33	4.55	6.40	6.31	3.60
8	5.00	3.40	5.22	1.99	2.80	4.71	3.10	4.45	4.49	5.61	6.00	3.27
24	3.47	2.30	3.10	1.34	1.59	2.47	1.63	2.73	2.27	2.88	4.00	1.85

Time refers to the time since caspofungin infusion ended. *NA* data not available

Table 2 Pharmacokinetics of caspofungin during continuous venovenous hemodiafiltration in 12 patients

Patient	AUC_{0-24} (mg h/L)			Vd (L)	Cl (L/h)	C_{max} (mg/L)	C_{trough} (mg/L)	$t_{½}$ (h)
	Arterial	Venous	Difference venous to arterial (%)					
1	140.0	180.0	29	14.1	0.356	12.5	3.47	27.4
2	88.3	106.0	20	17.1	0.567	7.8	2.1	21.0
3	124.0	152.0	23	10.9	0.402	8.8	3.1	18.8
4	65.4	77.4	18	26.8	0.765	6.9	1.3	24.3
5	68.0	90.0	32	17.5	0.735	4.8	1.5	16.5
6	102.0	107.0	5	13.6	0.683	10.7	2.5	13.8
7	65.6	78.8	20	15.0	0.762	8.3	1.6	13.6
8	100.0	113.0	13	13.9	0.499	9.5	2.7	19.3
9	102.0	127.0	25	14.1	0.685	9.2	2.3	14.3
10	121.0	142.0	17	12.5	0.578	12.6	2.9	15.0
11	190.0	224.0	18	13.9	0.368	11.5	4.0	26.2
12	60.1	74.5	24	27.7	1.165	8.5	1.9	16.5
Mean ± SD	102 ± 46	123 ± 46	20.3 ± 7.2	16.4 ± 5.4	0.630 ± 0.225	9.3 ± 2.3	2.4 ± 0.8	18.9 ± 4.9

SD standard deviation

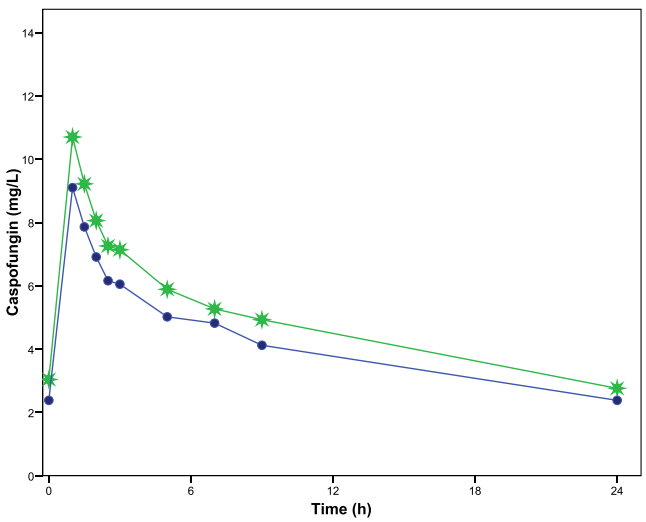

Fig. 1 Average caspofungin concentration over time. Infusion started at 0 h and continued over 1 h. $n = 12$ patients. *Solid dots*, arterial; *asterisks*, venous. (The figure is original for this article)

Abbreviations
AUC: Area under the concentration-time curve; C_{max}: Maximum concentration; C_{trough}: Trough concentration; CVVHD: Continuous venovenous hemodiafiltration; MIC_{90}: Minimum inhibitory concentration required to inhibit the growth of 90% of a microorganism; PK/PD: pharmacokinetic/pharmacodynamic; Vd: Volume of distribution

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Availability of data and materials
All relevant data are within the paper and its supporting information files. All data are fully available without restriction.

Authors' contributions
GA conceived the study, participated in its design, and drafted the manuscript. RF participated in designing and coordinating the study and helped to draft the manuscript. CE carried out the pharmacokinetics analysis and helped to revise the manuscript. AL, JAC, AJ, JC, and FS participated in analyzing and interpreting the data and helped to revise the manuscript. JP, DN, MA, and FJB participated in the design and coordination of the study and revised the manuscript. All authors read and approved the final manuscript.

Competing interests
G.A. received funds for speaking at meetings organized on behalf of Astellas, Gilead, Merck Sharp and Dohme (MSD), and Pfizer, as well as unrestricted research grants from Astellas, MSD, and Pfizer. D.N. received funds for speaking at meetings organized on behalf of Astellas, MSD, and Pfizer and received unrestricted research grants from Astellas and Pfizer. All other authors declare no competing interests.

Consent for publication
Written informed consent was obtained from the patients or their relatives for publication of their individual details. The consent form is held by the authors' institution and is available for review by the Editor-in-Chief.

Ethics approval and consent to participate
The study protocol (MER-CAS-2013-01) was approved by the local ethics committee (Instituto de Investigación Sanitaria, INCLIVA) and written informed consent obtained from the patients or their relatives prior to study inclusion.

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