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Short Communication

Low penetration of caspofungin into cerebrospinal fluid following intravenous administration of standard doses

Volker Strenger [a,*], Fedja Farowski [b], Carsten Müller [c], Nora Hofer [a], Hans Jürgen Dornbusch [a], Daniela Sperl [a], Herwig Lackner [a], Martin Benesch [a], Christian Urban [a]

[a] Department of Paediatrics and Adolescent Medicine, Medical University of Graz, Auenbruggerplatz 30, Graz A-8036, Austria
[b] Department I of Internal Medicine, University Hospital of Cologne, Cologne, Germany
[c] Centre of Pharmacology, Department of Therapeutic Drug Monitoring, University Hospital of Cologne, Cologne, Germany

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ABSTRACT

The kinetics of caspofungin (CAS) in cerebrospinal fluid (CSF) following intravenous (i.v.) administration has been studied exclusively in animal models. Human data are missing so far. In this study, 13 CSF samples were obtained at different time points following i.v. infusion of CAS in ten paediatric haemato-/oncological patients (age range 1.0–14.2 years, median 8.6 years) without signs of central nervous system (CNS) infection ($n = 10$ samples) or with infectious meningitis ($n = 3$ samples). Serum samples were obtained concurrently. Liquid chromatography–tandem mass spectrometry was used for CAS quantification. Whilst CAS serum levels were in the expected range, varying between 0.6 and 20.3 μg/mL (median 7.0 μg/mL), 11 of 13 CSF levels were below the limit of detection of 0.084 μg/mL at 3.0–48.0 h (median 23.3 h) following i.v. infusion. Only two (of three) levels in patients with bacterial meningitis were above the limit of detection (0.3 μg/mL and 0.09 μg/mL, respectively). These results indicate the low capacity of CAS to penetrate into the CNS even in inflamed meninges. Monotherapy with standard doses of CAS appears not to be suitable for treatment of fungal CNS infections.

1. Introduction

Increasing use of immunosuppressive treatment has resulted in a growing number of patients prone to fungal infections, including infections of the central nervous system (CNS). Whilst these infections are associated with high morbidity and mortality, only a limited number of antimycotic agents are available [1–7].

Caspofungin (CAS) was the first approved echinocandin, which acts as a non-competitive inhibitor of the β-(1,3)-D-glucan synthase, an important enzyme for cell wall synthesis in yeasts and moulds. Therefore, echinocandins are active against pathogenic *Aspergillus* as well as *Candida* species. All echinocandins have low oral bioavailability, high protein binding, and extensive distribution into most tissues including the liver, spleen, lungs and kidneys. Owing to their high protein binding and high molecular weights, they exhibit only low penetration into urine, cerebrospinal fluid (CSF), brain tissue and ocular fluid [8–10]. However, besides single case reports on the treatment of fungal CNS infections with CAS (in combination with other antifungals), there are only two published cases with reported measurements of CAS levels in CSF [11,12]. Whilst one patient with meningeal coccidioidomycosis had undetectable CAS levels [11], another patient with CNS aspergillosis receiving high doses of CAS (three to four times the standard dose) had sufficient levels at least during the acute inflammatory phase [12]. However, no further human data on CAS penetration across the blood–brain barrier (BBB) exist. So far, further data have only been derived from animal models, suggesting low CSF levels of CAS following systemic application [13,14].

The aim of this prospective study was to determine CAS levels in the CSF of paediatric haemato-/oncological patients of different age groups and to correlate these concentrations with concurrent serum levels.

2. Patients and methods

2.1. Ethics

This study was approved by the Ethics Committee of the Medical University of Graz (Graz, Austria). Informed consent by the patients' caregivers was obtained before enrolment of the patients.

* Corresponding author. Department of Paediatrics and Adolescent Medicine, Medical University of Graz, Auenbruggerplatz 30, Graz A-8036, Austria. Fax: +43 316 385 3300.
E-mail address: volker.strenger@medunigraz.at (V. Strenger).

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Table 1
Details of patient characteristics, caspofungin (CAS) administration, and CAS concentrations in cerebrospinal fluid (CSF) and serum.

Patient	Specimen	Sex	Age (years)	Underlying disease	Interval[a] (h)	Dose	Indication for CAS	Preceding CAS infusions[b]	CAS concentration (μg/mL)	
									CSF	Serum
1	A	M	2.4	AML	20.8	50 mg/m^2	Empirical therapy	2	<LLOQ	7.4
2	A	M	9.3	ALL	23.3	50 mg/m^2	Empirical therapy	15	<LLOQ	5.1
3	A	M	14.2	ic GCT	3.0	35 mg/m^2	Empirical therapy	22	<LLOQ	9.4
3	B	M	14.2	ic GCT	24.0	35 mg/m^2	Empirical therapy	28	<LLOQ	7.7
4	A	M	8.2	ALL	23.8	50 mg/m^2	Empirical therapy	8	<LLOQ	2.3
5	A	F	7.5	AML	6.8	50 mg/m^2	Empirical therapy	5	<LLOQ	19.4
6	A	M	3.3	ALL	41.5	35 mg/m^2	Prophylaxis	14[c]	<LLOQ	0.6
7	A	M	1.0	ALL	18.3	50 mg/m^2	Prophylaxis	27	<LLOQ	20.3
8	A	F	14.0	AML	48.0	50 mg	Prophylaxis	12[c]	<LLOQ	2.7
8	B	F	14.0	AML	20.5	50 mg	Prophylaxis	17	<LLOQ	7.4
9	A	F	11.0	AML	3.5	70 mg	Empirical therapy	1	0.3	0.7
10	A	M	8.6	AML	46.0	35 mg/m^2	Prophylaxis	5[c]	<LLOQ	n.d.
10	B	M	8.6	AML	24.0	35 mg/m^2	Empirical therapy	8	0.09	6.5

AML, acute myeloid leukaemia; ALL, acute lymphoblastic leukaemia; ic GCT, intracranial germ cell tumour; LLOQ, lower limit of quantitation; n.d., not done.
[a] Interval between administration and specimen collection.
[b] Prior to specimen collection.
[c] Every other day.

2.2. Clinical setting

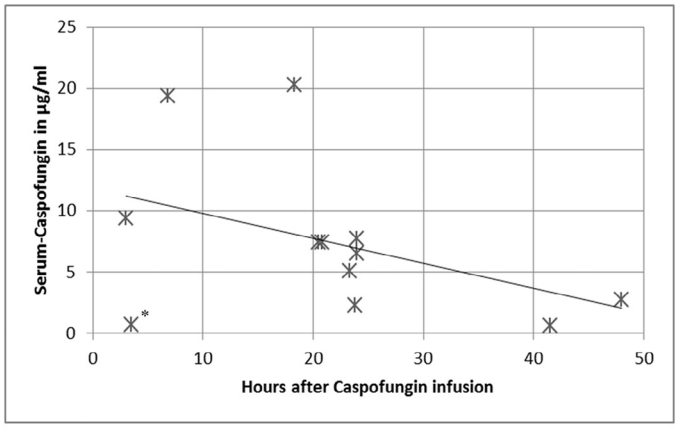
Blood (12 specimens) and CSF (13 specimens) were obtained from 10 paediatric haemato-/oncological patients (age range 1.0–14.2 years, median 8.6 years) (Table 1) who received CAS either as empirical therapy for possible fungal infection (eight episodes) or as antifungal prophylaxis (five episodes). Standard doses were 50 mg/m^2 body surface area (BSA) (max. 50 mg in patients with BSA > 1 m^2) once daily after an initial dose of 70 mg/m^2 BSA (max. 70 mg) on the first day. Patients with hepatic dysfunction (Child–Pugh score 7–9) received 35 mg/m^2 BSA (max. 35 mg in patients with BSA > 1 m^2) once daily after an initial dose of 50 mg/m^2 BSA (max. 50 mg). For antifungal prophylaxis, patients received CAS every day or every other day according to the patient's individual risk (Table 1). CAS doses were administered as 60-min infusions. Patients received 1–28 (median 12) CAS infusions prior to specimen collection (Table 1). CSF was obtained prior to routine administration of intrathecal therapy of the underlying malignant disease by means of lumbar puncture (11 punctures in 9 patients) or puncture of an Ommaya reservoir (2 punctures in 1 patient). In the latter case, 5 mL of CSF was discarded before obtaining CSF for analyses. Blood was obtained within 15 min before and 15 min after CSF puncture. Serum and CSF samples were stored at –80 °C until analysis. Whilst eight patients showed no signs and symptoms of CNS infection at the time of CSF puncture, two patients (three CSF specimens) had bacterial meningitis at the time of lumbar puncture caused by *Listeria monocytogenes* and *Rothia mucilaginosa*, respectively.

2.3. Laboratory methods

Serum samples were analysed using a previously described liquid chromatography–tandem mass spectrometry (LC-MS/MS) method [15]. However, the procedure was slightly modified to improve the peak quality of the analytes. The column was replaced by a Hypersil Gold™ column (50 × 2.1 mm; Thermo Hypersil–Keystone, Dreieich, Germany) allowing isocratic chromatography conditions with a constant flow rate of 350 μL/min. The performance characteristics were as follows: limit of detection of CAS, 0.032 μg/mL; lower limit of quantitation (LLOQ) of CAS, 0.084 μg/mL; intraday precision, ±8.1%; and intraday and interday accuracies (percent bias) within 13.8%. Mean extraction efficiency from diluted plasma for CAS was 78.0%. In addition to the existing CAS calibration serum standards, the final results were compared with a standard addition method for CSF matrix. The results were not significantly different.

3. Results

A total of 12 serum and 13 CSF specimens from 10 patients were analysed. Whilst CAS serum levels obtained 3.0–48.0 h (median 23.3 h) following i.v. CAS administration ranged from 0.6 to 20.3 μg/mL (median 7.0 μg/mL) (Table 1; Fig. 1), CSF levels of CAS were below the LLOQ of 0.084 μg/mL in 11 of 13 tested CSF specimens (Table 1). In two patients with bacterial meningitis, three CSF specimens were obtained. In one patient with meningitis due to *L. monocytogenes* (Table 1, patient 9) the CAS level in CSF was 43% of the correlating serum level 3.5 h after the first CAS infusion. Interestingly, this correlating serum level was only 0.7 μg/mL (Table 1; Fig. 1). In the other patient with severe sepsis and bacterial meningitis (due to *R. mucilaginosa*), two specimens were obtained at different time points (Table 1, patient 10). Whilst the CSF specimen obtained 24 h after CAS infusion showed a CAS level of only 1.4% of the correlating serum



* low serum level 3.5 hours after the first Caspofungin infusion in an 11-year old girl with bacterial meningitis (table 1, patient 9). In contrast, correlating CSF level was the highest in our series (0.3 μg/mL).

Fig. 1. Serum caspofungin levels at different time points following intravenous infusion. CSF, cerebrospinal fluid.