Caspofungin Shows Poor Penetration into Cerebrospinal Fluid Following Intravenous Administration of Standard Doses

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Background. While Caspofungin (CAS) has been used for the treatment of fungal infections of the central nervous system (CNS), CAS kinetics in cerebrospinal fluid (CSF) after intravenous administration has been studied exclusively in animal models. Human data are missing, so far.

Materials/Methods. In 10 paediatric haemato-/oncologic patients (aged 1 to 14.2, median 8.6 years), we obtained 13 CSF samples at different time points after therapeutic or prophylactic intravenous infusion of Caspofungin by means of routine punctures performed for intrathecal treatment of the underlying diseases in patients without signs of CNS infection (n=10) or for diagnostics of infectious meningitis (n=3). Concurrently, we obtained serum samples. Liquid chromatography-tandem mass spectrometry was used for Caspofungin quantification. The lower limit of quantitation (LLOQ) was 0.084 µg/ml.

Results. We analyzed 12 serum and 13 CSF specimens from 10 patients. While CAS serum levels obtained 3.0 to 48.0 (median 20.8) hours after intravenous CAS administration ranged from 0.6 to 20.3 (median 7.4) µg/mL (table 1, figure 1), CAS CSF levels were below the LLOQ of 0.084 µg/mL in 11 of 13 tested CSF specimens (table 1). In 2 patients with bacterial meningitis, 3 CSF specimens were obtained. In 1 patient with meningitis due to *Listeria monocytogenes* (table 1, patient 9) CAS level in CSF was 48% of the correlating serum level 3.5 hours after the first CAS infusion.

Results II. Interestingly, this correlating serum level was only 0.7 µg/mL (table 1, figure 1). In the other patient with severe sepsis and bacterial meningitis (due to *Rothia mucilaginosa*), 2 specimens were obtained at different time points (table 1, patient 10). While the CSF specimen obtained 24 hours after CAS infusion showed a CAS level of only 1.4% of the correlating serum level, in the specimen obtained 46 hours after infusion the CAS level was below the LLOQ.

pt	spec	sex	age (yrs)	underlying disease	interval[a] (hrs)	dose	indication for CAS	preceding CAS infusions[b]	CAS in CSF (µg/mL)	CAS in Serum (µg/mL)
1	A	m	2.4	AML	20.8	50mg/m^2	therap.	2	<LLOQ	7.4
2	A	m	9.3	ALL	23.3	50mg/m^2	therap.	15	<LLOQ	5.1
3	A	m	14.2	ic GCT	3.0	35mg/m^2	therap.	22	<LLOQ	9.4
3	B	m	14.2	ic GCT	24.0	35mg/m^2	therap.	28	<LLOQ	7.7
4	A	m	8.2	ALL	23.8	50mg/m^2	therap.	8	<LLOQ	2.3
5	A	f	7.5	AML	6.8	50mg/m^2	therap.	5	<LLOQ	19.4
6	A	m	3.3	ALL	41.5	35mg/m^2	proph.	14[c]	<LLOQ	0.6
7	A	m	1.0	ALL	18.3	50mg/m^2	proph.	27	<LLOQ	20.3
8	A	f	14.0	AML	48	50mg	proph.	12[c]	<LLOQ	2.7
8	B	f	14.0	AML	20.5	50mg	proph.	17	<LLOQ	7.4
9	A	f	11.0	AML	3.5	70mg	therap.	1	0.3	0.7
10	A	m	8.6	AML	46	35mg/m^2	proph.	5[c]	<LLOQ	n.d.
10	B	m	8.6	AML	24	35mg/m^2	therap.	8	0.09	6.5

Tab 1. Details on patient characteristics, Caspofungin (CAS) administration and CAS levels in cerebrospinal fluid (CSF) and serum. CAS doses were administered according to body surface and hepatic (dys-)function

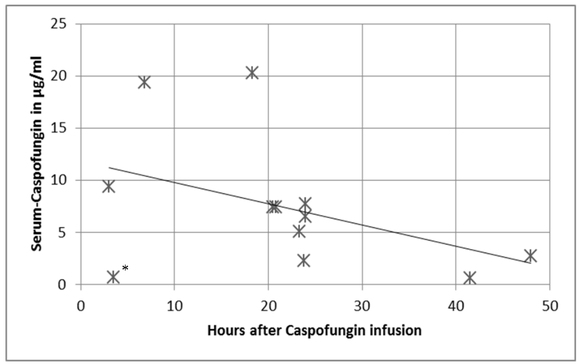
Tab.1, Abbreviations/Foot Notes:

pt – patient, spec – specimen, CAS – Caspofungin, CSF, cerebrospinal fluid, AML – acute myeloid leukemia, ALL – acute lympohblastic leukemia, ic GCT – intracranial germ cell tumor, therap. – therapeutic, proph. – prophylactic, LLOQ – lower limit of quantitation

[a]interval between administration and specimen collection

[b]prior to specimen collection,

[c]every other day (as antifungal prophylaxis)



* low serum level 3.5 hours after the first Caspofungin infusion in an 11-year old boy 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 (CAS) levels at different time points after intravenous CAS infusion.

Conclusions. Our results indicate **low capacity of Caspofungin to penetrate into the CNS** even in inflamed meninges. **Monotherapy with standard doses** of Caspofungin appears **not suitable for treatment of fungal CNS infections**.