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Very-High-Dose Caspofungin Combined with Voriconazole To Treat Central Nervous System Aspergillosis: Substantial Penetration of Caspofungin into Cerebrospinal Fluid

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Central nervous system (CNS) aspergillosis is a difficult-to-treat infection which remains associated with a severe outcome (1, 2). Among antifungals, voriconazole readily penetrates into both the cerebrospinal fluid (CSF) and brain abscesses and has shown encouraging efficacy in human CNS fungal infections (3). Although combination therapy in invasive aspergillosis is controversial, some authors advocate its use in the most severe forms of the disease, including CNS infection (4). It is commonly admitted that penetration of echinocandins into the CNS is poor (5), but human studies are scarce (6). Moreover, combination therapy to treat severe CNS aspergillosis could be an interesting therapeutic option. We report on the case of an immunocompromised patient with CNS aspergillosis successfully treated with a combination of voriconazole and a high dose of caspofungin. Substantial levels of caspofungin were found into the CSF.

Four months after receiving an orthotopic heart transplant, a 42-year-old man weighing 60 kg was admitted to the intensive care unit because of severe sepsis, altered consciousness, and left-sided hemiparesis. Brain computed tomography (CT) and magnetic resonance imaging (MRI) studies revealed a right cerebellar abscess and a left occipital abscess associated with signs of ventriculitis. Thorax CT showed diffuse nodular infiltrates. Renal failure present at admission required renal replacement therapy. The characteristics of CSF at admission (day 1 [D1]) are indicated in Table 1. At D1, galactomannan antigen titers (Platelia *Aspergillus* enzyme immunoassay; Bio-Rad Laboratory) in blood and CSF were 3 and 6.5, respectively, while PCR (7) was positive for *A. fumigatus* in both blood and CSF. Samples from bronchoalveolar lavage fluid (BAL fluid) grew *A. fumigatus*. Bilirubin, liver enzymes, and prothrombin time were all within normal ranges. Two days after admission, the patient was started on a combination of intravenous (i.v.) voriconazole (6 mg/kg body weight twice daily [b.i.d.] as a loading dose followed by 4 mg/kg b.i.d.) and i.v. caspofungin (280 mg as a loading dose followed by 140 mg/day). MICs of voriconazole and caspofungin, determined with Etest strips (AB Biodisk, Solna, Sweden), were 0.05 and 0.09 for the strain isolated from BAL fluid, respectively. Serum and CSF concentrations of antifungals were measured using high-performance liquid chromatography (HPLC).

The patient's neurological status remained poor, and external ventricular drainage was performed to relieve hydrocephalus on day 17. In addition, the patient underwent aspiration of the left occipital abscess. Caspofungin and voriconazole concentrations in cerebral pus were of 1.5 mg/liter and 1.6 mg/liter, respectively. Table 1 shows caspofungin and voriconazole concentrations in CSF and serum at different times. Notably, CSF concentrations of caspofungin were relatively high during the acute stage of the infection, well above the MIC for the pathogen. In contrast, these concentrations were lower in less-inflammatory CSF. These data are in line with data from experimental studies showing that brain caspofungin levels are higher in infected animals (8) and with numerous data showing that the penetration of hydrophilic anti-infective drugs increases with the intensity of blood-brain barrier inflammation. Moreover, in an animal model of CNS aspergillosis, caspofungin significantly reduced the fungal burden (9).

The patient received a 2-month course of voriconazole and

TABLE 1 Caspofungin and voriconazole concentrations in cerebrospinal fluid and serum at different time points

Parameter[a]	Day 1	Day 5	Day 11	Day 17[b]	Day 18[b]
CSF parameter					
WBC/μl	790	680	400	370	70
PMN (%)	80	80	75	60	60
Protein level (g/liter)	2.07	1.74	2.3	2.1	1.75
Glucose level (mmol/liter)	5.2	3.0	3.2	1.6	
Serum caspofungin concn (mg/liter)					
Trough		10	18.5	16.2	8.2
2 h and 8 h after administration				30.7 and 17.6	
CSF caspofungin concn (mg/liter)					
Trough		8	3.5	1	1
2 h and 8 h after administration				1.1 and 1	
Serum voriconazole concn (mg/liter)					
Trough		8.5	5.2	2.3	
2 h and 8 h after administration				4 and 2.9	
CSF voriconazole concn (mg/liter)					
Trough		3.7	3.4	0.9	1
2 h and 8 h after administration				1 and 1.1	

[a] CSF, cerebrospinal fluid; WBC, white blood cells; PMN, polymorphonuclear cells.
[b] On days 17 and 18, CSF samples were obtained from ventricular drainage.

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caspofungin, followed by oral voriconazole alone for 6 months, without any side effects attributable to antifungals. We conclude that relatively high concentrations of caspofungin may be obtained in the CSF provided that high doses are administered.

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REFERENCES

1. **Antinori S, Corbellino M, Meroni L, Resta F, Sollima S, Tonolini M, Tortorano AM, Milazzo L, Bello L, Furfaro E, Galli M, Viscoli C.** 2013. *Aspergillus* meningitis: a rare clinical manifestation of central nervous system aspergillosis. Case report and review of 92 cases. J. Infect. **66:**218–238. http://dx.doi.org/10.1016/j.jinf.2012.11.003.
2. **Spapen H, Spapen J, Taccone FS, Meersseman W, Rello J, Dimopoulos G, Charles P-E, Rao R, Pérez M, Martin C, Vogelaers D, Blot SI, AspICU Study Investigators.** 2014. Cerebral aspergillosis in adult critically ill patients: a descriptive report of 10 patients from the AspICU cohort. Int. J. Antimicrob. Agents **43:**165–169. http://dx.doi.org/10.1016/j.ijantimicag.2013.10.012.
3. **Schwartz S, Reisman A, Troke PF.** 2011. The efficacy of voriconazole in the treatment of 192 fungal central nervous system infections: a retrospective analysis. Infection **39:**201–210. http://dx.doi.org/10.1007/s15010-011-0108-6.
4. **Ehrmann S, Bastides F, Gissot V, Mercier E, Magro P, Bailly E, Legras A.** 2005. Cerebral aspergillosis in the critically ill: two cases of successful medical treatment. Intensive Care Med. **31:**738–742. http://dx.doi.org/10.1007/s00134-005-2605-5.
5. **Traunmüller F, Popovic M, Konz K-H, Smolle-Jüttner F-M, Joukhadar C.** 2011. Efficacy and safety of current drug therapies for invasive aspergillosis. Pharmacology **88:**213–224. http://dx.doi.org/10.1159/000331860.
6. **Okugawa S, Ota Y, Tatsuno K, Tsukada K, Kishino S, Koike K.** 2007. A case of invasive central nervous system aspergillosis treated with micafungin with monitoring of micafungin concentrations in the cerebrospinal fluid. Scand. J. Infect. Dis. **39:**344–346. http://dx.doi.org/10.1080/00365540600951333.
7. **Suarez F, Lortholary O, Buland S, Rubio MT, Ghez D, Mahé D, Quesne G, Poirée S, Buzyn A, Varet B, Berche, Bougnoux ME.** 2008. Detection of circulating Aspergillus fumigatus DNA by real-time PCR assay of large serum volumes improves early diagnosis of invasive aspergillosis in high-risk adult patients under hematologic surveillance. J. Clin. Microbiol. **46:**3772–3777. http://dx.doi.org/10.1128/JCM.01086-08.
8. **Flattery AM, Hickey E, Gill CJ, Powles MA, Misura AS, Galgoci AM, Ellis JD, Zhang R, Sandhu P, Ronan J, Abruzzo GK.** 2011. Efficacy of caspofungin in a juvenile mouse model of central nervous system candidiasis. Antimicrob. Agents Chemother. **55:**3491–3497. http://dx.doi.org/10.1128/AAC.01328-10.
9. **Clemons KV, Schwartz JA, Stevens DA.** 2012. Experimental central nervous system aspergillosis therapy: efficacy, drug levels and localization, immunohistopathology, and toxicity. Antimicrob. Agents Chemother. **56:**4439–4449. http://dx.doi.org/10.1128/AAC.06015-11.