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Favorable Outcome of Neonatal Cerebrospinal Fluid Shunt-Associated *Candida* Meningitis with Caspofungin

Jop Jans,[a] Roger J. M. Brüggemann,[b,e] V. Christmann,[c] Paul E. Verweij,[d,e] Adilia Warris[a,e]

Departments of Pediatric Infectious Diseases,[a] Pharmacy,[b] Neonatology,[c] and Medical Microbiology,[d] Radboud University Medical Centre, Nijmegen, Netherlands; Nijmegen Institute for Infection, Inflammation and Immunity, Radboud University Medical Centre, Nijmegen, Netherlands[e]

Invasive *Candida* infections associated with medical devices are very difficult to cure without device removal. We present a case of neonatal cerebrospinal fluid shunt-associated *Candida* meningitis, in which removal of the device was precluded, that was successfully treated with caspofungin. Pharmacokinetic assessment of caspofungin concentrations in cerebrospinal fluid showed that exposure was adequate in the presence of a high systemic exposure. In complex cases of neonatal *Candida* infections involving medical devices, the addition of caspofungin might be beneficial.

Candida spp. are the most common cause of invasive fungal infections in pediatric patients and are associated with substantial attributable mortality and morbidity, especially in premature neonates (1). Invasive *Candida* infections associated with medical devices, like central venous catheters and ventriculoperitoneal drains, are very difficult to cure without device removal. In some cases, removal is precluded, which significantly complicates patient management. The formation of *Candida* biofilms leads to an increased resistance to the antifungals commonly used in neonates, like fluconazole and amphotericin B (2). Recent *in vitro* data show that echinocandins retain their activity against *Candida* spp. in biofilms, while for the azoles and amphotericin B much higher MICs are measured (3–5).

For premature neonates, limited data are available about the safety, efficacy, and pharmacokinetics of echinocandins (6, 7). Optimal dosing schedules and cerebrospinal fluid (CSF) concentrations that correlate with a favorable outcome in the treatment of *Candida* meningoencephalitis are still subject to research (1, 8). In this report, we describe the successful treatment with caspofungin of a premature neonate suffering from *Candida* meningitis in the presence of a medical device. In addition, concentrations of caspofungin in both plasma and cerebrospinal fluid were measured.

A premature male Caucasian neonate, born by cesarean section after 26 weeks of gestation was admitted to our neonatal intensive care unit. Physical examination postpartum showed no abnormalities. Echography of the cerebrum showed intraventricular hemorrhage grade III. After the first week of life, the patient suffered from respiratory insufficiency requiring artificial ventilation, several episodes of infections caused by *Staphylococcus warneri* and *Ureaplasma urealyticum*, and a suspicion of a necrotizing enterocolitis requiring various antibiotic treatments. Development of increased ventricular dilatation and hydrocephaly required lumbar punctions to relieve the increased intraventricular pressure. At the age of 5 weeks, the lumbar punctions became ineffective and the patient received a subcutaneous cerebrospinal fluid reservoir (Omaya reservoir). A CSF sample taken during this surgical procedure grew *Candida albicans* associated with a high white blood cell count (454 cells/μl), elevated protein (5,470 mg/liter), and low glucose (0.5 mmol/liter). The concentration of C-reactive protein was 40 mg/liter (normal, <5 mg/liter). *In vitro* susceptibility was determined using the EUCAST broth microdilution method (http://mic.eucast.org/Eucast2/) (9). The isolated

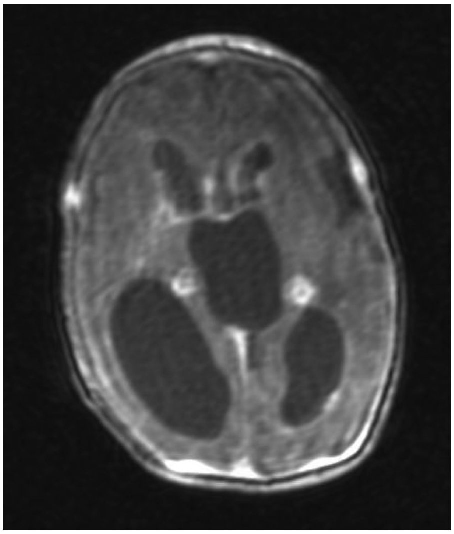

FIG 1 MRI-cerebrum showing progressive hydrocephalus and several thromboembolic foci in the parenchyma.

C. albicans was susceptible to fluconazole (MIC, 0.25 mg/liter), flucytosine (MIC, 0.125 mg/liter), amphotericin B (MIC, 0.5 mg/liter), and anidulafungin (MIC, 0.016 mg/liter). Isolates that test susceptible to anidulafungin are considered to be also susceptible to caspofungin (10). Cultures of urine and blood remained negative. Magnetic resonance imaging of the cerebrum (MRI-cerebrum) showed multiple foci consistent with *Candida* infection (Fig. 1). The fluconazole dose was increased to 12 mg/kg of body weight/day, flucytosine (100 mg/kg/day) was added, and the Omaya reservoir was replaced with a new one. After 2 weeks of treatment, the CSF remained positive for *C. albicans* and flucona-

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Address correspondence to Adilia Warris, A.Warris@cukz.umcn.nl.

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TABLE 1 Concentrations of caspofungin in plasma and cerebrospinal fluid obtained with an intravenous dosage of 25 mg/m^2 once daily

Day and time	Caspofungin concn[a] (mg/liter) Plasma	CSF	CSF/plasma ratio (%)
Day 1			
1 h	7.6		
6 h	6.4	0.12	2
12 h		0.16	
24 h	2.7		
Day 5			
6 h	6.4		
24 h	3.9	0.27	6.8
Day 12			
24 h		0.15	
Day 15			
24 h		0.27	
Day 18			
24 h	3.9		
Day 38			
24 h	3.5		

[a] For CSF, values are averages of samples taken from two or three different ventricular drains at the same time point.

zole was replaced by liposomal amphotericin B (3 mg/kg/day). C-reactive protein had decreased to normal values by that time. However, after another 2 weeks fundoscopy showed retinal *Candida* localizations and the CSF still remained positive for *C. albicans*. Caspofungin (25 mg/m^2) once daily was added after the patient's parents were informed about the off-label use and all national and local rules and regulations regarding this use were complied with. We refrained from intraventricular infusions due to the absence of data for caspofungin and due to reported arachnoidal inflammatory responses upon amphotericin B instillation. Sterilization of the CSF was achieved with normalization of the pleocytosis (29 cells/μl) and glucose levels (2.5 mmol/liter) without replacing the Omaya reservoir. After 7 weeks, the CSF remained sterile, the Omaya reservoir was replaced by a ventriculoperitoneal drain, and the combination antifungal therapy was switched to fluconazole (12 mg/kg/day) for another month. No increases in creatinine or liver enzymes were observed during the combination antifungal therapy. Follow-up at the outpatient clinic 1 year after treatment did not reveal any recurrence of the *Candida* infection, although the patient suffers from neurological sequelae.

Plasma and CSF concentrations of caspofungin were measured by means of a validated high-pressure liquid chromatography assay with fluorescence detection on day 1 and day 5 during the first week of caspofungin treatment and at later time points during treatment to monitor any variations during prolonged exposure (Table 1). After day 5 there was no further increase in plasma trough concentrations (C_{trough}), suggesting that a steady state had been reached.

To our knowledge, this is the first report evaluating concentrations of caspofungin in both plasma and CSF in the successful treatment of a neonatal cerebrospinal fluid shunt-associated *Candida* meningitis. We were able to achieve sterilization of the CSF in the presence of a cerebrospinal fluid shunt by adding caspofungin to the standard antifungal treatment. This supports results from *in vitro* studies showing an increased effectiveness of echinocandins against *Candida* infections associated with medical devices and biofilm formation (3, 5). Using the recommended dosage of 25 mg/m^2, we were able to detect adequate concentrations in plasma and CSF. Serial sampling showed increasing concentrations of caspofungin in the CSF while those in plasma decreased during the 24 h after administration, suggesting that a lower clearance of caspofungin from the CSF may be possibly beneficial. Penetration of an antifungal drug to the site of infection is a prerequisite for successful treatment. Previous reports observed low or undetectable levels of echinocandins in the CSF of adult patients because of their water solubility and high molecular mass (11, 12). Increased permeability of the blood-brain barrier of neonates compared to that of adults and inflammation of the meninges might explain the observed differences. In addition, a high systemic exposure of caspofungin being above the mean of the population predicted C_{trough} of 1.6 mg/liter reported by Neely et al. (13) and 1.9 mg/liter reported by Li et al. (14) will result in higher concentrations in the CSF and consequently might lead to improved efficacy of echinocandins. Support for an exposure-response relationship is provided by the observations from a rabbit model of neonatal *Candida* meningoencephalitis showing that relatively high micafungin concentrations in plasma were required to achieve therapeutic levels in the central nervous system (15).

A third aspect is that the relatively poor protein content of the CSF most likely results in a larger shift to a higher unbound fraction of caspofungin. The free-drug hypothesis states that only unbound drug is available for pharmacological activity. Hence, the combined effects of a higher systemic concentration, an increased permeability of the blood-brain barrier, and a higher free fraction of caspofungin in the CSF of neonates might result in an effective treatment option with a favorable outcome for complex *Candida* infections. However, the low echinocandin MIC of the isolate infecting our patient precludes extrapolation of our findings to neonates infected with *Candida* species with higher MICs such as observed for *Candida parapsilosis.*

With this report, the potential use of caspofungin in the treatment of *Candida* meningitis in neonates is illustrated. Sterilization of the CSF without removal of the shunt was obtained within only 72 h after adding caspofungin to the treatment regimen. Up to 7% of the caspofungin level in plasma was found in CSF, indicating that in this patient caspofungin penetrated into the CSF compartment. In complex cases of *Candida* infection in neonates that involve medical devices, the addition of caspofungin might be beneficial. In addition, therapeutic monitoring of caspofungin is a valuable tool to investigate the exposure-response relationship in the CSF in the treatment of neonatal *Candida* meningitis.

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