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

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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 punctures to relieve the increased intraventricular pressure. At the age of 5 weeks, the lumbar punctures 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

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-
trough concentrations (treatment to monitor any variations during prolonged exposure
week of caspofungin treatment and at later time points during
by means of a validated high-pressure liquid chromatography as-
sequelae.
Candida clinic 1 year after treatment did not reveal any recurrence of the
increases in creatinine or liver enzymes were observed during the
switched to fluconazole (12 mg/kg/day) for another month. No
peritoneal drain, and the combination antifungal therapy was
mained sterile, the Omaya reservoir was replaced by a ventriculo-
Sterilization of the CSF was achieved with normalization of the
complied with. We refrained from intraventricular infusions due
absence of the data for caspofungin and due to reported arach-
noidal 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) with-
out replacing the Omaya reservoir. After 7 weeks, the CSF re-
mained sterile, the Omaya reservoir was replaced by a ventriculo-
peritoneal drain, and the combination antifungal therapy was
switched to fluconazole (12 mg/kg/day) for another month. No
increases in creatine 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 as-
ay 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 concentra-
tions 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/m², 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 unetect-
able 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 echino-
candins. Support for an exposure-response relationship is pro-
vided by the observations from a rabbit model of neonatal Candida
meningoencephalitis showing that relatively high micaf-
fungin concentrations in plasma were required to achieve therape-
ugic 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 frac-
tion of caspofungin. The free-drug hypothesis states that only un-
bound 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 in-
festing our patient precludes extrapolation of our findings to ne-
onates infected with Candida species with higher MICs such as
observed for Candida parapsilosis.

With this report, the potential use of caspofungin in the treat-
ment 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 compart-
ment. In complex cases of Candida infection in neonates that in-
volve medical devices, the addition of caspofungin might be ben-
ficial. 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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