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Caspofungin for Refractory Fungal Infections in Infants and Children

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Invasive fungal disease is a life-threatening infection in immunocompromised children and premature infants.[1,2] On January 29, 2001, the Food and Drug Administration approved caspofungin acetate, a new antifungal for the treatment of *Candida* sp. infections. It is also indicated for the empirical treatment of fungal infections in febrile, neutropenic patients and the treatment of invasive aspergillosis in patients refractory to amphotericin or itraconazole. In clinical trials of adults, caspofungin has demonstrated an overall efficacy rate similar to amphotericin for the treatment of invasive candidal infections or fluconazole for the treatment of esophageal candidiasis.[1-5] Although not yet approved for use in children, caspofungin has been reported to be an effective therapy in infants and children with infections resistant to traditional antifungals.

Mechanism and Antifungal Spectrum

Caspofungin is the first of a new class of antifungals, the echinocandins, which inhibit the synthesis of β-(1,3)-D-glucan, an integral component of fungal cell walls. It has been demonstrated to have *in vitro* and *in vivo* activity against *Aspergillus* and *Candida* species. Activity against *Histoplasma capsulatum, Blastomyces dermatitidis, Pneumocystis carinii,* and *Coccidioides immitis* has also been reported. Resistance to caspofungin, resulting from mutations in *Candida* sp., has been reported in clinical use. The incidence of drug resistance is not known.[3-5]

Clinical Experience in Children

Within the last two years, a number of case reports have described the use of caspofungin, alone or in combination with other antifungals, in the treatment of refractory fungal infections in children.[6-11] The majority have involved invasive *Aspergillus* infections in immunocompromised children with chronic granulomatous disease or hematologic malignancies. Caspofungin has also been used successfully in the treatment of candidal endocarditis and in the treatment of persistent candidemia in an otherwise healthy 3 year old child. The loading dose of caspofungin in these reports has ranged from 1.4 to 5 mg/kg, given intravenously (IV), with a maintenance dose of 0.9 to 3 mg/kg/day. Some patients were treated without the use of a loading dose. The duration of treatment ranged from 2 to 8 weeks. Adverse effects were reported in only one patient, who developed mild elevations in liver enzymes, hypokalemia, and a decrease in hematocrit. All laboratory values returned to normal by the time of discharge.

In addition to these case reports, there have been several retrospective reviews of caspofungin use in children. In 2003, Franklin and colleagues at St. Jude Children's Research Hospital published a review of 25 immunocompromised children given caspofungin on a compassionate use protocol at their institution.[12] The patients ranged in age from 3 months to 26.2 years (median 9.8 years). Thirteen of the patients had a documented fungal infection, eight had suspected infection, and four were being given the drug as prophylaxis. Twenty-one patients were receiving concomitant liposomal amphotericin, three were receiving itraconazole, and three were receiving voriconazole.

Patients weighing 50 kg or more received standard adult doses (a 70 mg loading dose followed by a 50 mg/day maintenance dose). Patients less than 50 kg were treated with doses ranging from 0.8 to 1.6 mg/kg/day. The median duration of therapy was 32 days (range 1 to 116 days). Although the authors were unable to assess efficacy in this retrospective review, they reported that caspofungin appeared to be well tolerated. Only three patients experienced an adverse effect. All had hypokalemia, two also had elevated serum bilirubin levels, and one had an elevated alanine aminotransferase.[12]

The following year, Cesaro and colleagues published a prospective open-label study of the combination of liposomal amphotericin and caspofungin, followed by voriconazole, as prophylaxis in children and young adults with

refractory invasive fungal infections.[13] The authors enrolled 10 patients, with a median age of 13 years (range 6-24 years). All patients had hematologic malignancies and a proven or suspected fungal infection refractory to standard therapy. Liposomal amphotericin was initiated at 1-3 mg/kg/day, and increased to 5-6 mg/kg/day as needed. Caspofungin was administered according to data from a preliminary pharmacokinetic study in children,[14] with a loading dose of 70 mg/m^2 (maximum 70 mg), followed by 50 mg/m^2/day (maximum 50 mg).

In the eight patients with proven or probable fungal infection, response was classified as complete in four patients, stable in three, and as a treatment failure in one. At long-term follow-up (median 125 days), nine of the 10 patients were alive, with seven patients having had a complete response. The amphotericin-caspofungin combination was well tolerated. Hypokalemia occurred in eight patients, with thrombophlebitis and thrombosis in two patients. An increase in serum bilirubin was noted in two patients.

Caspofungin has also been used in the management of infants with invasive candidiasis. Hesseling and colleagues described the first use of caspofungin in an extremely low-birth-weight neonate in 2003.[15] The patient, a 24-week gestation neonate, developed a systemic candidiasis in the second week of life. Treatment with amphotericin and flucytosine failed to eradicate the organism. Because of mildly elevated liver enzymes, the patient was treated with a conservative caspofungin regimen consisting of a loading dose of 50 mg/m^2, followed by a daily dose of 35 mg/m^2. Caspofungin also failed to eradicate the infection and was discontinued after one week. The patient died two weeks later.

Subsequent reports have described successful treatment. In the December 2004 issue of the *Pediatric Infectious Disease Journal*, Odio and colleagues reported the results of treating 10 neonates (including nine premature neonates) with invasive infections caused by *C. albicans*, *C. prapsilosis*, *C. tropicalis*, and *C. glabrata*.[16] All of the neonates had been treated with amphotericin and/or fluconazole, but continued to have positive cultures during treatment. Because of the apparent resistance to amphotericin, caspofungin was initiated at a dose of 0.5 mg/kg/day for 3 days, followed by 1 mg/kg/day for 28 days in one patient and 1 mg/kg/day (10.5 mg/m^2/day) for two days, followed by 2 mg/kg/day (23.3 mg/m^2/day) for 15-21 days in the remaining patients. Caspofungin was given as a 1 hour infusion. All blood cultures became negative between days 3 and 7 of therapy (mean 4.3 days). Eight patients experienced a clinical cure, one patient had a relapse within 4 days after discontinuation but responded to a second course, and one patient expired. The authors reported no adverse effects.

In an abstract presented at the 2004 Pediatric Academic Societies meeting, Natarajan and colleagues reported similar results.[17] The authors conducted a retrospective review of 10 infants admitted to their neonatal intensive care unit who received caspofungin. All 10 were treated after failure to improve with conventional treatment (amphotericin with or without fluconazole). Five patients had *C. albicans*, four had *C. parapsilosis*, and one patient had both species. The median age at the time of diagnosis was 20 days (range 10 days to 5 months). Caspofungin was initiated at a median age of 38 days, at a dose of 1 mg/kg/day. Three of the 10 patients received an initial loading dose of 1.5 mg/kg.

Eight of the neonates achieved a cure, with a median time to negative cultures of 5 days. The median length of treatment was 24 days. The remaining two infants died shortly after therapy was initiated. Adverse effects were observed in two neonates: one developed thrombophlebitis and one had hypokalemia. Elevated liver enzymes were observed in three patients.

Pharmacokinetics

Caspofungin concentrations decline in a polyphasic pattern, resulting from its wide-spread distribution. A brief α–phase is followed by a longer β-phase, with an approximate half-life of 9 to 11 hours in adults. A final γ-phase exhibits a half-life of 40 to 50 hours. Approximately 90% of a dose is distributed to the tissues within 36 to 48 hours of administration. Caspofungin is highly protein bound (97%), primarily to albumin. It undergoes spontaneous chemical degradation, as well as metabolism through hydrolysis and N-acetylation. The metabolites are eliminated through the kidneys.[3-5]

A preliminary pharmacokinetic study in nine children given caspofungin 1 mg/kg/day revealed a β-phase half-life 32-42% lower than that reported in adults.[14] Caspofungin concentrations were lowest in the smaller, younger children. Based on these data, the investigators projected a dose of 50 mg/m^2/day would achieve serum caspofungin concentrations more like those observed in adults.

Drug Interactions

The concomitant use of caspofungin and cyclosporine is not recommended. In clinical

studies, some patients receiving this combination developed elevations in hepatic enzymes. In a retrospective study, 14 (35%) of the 40 patients on this combination developed elevated liver function tests. None of the patients developed clinical signs of hepatotoxicity. The mechanism of this interaction appears to be an increase in caspofungin concentrations. In two studies, cyclosporine increased the concentration of caspofungin by approximately 35%. If it is determined that the benefit of concomitant treatment outweighs the potential risk, liver function tests should be closely monitored.[3-5]

Caspofungin may reduce serum concentrations of tacrolimus by approximately 16 to 30%. Patients receiving both caspofungin and tacrolimus should have close monitoring of tacrolimus levels, with dose adjustment as necessary.[3-5]

Patients receiving caspofungin concomitantly with rifampin, an inducer of hepatic metabolism, should have their caspofungin dose increased to 70 mg/day. Patients receiving other hepatic enzyme inducers, such as carbamazepine, dexamethasone, efavirenz, nevirapine, or phenytoin, may also require an increase in caspofungin dose to 70 mg/day. The exact mechanism of these reactions is not yet known.[3-5]

Caspofungin is not stable in dextrose-containing solutions. Because of the lack of compatibility data at this time, caspofungin should not be mixed or infused with other medications.[3-5]

Adverse Effects

The most commonly reported adverse effects associated with caspofungin use during clinical trials in adults have included: phlebitis or thrombophlebitis (3.5-15.7%), headache (4.3-11.3%), fever and chills (2-17%), nausea and vomiting (1.8-6%), diarrhea (2-3%), and rash with or without pruritus (1-6.2%). In addition, eosinophilia has been reported in 3% of adults enrolled in clinical trials, as well as a decreased hemoglobin (3.1-12.3%), and a decreased white blood cell count (4.6-6.2%). Elevations in liver function tests and serum bilirubin have been reported in approximately 10-13% of adults in clinical trials. Hypokalemia has been reported in 2.9-10.8% of patients.[3-5] Similar changes in laboratory values have been reported in pediatric patients.[6-17]

Hypersensitivity reactions, including bronchospasm and anaphylaxis, have been reported in a small number of patients. Rare cases of clinically significant hepatic dysfunction, peripheral edema (including facial swelling), and hypercalcemia have been reported in clinical use. Pulmonary edema, adult respiratory distress syndrome, and pulmonary infiltrates have been reported in patients given caspofungin for *Aspergillus* infections.[3-5]

Dosing Recommendations

The recommended dosing regimen for caspofungin in adults consists of a 70 mg loading dose given IV on the first day of treatment, followed by a 50 mg dose given once daily, thereafter. Each infusion should be given over 1 hour. In patients who fail to respond to this regimen, the dose may be increased to 70 mg. Treatment is typically continued for a minimum of 2 weeks.[3-5] Based on the available literature, the recommended dosing regimen for infants and children is a 70 mg/m^2 loading dose, followed the next day by a maintenance dose of 50 mg/m^2 given once daily. As with adults, caspofungin should be administered IV over 1 hour.[1,13,17]

The maintenance dose of caspofungin should be reduced to 35 mg/day in adults with moderate hepatic function, after the standard 70 mg loading dose has been administered. It has been suggested that a comparable adjustment (a reduction to 35 mg/m^2/day) be made for children with moderate hepatic insuffiency.[1] No dosing guidelines are available for patients with severe hepatic dysfunction. Dosage adjustment is not necessary for patients with renal impairment. Caspofungin is not removed by hemodialysis.[3-5]

Availability and Cost

Caspofungin (Cancidas®; Merck) is available in 50 and 70 mg single-use vials.[5] The average wholesale price is $411.84 for the 50 mg vial and $530.55 for the 70 mg vial.

Summary

Caspofungin offers an alternative for the treatment of severe fungal infections in children. Its unique mechanism of action may be of benefit in patients who fail to respond to traditional therapy with amphotericin. More research is needed, however, to establish the efficacy and safety of this drug in the pediatric population before it can be considered first-line therapy.

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Pharmacology Literature Review

Acellular pertussis vaccine review

The authors of this review provide a concise history of the vaccine and the results of a meta-analysis of 52 studies conducted with this product. Information on adverse effects collected after routine implementation of the acellular product is also included. Casey JR, Pichichero ME. Acellular pertussis vaccine safety and efficacy in children, adolescents, and adults. **Drugs 2005;65:1367-89.**

Adherence to stimulants

A retrospective study of the Texas Medicaid prescription claims database was conducted to evaluate adherence, or compliance, with stimulant medication in children and adolescents. Three types of treatment were evaluated: amphetamine salts, immediate-release and extended-release methylphenidate. The overall level of adherence was low. The authors found the highest levels of persistence (consecutive refill history) and medication possession (actual number of days of therapy divided by the optimum days) in patients treated with extended-release methylphenidate. Younger patients (ages 5 to 9 years) had higher adherence rates than older patients. No gender-related differences were found. While this study can provide only a general impression of medication adherence, it generates several interesting ideas for future prospective studies. Sanchez RJ, Crismon ML, Barner JC, et al. Assessment of adherence measures with different stimulants among children and adolescents. **Pharmacotherapy 2005;25:909-17.**

Short-course therapy for pneumonia

Studies addressing the use of short-course (typically 3-day) treatment regimens for children with community-acquired pneumonia are the subject of this review. Based on the available data, the authors suggest that short-course regimens are equally as efficacious as traditional regimens, and may reduce the emergence of resistance, decrease cost, improve compliance, and produce fewer adverse effects. Qazi S. Short-course therapy for community-acquired pneumonia in paediatric patients. **Drugs 2005;65:1179-92.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 7/22/05:

1. An intravenous formulation of esomeprazole (Nexium® IV) was added to the Inpatient Formulary. It is restricted to use in the prevention of recurrent peptic ulcer bleeding, gastroesophageal reflux disease associated with a history of erosive esophagitis, pathologic hyersecretion, or stress ulcer prophylaxis. Intravenous pantoprazole was deleted.
2. Tegaserod (Zelnorm™), a partial serotonin-4 agonist, was added to both Inpatient and Outpatient Formularies for irritable bowel syndrome and chronic constipation. Prescribing is restricted to Gastroenterology.
3. The restriction on paricalcitol (Zemplar®) limiting it to patients unable to take calcitriol was removed.

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