

Caspofungin

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*Manuscript received: October 15, 2007; Initial review completed: February 1, 2008;
Revision accepted: February 18, 2008.*

ABSTRACT

Caspofungin is a new antifungal drug meant for intravenous use. It has been shown to be comparable to other antifungal agents such as amphotericin B and fluconazole for empirical therapy in febrile neutropenic patients, oropharyngeal/esophageal candidiasis and invasive aspergillosis. Its efficacy has also been documented in children in small uncontrolled trials. The biggest assets of caspofungin are its excellent tolerability/safety profile and minimal drug interactions.

Key words: *Caspofungin, Children, Fungal infections.*

Invasive fungal infections are important causes of morbidity and mortality especially in cancer patients on chemotherapy, post-transplant (renal, bone marrow) patients, immunodeficient children and premature neonates. The introduction of newer and less toxic antifungals like lipid formulations of amphotericin B, newer azoles/triazoles and echinocandins has improved the treatment of these subjects. Caspofungin belonging to a new class of antifungal drugs 'echinocandins' is the latest entry. This article briefly highlights the clinical pharmacology, indications, and therapeutic efficacy of this drug in the pediatric perspective.

PHARMACOLOGY

The oral bioavailability of caspofungin is low (<0.2%) and therefore it is given intravenously. It is extensively bound to albumin (~97%) and distribution into red blood cells is minimal. Caspofungin is metabolized in the liver by hydrolysis and N-acetylation to form inactive products. The metabolism is not dependent on renal or hepatic function and the cytochrome P450 enzyme system is

not involved. Since the half-life is long (12-16 hours), it can be given once daily.

Since the weight-based approach may result in sub-optimal plasma concentrations, body surface area is used for dose calculation(1). Loading dose of 70 mg/m² is followed by a maintenance dose of 50 mg/m². Loading dose is not required for oropharyngeal or esophageal candidiasis. Duration of treatment is based on the severity of the patient's underlying disease, recovery from immunosuppression, and clinical response to treatment. Empirical therapy in febrile neutropenic patients should be continued until resolution of neutropenia. Patients with proven fungal infection should be treated for at least 14 days and treatment should continue for at least 7 days after both neutropenia and clinical symptoms are resolved. The safety information on treatment durations of more than 4 weeks is inadequate; however limited data suggest that it continues to be well tolerated with prolonged courses (up to 162 days).

The drug is available commercially as 50 mg vial with dry white powder for intravenous (IV) infusion.

The lyophilized vials should be stored refrigerated at 2° to 8° C. After reconstitution with normal saline or distilled water (dextrose containing diluents are not recommended), the drug is recommended to be infused in 250 mL of normal saline or ringer lactate over one hour. In small children and neonates, the volume of the infusate should be reduced proportionately (20-30 mL for neonates, 50-100 mL for small children). It is contraindicated in patients with hypersensitivity to any component of this product.

Drug interactions: Since caspofungin is not an inhibitor of the enzymes in the cytochrome P450 (CYP) system, it does not induce the cytochrome dependent metabolism of other drugs. The pharmacokinetics of caspofungin is not altered by itraconazole, amphotericin B, mycophenolate, nelfinavir, and vice-versa. Caspofungin reduces the blood levels of tacrolimus, and standard monitoring of blood concentrations and appropriate dosage adjustments are recommended when these drugs are used simultaneously. Rifampicin has been shown to decrease the caspofungin trough concentrations by 30% and hence patients on rifampicin should receive a higher dosage of caspofungin. In addition, co-administration of other inducers of drug clearance (efavirenz, nevirapine, phenytoin, dexamethasone, carbamazepine) with caspofungin results in clinically meaningful reductions in caspofungin concentrations requiring a higher dosage. Cyclosporine increases the area under curve of caspofungin by about 35%, although plasma concentration of cyclosporine is not altered by co-administration of caspofungin. Patients who develop abnormal liver function tests during concomitant therapy should be monitored and the risk/benefit of continuing therapy should be evaluated.

Dose adjustments: No dose adjustment is necessary in mild hepatic insufficiency (Child-Pugh score 5-6). However, in patients with moderate hepatic insufficiency (Child-Pugh score 7-9), reduction of dose to 35 mg/m² daily is recommended after initial loading dose of 70 mg/m² on Day 1). There is no clinical experience in patients with severe hepatic insufficiency (Child-Pugh score >9). No dosage adjustment is necessary for patients with renal insufficiency. Caspofungin is not dialyzable, thus

supplementary dosing is not required following hemodialysis.

Mechanism of action: Caspofungin acetate inhibits the synthesis of β (1,3)-D-glucan (not present in mammalian cells), an essential component of the cell wall of the fungi by non-competitive inhibition of the enzyme β (1,3)-D-glucan synthase.

Anti-fungal spectrum: Caspofungin has shown fungicidal activity against yeasts (*Candida albicans*, *Candida glabrata*, *Candida parapsilosis*, and *Candida tropicalis*). It exhibits fungistatic activity against filamentous fungi such as *Aspergillus* species (*Aspergillus fumigatus* and *Aspergillus flavus*). Unlike amphotericin B and the triazoles, caspofungin is active against the cysts of *Pneumocystis jiroveci*. Caspofungin, however, lacks activity against *Cryptococcus* (the cell wall does not contain β (1,3)-D-glucan), *Histoplasma capsulatum*, *Fusarium* spp. and *Zygomycetes*. **Table I** compares caspofungin to other anti-fungal drugs.

CLINICAL EFFICACY

The efficacy of caspofungin in adults has been evaluated in large multicentric randomized controlled trials.

Adult studies: Caspofungin was non-inferior to liposomal amphotericin B (LMB) in a large double-blind multinational trial including 1095 patients(2) and itraconazole in open labeled study including 200 patients(3) as empirical therapy for febrile neutropenia, with significantly less toxicity. It has been shown to be equally efficacious and well tolerated as fluconazole in HIV patients with documented *Candida* esophagitis(4). Studies comparing caspofungin and amphotericin B for esophageal and oropharyngeal candidiasis in HIV infected patients have shown higher success rates with caspofungin with significantly less adverse effects(5). Similar results have been reported for the treatment of invasive candidiasis (including peritonitis, abdominal abscess, septic arthritis and endocarditis) or candidemia(6-9). Caspofungin has not been compared directly with voriconazole for febrile neutropenia or candidiasis.

Caspofungin has been used with favorable

TABLE I COMPARISON OF VARIOUS ANTI-FUNGAL AGENTS

	Caspofungin	Fluconazole	Voriconazole	Amphotericin B
Class	Echinocandins	First generation triazole	Second generation triazole	Polyenes
Antifungal Spectrum	Aspergillus species, Candida species (Rhizopus, Scedosporium, Fusarium less susceptible)	Cryptococcus, most Candida species, Coccidiomycosis, <i>H. capsulatum</i>	<i>Aspergillus</i> spp., <i>Candida</i> spp., <i>Fusarium</i> spp., <i>C. neoformans</i> , <i>H. capsulatum</i> , Malassezia species	Cryptococcus, Candida species, Coccidiomycosis, <i>Histoplasma capsulatum</i> , Blastomyces, Aspergillus,
Ineffective against	Cryptococcus, <i>Fusarium</i> spp and Zygomycetes	<i>Candida krusei</i> , <i>candida glabrata</i> , Aspergillus species	Rhizopus, non-albicans candida, zygomycosis	Dermatophytes, <i>Candida lusitanae</i> , scedosporium, fusarium, trichosporon
Metabolism and excretion	Liver by hydrolysis and N-acetylation; half-life, 12-16 hours; protein binding, ~97%	Cytochrome P450; Half-life, 24 hours; protein binding, 11%. Excretion: > 80% unchanged drug in urine	Cytochrome P450 (extensive); half-life, e ⁻ 24 hours; protein binding, 58% Excretion: renal (< 2%)	60 % in liver; Half-life 15 days; protein binding > 90%. Excretion: slowly in urine and bile
Route of administration	Intravenous	Intravenous, oral	Intravenous, oral	Intravenous
Common adverse effects	Fever, infusion-related complications, phlebitis, nausea, vomiting, rash, increased transaminases	Nausea, diarrhea, rash, elevated transaminases	Transient visual disturbances (increased brightness and blurred vision), rash	Acute infusion related reactions, nephrotoxic, hypokalemia, anemia, leucopenia,
Dose reduction in renal failure	Not Required	CrCl* > 50 mL/min: same; 10-50: reduce dose to 50%; <10: reduce dose to 25 %	Oral: not required. IV: if CrCl* < 50 mL/min, use oral formulation	CrCl* > 50 mL/min: same; 10-50: same; < 10: reduce dose by 50 %
Dose reduction in hepatic failure	Mild: Not required; moderate: 35 mg/m ² OD; Severe: No experience	Not required	Not required for acute hepatic injury; half maintenance dose in mild and moderate; drug not recommended in severe cirrhosis	Not required
Dose	Load: 70-mg/m ² day 1 OD; maintenance: 50 mg/m ² OD	6-12 mg/kg/day OD	Load: 6 mg/kg IV BD Day 1; maintenance: 4-8 mg/kg/day BD	1-1.5 mg/kg/day OD; liposomal 5 mg/kg/day

*CrCl, creatinine clearance

TABLE II PEDIATRIC STUDIES ON CASPOFUNGIN

Study Design	Study Population	Safety	Summary of Results
Multicenter, retrospective(12)	64 immuno compromised patients single agent (<i>n</i> =20) or in combination (<i>n</i> =44)	Clinical AEs mild to moderate, none severe to lead to discontinuation	Complete responses, partial responses or stabilization observed in 5/7/3 of 17 patients with proven, in 3/4/3 of 14 patients with probable & in 7/6/1 of 15 patients with possible invasive infections. 13/16 patients on empirical therapy completed without breakthrough infection
Retrospective(13)	40 children with invasive aspergillosis, Severe neutropenia in 31 (78%)	Combination therapy well tolerated	Favorable response, 21 patients (53%); probability of 100-day survival, 70%
Retrospective (14)	20 children (11 aspergillosis, 7 candidiasis, 2 Rhodotorula 1st line (<i>n</i> = 7) or salvage (<i>n</i> = 13)	CAS well tolerated. 9 patients experienced 11 AEs, none severe to lead to discontinuation	Successful as a 1st line (75 % CR and 5% survival) or as monotherapy (100 % CR and 75 % survival). Salvage therapy rescued 8 of 13 children (only 5 survived) Sample size small and combination anti-fungal used
Retrospective (15)	56 patients with febrile neutropenia	10 (15% of courses) had adverse drug-related event. Rash and hypokalemia was the most common.	53 (79%) courses resulted in an overall favorable response
Case series(16)	10 neonates with invasive candidiasis resistant to amphotericin B	Renal and hepatic function tests, normal. There were no attributable clinical AEs	All positive blood cultures cleared between 3-7 days after initiation, the atrial vegetation resolved and the renal Candida bezoars disappeared

AE, adverse events

response rates either alone(10) or in combination with other antifungals(11) for documented or probable invasive aspergillosis as a salvage therapy in patients either intolerant or refractory to other antifungals. No data regarding use of caspofungin monotherapy for initial treatment of aspergillosis are available.

Pediatric and neonatal studies: Data regarding efficacy in children is limited to uncontrolled studies and case series (**Table II**). Most pediatric or neonatal studies evaluating caspofungin have small sample size and are non-randomized(12-16). Moreover, most studies have included heterogeneous group of patients having candidiasis or aspergillosis. A multicentric retrospective survey on immunocompromised children included 64 patients (median age: 11.5 years) with hematological malignancies ($n=48$), marrow failure ($n=9$), solid tumors ($n=3$), hematological disorders ($n=2$) and congenital immunodeficiency ($n=2$) who received caspofungin for proven ($n=17$), probable ($n=14$) and possible ($n=17$) invasive fungal infections or empirically ($n=16$). Overall, caspofungin displayed favorable safety and tolerance(12).

A favorable response to antifungal therapy was documented in 53% (21 out of 40) children having malignant disease who developed invasive aspergillosis(13). A retrospective review evaluating the response to caspofungin in 56 febrile neutropenic children has shown overall favorable response in 79% (15). Caspofungin has also been shown to be effective, safe and well tolerated as an alternative therapy for persistent and progressive candidiasis in neonates who were unresponsive or intolerant to amphotericin B (16).

ADVERSE DRUG REACTIONS (ADR)

Toxicity associated with echinocandins is infrequent because their action is specific to fungal cell walls (glucan is not found in mammalian cells). The most commonly encountered ADR include fever (12-39%), phlebitis at the infusion site (12-18%), headache (up to 15%) and nausea (up to 9%). Rare cases of skin rashes and pruritus have been reported. Renal tolerability is excellent, even on prolonged treatment. Transient mild-to-moderate elevations in alanine and aspartate transaminases levels have been noted.

These were not more common than in patients receiving amphotericin B or fluconazole.

COST ANALYSIS

The pharmacoeconomic analysis suggests that based only on differences in drug acquisition cost and renal toxicity, the use of caspofungin instead of amphotericin B in patients with candidaemia may be a cost-saving strategy from the hospital perspective(17). Similarly, the comparisons of cost estimates are lower for caspofungin than for liposomal amphotericin B in febrile neutropenia(18). In another analysis from Spain, voriconazole was more cost-effective option than caspofungin in invasive aspergillosis(19).

CONCLUSIONS

Caspofungin appears to be a promising new drug for invasive fungal infections. Antifungal spectrum includes yeasts like *Candida* (including those resistant to amphotericin B and azoles), filamentous fungi including aspergillosis, certain dimorphic fungi and *Pneumocystis jiroveci*. It appears to be an effective treatment option for empirical antifungal therapy in febrile neutropenic patients, invasive/oropharyngeal/oesophageal candidiasis and salvage therapy for invasive aspergillosis. The biggest assets of caspofungin are its excellent tolerability/safety profile and minimal drug interactions. However, use in children is limited to uncontrolled studies enrolling a small number of patients, and large scale randomized studies are required to evaluate its comparative efficacy with other antifungal drugs.

Contributors: AP contributed towards literature search and prepared the manuscript. APD conceptualized the idea, edited and approved the final version. He will act as guarantor. DS contributed towards literature search and draft.

Funding: None.

Competing Interests: None stated.

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