

Caspofungin: the first agent available in the echinocandin class of antifungals

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Caspofungin acetate (Cancidas, MK-0991, L-743,872) is a parenteral antifungal agent indicated in the treatment of invasive aspergillosis in patients who are intolerant of or whose infection is refractory to other antifungal therapies. It is the first member of a novel class of antifungals, the echinocandins, to be made available in the USA. As a class, the echinocandins possess a mechanism of action that is distinct from those of the polyenes, azoles, allylamines, or flucytosine. Echinocandins inhibit synthesis of β -(1,3)-D-glucan, a component of fungal cell walls (1).

SPECTRUM OF ACTIVITY

Caspofungin has demonstrated in vitro antifungal activity against *Aspergillus fumigatus*, *A. flavus*, *Candida albicans* (including fluconazole-resistant strains), *C. glabrata*, *C. krusei*, *C. tropicalis*, *C. parapsilosis*, and other *Candida* species. Intermediate in vitro activity has been demonstrated against *Histoplasma capsulatum* and *Blastomyces dermatitidis*. *Cryptococcus neoformans*, *Trichosporon beigelii*, and *Fusarium* spp. have demonstrated in vitro resistance to caspofungin. Caspofungin has also demonstrated some efficacy in animal models of *Pneumocystis carinii* infection (1–9).

PHARMACOKINETICS

Oral bioavailability was demonstrated to be poor in animal studies (0.3% to 1% in mice), resulting in a 300-fold reduction in clinical activity. As a result, caspofungin is available only as a parenteral agent. Approximately 92% of a single dose is distributed to tissues after 36 to 48 hours. Plasma concentration declines in a triphasic manner following each dose; the second phase is predominant, with an associated plasma half-life of 9 to 11 hours. However, because distribution to peripheral tissue is the primary mechanism by which caspofungin is cleared from the plasma, rather than metabolism or excretion, this is not reflective of the total body half-life of the drug. Caspofungin is approximately 97% bound to albumin; therefore, its apparent volume of distribution is only slightly greater than the plasma volume (10, 11).

Caspofungin is slowly metabolized by hydrolysis and *N*-acetylation. These metabolites are further degraded before being eliminated renally. No clinically significant differences in metabolism were observed in individuals of different sexes (12, 13), ages (12), or races (1).

Single-dose and multiple-dose studies have been performed in volunteers with varying degrees of renal impairment (includ-

ing end-stage renal disease). Although renal insufficiency caused a modest increase in caspofungin concentrations after a single dose (30% to 49% increase in area under the curve [AUC]), no differences were observed in caspofungin trough concentrations in multiple-dose studies. Modest increases in caspofungin AUC (19% to 55%) have been observed in single-dose and multiple-dose studies in patients with mild hepatic insufficiency (Child-Pugh score, 5–6). An average increase in caspofungin AUC of 76% was observed in patients with moderate hepatic insufficiency (Child-Pugh score, 7–9). No studies have been performed in patients with severe hepatic insufficiency (Child-Pugh score >9) (1).

ADVERSE EFFECTS

Most of the commonly reported adverse effects associated with caspofungin are mild in severity. Fever (16.2%), phlebitis (13.6%), infused-vein complications (5.7%), headache (8.3%), and nausea (3.9%) were the most commonly observed adverse effects in 228 patients with fungal infections other than aspergillosis enrolled in amphotericin B–controlled clinical trials. The most common laboratory abnormalities in these studies were elevations in aspartate aminotransferase (AST) (12.3%), alanine aminotransferase (ALT) (10.6%), and alkaline phosphatase (9.7%) and decreases in hemoglobin concentration (9.6%), serum potassium level (5.7%), and white blood cell count (5.7%). Each of these adverse effects was more common in patients receiving amphotericin B than in those receiving caspofungin (1).

In a smaller ($n = 69$) noncomparative trial for the treatment of invasive aspergillosis, caspofungin was somewhat better tolerated. Fever, infused-vein complications, nausea, vomiting, and flushing were each reported in 2 patients (2.9%). Laboratory abnormalities that were reported included increased urine protein (4.9%), eosinophilia (3.2%), increased alkaline phosphatase (2.9%), decreased serum potassium (2.9%), and increased urine red blood cells (2.2%). Serious adverse events were noted in 2 patients during this study, one with hypercalcemia and one with pulmonary infiltrates/adult respiratory distress syndrome. The latter patient was withdrawn from the study because of the ad-

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verse effect; 2 other patients also withdrew because of adverse effects. In contrast to the previously mentioned studies of patients with nonaspergillosis infections, no increases in serum transaminases were noted in this study (1, 14).

While the adverse effects in both studies were judged by the investigators to be possibly, probably, or definitely related to the drug, it should be noted that patients in these clinical studies often had serious underlying conditions (e.g., HIV disease, bone marrow transplant, hematologic malignancy) requiring multiple concomitant medications.

DRUG INTERACTIONS

Caspofungin has not inhibited any cytochrome P450 isozyme in *in vitro* studies, nor has it inhibited the metabolism of CYP3A4 substrates in clinical studies. Caspofungin itself is not an *in vitro* substrate for P-glycoprotein and is a poor substrate for cytochrome P450 enzymes. Pharmacokinetic studies in healthy volunteers demonstrated a lack of interactions between caspofungin and itraconazole, mycophenolate, the active metabolite of mycophenolate, or amphotericin B (1).

Although caspofungin demonstrates poor affinity for the cytochrome P450 system *in vitro*, regression analyses of patient pharmacokinetic data suggest that coadministration of caspofungin with inducers or mixed inducer/inhibitors of drug clearance may result in clinically significant reductions in caspofungin concentrations. Results in a small number of patients receiving efavirenz, nelfinavir, nevirapine, phenytoin, rifampin, dexamethasone, or carbamazepine prior to and/or concurrent with caspofungin indicate that an increase in the maintenance dose from 50 mg to 70 mg daily (after a 70-mg loading dose) may be considered in patients receiving any of these drugs with caspofungin who do not respond clinically (1).

In one clinical study, 4 healthy subjects received caspofungin 70 mg on days 1 through 10, as well as two 3-mg/kg doses of cyclosporine 12 hours apart on day 10. On day 11, 3 of the 4 patients developed transient elevations of ALT that were 2 to 3 times the upper limit of normal. In a separate panel of subjects in the same study, 8 patients received caspofungin 35 mg daily for 3 days and cyclosporine 3 mg/kg on day 1. Two of the 8 patients developed small increases in ALT on day 2. In both studies, AST elevations paralleled those of ALT but were of smaller magnitude. The manufacturer recommends not using cyclosporine concomitantly with caspofungin unless the potential benefit outweighs the potential risk to the patient. However, given the potential interactions of alternative therapies with cyclosporine (e.g., additive nephrotoxicity with amphotericin B, significant pharmacokinetic interaction with itraconazole), concurrent therapy with appropriate monitoring is probably reasonable (1).

In other clinical studies, one 4-mg/kg dose or two 3-mg/kg doses of cyclosporine increased the AUC of caspofungin by approximately 35%. Caspofungin did not cause an increase in cyclosporine levels (1).

In a study of healthy subjects, caspofungin 70 mg was given on days 1 through 10, as well as two 0.1-mg/kg doses of tacrolimus 12 hours apart on day 10. The 12-hour tacrolimus AUC, the peak tacrolimus concentration, and the trough (12-hour) tacrolimus concentration were compared with the same values from a control period in which tacrolimus was administered alone. Co-

administration of caspofungin reduced the 12-hour tacrolimus AUC by 20%, the peak concentration by 16%, and the trough concentration by 26% compared with the control period. The manufacturer recommends monitoring tacrolimus blood concentrations and adjusting the dose accordingly, if necessary, if the agents are used together (1).

DOSING RECOMMENDATIONS

The manufacturer's recommended dose of caspofungin for patients with normal or mildly impaired hepatic function is 70 mg intravenously on day 1, followed by 50 mg daily. Patients with moderately impaired hepatic function should receive 70 mg on day 1, followed by 35 mg daily. There is no clinical experience in patients with severe (Child-Pugh score >9) hepatic insufficiency.

Limited safety data suggest that an increase to a daily dose of 70 mg is well tolerated, although efficacy in patients who do not respond clinically to 50 mg is unknown (1).

CLINICAL TRIALS

Efficacy and safety of caspofungin in the treatment of invasive aspergillosis was established in an open-label, multicenter, noncomparative study of adults with invasive aspergillosis who did not respond to or were intolerant of conventional amphotericin B, lipid formulations of amphotericin B, or azoles. A total of 69 patients were enrolled, and clinical outcome data were available for 63. Details on 56 of these patients (54 with outcome data) were presented at the 2000 Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) but have not been published in the scientific literature. The investigators concluded that caspofungin is effective and generally well tolerated in the treatment of well-documented aspergillosis in patients who did not respond to or were intolerant of other therapy.

Preliminary results from phase II trials comparing caspofungin 50 or 70 mg/day with conventional amphotericin B 0.5 mg/kg/day for 2 weeks in the treatment of endoscopically verified candidal esophagitis have been presented in a meeting abstract (15). Data for a total of 128 patients were presented. Decreases in symptoms and endoscopic lesions were documented in 85.1% of caspofungin-treated patients and 66.7% of amphotericin B-treated patients. Similar results were reported in another meeting abstract for a comparative trial of conventional amphotericin B 0.5 mg/kg/day and caspofungin 35, 50, or 70 mg/day for oropharyngeal or esophageal candidiasis in 105 HIV-infected patients. Since the same group conducted both of these studies, many patients were probably described in both (2).

Caspofungin has been evaluated in mouse models of histoplasmosis (16, 17), *Pneumocystis carinii* pneumonia (10), candidiasis (18, 19), and cryptococcosis (19).

ECONOMIC ISSUES

Although the cost impact of invasive aspergillosis has not been specifically studied, fungal infections have a significant economic impact in pharmacy and nonpharmacy costs. The *Table* lists acquisition costs and year 2000 usage for several systemic antifungal agents. Fluconazole is included because of the *in vitro* and limited clinical data supporting the use of caspofungin in candidal infections. It should be noted that caspofungin has not

Table. Costs and expenditures for selected systemic antifungal agents

Product, route	Reference dose	Acquisition cost/day
Amphotericin B deoxycholate, IV	50 mg	\$4.45
Amphotericin B liposomal, IV	350 mg	\$496.44
Itraconazole, IV	200 mg	\$135.59
Itraconazole, oral	200 mg	\$11.52–\$12.83
Fluconazole, IV	400 mg	\$100.96
Fluconazole, oral	400 mg	\$19.14–\$24.81
Caspofungin, IV	70 mg	\$367.66
Caspofungin, IV	50 mg	\$285.40

been thoroughly evaluated for treatment of infections in which any of the other agents would be appropriate.

SUMMARY

Caspofungin represents a useful option for the treatment of invasive aspergillosis. It was approved by the Food and Drug Administration on the basis of one noncomparative trial in <100 patients whose disease was refractory to other therapies. This agent has not been studied as a first-line therapy for invasive aspergillosis, nor has it been extensively studied in invasive fungal infections caused by other organisms. At present, caspofungin's use should be restricted to single-agent therapy of documented invasive aspergillosis in patients who are intolerant of or whose disease is refractory to amphotericin B and/or itraconazole therapy. Its lower cost and probable superior tolerability compared with liposomal amphotericin B make caspofungin an intriguing candidate for first-line therapy when more data are available.

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