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Safety and tolerability of caspofungin acetate in the treatment of fungal infections

Key words:
caspofungin; echinocandin; esophageal candiasis; aspergillosis; safety

Note: The institutional review boards at the participating centers approved the protocols included in this summary. Informed consent was obtained from all enrolled patients.

Abstract: Caspofungin acetate is the first member of the novel echinocandin class of antifungal drugs to be marketed in the United States. It has recently been approved for use in patients with invasive aspergillosis who are refractory to or intolerant of conventional therapy. Accordingly, its safety profile is particularly important to review. The safety and tolerability of caspofungin have been examined in 623 persons, including 295 patients who received ≥ 50 mg/day for at least one week in clinical studies. In the 263 patients, given caspofungin in randomized double-blind active-control trials to date, there have been no serious clinical or laboratory drug-related adverse events; caspofungin was discontinued in only 2% of these patients because of drug-related adverse experiences. Caspofungin may have potentially important drug interactions with cyclosporine and tacrolimus.

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Caspofungin acetate (MK-0991, Cancidas®) is a semisynthetic lipopeptide derivative of pneumocandin B_0 that noncompetitively inhibits the synthesis of the β-(1, 3)-D-glucan component of the cell wall of many fungi, including *Candida*, *Aspergillus*, and the cyst form of *Pneumocystis carinii* (1). Since caspofungin and other drugs of the novel echinocandin class act on a component of fungal cell walls not present in mammalian cells, these drugs were expected to have a high therapeutic index (2). Caspofungin was recently approved by the Food and Drug Administration for patients with invasive aspergillosis who are refractory to or intolerant of standard therapy and is currently the only drug of its class to be marketed in the United States.

Patients and methods

This review of safety and tolerability is largely based upon the 3 completed double-blind randomized studies of patients with esophageal or oropharyngeal candidiasis in which caspofungin at doses of 35, 50, or 70 mg was compared to amphotericin B deoxycholate 0.5 mg/kg/day

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or fluconazole 200 mg/day, all given as intravenous infusions once daily (3–5). The similar study designs (randomized double-blind active-control trials), patient populations (largely men with advanced HIV-infection), and treatment durations (7–14 days) in these studies allows them to be readily combined and summarized. Descriptive comparisons of the incidence of clinically important drug-related adverse events among treatment groups are presented for the combined data from the three trials; however, the nature of our retrospective analysis precludes hypothesis testing of these differences for statistical significance. A noncomparative study of caspofungin in severely compromised patients with invasive aspergillosis who were refractory to or intolerant of standard treatment provides the only available data on prolonged use (6).

For the purposes of this review, standard definitions of adverse experiences were used. An adverse experience was defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the study drug, whether or not determined to be related to that drug. An adverse experience was considered serious if life-threatening or the consequence of an overdose, or when the event resulted in any of the following outcomes: death; permanent or substantial disability; new or prolonged hospitalization; cancer or a congenital anomaly; or a medical or surgical intervention to prevent one of the above-mentioned complications. Clinical adverse experiences determined by the investigator or volunteered by the patient were recorded at each patient visit. Results from periodic laboratory tests were reviewed by the investigators to determine if abnormal findings should be classified as adverse events. When adverse experiences occurred, the investigator also assessed the seriousness of the event and its causal relationship to the study drug. Investigators recorded whether the adverse experience resulted in discontinuation of therapy. Any adverse experience judged even possibly related to the study drug was designated as "drug-related." All adverse experiences were recorded; however, since the occurrence of total adverse events is likely influenced to some degree by the patients' underlying disease processes, concurrent infections, and concomitant medications, we shall focus on drug-related adverse experiences.

Results

In Phase 1 studies comprising 274 subjects, caspofungin was generally well tolerated in single and multiple doses. The most common clinical adverse experiences in normal volunteers receiving caspofungin were headache and phlebitis at the infusion site. Most clinical adverse events were transient, mild to moderate in intensity, and did not result in discontinuation of therapy. Drug-related laboratory events, including elevations of serum alanine transferase (ALT) and/or aspartate transferase (AST) levels, were uncommon (3 out of 162 patients; $< 2\%$) in subjects given caspofungin without concomitant medications. Coadministration of cyclosporin A for 2 doses with caspofungin was associated with transient elevations of ALT levels to ≤ 3 times the upper limit of the normal range in 5 (42%) of 12 healthy subjects.

Caspofungin has now been administered to 349 patients in Phase II/III clinical trials as a one-hour intravenous infusion of 35 ($n = 34$), 50 ($n = 244$), or 70 mg ($n = 71$) dissolved in 0.9% saline solution to treat *Candida* ($n = 277$; 79%) or *Aspergillus* ($n = 72$; 21%) infections where it appeared to offer a similarly efficacious option to standard therapies (3–6). Detailed safety data are available from all but three of these patients who received 50 mg daily as part of a compassionate use protocol for invasive aspergillosis (6). The median duration of therapy was less than 2 weeks, but 35 patients (10%) received at least 50 mg/day of caspofungin for ≥ 4 weeks. The overwhelming majority (~90%) of patients enrolled in the studies of mucosal candidiasis were HIV-seropositive, almost all of whom had advanced immunodeficiency (median CD4 count < 50 cells/mL). Of the 72 patients with invasive aspergillosis, 20 (28%) had undergone bone marrow transplantation, 16 of which were allogeneic transplants. In addition, five patients (7%) had received allogeneic ($n = 2$) or autologous ($n = 3$) peripheral stem cells. Solid organs were transplanted in nine patients (13%), including five lung transplants.

In the three randomized double-blind active-control studies of caspofungin in the treatment of oropharyngeal and esophageal candidiasis, adverse experiences related to the study drugs were common in patients in all five treatment arms (caspofungin 35, 50, and 70 mg; amphotericin B 0.5 mg/kg; and fluconazole 200 mg), as might be expected in a population with advanced HIV-infection. Nonetheless, caspofungin was generally well tolerated at all doses tested (Table 1). There were no serious clinical or laboratory adverse experiences attributed to caspofungin; therapy was stopped in only 6 (2%) of 263 caspofungin-treated patients because of drug-related adverse events. Although patients died in each treatment arm, no deaths were directly related to caspofungin therapy.

The most commonly encountered drug-related clinical adverse experiences in the three caspofungin treatment groups were fever (12–26%) and phlebitis at the infusion site (12–18%) (Fig. 1A). Similar local complications were also observed in 17% of the fluconazole group and 23% of the amphotericin group. Although uncommon with both caspofungin and fluconazole, chills, headache, and rash were seen slightly more often in patients given caspofungin than with fluconazole, but less frequently than with amphotericin. In these composite data (3–5), the most apparent difference in drug-related clinical adverse events between the caspofungin and fluconazole groups was the reported incidence of drug-related fever. However, in the head-to-head comparison of caspofungin vs. fluconazole, drug-related fever developed only slightly more often in patients receiving caspofungin (3.6%) than fluconazole (1.1%). The discrepancy between the reported incidence of caspofungin-associated fever in the double-blind trials with fluconazole and amphotericin (Fig. 1B)

Frequency of clinical and laboratory adverse experiences in three randomized double-bind trials of treatment for esophageal and oropharyngeal candidiasis

Phase II/III Randomized Double-Blind Mucosal Candidiasis Studies	Caspofungin 35 mg		Caspofungin 50 mg		Caspofungin 70 mg		Amphotericin B 0.5 mg/kg		Fluconazole 200 mg	
	[N = 34]		[N = 164]		[N = 65]		[N = 89]		[N = 93]	
Adverse Experiences [AEs]	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Clinical AEs										
Drug-related[1]	17	(50)	74	(45)	36	(55)	84	(94)	30	(32)
Serious drug-related[1]	0	(0)	0	(0)	0	(0)	4	(5)	1	(1)
Therapy stopped due to drug-related[1]	2	(6)	0	(0)	1	(1)	3	(3)	0	(0)
Deaths[2]	3	(9)	9	(6)	3	(5)	7	(8)	6	(7)
Laboratory AEs										
Drug-related[1]	16	(49)	67	(41)	22	(34)	74	(83)	32	(35)
Serious drug-related[1]	0	(0)	0	(0)	0	(0)	1	(1)	0	(0)
Therapy stopped due to drug-related[1]	0	(0)	2	(1)	1	(2)	11	(12)	1	(1)

[1]AEs considered by the investigator to be possibly, probably, or definitely drug- related.

[2]No deaths were considered drug-related.

Table1

suggests that the reputation of an established comparator may influence the attribution of adverse events to the less familiar investigational drug even with adequate blinding.

The type and incidence of drug-related laboratory adverse experiences with caspofungin were generally similar to those observed with fluconazole therapy. The most common drug-related laboratory adverse experiences in the caspofungin treatment arms were increased levels of AST, ALT and alkaline phosphatase and decreased hematocrit and hemoglobin concentrations (Fig. 1C). Drug-related elevations in ALT levels were noted in 11–24% of patients treated with caspofungin. AST and alkaline phosphatase levels were typically increased in concert with ALT levels. Most of the elevations in these levels were < 5 times the upper limit of the normal range, transient, and did not limit therapy. Interpretation of these laboratory tests was often confounded by elevated baseline values, concurrent diseases, and concomitant medications. Serum concentrations of ALT, AST, and alkaline phosphatase were less commonly elevated in patients given the higher 2 doses of caspofungin compared to the 35 mg dose; the overall incidence of drug-related abnormalities in these enzyme levels was similar in patients receiving caspofungin, fluconazole or amphotericin. Drug-related reductions in hemoglobin levels developed in 3–12% of patients in the 3 caspofungin and fluconazole groups in contrast to more than a third of the amphotericin recipients. Small numbers (< 4%) of patients also experienced drug-associated leukopenia and/or thrombocytopenia, an incidence similar to that observed with fluconazole and amphotericin. None of the caspofungin-related cytopenias were regarded as serious adverse experiences.

Amphotericin recipients experienced more drug-related hypokalemia (32%) and elevated serum creatinine levels (28%) than patients receiving caspofungin or fluconazole. Hypokalemia occurred more often in the 70 mg caspofungin group (11%) relative to patients given the lower 2 doses of caspofungin (< 4%) or fluconazole (4%). Nephrotoxicity was rarely attributed to patients treated with either fluconazole or caspofungin; only one of 263 patients was felt to have developed a "probably" caspofungin-related increase in serum creatinine level to ~1.5 times his baseline value.

Although fewer patients with *Aspergillus* infections have been evaluated to date, the occurrence and pattern of drug-related adverse events associated with caspofungin therapy have resembled those observed in the *Candida* protocols despite longer durations of therapy (6). Figure 2 summarizes the drug-related adverse experiences in 69 patients from an on-going open-label noncomparative study of caspofungin as salvage therapy for documented invasive aspergillosis. The incidence of drug-related fever in this acutely ill population was 2.9%, similar to the rate of caspofungin-related fever observed in the direct comparative trial vs. fluconazole for the treatment of mucosal candidiasis.

Allergic reactions to caspofungin were uncommon in the 623 persons for whom data are presently available. Possible histamine-mediated symptoms have been reported in a few patients in the clinical studies, usually as isolated findings. One case of anaphylaxis occurred during the initial infusion in a patient receiving caspofungin on a compassionate use basis. The safety database has also been specifically reviewed for potential reactions to caspofungin-degradation products covalently bound to plasma proteins (7, 8). Across studies, no toxicity attributable to the low circulating levels of these complexes has yet been identified.

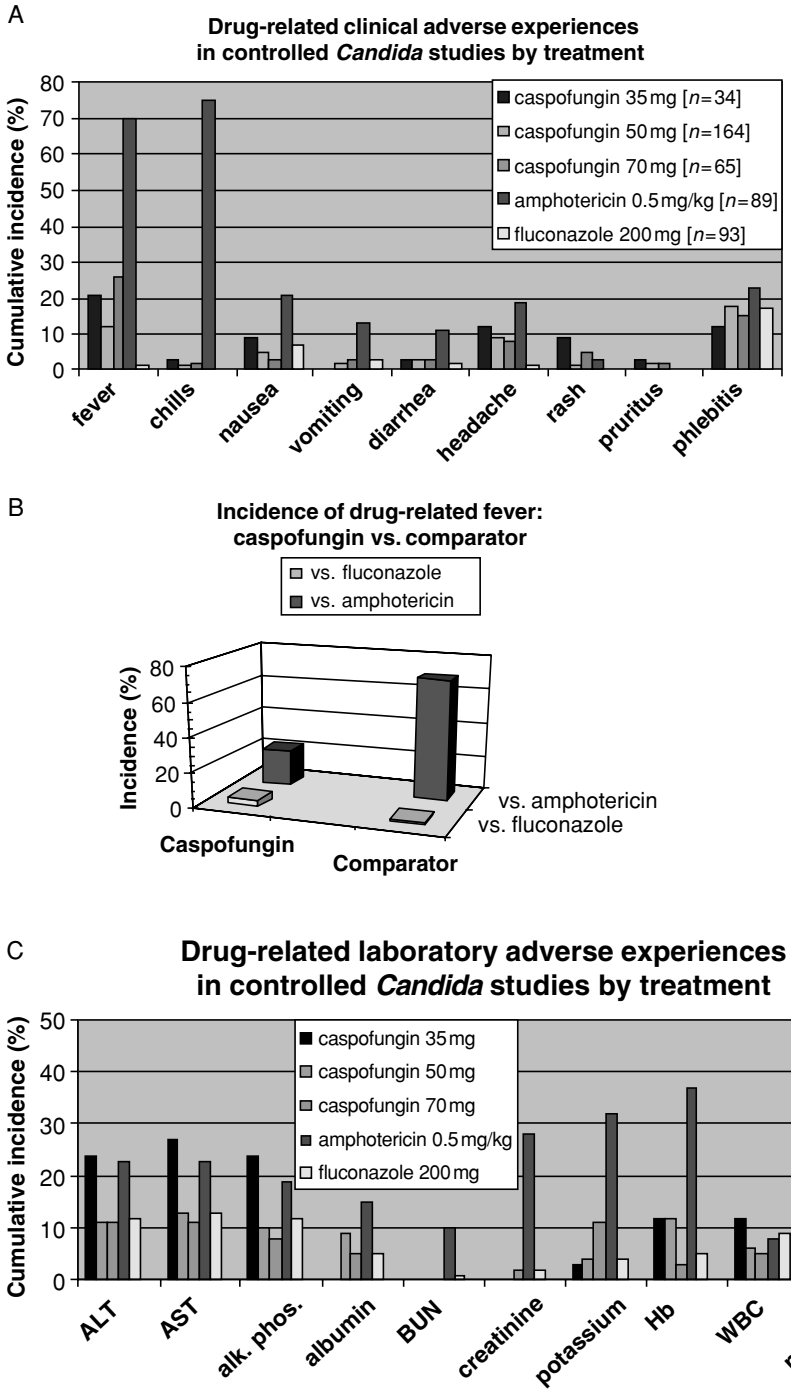

Fig. 1. **Selected drug-related clinical adverse experiences in the randomized double-blind studies of mucosal candidiasis. A. Cumulative incidence of the most frequent drug-related clinical adverse experiences in the 3 randomized double-blind active-control trials of caspofungin in the treatment of esophageal and oropharyngeal candidiasis**. Phlebitis refers to any signs of irritation or inflammation, with or without thrombosis, at the infusion site. **B. Cumulative incidence of drug-related fever in patients treated with caspofungin vs. the comparator drug (fluconazole or amphotericin) used in the randomized double-blind trials of esophageal and oropharyngeal candidiasis.** The graph presents the cumulative incidence of drug-related fever in 84 patients receiving caspofungin 50 mg vs. 93 patients given fluconazole 200 mg intravenously once daily from a single head-to-head study (*light block*) and 80 patients receiving caspofungin 50 mg vs. 89 patients given amphotericin 0.5 mg/kg intravenously once daily from two similar studies (*dark block*). **C. Cumulative incidence of the most frequent drug-related laboratory adverse experiences in the 3 randomized double-blind active-control trials of caspofungin in the treatment of esophageal and oropharyngeal candidiasis.** The bars give the frequency of abnormal elevations of serum levels of ALT, AST, alk. phos., BUN, and creatinine, and decreases in albumin level, Hb concentration, WBC, and platelet count. ALT, alanine transferase; AST, aspartate transferase; BUN, blood urea nitrogen levels; Hb, hemoglobulin; WBC, white blood count.

Caspofungin appears to have few significant drug interactions based on data from formal Phase I studies and population pharmacokinetic analyses (8, 9). Dosing need not be altered for patients on the basis of age > 18 years, race, gender, renal impairment or hemodialysis (10–12), but dose reductions are suggested for persons with moderate hepatic insufficiency. No dosing guidelines have been established for severe liver disease. Caspofungin is neither a substrate for nor an inhibitor of the cytochrome P-450 system, but some inducers of these enzyme systems (e.g., rifampin) may interact with caspofungin through different mechanisms.

Although caspofungin had no significant effect on cyclosporin A pharmacokinetics, plasma concentrations of caspofungin were moderately elevated by coadministration of cyclosporine, probably due to reversible inhibition of hepatic uptake of caspofungin. Two

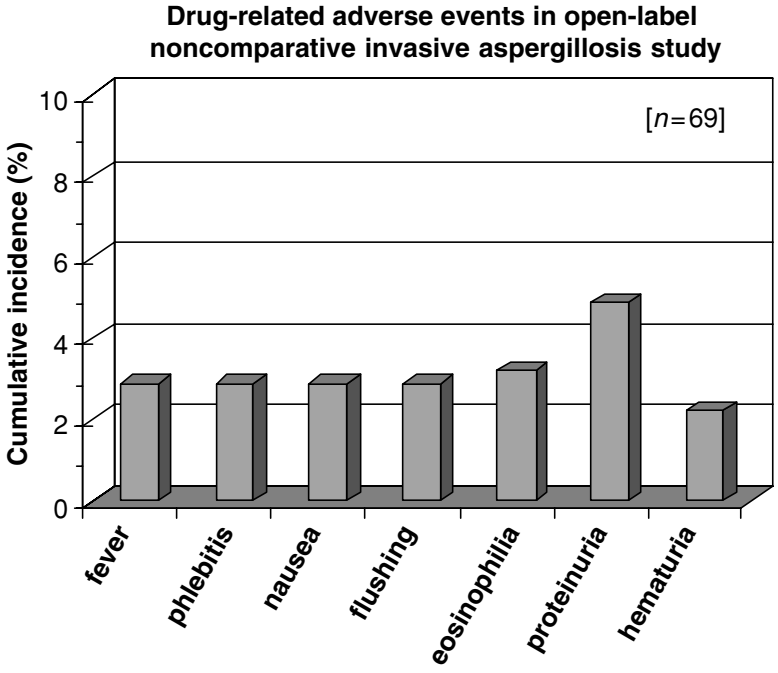

Fig. 2. **Cumulative incidence of selected drug-related adverse experiences in an open-label noncomparative study of caspofungin as salvage therapy for documented invasive aspergillosis**. The interim analysis of safety included 69 patients enrolled in this ongoing study.

studies were conducted in healthy volunteers to assess potential interactions between caspofungin and cyclosporine. Five of 12 subjects (43%) given 1 or 2 doses of cyclosporine while receiving caspofungin 70 mg daily experienced transient elevations of serum ALT levels to $\leq$3 times the upper limit of normal within 48 h of the administration of cyclosporine. Similar but smaller increases in AST concentrations were also seen in the same 5 subjects. These results led to the exclusion of patients receiving cyclosporine from the initial Phase II/III clinical studies. Pending further data, it is recommended that caspofungin be avoided in patients receiving cyclosporine.

The pharmacokinetics of caspofungin were unaltered by coadministration of tacrolimus, but caspofungin may reduce tacrolimus concentrations by up to 20%. Since tacrolimus has a narrow therapeutic index, standard monitoring of tacrolimus blood concentrations is advised for patients receiving concurrent therapy with caspofungin and tacrolimus. In healthy volunteers given 2 doses of tacrolimus while receiving caspofungin 50 or 70 mg/day, 7 subjects (37%) developed transient elevations of serum transaminase levels to $\leq$ twice the upper limit of normal (13).

Mycophenolate did not affect the pharmacokinetics of caspofungin; conversely, coadministration of caspofungin had no effect on the pharmacokinetic profile of mycophenolic acid or its active metabolite. The concurrent administration of these 2 drugs appeared to be well tolerated in healthy subjects.

Discussion

New and effective therapies are needed for invasive fungal infections. Caspofungin represents the first drug from the novel echinocandin class to be introduced into clinical practice. This drug was recently approved in the United States as salvage therapy for patients with invasive aspergillosis. Based on the presently available database, caspofungin appears to be generally well tolerated at doses between 35 and 70 mg daily. In a largely HIV-infected population of adult men with mucosal candidiasis, the nature and frequency of caspofungin-related adverse experiences were similar to those seen with parenteral fluconazole. Comparable tolerability has been seen with longer courses of caspofungin in the treatment of *Aspergillus* infections.

Serious drug-related adverse experiences and discontinuation of therapy because of drug-related adverse events have been uncommon in caspofungin recipients. Unlike conventional and lipid preparations of amphotericin, renal dysfunction has only rarely been attributed to caspofungin. There has been little apparent dose-dependent toxicity over the dosing range (35–70 mg daily) examined in Phase II/III trials to date, so higher doses could potentially provide a better therapeutic index for some cases of life-threatening angioinvasive mold infections. Possible adverse drug interactions with cyclosporine require further study. As with all new drugs, further experience and postmarketing surveillance are required to exclude unexpected toxicities.

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