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In Vitro Activities of Caspofungin Compared with Those of Fluconazole and Itraconazole against 3,959 Clinical Isolates of *Candida* spp., Including 157 Fluconazole-Resistant Isolates

M. A. Pfaller,[1,2]* D. J. Diekema,[1,3] S. A. Messer,[1] R. J. Hollis,[1] and R. N. Jones[4,5]

Departments of Pathology,[1] Epidemiology,[2] and Medicine,[3] University of Iowa College of Medicine and College of Public Health, Iowa City, and The Jones Group/JMI Laboratories, North Liberty,[4] Iowa, and Tufts University School of Medicine, Boston, Massachusetts[5]

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Caspofungin is an echinocandin antifungal agent with broad-spectrum activity against *Candida* and *Aspergillus* spp. The in vitro activities of caspofungin against 3,959 isolates of *Candida* spp. obtained from over 95 different medical centers worldwide were compared with those of fluconazole and itraconazole. The MICs of the antifungal drugs were determined by broth microdilution tests performed according to the NCCLS method using RPMI 1640 as the test medium. Caspofungin was very active against *Candida* spp. (MIC at which 90% of the isolates were inhibited [MIC_{90}], 1 μg/ml; 96% of MICs were ≤2 μg/ml). *Candida albicans*, *C. dubliniensis*, *C. tropicalis*, and *C. glabrata* were the most susceptible species of *Candida* (MIC_{90}, 0.25 to 0.5 μg/ml), and *C. guilliermondii* was the least susceptible (MIC_{90}, >8 μg/ml). Caspofungin was very active against *Candida* spp., exhibiting high-level resistance to fluconazole and itraconazole (99% of MICs were ≤1 μg/ml). These results provide further evidence for the spectrum and potency of caspofungin activity against a large and geographically diverse collection of clinically important isolates of *Candida* spp.

Presently we are witnessing the development and introduction into clinical practice of several new systemic antifungal agents, including both extended-spectrum triazoles and echinocandin antifungal agents (2, 3, 6, 15, 19–21, 23, 26). Both the new triazoles and the echinocandins exhibit a spectrum of activity that includes *Candida* and *Aspergillus* (6, 10, 15, 20, 21, 23). Whereas the new triazoles have the same mechanism of action (inhibition of ergosterol synthesis) as the licensed antifungal agents, fluconazole and itraconazole, the echinocandins exhibit a novel mechanism of action based on the inhibition of cell wall glucan synthesis (6, 23). In contrast to the triazoles, which are fungistatic for *Candida* spp., the echinocandins exhibit concentration-dependent fungicidal activity against *Candida* spp. but not against *Aspergillus* spp. (6–11, 19).

Caspofungin is an echinocandin antifungal agent which has recently been approved for treatment of aspergillosis in patients refractory to or intolerant of other therapies (6, 11). Caspofungin also has demonstrated potent in vitro and in vivo activity against *Candida* spp. and has approved indications for treatment of candidemia, intra-abdominal abscesses, peritonitis, pleural space infections, and esophageal candidiasis (1, 15, 16a, 26). Although numerous studies documenting the in vitro activity of caspofungin against *Candida* spp. have been published, these studies are limited in the number of isolates of the various species of *Candida* tested and also are restricted in the geographic distribution of the tested strains (5, 10, 13, 15, 20, 21, 25). In the present study we determined the in vitro activity of caspofungin against an international collection of 3,959 clinical isolates of *Candida* spp. representing predominantly bloodstream infection and other invasive forms of candidiasis. We compare the activity of caspofungin against those of the licensed agents, fluconazole and itraconazole, and provide an evaluation of the activity of caspofungin against 157 isolates demonstrating high-level resistance (MIC, ≥64 μg/ml) to fluconazole.

* Corresponding author. Mailing address: Medical Microbiology Division, C606 GH, Department of Pathology, University of Iowa College of Medicine, Iowa City, Iowa 52242. Phone: (319) 384-9566. Fax: (319) 356-4916. E-mail: michael-pfaller@uiowa.edu.

MATERIALS AND METHODS

Organisms. A total of 3,959 clinical isolates of *Candida* spp. obtained from more than 95 different medical centers internationally were tested. The collection included the following numbers of isolates: *C. albicans*, 2,453; *C. glabrata*, 512; *C. parapsilosis*, 420; *C. tropicalis*, 285; *C. dubliniensis*, 88; *C. guilliermondii*, 75; *C. krusei*, 72; *C. lusitaniae*, 26; *C. famata*, 9; *C. kefyr*, 4; *C. rugosa*, 6; *C. pelliculosa*, 3; *C. lambica*, 2; *C. lipolytica*, 1; *C. humicola*, 1; *C. zeylanoides*, 1. The isolates were all recent clinical isolates, and the majority (>80%) were from blood or normally sterile body fluid (cerebrospinal fluid, pleural fluid, or peritoneal fluid). The *C. dubliniensis* isolates were from mucosal sources. The isolates were identified by standard methods (27) and were stored as water suspensions until they were used in the study. Prior to testing, each isolate was passaged at least twice on potato dextrose agar (Remel, Lenexa, Kans.) to ensure purity and viability.

Antifungal agents. Standard antifungal powders of caspofungin (Merck Co., Whitehouse Station, Pa.), fluconazole (Pfizer, Inc., New York, N.Y.), and itraconazole (Janssen, Beerse, Belgium) were obtained from their respective manufacturers. Stock solutions were prepared in water (caspofungin and fluconazole) or polyethylene glycol (itraconazole). Serial twofold dilutions were prepared exactly as outlined in NCCLS document M27-A2 (17). Final dilutions were made in RPMI 1640 medium (Sigma, St. Louis, Mo.) buffered to pH 7.0 with 0.165 M morpholinepropanesulfonic acid (MOPS) buffer (Sigma). Aliquots (0.1 ml) of each antifungal agent at a 2× final concentration were dispensed into wells of plastic microdilution trays by using a Quick Spense II system (Dynatech Laboratories, Chantilly, Va.). The trays were sealed and frozen at −70°C until they were used.

Antifungal susceptibility studies. Broth microdilution (BMD) testing was performed in accordance with the guidelines in NCCLS document M27-A2 (17) by using the spectrophotometric method of inoculum preparation, an inoculum concentration of $(1.5 \pm 1.0) \times 10^3$ cells/ml, and RPMI 1640 medium buffered to pH 7.0 with MOPS. A 0.1-ml yeast inoculum was added to each well of the microdilution trays. The final concentrations of the antifungal agents were 0.007

TABLE 1. In vitro susceptibilities of 3,959 clinical isolates of *Candida* spp. to caspofungin, fluconazole, and itraconazole[a]

Organism (no. tested) and antifungal agent	MIC (μg/ml)[b]			% Susceptible at MIC (μg/ml) of:						
	Range	50%	90%	0.12	0.25	0.5	1	2	4	8
C. albicans (2,453)										
Caspofungin	0.007–>8	0.12	0.25	79	97	99	99	99	99	99
Fluconazole	0.12–>128	0.25	0.5	24	82	91	94	95	96	97[c]
Itraconazole	0.007–>8	0.03	0.12	93[d]	96	98	99	99	99	99
C. glabrata (512)										
Caspofungin	0.007–>8	0.12	0.25	58	91	99	99	99	99	99
Fluconazole	0.12–>128	8	32	0.2	0.6	1	2	12	33	60[c]
Itraconazole	0.007–>8	1	2	4[d]	18	46	80	91	94	96
C. parapsilosis (420)										
Caspofungin	0.03–>8	1	4	2	6	25	60	87	95	99
Fluconazole	0.12–64	0.5	2	1	11	51	78	93	97	99[c]
Itraconazole	0.015–2	0.12	0.25	54[d]	90	99	99	100		
C. tropicalis (285)										
Caspofungin	0.03–>8	0.12	0.5	60	86	96	98	98	98	98
Fluconazole	0.12–>128	0.5	2	2	20	55	82	95	97	98[c]
Itraconazole	0.015–>8	0.12	0.5	58[d]	86	96	99	99	99	99
C. dubliniensis (88)										
Caspofungin	0.015–1	0.25	0.5	35	83	98	100			
Fluconazole	0.12–>128	0.25	16	45	81	84	85	85	85	89[c]
Itraconazole	0.015–>8	0.06	0.25	84[d]	94	98	98	98	98	98
C. guilliermondii (75)										
Caspofungin	0.12–>8	>8	>8	1	3	5	5	7	11	13
Fluconazole	0.25–>128	4	16	0	1	2	6	21	64	81[c]
Itraconazole	0.03–>8	1	1	7[d]	24	48	97	97	99	99
C. krusei (72)										
Caspofungin	0.12–2	1	1	1	10	43	99	100		
Fluconazole	4–128	32	64	0	0	0	0	0	1	5[c]
Itraconazole	0.12–2	0.5	1	2[d]	18	57	95	100		
C. lusitaniae (26)										
Caspofungin	0.12–2	0.5	1	11	23	81	96	100		
Fluconazole	0.12–16	0.5	2	2	38	64	86	97	97	98[c]
Itraconazole	0.03–2	0.12	0.25	50[d]	91	98	98	100		
C. famata (9)										
Caspofungin	0.06–>8	4		11	11	22	33	44	56	56
Fluconazole	0.25–16	2		0	13	33	47	53	73	89[c]
Itraconazole	0.06–1	0.25		33[d]	60	80	100			
Candida spp.[e] (19)										
Caspofungin	0.03–8	0.5	1	25	31	75	94	94	94	100
Fluconazole	0.12–128	4	64	4	7	11	25	39	75	86[c]
Itraconazole	0.015–>8	0.25	1	29[d]	68	86	96	96	96	96

[a] BMD testing according to NCCLS M27-A2 (17).
[b] 50% and 90%, MICs encompassing 50 and 90% of isolates tested, respectively.
[c] Percentage of isolates susceptible to fluconazole at the NCCLS breakpoint of ≤8 μg/ml.
[d] Percentage of isolates susceptible to itraconazole at the NCCLS breakpoint of ≤0.12 μg/ml.
[e] Includes *C. kefyr* (four isolates), *C. rugosa* (six isolates), *C. pelliculosa* (three isolates), *C. lambica* (two isolates), and one isolate each of *C. lipolytica*, *C. humicola*, and *C. zeylanoides*.

to 8 μg/ml for caspofungin and itraconazole and 0.12 to 128 μg/ml for fluconazole. The trays were incubated at 35°C, and MIC end points were read after 48 h. Drug-free and yeast-free controls were included.

Following incubation, the BMD wells were examined with the aid of a reading mirror and the growth in each well was compared to that in the growth control well. The MIC of caspofungin was defined as complete inhibition of growth, and the MICs of fluconazole and itraconazole were defined as the lowest concentrations that produced a prominent decrease in turbidity (approximately 50%) relative to that of the drug-free control well (15). The interpretative criteria for fluconazole and itraconazole were those published by Rex et al. (22) and the NCCLS (17).

Quality control. Quality control was performed by testing the NCCLS-recommended strains, *C. krusei* ATCC 6258 and *C. parapsilosis* ATCC 22019 (4, 17).

RESULTS AND DISCUSSION

Table 1 summarizes the in vitro susceptibilities of 3,959

TABLE 2. Antifungal susceptibility of 3,959 isolates of *Candida* spp. stratified by fluconazole susceptibility

Fluconazole susceptibility category[a]	No. tested	Antifungal agent	Cumulative % inhibited at MIC (μg/ml) of:						
			0.12	0.25	0.5	1	2	4	8
S	3,479	Caspofungin	64	82	88	93	96	97	98
		Itraconazole	77	89	96	99	99	100	100
S-DD	323	Caspofungin	57	82	90	95	95	96	96
		Itraconazole	2	12	33	77	95	98	99
R	157	Caspofungin	47	68	82	99	99	99	99
		Itraconazole	0	5	29	49	56	62	70

[a] Fluconazole susceptibility category according to NCCLS M27-A2. S, susceptible (≤8 μg/ml); S-DD, dose-dependently susceptible (16 to 32 μg/ml); R, resistant (≥64 μg/ml).

isolates of *Candida* spp. to caspofungin, fluconazole, and itraconazole. Overall, caspofungin was quite active (MIC at which 90% of the isolates were inhibited [MIC_{90}], 1 μg/ml; 96% of isolates were inhibited by ≤2 μg/ml). *C. albicans*, *C. dubliniensis*, *C. tropicalis*, and *C. glabrata* were the species most susceptible to caspofungin (MIC_{90}, 0.25 to 0.5 μg/ml), and *C. guilliermondii* was the least susceptible (MIC_{90}, >8 μg/ml). Notably, 99 to 100% of *C. glabrata* and *C. krusei* isolates were inhibited by ≤2 μg of caspofungin/ml.

Among the 3,959 isolates of *Candida* spp. studied, a total of 157 were resistant to fluconazole, and 71% of those isolates were also resistant to itraconazole (MIC, ≥1 μg/ml) (Table 2). Among these resistant isolates, 99% were susceptible to caspofungin at an MIC of ≤1 μg/ml. Caspofungin was at least as active against fluconazole-resistant isolates as it was against isolates susceptible and dose-dependently susceptible to fluconazole, confirming the complete lack of cross-resistance between these two classes of antifungal agents (15, 16, 18, 25).

These findings confirm and extend those reported previously regarding the anticandidal activity of caspofungin (5, 10, 13, 15, 16, 18, 20, 21, 25). Caspofungin was as active or more potent than either fluconazole or itraconazole against all *Candida* spp. with the exception of *C. guilliermondii* and *C. famata*. Although lower caspofungin MICs against these species may be demonstrated by testing in antibiotic medium 3 (14, 18; M. A. Pfaller, unpublished data on file), they still remain higher than those obtained for other *Candida* spp. It is unclear what this may mean clinically at this time, as both *C. guilliermondii* and *C. famata* are very unusual causes of fungal infection and the recommended dosing of caspofungin provides peak plasma concentrations well in excess of 8 μg/ml (11, 12, 19, 24).

Notably, caspofungin demonstrated excellent activity against *C. glabrata* and *C. krusei*, two species of *Candida* that are not covered optimally by the triazoles. In addition, caspofungin was active against isolates of *Candida* spp., including *C. glabrata* and *C. krusei* as well as *C. albicans*, exhibiting high-level resistance to both fluconazole and itraconazole. Caspofungin has been shown to be fungicidal against *Candida* spp. (7, 8); however, minimum-fungicidal-concentration determinations were not performed in this study.

Consistent with these in vitro results, in vivo studies have demonstrated the efficacy of treating infections due to *Candida* spp. with caspofungin (1, 16a, 26). Pharmacokinetic studies have demonstrated peak concentrations of caspofungin in plasma in excess of 16 μg/ml with dosing of 1 mg/kg of body weight daily (12, 19, 24). Pharmacodynamic studies have demonstrated concentration-dependent killing that is optimized at four or more times the MIC and a postantifungal effect of more than 12 h (7, 8). Given the MIC data presented in Tables 1 and 2 (overall MIC_{90}, ≤1 μg/ml), plasma caspofungin concentrations exceeding the MIC by fourfold or more should be attainable for virtually all clinical isolates of *Candida* spp. treated with caspofungin.

In summary, we have demonstrated that caspofungin is more potent than fluconazole and itraconazole against significant clinical isolates of *Candida* spp. The emerging in vivo data from animal models as well as from clinical trials appear to support the in vitro data regarding the efficacy of caspofungin in the treatment of invasive candidiasis. Caspofungin has very favorable pharmacokinetic and pharmacodynamic properties that make it a highly promising new systemic antifungal agent. Caspofungin may prove to be very useful in the treatment of serious *Candida* infections that are refractory to existing antifungal agents.

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