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Comparative In Vitro Activities of Caspofungin and Micafungin, Determined Using the Method of the European Committee on Antimicrobial Susceptibility Testing, against Yeast Isolates Obtained in France in 2005-2006▽

E. Dannaoui,[1,2]* O. Lortholary,[1,3] D. Raoux,[1] M. E. Bougnoux,[4] G. Galeazzi,[5] C. Lawrence,[6] D. Moissenet,[7] I. Poilane,[8] D. Hoinard,[1] F. Dromer,[1] and the YEASTS Group

Centre National de Référence Mycologie et Antifongiques, Unité de Mycologie Moléculaire, CNRS URA3012, Institut Pasteur, 75724 Paris Cedex 15, France[1]; Université Paris Descartes, Faculté de Médecine, AP-HP, Hôpital Européen Georges Pompidou, Unité de Parasitologie—Mycologie, 75015 Paris, France[2]; Université Paris Descartes, Faculté de Médecine, AP-HP, Hôpital Necker-Enfants-Malades, Centre d'Infectiologie Necker-Pasteur, 75015 Paris, France[3]; Université Paris Descartes, Faculté de Médecine, AP-HP, Hôpital Necker-Enfants-Malades, Laboratoire de Microbiologie, 75015 Paris, France[4]; AP-HP, Hôpital Louis Mourier, Unité de Parasitologie-Mycologie, 92701 Colombes Cedex, France[5]; AP-HP, Hôpital Raymond Poincaré, Laboratoire de Microbiologie, 92380 Garches, France[6]; AP-HP, Hôpital Armand Trousseau, Laboratoire de Bacteriologie-Virologie, 75012 Paris, France[7]; and AP-HP, Hôpital Jean Verdier, Laboratoire de Microbiologie, 93140 Bondy, France[8]

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The in vitro activities of caspofungin and micafungin against 1,038 yeast isolates have been determined. The caspofungin and micafungin MICs were lower for *Candida albicans*, *Candida glabrata*, and *Candida tropicalis* than for *Candida parapsilosis*, *Candida guilliermondii*, and *Candida krusei*. A clear correlation was seen between the MICs for the two drugs.

Echinocandins are lipopeptide antifungal drugs targeting the fungal cell wall by inhibition of the beta-1-3-glucan synthase (9, 10).

For any given method, the matter of the best technical parameters for antifungal susceptibility testing of echinocandins, particularly for distinction between isolates with low and high MICs, is still debated (5, 21, 23). In this study, we used the broth microdilution reference procedure of the Antifungal Susceptibility Testing Subcommittee of the European Committee on Antimicrobial Susceptibility Testing (AFST-EUCAST) to test a large collection of yeast clinical isolates from France for their in vitro susceptibilities to caspofungin and micafungin. For caspofungin, good agreement between results obtained with the EUCAST method and those obtained with the Clinical and Laboratory Standards Institute (CLSI) technique has been shown (6), and the EUCAST methodology has previously been used to generate in vitro data for this drug (7, 8).

A total of 1,038 yeast isolates, mostly (84%) recovered from blood or sterile sites, consecutively received at the French National Reference Center for Mycoses and Antifungals in 2005-2006, were prospectively analyzed for their in vitro susceptibilities to caspofungin and micafungin. Identification was confirmed using ID32C strips (BioMérieux, Marcy-l'Etoile, France) and ITS1-5.8S–ITS2 sequencing for species other than *Candida albicans*, *Candida glabrata*, *Candida tropicalis*, *Candida parapsilosis*, and *Cryptococcus neoformans*. A specific PCR (11) was performed to differentiate *Candida dubliniensis* from *C. albicans*.

In vitro susceptibility was determined by following the guidelines of AFST-EUCAST discussion document 7.1 (29). Pure powders of caspofungin and micafungin were used. Microplates were prepared and stored frozen at −20°C. Testing was performed with RPMI-1640 medium supplemented with 2% glucose and adjusted to a final inoculum size of 10^5 CFU/ml. The final concentrations of the antifungals were 0.015 to 8 μg/ml for both echinocandins. MICs were determined spectrophotometrically after 24 h or 48 h of incubation (depending on the species) at 35°C. The MIC endpoint was defined as 50% or more reduction in growth compared to that in the drug-free well. Two reference strains, *Candida krusei* ATCC 6258 and *C. parapsilosis* ATCC 22019, were included in each set of determination.

The MIC_{50}s and MIC_{90}s of the isolates tested were determined for genera for which ≥5 and ≥10 isolates, respectively, were available. MIC distributions were compared by the Mann-Whitney test. Correlation between MIC results for the two echinocandins was assessed by the Pearson correlation coefficient after $\log_2$ transformation.

The in vitro activities of caspofungin and micafungin against all isolates are presented in Table 1. The most susceptible species (MIC_{90}s of ≤1 μg/ml and ≤0.125 μg/ml for caspofungin and micafungin, respectively) were *C. albicans*, *C. glabrata*, and *C. tropicalis*, whereas *C. parapsilosis*, *C. guilliermondii*, and *C. krusei* exhibited higher MICs (MIC_{90}s of ≥2 μg/ml and ≥0.25 μg/ml for caspofungin and micafungin, respectively).

* Corresponding author. Mailing address: Centre National de Référence Mycologie et Antifongiques, Unité de Mycologie Moléculaire, CNRS URA3012, Institut Pasteur, 25, rue du Dr. Roux, 75724 Paris Cedex 15, France. Phone: 33 1 40 61 32 50. Fax: 33 1 45 68 84 20. E-mail: dannaoui@pasteur.fr.

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TABLE 1. In vitro activities of caspofungin and micafungin against 1,038 yeast isolates in France (2005-2006)

Species (n^b)	MIC (μg/ml)[a] of:							
	Caspofungin				Micafungin			
	Range	MIC_{50}	MIC_{90}	GMIC	Range	MIC_{50}	MIC_{90}	GMIC
C. albicans (404)	0.125–4	0.5	0.5	0.38	0.015–1	0.03	0.06	0.03
C. glabrata (157)	0.25–8	0.5	1	0.51	0.015–8	0.03	0.06	0.03
C. parapsilosis (109)	0.5–4	2	2	1.57	0.25–2	2	2	1.47
C. tropicalis (62)	0.25–2	0.5	1	0.60	0.03–2	0.06	0.125	0.08
C. guilliermondii (27)	0.06–2	2	2	1.32	0.5–2	1	2	1.00
C. krusei (21)	0.5–8	1	2	1.10	0.125–4	0.25	0.25	0.27
C. kefyr (21)	0.125–0.5	0.25	0.5	0.27	0.06–0.5	0.125	0.25	0.12
C. haemulonii (12)	0.25–8	1	2	0.89	0.06–0.25	0.25	0.25	0.18
C. lusitaniae (12)	1–2	1	1	1.06	0.06–0.5	0.25	0.5	0.23
C. fermentati (10)	1–2	1	2	1.41	0.25–1	1	1	0.66
Other *Candida* spp.[c] (27)	0.125–2	0.5	1	0.68	0.03–1	0.06	1	0.09
Other *Ascomycota* yeasts[d] (13)	0.25–16	1	16	1.38	0.03–16	0.25	16	0.29
C. neoformans (158)	1–16	8	16	9.59	2–16	16	16	11.31
Other *Basidiomycota* yeasts[e] (5)	8–16	16	ND	ND	8–16	16	ND	ND

[a] MICs were determined by the EUCAST method in RPMI medium. High off-scale MICs (>8 μg/ml) were converted to the next higher concentration (16 μg/ml). GMIC, geometric mean MIC; ND, not determined.
[b] Number of isolates.
[c] Other *Candida* spp.: *C. dubliniensis* ($n = 7$), *C. lipolytica* ($n = 5$), *C. famata* ($n = 2$), *C. pelliculosa* ($n = 2$), *C. rugosa* ($n = 2$), *C. utilis* ($n = 2$), and one each of *C. inconspicua, C. intermedia, C. africana*, *C. lambica, C. nivariensis, C. norvegensis*, and *C. sphaerica*.
[d] Other *Ascomycota* yeasts: *Saccharomyces cerevisiae* ($n = 8$), *Geotrichum* spp. ($n = 2$), and *Williopsis saturnus, Kodamaea ohmeri,* and a *Zygosaccharomyces* sp. ($n = 1$ each).
[e] Other *Basidiomycota* yeasts: *Trichosporon* spp. ($n = 3$) and *Rhodotorula mucilaginosa* ($n = 2$).

Among other *Candida* spp., less commonly isolated, 90% of the isolates tested (belonging to 17 different species) were inhibited by 2 μg/ml of caspofungin and 1 μg/ml of micafungin. Nevertheless, there was a trend toward higher MICs recorded for both echinocandins against the closely related species *Candida fermentati* and *Candida guilliermondii*. Among the other *Ascomycota* yeast isolates, *Geotrichum* spp. showed high MICs (>8 μg/ml) for both drugs. Both echinocandins had no activity against *C. neoformans*, with MIC_{90}s of >8 μg/ml, and similar high MICs were found for the other *Basidiomycota* yeasts (*Trichosporon* spp. and *Rhodotorula* spp.).

Globally, micafungin MICs were significantly lower than caspofungin MICs ($P < 0.0001$). Nevertheless, a clear correlation ($P < 0.0001$, Pearson coefficient $R^2 = 0.82$) was seen between the MICs for the two drugs, as shown in Table 2.

TABLE 2. Distribution of micafungin MICs according to caspofungin MICs by use of the EUCAST method in RPMI medium for yeast isolates collected in France

Caspofungin MIC[a] (μg/ml)	No. of isolates with indicated micafungin MIC[a] (μg/ml)										
	0.015	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16
0.015											
0.03											
0.06											
0.125	2	9		2	1						
0.25	26	147	20	8	2						
0.5	22	265	82	20	11	1	1				
1	1	24	16	18	21	13	27	28	1		
2		1		1	10	7	34	48	2		
4						1	2	3	3	4	8
8					1			1	9	19	43
16								1	1	12	59

[a] Isolates with MICs of ≥8 μg/ml for both echinocandins were of *C. neoformans* ($n = 125$), *Trichosporon* spp. ($n = 3$), *Rhodotorula mucilaginosa* ($n = 2$), *Geotrichum* spp. ($n = 2$), and *C. glabrata* ($n = 1$).

Good activities of caspofungin and micafungin against most of the *Candida* species were found, with *C. albicans*, *C. tropicalis*, and *C. glabrata* being the more susceptible species. Similar susceptibilities to caspofungin were previously reported for isolates in the United States (18, 22, 26, 27) and in Europe (28), as demonstrated by surveys in Spain (7, 8), Germany (13), Denmark (1), and Italy (32). These species were also among the most susceptible to micafungin (16, 22, 25, 30). In contrast, *C. parapsilosis* and *C. guilliermondii* showed higher MICs for both echinocandins, as reported in different studies (7, 8, 13, 16, 18, 22, 25–28, 30). A recent animal study showed that although caspofungin treatment significantly reduced renal fungal burden in mice infected by *C. parapsilosis* or *C. guilliermondii*, the CFU reduction was 100-fold less than that for *C. albicans* (4), thereby suggesting intrinsic in vivo reduced susceptibility against the former species. Of note, 2008 Infectious Diseases Society of America guidelines suggested the use of another antifungal class against *C. parapsilosis* (24). Among less frequently isolated species, *C. fermentati*, a species phylogenetically closely related to *C. guilliermondii* but indistinguishable by standard phenotypic criteria (2), exhibited caspofungin MICs similar to those of *C. guilliermondii*.

Both echinocandins lack in vitro activity against *C. neoformans*, as previously reported (5, 12, 15, 31), although the reason remains uncertain (10). This lack of in vitro activity is extended to other yeasts belonging to the *Basidiomycetes*, such as *Trichosporon* spp. and *Rhodotorula* spp. Since these yeasts currently emerge in immunocompromised hosts, empirical therapy using an echinocandin in this setting may be inappropriate.

Few studies have compared the in vitro activities of the different echinocandins (19, 22, 25). In some of these studies, MICs were similar for caspofungin and micafungin (19, 25), while in others, such as the present study, micafungin

MICs were lower than caspofungin MICs (22). The reason for these differences remains unclear and warrants further investigations. In the present study, the isolates less susceptible to caspofungin were also less susceptible to micafungin and this is in accordance with the results of a recent study (26). Moreover, in several case reports, the clinical failure of echinocandin treatment was associated with elevated caspofungin MICs for the infecting isolates and it was shown that these isolates also had elevated MICs for micafungin and/or anidulafungin (3, 14, 17, 20). Together, these data suggest that there is a "cross-resistance" between caspofungin and micafungin in yeasts.

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