In Vitro Susceptibility to Posaconazole of 1,903 Yeast Isolates Recovered in France from 2003 to 2006 and Tested by the Method of the European Committee on Antimicrobial Susceptibility Testing[▽]

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The posaconazole MIC₉₀ for 1,903 yeast isolates from France was 1 µg/ml (range, ≤0.015 to 8 µg/ml). Ninety percent of isolates with fluconazole MICs of ≥8 µg/ml (*n* = 509) and 90% of those with voriconazole MICs of ≥2 µg/ml (*n* = 80) were inhibited by 2 and 8 µg/ml of posaconazole, respectively.

Yeasts, especially *Candida* spp., are among the most frequent causes of nosocomial bloodstream infections. Several non-*albicans* *Candida* spp. and rare species are often less susceptible to fluconazole (5). Among the new antifungals available, posaconazole has emerged as the one with the broadest spectrum of in vitro activity against yeasts and filamentous and dimorphic fungi (8, 13). Using the method standardized by the Antifungal Susceptibility Testing Subcommittee of the European Committee on Antimicrobial Susceptibility Testing (AFST-EUCAST), we report here the in vitro susceptibility profiles to posaconazole of 1,903 yeast isolates.

(This work was presented in part at the 46th Interscience Conference on Antimicrobial Agents and Chemotherapy, 27 to 30 September 2006, San Francisco, CA [2b].)

A total of 1,903 yeast isolates from 79 medical centers were collected at the French National Reference Center for Mycoses and Antifungals (Institut Pasteur, Paris, France) between 1 January 2003 and 31 July 2006. Isolates were recovered from 1,443 blood cultures, including 1,241 consecutive fungemia cultures obtained through the active prospective surveillance program in the Paris area (2a), from other sterile sites (*n* = 187), and from superficial infections (*n* = 273).

Active powders of known potency of posaconazole (Schering-Plough Research Institute, Kenilworth, NJ), fluconazole, and voriconazole (both from Pfizer Central Research, Sandwich, United Kingdom) were used. The final concentrations tested were 0.015 to 8 µg/ml for posaconazole and voriconazole and 0.125 to 64 µg/ml for fluconazole.

The MICs of posaconazole, fluconazole, and voriconazole were determined according to AFST-EUCAST discussion doc-

ument 7.1 (12). Quality control strains were included in each set. Since breakpoints have not yet been published, we used thresholds that defined 95% of the *C. albicans* isolates as susceptible and 98% of the *C. krusei* isolates as resistant to fluconazole. Thus, isolates were considered fluconazole resistant or susceptible when MICs were ≥8 µg/ml or ≤4 µg/ml, respectively. Likewise, an arbitrary threshold of ≥2 µg/ml defined isolates with decreased susceptibility to voriconazole and posaconazole.

The overall susceptibilities to posaconazole, divided into those for yeast isolates from blood (*n* = 1,383) and those for isolates from other sites (*n* = 428), are reported in Table 1 for the 10 most frequently isolated species of our collection. The MIC₅₀ (range) value for the 1,535 *Candida* sp. isolates was 0.06 µg/ml (≤0.015 to ≥8 µg/ml). Twenty-nine percent (74/254 isolates) of *C. glabrata* isolates exhibited posaconazole MICs of ≥2 µg/ml. Considering the *C. glabrata* isolates with fluconazole MICs of ≥8 µg/ml (*n* = 230), 68% were inhibited by 1 µg/ml of posaconazole and 83% were inhibited by 1 µg/ml of voriconazole. Considering the *C. glabrata* isolates with voriconazole MICs of ≥2 µg/ml (*n* = 41), the posaconazole MIC₅₀ was ≥8 µg/ml. For *C. krusei*, the activity of posaconazole was similar to that of voriconazole, although 3/50 isolates presented voriconazole MICs of ≥2 µg/ml and remained inhibited by ≤1 µg/ml of posaconazole. Table 2 summarizes the in vitro susceptibilities to posaconazole, in comparison to those to fluconazole and voriconazole, of 79 uncommon yeasts (i.e., at least 2 but less than 12 isolates per species). Posaconazole MICs were lower than the corresponding fluconazole MICs, and overall, voriconazole had equal or lower MICs than those of posaconazole. MICs for posaconazole against *Rhodotorula* spp. were lower than those of voriconazole. Yeast species with reduced intrinsic activity of fluconazole had higher posaconazole and voriconazole MICs, with the highest MICs of the three azoles tested being observed for *C. haemulonii* isolates.

Overall, considering the 1,903 isolates, comparative MIC₅₀s (range) were 0.5 µg/ml (≤0.125 to ≥64 µg/ml), ≤0.015 (≤0.015 to ≥8 µg/ml), and 0.125 (≤0.015 to 8 µg/ml) for fluconazole,

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TABLE 1. Susceptibility to posaconazole of yeast clinical isolates corresponding to the 10 most frequently isolated species in the collection of the French National Reference Center for Mycoses and Antifungals

Species	All isolates (n = 1,811)			Blood isolates (n = 1,383)			Isolates from superficial sites (n = 428)		
	n (%)	MIC ₅₀ /MIC ₉₀	MIC range	n	MIC ₅₀ /MIC ₉₀	MIC range	n	MIC ₅₀ /MIC ₉₀	MIC range
<i>C. albicans</i>	808 (44.6)	0.06/0.125	≤0.015–8	658	0.03/0.125	≤0.015–8	150	0.06/0.25	≤0.015–1
<i>C. glabrata</i>	254 (14.0)	1/≥8	0.125–≥8	211	1/≥8	0.125–≥8	43	1/≥8	0.25–≥8
<i>C. parapsilosis</i>	186 (10.3)	0.125/0.25	0.03–0.5	177	0.125/0.25	0.03–0.5	9	0.125/0.25	0.03–0.25
<i>C. tropicalis</i>	140 (7.7)	0.125/0.25	≤0.015–≥8	125	0.125/0.50	≤0.015–≥8	15	0.125/4	0.03–≥8
<i>Cryptococcus neoformans</i>	276 (15.2)	0.125/0.50	≤0.015–1	103	0.125/0.50	≤0.015–0.5	173	0.125/0.50	≤0.015–1
<i>C. krusei</i>	50 (2.8)	0.25/0.50	0.06–1	35	0.25/0.50	0.06–1	15	0.25/0.50	0.125–0.5
<i>C. kefyr</i>	30 (1.7)	0.125/0.25	0.03–0.50	30	0.125/0.50	0.03–0.50			
<i>C. dubliniensis</i>	21 (1.2)	0.06/0.125	≤0.015–0.125	12	0.06/0.125	0.03–0.125	9		≤0.015–0.06
<i>C. guilliermondii</i>	30 (1.7)	0.25/0.5	0.125–1	18	0.25/1	0.125–1	12	0.50/0.50	0.125–0.50
<i>C. lusitanae</i>	16 (0.9)	0.06/0.25	0.03–0.25	14	0.06/0.25	0.03–0.25	2		0.03–0.06

voriconazole, and posaconazole, respectively, showing that posaconazole was more active than fluconazole, but slightly less active than voriconazole, against these clinical isolates.

Table 3 shows the distribution of posaconazole MICs according to those of fluconazole or voriconazole for all isolates. There was a clear correlation ($P < 0.0001$) between posaconazole MICs and either fluconazole ($R^2 = 0.63$) or voriconazole ($R^2 = 0.69$) MICs. Considering isolates with fluconazole MICs of ≤4 µg/ml ($n = 1,394$), the posaconazole MIC₅₀ and MIC₉₀ were 0.06 and 0.25 µg/ml, respectively, and for those with fluconazole MICs of ≥8 µg/ml ($n = 509$), the posaconazole MIC₅₀ and MIC₉₀ were 0.5 and 2 µg/ml, respectively. Considering yeast isolates with voriconazole MICs of ≤1 µg/ml ($n = 1,823$), the posaconazole MIC₅₀ and MIC₉₀ were 0.06 and 1 µg/ml, respectively, and for those with voriconazole MICs of ≥2 µg/ml ($n = 80$), the posaconazole MIC₅₀ and MIC₉₀ were 4 and 8 µg/ml, respectively.

We report here the in vitro susceptibilities to posaconazole of 1,903 yeast isolates recently collected in France, mostly from blood, with a MIC₅₀ of 0.125 µg/ml. In previous studies and here, clinical isolates of *C. albicans* and *C. dubliniensis* were the

most susceptible species to posaconazole (1, 3, 5, 11, 14). In considering *C. glabrata* isolates, the posaconazole MIC₉₀ values determined here were slightly higher than those reported elsewhere (1, 11). Posaconazole was slightly less active than voriconazole against *C. glabrata*, as shown in at least two other studies (10, 11). *Cryptococcus neoformans* isolates were highly susceptible to posaconazole, and slightly higher posaconazole MIC₅₀ values than those of voriconazole were found, in accordance with previous data for a smaller sample (1, 6, 11). Interestingly, posaconazole was also active against several rare but potentially emerging yeast species known to be less susceptible to antifungals, including fluconazole. Few reports have emphasized that the activity of voriconazole is reduced against *Candida* sp. isolates with decreased susceptibility to fluconazole (2, 4, 9). Cross-resistance between extended-spectrum azoles has been mentioned previously, especially for *C. glabrata* isolates. Indeed, Pfaller et al. reported that among fluconazole-resistant *C. glabrata* isolates, only 4% remained susceptible to posaconazole and 13% remained susceptible to voriconazole with a cutoff MIC of ≤1 µg/ml for posaconazole and voriconazole (7). In this study, we also evidenced such

TABLE 2. Susceptibility to posaconazole of 79 uncommon yeast clinical isolates recovered from various sites of infection (blood cultures or deep or superficial sites) in France

Species	No. of isolates	MIC ₅₀ /MIC ₉₀ (range)		
		Posaconazole	Fluconazole	Voriconazole
<i>C. haemulonii</i>	11	≥8/≥8 (1–≥8)	32/≥64 (8–≥64)	≥8/≥8 (4–≥8)
<i>C. fermentati</i>	10	0.25/1 (0.125–1)	8/≥64 (4–≥64)	0.125/1 (0.125–≥8)
<i>Saccharomyces cerevisiae</i>	9	0.03–1	0.25–16	≤0.015–0.25
<i>C. utilis</i>	7	0.125–0.50	1–4	0.03–0.125
<i>C. lipolytica</i>	5	0.125–1	2–8	≤0.015–0.125
<i>C. pelliculosa</i>	5	0.06–0.50	2–4	0.03–0.125
<i>C. palmiophila</i>	5	0.125–0.25	8–16	0.06–0.25
<i>Geotrichum capitatum</i>	4	0.5–2	4–≥64	≤0.015–1
<i>Rhodotorula mucilaginosa</i>	4	1–2	≥64–≥64	2–4
<i>C. inconspicua</i>	3	0.125–0.25	16–≥64	0.06–0.25
<i>C. africana</i>	3	≤0.015–≤0.015	0.25–1	≤0.015–≤0.015
<i>Trichosporon</i> spp. ^a	3	0.06–0.50	2–2	0.03–0.125
<i>C. famata</i>	2	0.125–0.25	0.125–2	≤0.015–≤0.015
<i>Trichosporon asahii</i>	2	0.25–1	2–16	0.03–0.25
<i>Trichosporon inkin</i>	2	0.06–0.50	0.5–16	≤0.015–0.25
<i>C. rugosa</i>	2	0.06–0.25	1–4	≤0.015–0.06
<i>Pichia ohmeri</i>	2	0.06–0.125	8–16	0.03–0.03

^a Including *Trichosporon loubieri*, *Trichosporon mucoides*, and *Trichosporon* sp. ($n = 1$ of each).

TABLE 3. Distribution of posaconazole MICs according to fluconazole or voriconazole MICs for 1,903 yeast isolates collected in France

Fluconazole or voriconazole MIC (μg/ml)	No. of isolates with posaconazole MIC (μg/ml)									
	0.015	0.03	0.06	0.125	0.25	0.5	1	2	4	8
Fluconazole MICs										
0.125	50	111	81	15	0		1			
0.25	27	176	178	53	3	1				
0.5	4	65	121	66	20	1	1			1
1	3	10	45	65	32	2	1			
2	4	11	14	46	36	8				1
4		5	18	37	43	21	16			1
8		1	5	32	43	36	52	9	1	3
16			1	3	15	26	21	42	15	1
32				1	9	14	12	21	7	1
64					10	14	36	27	13	6
										29
Voriconazole MICs										
0.015	86	360	396	170	31	1	1			1
0.03	2	12	47	84	52	6				
0.06		6	15	56	71	17	1			
0.125		1	4	19	37	52	20			
0.25			2	9	26	38	65	6		
0.5				6	7	11	60	17		
1				4	4	3	6	11		
2					1	2	3	4		3
4					1	6	2	4	5	11
8		1	2		1	2	3	2	4	23

reduced posaconazole activity against yeast isolates with reduced susceptibility to fluconazole and voriconazole.

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