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In Vitro Susceptibilities of Clinical Isolates of *Candida* Species, *Cryptococcus neoformans*, and *Aspergillus* Species to Itraconazole: Global Survey of 9,359 Isolates Tested by Clinical and Laboratory Standards Institute Broth Microdilution Methods

M. A. Pfaller,[1,3]* L. Boyken,[1] R. J. Hollis,[1] S. A. Messer,[1] S. Tendolkar,[1] and D. J. Diekema[1,2]

Departments of Pathology[1] and Medicine,[2] Roy J. and Lucille A. Carver College of Medicine, and Department of Epidemiology, College of Public Health,[3] University of Iowa, Iowa City, Iowa 52242

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The in vitro activity of itraconazole was determined against 7,299 isolates of *Candida* spp., 1,615 isolates of *Cryptococcus neoformans*, and 445 isolates of *Aspergillus* spp. obtained from over 200 medical centers worldwide. Itraconazole was active against all *Candida* spp. (96% of MICs were ≤1 μg/ml) with the exception of *C. glabrata* (77% of MICs were ≤1 μg/ml). Itraconazole inhibited 94% of *C. krusei* and 84% of other fluconazole-resistant *Candida* species, exclusive of *C. glabrata*, at a MIC of ≤1 μg/ml. Itraconazole was not active against fluconazole-resistant isolates of *C. glabrata*. Only modest activity was seen against *C. neoformans* (80% of MICs were ≤1 μg/ml); however, itraconazole showed excellent activity against *Aspergillus* spp. (94% of MICs were ≤1 μg/ml). These results provide an update on the antifungal activity of itraconazole against major opportunistic fungal pathogens. In light of the new intravenous formulation of itraconazole these data suggest that this agent remains a viable systemically active antifungal agent.

Invasive fungal infections remain a major threat to the health of immunocompromised hosts worldwide (3, 4, 10, 15, 16, 26, 29, 36, 40). Among the myriad of opportunistic fungal pathogens, the three most important groups include *Candida* spp., *Cryptococcus neoformans*, and *Aspergillus* spp. (6, 9, 13, 15, 22, 24, 25, 28, 29). In recent years, several new developments in the area of antifungal therapy have improved the ability of physicians to prevent and treat these important mycoses (14, 23, 29, 31–33, 35, 37). Certainly a great deal of attention has been paid to the new triazoles (e.g., voriconazole, posaconazole, and ravuconazole), with their potency and improved spectrum of activity, including activity against fluconazole-resistant *Candida* spp., *C. neoformans*, and *Aspergillus* spp. (6, 7, 12, 13, 22, 24, 32, 33, 37, 38). Despite the well-founded enthusiasm for the new antifungal agents, it is important to continue to assess the activity of the older, more established agents, especially those, such as itraconazole, for which the development of new formulations has overcome some of the major deficiencies (i.e., bioavailability) of the drug when it was first introduced (2–5, 10, 16, 18, 19, 29, 36, 39, 40). The inherent potency and broad spectrum of itraconazole (1, 5, 13, 16, 17, 22, 24, 29, 38), coupled with the availability of an intravenous formulation (IVF), suggests that the use of itraconazole as first-line therapy for some of the opportunistic mycoses may well become an option (29).

The development of itraconazole as an important antifungal agent has lagged due to the lack of an IVF and the poor and erratic bioavailability of the oral capsule formulation (2, 5, 29, 39). Although bioavailability was much improved with the oral solution, it remains somewhat variable and is clearly inferior to that of fluconazole or voriconazole (2, 29, 36, 39). The introduction of the IVF of itraconazole in 1999 broadened the potential utility of itraconazole (29, 39). Whereas the suggested "target" concentration of ≥0.5 μg/ml in serum (29, 30) was difficult to achieve reliably with either oral formulation, it is now very easy to obtain peak concentrations of 2 to 4 μg/ml and troughs of ≥1 μg/ml using the IVF (4, 19, 29, 36, 39).

Although itraconazole has often been used as a comparator in surveys of the in vitro antifungal susceptibility of opportunistic fungal pathogens, it has rarely been the primary focus of such studies; thus, its activity against opportunistic fungi is generally underappreciated (5, 8, 9, 13, 22, 24, 25). In part, this may also be due to a perception of rather poor activity of itraconazole against *Candida* spp. given the very conservative breakpoints (susceptible MIC, ≤0.12 μg/ml; susceptible-dose dependent MIC, 0.25 to 0.5 μg/ml; resistant MIC, ≥1 μg/ml) assigned by the Clinical and Laboratory Standards Institute (CLSI; formerly the National Committee for Clinical Laboratory Standards) (30). These breakpoints were assigned based entirely on MICs for isolates of *Candida* spp. obtained from patients with oropharyngeal candidiasis who were treated with oral itraconazole (capsule and/or solution) and in whom serum concentrations of <0.5 μg/ml were common (30). The category of susceptible-dose dependent was applied to those isolates for which the MIC was determined to be 0.25 to 0.5 μg/ml on the basis of the recognition of improved clinical and microbiological response when serum concentrations were ≥0.5 μg/ml

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

TABLE 1. In vitro susceptibilities of 7,299 isolates of *Candida* spp. and 1,615 isolates of *Cryptococcus neoformans* to itraconazole

Organism (no. of isolates tested)	Cumulative % at MIC (μg/ml):								
	0.03	0.06	0.12	0.25	0.5	1	2	4	8
C. albicans (3,895)	46	88	98	99	99	99	99	99	99
C. glabrata (1,054)	1	1	2	9	37	77	91	94	95
C. parapsilosis (1,028)	1	10	48	87	97	99	100		
C. tropicalis (839)	7	25	61	90	99	99	99	99	99
C. krusei (206)		1	2	10	53	94	99	100	
C. guilliermondii (90)		1	4	14	73	99	99	100	
C. lusitaniae (89)	2	5	54	93	98	100			
C. kefyr (29)		24	83	97	100				
C. pelliculosa (28)			4	32	68	100			
C. rugosa (15)	7	27	60	80	100				
Candida spp. (26)[a]		20	38	54	80	92	96	96	100
All *Candida* (7,299)	25	51	68	80	88	96	99	99	99
Cryptococcus neoformans (1,615)	2	6	26	61	76	80	83	92	98

[a] Includes *C. dubliniensis* (7), *C. lipolytica* (7), *C. famata* (6), and *C. zeylanoides* (6).

(30). Given the ability to reliably achieve serum concentrations of itraconazole of ≥1 μg/ml throughout the dosing interval with the IVF (4, 19, 36, 39), it is now reasonable to reassess the potency and spectrum of activity of itraconazole against the major opportunistic fungi. As such, we will discuss the data presented herein with a focus on the proportion of isolates tested for which the itraconazole MIC is ≤1 μg/ml. Such data are necessary to more accurately assess the "treatability" of the pathogens in light of the new formulation (IVF) of itraconazole and can be considered the first step towards a readjustment of the interpretive breakpoints.

In the present study we determined the in vitro activity of itraconazole against an international collection (representing over 200 medical centers) of more than 9,000 clinical isolates of *Candida* spp. (7,299 isolates), *C. neoformans* (1,615 isolates), and *Aspergillus* spp. (445 isolates). This report represents the largest experience with itraconazole tested by CLSI reference methods (20, 21). The results are presented as the cumulative percentage of isolates inhibited at each concentration throughout the dilution series (full-range MICs) to facilitate comparison with other studies using the CLSI methods.

MATERIALS AND METHODS

Organisms. A total of 9,359 clinical isolates of *Candida* spp. (7,299 isolates), *Cryptococcus neoformans* (1,615 isolates), and *Aspergillus* spp. (445 isolates) obtained from more than 200 medical centers worldwide were tested. These were all clinical isolates collected between 1992 and 2004. The *Candida* and *C. neoformans* isolates were obtained from blood and normally sterile body fluids, and the *Aspergillus* isolates were from respiratory specimens. Isolates were identified by standard methods (11, 34) and stored as water suspensions until they were used. Prior to testing, each isolate was subcultured on potato dextrose agar (Remel, Lenexa, Kans.) to ensure viability and purity.

Susceptibility testing. Standard antifungal powder of itraconazole (Janssen, Beerse, Belguim) was obtained from the manufacturer. Broth microdilution trays were prepared in house at the University of Iowa as described previously (7, 24, 25, 28). Broth microdilution testing of *Candida* spp. and *C. neoformans* was performed in the Molecular Epidemiology and Fungus Testing Laboratory (Iowa City) exactly as outlined in CLSI document M27-A2 (20), and testing of *Aspergillus* was performed as described in CLSI document M38-A (21). The concentrations of itraconazole tested ranged from 0.007 to 8 μg/ml. MIC endpoints for *Candida* and *Aspergillus* spp. were determined after 48 h of incubation and for *C. neoformans* after 72 h of incubation. The MICs of itraconazole were defined as the lowest concentrations that produced either a prominent (approximately 50%) decrease (*Candida* and *Cryptococcus* spp.) or a complete (100%; *Aspergillus* spp.) inhibition of growth relative to that of the drug-free control well (20, 21).

Quality control. Quality control was ensured by testing the following strains (20, 31): *A. flavus* ATCC 204304, *C. parapsilosis* ATCC 22019, and *C. krusei* ATCC 6258. All results were within the recommended limits of the CLSI (20, 21).

RESULTS AND DISCUSSION

Table 1 summarizes the in vitro susceptibility of 7,299 isolates of *Candida* spp. and 1,615 isolates of *C. neoformans* to itraconazole. Overall, itraconazole was quite active against all species of *Candida* (96% of isolates were inhibited by ≤1 μg/ml) with the exception of *C. glabrata* (77% inhibited by ≤1 μg/ml). This level of activity was unchanged over time and when stratified by geographic regions of the world (data not shown). Itraconazole had little meaningful activity against flu-

TABLE 2. In vitro activity of itraconazole against fluconazole-resistant isolates of *Candida* spp.

Organism (no. of isolates tested)	No. of resistant isolates[a]	No. of isolates at MIC (μg/ml)[b]:									
		0.03	0.06	0.12	0.25	0.5	1	2	4	8	>8
C. albicans (3,895)	4			1		1	1	1			
C. glabrata (1,054)	88					2	2	15	18	9	42
C. parapsilosis (1,028)	8				2	4	2				
C. tropicalis (829)	3				1	1		1			
C. krusei (206)	70				1	16	44	9			
All *Candida* spp. (7,299)	175			1	4	25	49	26	18	10	42

[a] No. of isolates for which the fluconazole MIC was ≥64 μg/ml.
[b] MICs for itraconazole.

TABLE 3. In vitro susceptibilities of 445 isolates of *Aspergillus* spp. to itraconazole

Organism (no. of isolates tested)	Cumulative % at MIC (μg/ml):							
	0.06	0.12	0.25	0.5	1	2	4	8
A. fumigatus (331)	1	4	11	50	96	100		
A. flavus (48)			8	83	100			
A. terreus (23)		9	39	96	100			
A. niger (21)			10	24	71	100		
All *Aspergillus* spp. (445)[a]	1	4	13	55	94	99	88	99

[a] Includes *A. versicolor* (9), *A. ustus* (3), *A. nidulans* (2), *A. sydowii* (1), *A. glaucus* (1), *Aspergillus* spp. (6).

conazole-resistant isolates of *C. glabrata* (Table 2); however, 86% of the fluconazole-resistant isolates of *C. albicans*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei* were inhibited by ≤1 μg of itraconazole per ml. Overall, 94% of all isolates of *C. krusei* (those for which fluconazole MICs were either ≤64 or ≥64 μg/ml) were susceptible to itraconazole at concentrations of ≤1 μg/ml (Table 1).

Itraconazole was less active against *C. neoformans* (Table 1). Although 80% of the isolates tested were inhibited by ≤1 μg of itraconazole per ml, the poor penetration of itraconazole into the central nervous system makes this drug a less attractive option for treating cryptococcosis than other azoles (39).

In similarity to the results recently reported by Verweij et al. (38), itraconazole showed good activity (94% inhibited by ≤1 μg/ml) against a large collection of *Aspergillus* spp. (Table 3). Notably, there were no isolates of *A. fumigatus* for which the MICs of itraconazole were greater than 2 μg/ml. Likewise, Verweij et al. (38) reported only three isolates of *A. fumigatus* for which itraconazole MICs were >2 μg/ml.

These findings provide a contemporary look at the spectrum and potency of itraconazole against three major groups of opportunistic fungal pathogens as determined by standardized reference broth microdilution methods. Given the changes in formulation of itraconazole and the ability to reliably maintain serum concentrations above 1 μg/ml, one can now begin to assess the data presented in Table 1 to Table 3 in terms of those species that may be covered by this agent (i.e., those for which the MIC is ≤1 μg/ml). In this regard, more than 90% of invasive isolates of *Candida* and *Aspergillus* spp. from throughout the world may be considered "susceptible" to itraconazole at concentrations of ≤1 μg/ml. Indeed, elevated itraconazole MICs (>2 μg/ml) were extremely uncommon among isolates of *Candida* and *Aspergillus* spp. (Table 1 to Table 3). Aside from *C. glabrata*, even strains of fluconazole-resistant *Candida* spp. show itraconazole MICs of ≤1 μg/ml.

As seen with fluconazole and *Candida* spp. (27), and as reported by Verweij et al. (38) for *Aspergillus*, we have found no evidence that the in vitro activity of itraconazole has decreased over time (data not shown). Thus, primary resistance to itraconazole among clinical isolates of *Candida* (except for *C. glabrata*) and *Aspergillus* spp. appears to be very low. The fact that the spectrum and potency of the drug has been sustained over a 13-year period (1992 to 2004) despite the use of itraconazole for treatment and prophylaxis indicates that acquired resistance is low as well.

The availability of more readily bioavailable oral and parenteral formulations of itraconazole has given this established antifungal agent "new life" (29, 39). We report the MIC data herein as a continuous distribution of results throughout the range of concentrations tested to allow one to better evaluate the activity of the drug against readily achievable serum and tissue concentrations. Such data should prove useful in reevaluating the MIC interpretive breakpoints for itraconazole and serve as an aid in guiding the application of this drug clinically.

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