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In Vitro Studies of Two Triazole Antifungal Agents (Voriconazole [UK-109,496] and Fluconazole) against *Candida* Species

ARTHUR L. BARRY* AND STEVEN D. BROWN

The Clinical Microbiology Institute, Tualatin, Oregon 97062

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A new triazole derivative (voriconazole or UK-109,496) and fluconazole were tested against 249 isolates of *Candida* spp. representing six species. Voriconazole was 10 to 100 times more potent than fluconazole. Strains with decreased susceptibility to fluconazole were inhibited by relatively low concentrations of voriconazole.

Fluconazole is a triazole antifungal agent that is widely used for treating human infections, especially candidiasis. The chemical structure of fluconazole has been modified in order to broaden its antifungal spectrum of activity and to increase its in vitro potency (8, 9). Figure 1 shows the chemical structure of the new triazole, voriconazole (UK-109,496), which is well tolerated by humans following oral or parenteral administration (7). In vitro and animal studies have demonstrated that voriconazole is very active against many molds, including *Aspergillus* spp. (2, 3, 5), as well as *Candida* spp., *Cryptococcus* spp., and other yeasts (1, 4, 10).

In this report we describe the results of in vitro studies carried out with 249 isolates of *Candida* spp. representing six different species. The study strains were kindly provided by Chris Hitchcock (Pfizer Central Research, Sandwich, United Kingdom) and were selected to include strains with a broad range of fluconazole MICs. The reference broth dilution procedure of the National Committee for Clinical Laboratory Standards (6) was used to compare MICs of voriconazole to those of fluconazole. Serial dilutions of both drugs were dispensed into plastic tubes (12 by 75 mm) and then frozen at −20°C until needed. The drugs were further diluted when the tubes were inoculated with 1.0 ml of a suspension of freshly isolated colonies in RPMI 1640 broth. The inoculum was a saline suspension of 3 to 5 fresh colonies, adjusted to match the turbidity of a McFarland 0.5 standard as determined with a spectrophotometer set at 530 nm. For each test, colony counts were performed and the strain was retested if the inoculum was not 0.5×10^3 to 2.5×10^3 CFU/ml. MICs were recorded after 48 h of incubation; 90% of the 24-h determinations were found to be essentially identical (±1 doubling concentration) to the 48-h values. A few strains that failed to grow well during the first 24 h showed greater shifts in 48-h MICs. All MICs were defined as the lowest concentration with at least 80% inhibition of growth. That endpoint was determined by visually contrasting turbidity to that of a 1:5 dilution of the growth control.

Table 1 summarizes the results of this exercise. In all cases, voriconazole was more potent than fluconazole. There were only three strains of *C. kefyr* and all three voriconazole MICs were ≤0.06 μg/ml. For the five other species, geometric mean MICs of fluconazole were at least 10 times greater than those of voriconazole. The difference in potencies of the two drugs

TABLE 1. In vitro activity of voriconazole and fluconazole against 249 *Candida* isolates as determined by a standard tube dilution procedure[a]

Species (no. tested)	Antimicrobial agent	48-h MIC (μg/ml)[b]			Geometric mean[c]
		Range	50%	90%	
C. albicans (100)	Voriconazole	≤0.06–16	≤0.06	0.5	0.12
	Fluconazole	0.12–>128	0.5	32	1.49
C. guilliermondii (26)	Voriconazole	≤0.06–8.0	0.5	4.0	0.59
	Fluconazole	2.0–>128	32	128	28.8
C. krusei (42)	Voriconazole	≤0.06–2.0	0.5	0.5	0.39
	Fluconazole	2.0–>128	64	64	48.3
C. kefyr (3)	Voriconazole	≤0.06–≤0.06	≤0.06	—[d]	≤0.06
	Fluconazole	0.25–0.5	0.5	—	0.40
C. parapsilosis (40)	Voriconazole	≤0.06–0.25	≤0.06	0.12	0.07
	Fluconazole	0.12–8.0	1.0	2.0	0.86
C. tropicalis (38)	Voriconazole	≤0.06–1.0	≤0.06	0.25	0.10
	Fluconazole	0.25–64	1.0	2.0	1.06

[a] The standard reference method of the National Committee for Clinical Laboratory Standards (6) was used throughout with RPMI 1640 broth medium in tubes (12 by 75 mm).
[b] After 48 h of incubation, the MIC was defined as the lowest concentration inhibiting at least 80% of the growth (turbidity less than that of a 1:5 dilution of the 48-h growth control tube).
[c] For calculation purposes, an MIC ≤0.06 μg/ml was assumed to be 0.06 μg/ml and an MIC >128 μg/ml was assumed to be 256 μg/ml.
[d] MIC_{90}s were not calculated since there were only three strains tested.

* Corresponding author. Mailing address: Clinical Microbiology Institute, P.O. Box 947, Tualatin, OR 97062. Phone: (503) 692-4690. Fax: (503) 692-6184.

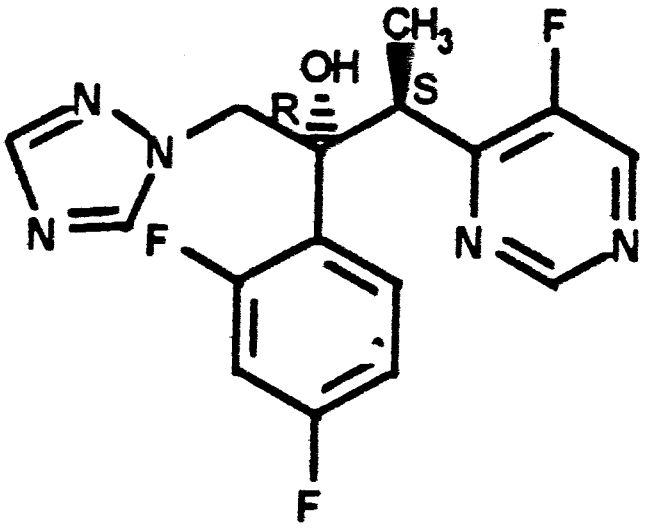

FIG. 1. Chemical structure of voriconazole (UK-109,496).

was particularly noteworthy for *C. krusei* (124-fold) and *C. guilliermondii* (49-fold). Most strains belonging to the latter two species were relatively resistant to fluconazole (the MICs at which 90% of the isolates were inhibited [MIC_{90}s] were 64 and 128 μg/ml, respectively) but they were much more susceptible to voriconazole (MIC_{90}s, 0.5 and 4.0 μg/ml, respectively). The *C. albicans* collection included seven strains with elevated MICs of fluconazole (MIC ≥64 μg/ml), and for those strains, MICs of voriconazole were either 0.5 μg/ml (3 strains), 4.0 μg/ml (3 strains), or 16 μg/ml (1 strain). There were 17 *C. albicans* strains for which the fluconazole MIC was 16 or 32 μg/ml, and for those strains, MICs of voriconazole ranged from 0.06 to 1.0 μg/ml. The 76 remaining strains were susceptible to ≤8.0 μg of fluconazole per ml, and for those strains, MICs of voriconazole were ≤0.25 μg/ml.

The in vitro data presented in this brief note demonstrate that voriconazole is a very potent drug against *Candida* species. This increased potency is expected to be sufficient to permit treatment of infections due to strains with diminished susceptibility to fluconazole but that remains to be determined. Its activity against *C. krusei* is particularly noteworthy. Clinical studies that are currently in progress should determine whether this in vitro potency accurately predicts clinical utility.

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