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In Vitro Comparative Efficacy of Voriconazole and Itraconazole against Fluconazole-Susceptible and -Resistant *Cryptococcus neoformans* Isolates

M. HONG NGUYEN* AND CHRISTINE Y. YU

Department of Medicine, Division of Infectious Disease, University of Florida College of Medicine, and VA Medical Center, Gainesville, Florida

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In vitro susceptibility testing for 50 clinical isolates of fluconazole-susceptible or -resistant *Cryptococcus neoformans* was performed with itraconazole and voriconazole. Voriconazole was more potent than itraconazole for fluconazole-susceptible isolates and as potent as itraconazole for fluconazole-susceptible dose-dependent isolates and for fluconazole-resistant isolates. For fluconazole-resistant isolates, the voriconazole and itraconazole MICs ranged from 1 to 2 μg/ml.

Cryptococcus neoformans is the leading cause of meningitis in human immunodeficiency virus-infected patients. Amphotericin B is the current standard therapy but is associated with a high toxicity profile. Fluconazole is better tolerated, but with increasing reports of fluconazole-resistant *C. neoformans* (3), the use of this agent might be limited in the future. Itraconazole is less effective than fluconazole in the treatment of cryptococcal meningitis in human immunodeficiency virus-infected patient (5, 10). For these reasons, the evaluation of newer antifungal agents against *C. neoformans* is clearly indicated.

Voriconazole is a new triazole antifungal agent that has in vitro activity against *Candida* isolates, including those that are resistant in vitro to fluconazole (1, 2, 9). Its activity against *C. neoformans* is unknown. Furthermore, the in vitro activity of voriconazole has not been compared with that of itraconazole against this yeast. The goal of this study was to compare the in vitro activities of fluconazole, itraconazole, and voriconazole against 50 clinical isolates of *C. neoformans*; fluconazole had a wide range of MICs for the isolates studied.

Fifty clinical isolates of *C. neoformans* obtained from our clinical microbiology laboratory or from the Fungus Testing Laboratory at the University of Texas Health Science Center (San Antonio, Tex.) were tested; previously, fluconazole demonstrated a wide range of MICs for these isolates. *Candida albicans* ATCC 90028, *Candida glabrata* ATCC 90030, and *C. neoformans* ATCC 90113 were incorporated into each set of experiments as quality control isolates.

The susceptibility testing was performed by a macrodilution method adhering to the National Committee for Clinical Laboratory Standards (NCCLS) protocol (7). The stock solutions for fluconazole and voriconazole (Pfizer Central Research, Groton, Conn.) were prepared in sterile water. Stock solutions for itraconazole (Janssen Research Foundation, Beerse, Belgium) were prepared in dimethyl sulfoxide. The concentrations of drugs tested were 0.125 to 64 μg/ml for fluconazole and 0.015 to 16 μg/ml for itraconazole and voriconazole.

Fluconazole and itraconazole breakpoint values for susceptibility have not yet been proposed by the NCCLS for *C. neoformans*; for simplicity, we adapted the breakpoint values proposed by the NCCLS for *Candida* spp. to *Cryptococcus* (8).

The fluconazole, itraconazole, and voriconazole MICs for the ATCC isolates were 0.5, 0.125, and 0.03 μg/ml, respectively, for ATCC 90028; 16, 0.125, and 0.03 μg/ml, respectively, for ATCC 90030; and 2, 0.06, and 0.125 μg/ml, respectively, for ATCC 90113.

Fluconazole had MICs of ≤8 μg/ml for 82% (41 of 50) of the *C. neoformans* isolates (fluconazole susceptible), 16 to 32 μg/ml for 14% (7 of 50) of these isolates (susceptible, dose dependent), and 64 μg/ml for 4% (2 of 50) of these isolates (resistant). The itraconazole and voriconazole MICs paralleled the fluconazole MICs: the higher the fluconazole MICs, the higher the itraconazole and voriconazole MICs ($P < 0.001$, linear regression). Itraconazole and voriconazole had MICs of ≤0.5 μg/ml for all isolates demonstrating in vitro susceptibility or susceptibility, dose dependent to fluconazole.

Itraconazole and voriconazole had MICs of ≤0.125 μg/ml, for 56% (23 of 41) and 88% (36 of 41) respectively, of fluconazole-susceptible isolates and MICs of 0.25 to 0.5 μg/ml for 44% (18 of 41) and 12% (5 of 41), respectively, of these same isolates. For these isolates, voriconazole was more potent than itraconazole in vitro: the voriconazole geometric mean MIC (0.07 μg/ml) was significantly lower than the itraconazole geometric mean MIC (0.14 μg/ml; $P = 0.001$, analysis of variance).

Itraconazole and voriconazole had MICs of ≤0.125 μg/ml for 43% (three of seven) and 28% (two of seven), respectively, of susceptible, dose dependent isolates and MICs of 0.25 to 0.5 μg/ml for 57% (four of seven) and 72% (five of seven), respectively, of these same isolates. For these isolates, there was no difference between the voriconazole and itraconazole geometric mean MICs (0.37 and 0.29 μg/ml, respectively).

For fluconazole-resistant isolates, the itraconazole and voriconazole MICs were either 1 or 2 μg/ml. To our knowledge, this is the first report documenting such high itraconazole and voriconazole MICs for *C. neoformans* isolates. Extrapolating from the known pharmacokinetics of itraconazole, and the clinical experience with *C. albicans* where itraconazole MICs of ≥1 μg/ml indicate resistance (8), the itraconazole MICs of 1 or 2 μg/ml observed for fluconazole-resistant isolates might represent itraconazole resistance for *C. neoformans* as well. Although the evaluation of the pharmacokinetics and clinical efficacy of voriconazole is still in progress, there has been evidence in animals that voriconazole is better absorbed and

* Corresponding author. Mailing address: Department of Medicine, University of Florida College of Medicine, P.O. Box 100277, JHMHC, Gainesville, FL 32610. Phone: (352) 379-4027. Fax: (352) 379-4015. E-mail: nguyemt@medicine.ufl.edu.

can achieve higher and more prolonged concentrations in serum than can itraconazole (4, 6). For example, in a rat model of invasive aspergillosis, the maximum concentration of drug in serum after an oral administration of 30 mg/kg was 4.6 μg/ml for voriconazole, compared to only 0.4 μg/ml for itraconazole (6). This favored pharmacokinetics of voriconazole might explain the better outcome observed in infected rats treated with voriconazole than in those treated with itraconazole and might therefore represent an advantage of voriconazole over itraconazole (6).

In summary, voriconazole was more potent than itraconazole in vitro against fluconazole-susceptible *C. neoformans* isolates and was as potent as itraconazole against fluconazole-susceptible, dose-dependent and fluconazole-resistant isolates. Given the high oral bioavailability and the well-tolerated nature of voriconazole, this drug might become an important addition to the armamentarium of antifungal agents. It should be stressed, however, that clinical confirmation of these promising in vitro results is needed to elucidate the role of this new antifungal agent in the management of cryptococcal infection.

REFERENCES

1. **Barry, A. L., and S. D. Brown.** 1996. In vitro studies of two triazole antifungal agents (voriconazole [UK-109,246] and fluconazole) against *Candida* species. Antimicrob. Agents Chemother. **40:**1948–1949.
2. **Belanger, P., C. C. Nast, R. Fratti, H. Sanati, and M. Ghannoum.** 1997. Voriconazole (UK-109,496) inhibits the growth and alters the morphology of fluconazole-susceptible and -resistant *Candida* species. Antimicrob. Agents Chemother. **41:**1840–1842.
3. **Berg, J., C. J. Clancy, and M. H. Nguyen.** The hidden danger of primary fluconazole prophylaxis in patients with acquired immunodeficiency syndrome. Clin. Infect. Dis., in press.
4. **Martin, M. V., J. Yates, and C. A. Hitchcock.** 1997. Comparison of voriconazole (UK-109,496) and itraconazole in prevention and treatment of *Aspergillus fumigatus* endocarditis in guinea pigs. Antimicrob. Agents Chemother. **41:**13–16.
5. **Moskowitz, B. L.** 1993. Randomized, comparative study of itraconazole and fluconazole for treatment of AIDS-related cryptococcal meningitis. *In* Proceedings of the First National Conference on Human Retroviruses and Related Infections, Washington, D.C. (Abstract.)
6. **Murphy, M., E. M. Beranard, T. Ishimary, and D. Armstrong.** 1997. Activity of voriconazole (UK-109,496) against clinical isolates of *Aspergillus* species and its effectiveness in an experimental model of invasive pulmonary aspergillosis. Antimicrob. Agents Chemother. **41:**696–698.
7. **National Committee for Clinical Laboratory Standards.** 1995. Development of in vitro susceptibility testing criteria and quality control parameters. Approved guideline M27-A. National Committee for Clinical Laboratory Standards, Villanova, Pa.
8. **Rex, J. H., M. A. Pfaller, J. N. Galgiani, et al.** 1997. Development of interpretive breakpoints for antifungal susceptibility testing: conceptual framework and analysis of in vitro-in vivo correlation data for fluconazole, itraconazole, and candida infections. Clin. Infect. Dis. **24:**235–247.
9. **Ruhnke, M., A. Schmidt-Westhausen, and M. Trautmann.** 1997. In vitro activities of voriconazole (UK-109,496) against fluconazole-susceptible and -resistant *Candida albicans* isolates from oral cavities of patients with human immunodeficiency virus infection. Antimicrob. Agents Chemother. **41:**575–577.
10. **Saag, M. S., G. C. Cloud, J. R. Graybill, J. Sobel, C. Tuazon, B. Wiesinger, L. Riser, B. L. Moskovitz, W. E. Dismukes, and the NIAID Mycoses Study Group.** 1995. Comparison of fluconazole (FLU) versus itraconazole (ITRA) as maintenance therapy of AIDS-associated cryptococcal meningitis (CM), abstr. I218, p. 244. *In* Program and Abstracts of the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy. American Society for Microbiology, Washington, D.C.