ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2006, p. 1570–1572 Vol. 50, No. 4
0066-4804/06/$08.00+0 doi:10.1128/AAC.50.4.1570–1572.2006


# Voriconazole Therapeutic Drug Monitoring

J. Smith,[1] N. Safdar,[1] V. Knasinski,[1] W. Simmons,[2] S. M. Bhavnani,[3] P. G. Ambrose,[3] and D. Andes[1,4]*

*University of Wisconsin, Department of Medicine, Section of Infectious Diseases, Madison, Wisconsin[1]; University of Wisconsin, Department of Pharmacy, Madison, Wisconsin[2]; Institute for Clinical Pharmacodynamics, Ordway Research Institute, Albany, New York[3]; and University of Wisconsin, Department of Medical Microbiology and Immunology, Madison, Wisconsin[4]*

Received 22 September 2005/Returned for modification 4 December 2005/Accepted 9 January 2006

**We report on 28 patients who underwent voriconazole monitoring because of disease progression or toxicity. A relationship ($P < 0.025$) between disease progression and drug concentration was detected. Favorable responses were observed in 10/10 patients with concentrations above 2.05 μg/ml, while disease progressed in 44% ($n = 18$) of patients with concentrations below 2.05 μg/ml.**

Most drugs display linear pharmacokinetic profiles. Drugs with nonlinear elimination characteristics that also have narrow therapeutic toxicity widows are candidates for monitoring. This is especially true in the circumstance where low drug exposures are life threatening and high drug exposures result in significant toxicities. Voriconazole is a triazole antifungal with enhanced activity against a broad spectrum of fungal pathogens, including *Aspergillus* and *Candida* species (11, 26). We provide a succinct review of voriconazole's pharmacokinetics (PK) and present new PK-pharmacodynamic (PD) data relating drug concentration to therapeutic response.

The pharmacokinetics of voriconazole in volunteers and patients have shown that voriconazole exhibits a nonlinear pharmacokinetic profile, secondary to saturable clearance (6, 16, 24, 25). Voriconazole is metabolized by the cytochrome P450 system, with less than 2% of the dose excreted unchanged (12, 13, 24, 25). Most voriconazole metabolism is mediated through CYP2C19. Allelic polymorphisms of CYP2C19 have been shown to be the most important determinants of the clearance of voriconazole, resulting in two phenotypes: poor and extensive metabolizers (both homozygous and heterozygous). There is extensive genetic variability in the incidence of poor and extensive metabolizers (5, 10, 18, 28). The proportions of CYP2C19 extensive metabolizers in the U.S. population are estimated to be 2% homozygous extensive and 26% heterozygous extensive. Homozygous extensive metabolizers have a twofold lower exposure than heterozygous extensive metabolizers and fourfold lower drug exposure than poor metabolizers (12, 13).

In 10 trials, the median values for the average and maximum voriconazole plasma concentrations in individual patients ($n$ = 1,121) were 2.51 μg/ml and 3.79 μg/ml, respectively (6, 16, 23, 24, 25). The values for area under the plasma concentration-time curve on day 10 in 200- and 300-mg administration groups were approximately 5.8 and 3.8 times higher, respectively, among the poor metabolizers than among the extensive metabolizers. Trough concentrations also suggested that poor metabolizers were exposed to higher concentrations than were extensive metabolizers. The pharmacokinetics exhibited minimal intrapatient variation but marked interpatient variation, which was postulated to be secondary to genetic factors, enzyme inhibition and induction, old age, and liver disease.

A PK-PD analysis of 6 of the 10 clinical trials ($n$ = 280) did not reveal an association between voriconazole concentration and efficacy (19). This is likely because the antifungal exposure far exceeded the MICs of most pathogens ($MIC_{90}$, ≤0.5 μg/ml) (26). However, analysis of the clinical trials did suggest a trend towards worse outcome in those patients with voriconazole concentrations of <0.5 μg/ml (http://www.fda.gov).

Despite voriconazole's efficacy, breakthrough fungal infections have been reported (1, 14, 20, 29). Among the 13 patients described in a report by Imhof et al., pathogen MICs were ≥1 μg/ml for available isolates (14). Unfortunately, data regarding voriconazole serum concentrations in these patients were unavailable.

We retrospectively studied voriconazole monitoring at our institution. Data variables included patient age, gender, voriconazole indication and dose, other potentially interacting pharmaceuticals, voriconazole concentration, reason for the lab request, timing of dose relative to sampling, and outcome. Serum concentrations were determined by a validated high-pressure liquid chromatography method. Progression was defined as an increase in size or number of lesions on follow-up imaging. Survival was defined at time of last follow-up.

A total of 188 patients received voriconazole from 2002 to 2005. The indications for voriconazole were as follows: invasive aspergillosis (82 patients), prophylaxis (13), blastomycosis (3), febrile neutropenia (56), and other fungal infections (34). Twenty-eight patients had at least one drug concentration determination (Table 1). All patients received voriconazole loading and were on 200 mg orally twice daily for at least 2 weeks. Seventeen patients had concentrations determined because of disease progression, while 11 were determined for toxicity. Of those patients who were failing therapy, 15 of 17 patients had a transplant and received voriconazole for aspergillosis. All 17 patients had serum concentrations below the median value from clinical trials (2.51 μg/ml). The voriconazole range, median, mean and standard deviation in this study were <0.2 to 4.8, 1.05, 1.10, and 0.76 μg/ml, respectively. Five patients had duplicate determinations of concentrations prior to dose adjustments (concentrations remained below the median value from the trials until dose adjustment). No concomitant CYP-

* Corresponding author. Mailing address: 600 Highland Avenue, Room H4/572, Madison, WI 53792. Phone: (608) 263-1545. Fax: (608) 263-4464. E-mail: dra@medicine.wisc.edu.

TABLE 1. Patient demographics, voriconazole levels, indications, and outcomes for patients with lower serum concentrations

| Patient no. | Age range (yr) | Gender[a] | Wt (kg) | Comorbidity[b] | Fungal disease[c] | Level (μg/ml) | Progression | Voriconazole dose changed as result of level | Survival |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 36–40 | F | 56 | Lung Tx | IA | 1.0 | Yes | Yes | No |
| 2 | 36–40 | F | 43 | Kidney Tx | IA | 0.3, 0.9 | Yes | Yes | Yes |
| 3 | 41–45 | M | 51 | BMT | IA | 1.5 | No | No | No |
| 4 | 36–40 | M | 64 | Lung Tx | IA | 0.9, 1.2 | No | Yes | Yes |
| 5 | 56–60 | M | 64 | CLL | IA | 1.2 | Yes | No | No |
| 6 | 46–50 | M | 43 | BMT | IA | 0.7 | No | No | Yes |
| 7 | 26–30 | F | 99 | Hodgkin's disease | IA | 0.3 | Yes | No | No |
| 8 | 31–35 | F | 41 | BMT | IA | 1.8 | Yes | No | No |
| 9 | 36–40 | F | 58 | Lung Tx | IA | 0.4 | No | Yes | Yes |
| 10 | 36–40 | M | 60 | ALL, BMT | IA | 0.2 | Yes | No | No |
| 11 | 51–55 | M | 105 | Renal Tx | IA | 0.8, 1.5 | Yes | Yes | Yes |
| 12 | 41–55 | M | 82 | Renal Tx | IA | <0.2, <0.2 | Yes | Yes | Yes |
| 13 | 36–40 | M | 137 | Liver Tx | IA | 0.7, 4.4 (peak), 4.8 (trough) | Yes | Yes | No |
| 14 | 16–20 | F | 48 | Lung Tx | *Scedosporium* | 0.8, 0.7, 2.9 | Yes | Yes | Yes |
| 15 | 51–55 | M | 175 | Liver Tx | Blastomycosis | <0.2, 0.3, 2.4 | Yes | Yes | Yes |
| 16 | 61–65 | M | 78 | Lung Tx | IA | 0.6, 1.2, 1.5 | Yes | Yes | Yes |
| 17 | 66–70 | M | 100 | Liver Tx | IA, blastomycosis | 0.9, 2.4, 2.3 | Yes | Yes | No |
| 18 | 56 | F | 59 | Heart Tx | IA | 2.8 | No | No | Yes |
| 19 | 39 | F | 46 | Heart Tx | IA | 3.9 | No | No | Yes |
| 20 | 36 | M | 80 | Renal Tx | *Candida* | 2.9 | No | No | Yes |
| 21 | 52 | M | 90 | | IA | 3.5 | No | No | Yes |
| 22 | 32 | F | 48 | Lung Tx | IA | 2.2 | No | No | Yes |
| 23 | 40 | M | 58 | Liver | IA | 4.0 | No | No | Yes |
| 24 | 40 | F | 63 | BMT | IA | 1.6 | No | No | Yes |
| 25 | 0.8 | F | 61 | Renal Tx | IA | 0.8 | Yes | Yes | Yes |
| 26 | 64 | M | 64 | AML | IA | 13.2 | No | Yes | Yes |
| 27 | 46 | F | 46 | Unknown | *Cryptococcus* | 2.5 | No | No | Yes |
| 28 | 41 | F | 45 | Renal Tx | IA | 2.9 | No | No | Yes |

[a] F, female; M, male.
[b] Tx, transplant; BMT, bone marrow transplant; CLL, chronic lymphocytic leukemia; ALL, acute lymphocytic leukemia; AML, acute myelogenous leukemia.
[c] IA, invasive aspergillosis.

inducing drugs were identified. Weight did not appear to affect the concentrations in this small cohort. Eight of the 17 patients in whom a concentration was checked for disease progression died due to invasive aspergillosis. Voriconazole concentrations below 2.0 μg/ml prompted an increase in dose in 11 patients, 8 of whom survived the infection. A subsequent concentration, which was available for six patients, was above 2.5 μg/ml in three patients. The mean follow-up period was 13 months after the serum concentration was obtained.

Using data from all 28 patients, PK-PD breakpoints for a clinical response were determined using classification and regression tree-based modeling. A significant ($P < 0.025$) relationship between disease progression and drug concentration was detected. A positive clinical response was observed in 100% (10/10) of patients with random voriconazole concentrations of above 2.05 μg/ml, while disease progressed (and patients died) in 8/18 patients with concentrations of below 2.05 μg/ml.

Therapeutic drug monitoring is well established when using medicines with narrow therapeutic indices to minimize toxicity (3). Therapeutic drug monitoring is also well established when variable absorption or pharmacokinetics could result in insufficient drug exposures. Drug monitoring is common with a large number of anti-infective agents, including the antifungal agents flucytosine and itraconazole (3, 8, 9, 15, 17, 21, 22). The rationale for monitoring itraconazole concentrations is the erratic oral bioavailability. A relationship between plasma concentrations (0.5 μg/ml) and antifungal efficacy was demonstrated in postmarketing data analyses (9, 15). CYP metabolizer status has been shown to affect clinical responses for other disease states. For example, extensive metabolizers of the proton pump inhibitors have a five-times-lower exposure and experience less effective healing of ulcers (5, 18).

The main limitation of the current report is the small cohort size and the retrospective design. However, the cohort is similar to those utilized in demonstrating the importance of exposure with other anti-infectives. The study most closely related to the current investigation was that which demonstrated the relevance of itraconazole therapeutic drug monitoring (9; A. Glasmacher, C. Hahn, E. Molitor, et al., Abstr. 40th Intersci. Conf. Antimicrob. Agents Chemother., abstr. 700, 2000). There are other examples of cohorts of similar size (five to eight patients with low exposure and failure) which have been used to examine the relationship between drug exposure and outcome with antibacterials (2, 4, 7).

Additionally, we were unable to assess the genotype for this cohort, and we do not have susceptibility data for the fungal isolates. Despite these limitations, this study suggests that clinical failure may be related to subtherapeutic drug exposures. The presence of low concentrations altered management of patients when the concentration was known prior to the patient death. Both the prior breakthrough infection reports and the current data suggest that clinicians should escalate doses for serum concentrations of below 2 μg/liter in patients failing therapy.

## REFERENCES


1. **Alexander, B., W. A. Schell, J. L. Miller, G. D. Long, and J. R. Perfect.** 2005. Candida glabrata fungemia in transplant patients receiving voriconazole after fluconazole. Transplantation **27:**868–871.
2. **Ambrose, P. G., D. M. Grasela, T. H. Grasela, J. Passarell, H. B. Mayer, and P. F. Pierce.** 2001. Pharmacodynamics of fluoroquinolones against *Streptococcus pneumoniae* in patients with community-acquired respiratory tract infections. Antimicrob. Agents Chemother. **45:**2793–2797.
3. **Begg, E. J., B. L. Murray, and C. J. Kirkpatrick.** 1999. The therapeutic monitoring of antimicrobial agents. Br. J. Clin. Pharmacol. **47:**23–30.
4. **Craig, W. A., and D. Andes.** 1996. Pharmacokinetics and pharmacodynamics of antibiotics in otitis media. Pediatr. Infect. Dis. J. **15:**255–259.
5. **Desta, Z., X. Zaho, J. G. Shin, and D. A. Flockhart.** 2002. Clinical significance of the cytochrome P450 2C19 genetic polymorphism. Clin. Pharmacokinet. **41:**913–958.
6. **Europen Medicines Agency.** 2002. EPAR for Vfend. Europen Medicines Agency, London, United Kingdom.
7. **Forrest, A., D. E. Nix, C. H. Ballow, T. F. Goss, M. C. Birmingham, and J. J. Schentag.** 1993. Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. Antimicrob. Agents Chemother. **37:**1073–1081.
8. **Francis, P., and T. J. Walsh.** 1992. Evolving role of flucytosine in immunocompromised patients: new insights into safety, pharmacokinetics, and antifungal therapy; Clin. Infect. Dis. **15:**1003–1018.
9. **Glasmacher, A., C. Hahn, C. Leutner, E. Molitor, E. Wardelmann, C. Losem, T. Sauerbruch, G. Marklein, and I. G. Schmidt-Wolf.** 1999. Breakthrough invasive fungal infections in neutropenic patients after prophylaxis with itraconazole. Mycoses **42:**443–451.
10. **Goldstein, J. A., and S. M. F. de Morais.** 1994. Biochemistry and molecular biology of the human CYP2C subfamily. Pharmacogenetics **4:**285–299.
11. **Herbrecht, R., D. W. Denning, T. F. Patterson, J. E. Bennett, R. E. Greene, J. W. Oestmann, W. V. Kern, K. A. Marr, P. Ribaud, O. Lortholary, R. Sylvester, R. H. Rubin, J. R. Wingard, P. Stark, C. Durand, D. Caillot, E. Thiel, P. H. Chandrasekar, M. R. Hodges, H. T. Schlamm, P. F. Troke, and B. de Pauw.** 2002. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N. Engl. J. Med. **347:**408–415.
12. **Hyland, R., B. C. Jones, and D. A. Smith.** 2003. Identification of the cytochrome P450 enzymes involved in the N-oxidation of voriconazole. Drug Metab. Dispos. **31:**540–712.
13. **Ikeda, Y., K. Umemura, K. Kondo, K. Sekiguchi, and M. Nakashima.** 2004. Pharmacokinetics of voriconazole and cytocrome P450 and 2C19 genetic status. Clin. Pharmacol. Ther. **75:**586–588.
14. **Imhof, A., S. A. Balajee, D. N. Fredricks, J. A. Englund, and K. A. Marr.** 2004. Breakthrough fungal infections in stem cell transplant recipients receiving voriconazole. Clin. Infect. Dis. **39:**743–746.
15. **Lampe, D., S. Kreutzberg, and H. J. Prumke.** 1994. Therapeutic drug monitoring of itraconazole—a report of experiences. Mycoses **37**(Suppl. 2)**:**34–39.
16. **Lazarus, H. M., J. L. Blumer, S. Yanovich, H. Schlamm, and A. Romero.** 2002. Safety and pharmacokinetics of oral voriconazole in patients at risk of fungal infection: a dose escalation study. J. Clin. Pharmacol. **42:**395–402.
17. **Lazo de la Vega, S., P. Volkow, R. A. Yeates, and G. Pfaff.** 1994. Administration of the antimycotic agents fluconazole and itraconazole to leukaemia patients: a comparative pharmacokinetic study. Drugs Exp. Clin. Res. **20:** 69–75.
18. **Lehman, D. F., J. J. Medicis, and P. D. Franklin.** 2003. Polymorphisms and the pocketbook: the cost-effectiveness of cytochrome P450 2c19 genotyping in the eradication of Helicobacter pylori infection associated with duodenal ulcer. J. Clin. Pharmacol. **43:**1316–1323.
19. **Lutsar, I., M. R. Hodges, K. Tomaszewski, P. F. Troke, and N. Wood.** 2003. The safety of voriconazole and dose individualization. Clin. Infect. Dis. **36:**1087–8813.
20. **Marty, F. M., L. A. Cosimi, and L. Baden.** 2004. Breakthrough zygomycosis after voriconazole treatment in recipients of hematopoietic stem-cell transplants. N. Engl. J. Med. **350:**950–952.
21. **Petersen, D., S. Demertzis, M. Freund, G. Schumann, and M. Oellerich.** 1994. Individualization of 5-fluorocytosine therapy. Chemotherapy **40:**149–156.
22. **Poirier, J. M., and G. Cheymol.** 1998. Optimization of itraconazole therapy using target drug concentrations. Clin. Pharmacokinet **35:**461–473.
23. **Potoski, B. A., and J. R. Brown.** 2002. The safety of voriconazole. Clin. Infect. Dis. **35:**1273–1275.
24. **Purkins, L., N. Wood, K. Greenhalgh, M. J. Allen, and S. D. Oliver.** 2003. Voriconazole, a novel wide spectrum triazole: oral pharmacokinetics and safety. Br. J. Clin. Pharmacol. **56**(Suppl. 1)**:**10–16.
25. **Purkins, L., N. Wood, P. Ghahramani, K. Greenhalgh, M. J. Allen, and D. Kleinermans.** 2002. Pharmacokinetics and safety of voriconazole following intravenous-to oral-dose escalation regimens. Antimicrob. Agents Chemother. **46:**2546–2553.
26. **Radford, S. A., E. M. Johnson, and D. W. Warnock.** 1997. In vitro studies of activity of voriconazole (UK-109,496), a new triazole antifungal agent, against emerging and less common mold pathogens. Antimicrob. Agents Chemother. **41:**841–843.
27. **Schafer-Korting, M.** 1993. Pharmacokinetic optimization of oral antifungal therapy. Clin. Pharmacokinet. **25:**329–341.
28. **Service, R. F.** 2005. Going from genome to pill. Science **308:**1858–1860.
29. **Siwek, G. T., K. J. Dodgson, M. de Magalhaes-Silvermanet, L. A. Bartlet, S. B. Kilborn, P. L. Hoth, D. J. Diekema, and M. A. Pfaller.** 2004. Invasive zygomycosis in hematopoietic stem cell transplant recipients receiving voriconazole prophylaxis. Clin. Infect. Dis. **39:**584–587.