Utilization of Omeprazole To Augment Subtherapeutic Voriconazole Concentrations for Treatment of *Aspergillus* Infections

Natalie K. Boyd,^a Cindy L. Zoellner,^{a,b} Mark A. Swancutt,^{a,b} and Kavita P. Bhavan^{a,b}

Parkland Health and Hospital System^a and University of Texas Southwestern Medical Center, Dallas, Texas, USA^b

Voriconazole is the preferred antifungal agent for *Aspergillus* infections. Therapeutic drug monitoring is recommended to achieve target concentrations and prevent toxicity. However, variable pharmacokinetics, cytochrome P450 polymorphisms, and extensive drug-drug interactions can contribute to subtherapeutic concentrations. We report a voriconazole “boosting” effect of omeprazole to achieve target concentrations for the treatment of *Aspergillus* in a patient who had persistently subtherapeutic trough concentrations.

Voriconazole is a triazole antifungal agent that is the mainstay of therapy for invasive *Aspergillus* infections (2, 5). Multiple factors, such as age, liver function, and cytochrome P450 (CYP) polymorphisms, affect the systemic exposure of voriconazole (6). Additionally, drug interactions, saturable pharmacokinetics, and significant inter- and inpatient variability produce unpredictable concentrations. Therapeutic drug monitoring (TDM) is therefore necessary to optimize voriconazole concentrations during the management of invasive fungal infections (IFIs), such as aspergillosis. However, the optimal target range remains undefined. Pascual et al. observed a higher response rate for patients with IFIs when trough concentrations were >1 $\mu\text{g/ml}$ (4). A retrospective cohort study found that steady-state concentrations of >2.05 $\mu\text{g/ml}$ were associated with an increased invasive aspergillosis survival rate (10/10 versus 8/18, $P < 0.025$) (8). In contrast, voriconazole trough concentrations of >5.5 $\mu\text{g/ml}$ were correlated with toxicity (4).

Voriconazole concentrations that fall outside the therapeutic range can occur as a result of drug-drug interactions due to extensive metabolism by CYP enzymes. Voriconazole is a major substrate of CYP2C19, an isoenzyme known for polymorphisms (5). Phenotypic expression of CYP2C19 allelic variants ranges from poor metabolism to ultrarapid metabolism (7). Voriconazole systemic concentrations increase in the presence of CYP2C19 inhibitors. Omeprazole, a widely available proton pump inhibitor, competitively inhibits the CYP2C19 enzyme (3). Wood et al. investigated the effect of omeprazole, given orally at standard doses, on voriconazole pharmacokinetics in 16 patients (11). Omeprazole coadministration increased the mean voriconazole peak concentration in plasma and the area under the curve over the dosing interval by 15 and 41%, respectively. Higher trough concentrations also occurred in the omeprazole-cotreated group. Additionally, other prospective clinical observational data suggest that 44% of patients with supratherapeutic voriconazole concentrations (>5.5 $\mu\text{g/ml}$) were concomitantly receiving omeprazole (4). Here we report a case of the therapeutic use of omeprazole to “boost” subtherapeutic voriconazole concentrations in a patient with chronic intracranial aspergillosis.

In June 2011, a 22-year-old immunocompetent male with a history of intracranial *Aspergillus* infections was admitted to the Parkland Health and Hospital System (Dallas, TX) after brain magnetic resonance imaging (MRI) showed new abscess formation. The patient had a traumatic brain injury after a motor vehicle

accident in June 2007 necessitating craniotomy, ventricular-peritoneal shunt placement, and cranioplasty in October 2007. Right frontal lobe aspergillosis, first diagnosed in mid-2008 and confirmed by multiple cultures for *Aspergillus fumigatus*, subsequently complicated his course. He has taken multiple courses of voriconazole, posaconazole, micafungin, and amphotericin B without resolution. Before his most recent admission, the patient was maintained on a higher-than-average dose of 400 mg orally (p.o.) every 12 h (6 mg/kg/dose q12h) because of subtherapeutic trough concentrations. Initially, liposomal amphotericin B was added to voriconazole. Lesion proximity to the motor strip was a contraindication to operative intervention. Our goal voriconazole trough concentration range was >1 to ≤ 5.5 $\mu\text{g/ml}$. The first trough concentration, obtained 5 days after admission, was subtherapeutic (0.3 $\mu\text{g/ml}$) (Fig. 1). We increased the dose to 300 mg p.o. q8h. Since his trough concentration remained subtherapeutic (0.3 $\mu\text{g/ml}$), we briefly changed from p.o. to intravenous (i.v.) drug administration with no change in the dose. Eight days after i.v. administration, the trough concentration increased to 0.9 $\mu\text{g/ml}$. Although this nearly achieved the target concentration of >1 $\mu\text{g/ml}$, it was suboptimal considering the history of readmissions due to persistent *Aspergillus* infection. Furthermore, the 13.5-mg/kg/day dose was already exceeding the recommended maintenance dose (5). Further dose titration would increase the outpatient pill burden and the risk of noncompliance. Therefore, on day 42, omeprazole at 40 mg p.o. daily was added with the intention of creating a modest “boost” of voriconazole levels via CYP2C19 interaction (11). After 4 weeks, the patient was discharged on i.v. micafungin at 100 mg daily, voriconazole at 300 mg p.o. q8h, and omeprazole at 40 mg p.o. daily. There were no other medication changes. His liver function enzymes remained within normal limits. Another trough voriconazole concentration obtained approximately 6 weeks later was therapeutic at 1.5 $\mu\text{g/ml}$. Micafungin was discontinued. To date, the patient remains asymptomatic and

Received 4 April 2012 Returned for modification 18 June 2012

Accepted 7 August 2012

Published ahead of print 13 August 2012

Address correspondence to Natalie Boyd, natalie.boyd@phhs.org.

Copyright © 2012, American Society for Microbiology. All Rights Reserved.

doi:10.1128/AAC.00700-12

FIG 1 Plasma voriconazole concentrations over the course of treatment. Superscripts: a, dose increased from 400 mg p.o. q12h to 300 mg q8h; b, switched to i.v. formulation (300 mg q8h); c, i.v. dose transitioned back to voriconazole at 300 mg p.o. q8h and omeprazole at 40 mg p.o. daily added.

repeat brain MRI findings from April 2012 showed near resolution of the ring-enhancing lesion in the right parietal lobe. After 10 months of therapy, he remains 100% compliant without reported adverse effects. Subsequent voriconazole concentrations have ranged from 1.5 to 1.8 µg/ml.

Although voriconazole has >95% oral bioavailability, variable pharmacokinetics and drug-drug interactions produce unpredictable concentrations. Trifilio et al. evaluated steady-state concentrations in patients who had undergone allogeneic hematopoietic stem cell transplantation and found that 27% had subtherapeutic drug concentrations, although they received equivalent doses (9). Although the exact therapeutic range has not been fully delineated, trough concentrations between 1 and 5 µg/ml have been proposed as optimal. Pascual et al. noted that patients with voriconazole concentrations of <1.1 µg/ml had increased failure rates during treatment for IFIs (46% versus 12%, $P = 0.02$), while those with levels of >5.5 µg/ml (5/16) experienced adverse neurological effects (4). In a recent meta-analysis, investigators concluded that minimum voriconazole concentrations of 1 µg/ml may be necessary for efficacy, but levels of >4 µg/ml should be avoided for safety (1). Others advise targeting a higher minimum concentration of ≥ 2 µg/ml to exceed the MICs of most fungal pathogens. Troke et al. evaluated nine published clinical trials to assess the voriconazole exposure-response relationship (10). The MIC₉₀s for yeast ($n = 259$) and molds ($n = 109$) were 1 and 0.5 µg/ml, respectively. A trough concentration/MIC ratio of 2 to 5 was associated with a higher probability of response. Interestingly, the lowest response rates were observed at both low (<0.5) and high (≥ 5) voriconazole trough concentrations.

Individualized dosing based on TDM is key to managing supra- or subtherapeutic voriconazole exposure. We report a case of an immunocompetent patient with chronic intracranial *Aspergillus* infections who achieved target voriconazole trough concentrations after the coadministration of omeprazole. The magnitude of the effect of omeprazole on voriconazole pharmacokinetics and

the general applicability of this strategy are unknown. Further systematic investigation is warranted to define the true “boosting” effect of omeprazole on plasma voriconazole concentrations and determine whether this combination will play a role in clinical practice.

ACKNOWLEDGMENTS

We thank Sujata Bhavnani, Paul Ambrose, George Drusano, and Kristin Alvarez for their guidance and constructive feedback.

REFERENCES

- Hamada Y, Yoshinori S, Kazuo Y, Kuroyama M. 2012. Investigation and threshold of optimum blood concentration of voriconazole: a descriptive statistical meta-analysis. *J. Infect. Chemother.* 18:501–507.
- Herbrecht R, et al. 2002. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N. Engl. J. Med.* 347:408–415.
- Ko JW, Sukhova N, Thacker D, Chen P, Flockhart DA. 1997. Evaluation of omeprazole and lansoprazole as inhibitors of cytochrome P450 isoforms. *Drug Metab. Dispos.* 25:853–862.
- Pascual A, et al. 2008. Voriconazole therapeutic drug monitoring in patients with invasive mycoses improves efficacy and safety outcomes. *Clin. Infect. Dis.* 46:201–211.
- Pfizer Inc. 2010. Vfend—U.S. prescribing information (revised June 2010). Pfizer Inc., New York, NY.
- Purkins L, et al. 2002. Pharmacokinetics and safety of voriconazole following intravenous to oral-dose escalation regimens. *Antimicrob. Agents Chemother.* 46:2546–2553.
- Scott SA, et al. 2011. Clinical pharmacogenetics implementation consortium guidelines for cytochrome P450-2C19 (*CYP2C19*) genotype and clopidogrel therapy. *Clin. Pharmacol. Ther.* 90:328–332.
- Smith J, et al. 2006. Voriconazole therapeutic drug monitoring. *Antimicrob. Agents Chemother.* 50:1570–1572.
- Trifilio S, et al. 2007. Monitoring plasma voriconazole levels may be necessary to avoid subtherapeutic levels in hematopoietic stem cell transplant recipients. *Cancer* 109:1532–1535.
- Troke PF, Hockey HP, Hope WW. 2011. Observational study of the clinical efficacy of voriconazole and its relationship to plasma concentrations in patients. *Antimicrob. Agents Chemother.* 55:4782–4788.
- Wood N, et al. 2003. Effect of omeprazole on the steady-state pharmacokinetics of voriconazole. *J. Clin. Pharmacol.* 56(Suppl 1):56–61.