Published in final edited form as:
Mycoses. 2011 November ; 54(6): e877–e879. doi:10.1111/j.1439-0507.2011.02016.x.

Prolonged Half-life of Voriconazole in a CYP2C19 Homozygous Poor Metabolizer Receiving Vincristine Chemotherapy: Avoiding a Serious Adverse Drug Interaction

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Summary

We report a case of prolonged half-life of voriconazole due to *CYP2C19*2/*2* poor metabolizer genotype in a patient receiving vincristine chemotherapy. Voriconazole was discontinued three days before start of vincristine to avoid a serious drug interaction. Therapeutic drug monitoring and genotyping are valuable tools in managing patients receiving voriconazole and vincristine.

Keywords

voriconazole; vincristine; CYP2C19; poor metabolizer

Introduction

The concomitant use of triazole antifungal agents with vincristine may lead to severe neurotoxicity (Bermudez M et al., J Pediatr Hematol Oncol 2005;**27**:389–92; Porter CC et al., Pediatr Blood Cancer 2009;**52**:298–300; Eiden C et al., J Pediatr Hematol Oncol 2009;**31**:292–5; Gubbins PO et al., Mycoses 2010;**53**:95–113; Mantadakis E et al., J Pediatr Hematol Oncol 2007;**29**:130; Jain S et al., Pediatr Blood Cancer 2010;**54**:783). Prevention and management of this serious drug interaction are not well understood. We report herein an obese patient who demonstrated slow metabolism of voriconazole, necessitating discontinuation of voriconazole three days before vincristine chemotherapy and replacement by an echinocandin in order to avoid this potentially life-threatening drug interaction.

Case Description

A 41-year-old Caucasian male with peripheral T-cell lymphoma and hemophagocytic syndrome was admitted to the Intensive Care Unit with septic shock from methicillin-

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Financial Disclosures: Dr. Walsh is the recipient of a research grant from Vestagen and has served on advisory boards of Novartis, Ico, and Trius.

susceptible *Staphylococcus aureus*, and *Pasteurella dagmatis* bacteremia. In addition, *Aspergillus fumigatus* was recovered from a bronchoalveolar lavage and liposomal amphotericin B and caspofungin were initiated. The patient's underlying conditions included obesity with a body mass index (BMI) of 36 kg/m^2, bilateral lower extremity neuropathy, and chronic renal insufficiency.

After completing the first cycle of EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) chemotherapy for peripheral T-cell lymphoma, voriconazole was added to the patient's antifungal regimen. He received two loading doses of voriconazole 6 mg/kg (605 mg) IV every 12 hours followed by a maintenance dose of 4 mg/kg (405 mg) IV every 12 hours. Liposomal amphotericin B and caspofungin were then discontinued. As there were no published data to our knowledge on the pharmacokinetics of voriconazole in obese patients, serum concentrations were measured to assist dosing. Serum concentrations were determined by liquid chromatography-tandem mass spectrometry assay at the Mayo Medical Laboratories, Rochester, MN. Voriconazole pharmacokinetics were determined using standard noncompartmental methods with the WinNonlin Professional computer program (version 5.0, Pharsight Corporation, Mountain View, CA).

Voriconazole pharmacokinetic parameter values after five days of voriconazole 405 mg IV every 12 hours are displayed in Table 1 (Purkins L et al., Antimicrob Agents Chemother 2002;**46**:2546–53). The serum area under the concentration versus time curve over the course of a single dosing interval ($AUC_{0–12}$)of 77,790 ng · h/ml was unexpectedly elevated in relation to a reduced clearance. Based on these pharmacokinetic data, the voriconazole dose was decreased to 325 mg IV every 12 hours. However, despite 2.5 days at this dosage, the clearance further diminished with the $AUC_{0–12}$ measured at 104,245 ng · h/ml (Table 1). In addition, the prolonged voriconazole half-lives ($t_{1/2}$) of 24 hours and 30 hours (Table 1) were approximately 3 to 4 times those observed in normal adult volunteers.

Due to the patient's prolonged voriconazole $t_{1/2}$ and decreased clearance, voriconazole was discontinued three days before the second cycle of EPOCH chemotherapy in the hope of diminishing the inhibitory impact of voriconazole on the CYP3A4-mediated metabolism of vincristine. Voriconazole serum concentrations approximately 24 hours and 72 hours after the last dose had slowly declined to 3.9 mcg/ml and 1.6 mcg/ml, respectively. Although an increase in volume of distribution secondary to the patient's obesity may have contributed to the extended voriconazole $t_{1/2}$, it cannot explain the unusually low voriconazole clearance. To further understand reduced voriconazole clearance in this patient, CYP2C19 genotyping was performed using PCR methodology (Mayo Medical Laboratories, Rochester, MN). The patient was found to be a homozygous slow metabolizer with a genotype of *CYP2C19*2/*2*.

After withholding voriconazole for three days, the patient tolerated the second cycle of EPOCH chemotherapy, but complained of tingling and numbness of his finger tips. Thus, caspofungin was initiated in place of voriconazole as voriconazole's prolonged $t_{1/2}$ in this patient would make administration difficult with subsequent cycles of EPOCH chemotherapy.

Discussion

The vinca alkaloid vincristine is a substrate for CYP3A4 and P-glycoprotein (P-gp). Severe vincristine toxicity potentiated by itraconazole, a CYP3A4 and P-gp inhibitor, has been well described in the literature (Bermudez M et al., J Pediatr Hematol Oncol 2005;**27**:389–92). Adverse drug interactions between vincristine and itraconazole include abdominal pain, constipation, paralytic ileus, hypertension, weakness, neuropathy, seizures, hyponatremia, and syndrome of inappropriate antidiuretic hormone secretion. Voriconazole is an inhibitor

of CYP3A4, CYP2C9, and CYP2C19, and neurotoxicity also has been reported with concurrent administration of vincristine (Porter CC et al., Pediatr Blood Cancer 2009;**52**:298–300; Harnicar S et al., J Oncol Pharm Pract 2009;**15**:175–82). Porter and colleagues reported a 5 year old patient with acute lymphoblastic leukemia who developed severe foot drop and loss of deep tendon reflexes with concomitant administration of vincristine and voriconazole (Porter CC et al., Pediatr Blood Cancer 2009;**52**:298–300).

Our patient demonstrated a prolonged voriconazole $t_{1/2}$ and decreased clearance requiring discontinuation of the drug three days before vincristine chemotherapy. One possible cause of the patient's prolonged voriconazole $t_{1/2}$ and decreased clearance is his *CYP2C19*2/*2* genotype. This poor metabolizer phenotype occurs in 12% to 23% of Asians, 1% to 6% of Caucasians, and 1% to 7.5% of Black Africans (Desta Z et al., Clin Pharmacokinet 2002;**41**:913–58). Several reports indicate a voriconazole $t_{1/2}$ and clearance in CYP2C19 poor metabolizers of 9.4 to 14.3 hours and 8.8 to 9.8 L/hour, respectively (Weiss J et al., J Clin Pharmacol 2009;**49**:196–204; Scholz I et al., Br J Clin Pharmacol 2009;**68**:906–15; Lei HP et al., Ann Pharmacother 2009;**43**:726–31; Wang G et al., Eur J Clin Pharmacol 2009;**65**:281–5; Meletiadis J et al., Pharmacogenomics 2008;**9**:561–84). Our patient's voriconazole $t_{1/2}$ was longer than in the above studies, possibly due to his obesity. Consistent with this patient's BMI of 36 kg/m^2, his total volume of distribution (Vd) was markedly elevated. Given the relation of $t_{1/2} = 0.693\ Vd/Cl$, an increase in Vd would lead to prolongation of $t_{1/2}$. While little is known about the effect of obesity on pharmacokinetics of voriconazole, we hypothesize that this patient's increased total Vd contributed further to the already prolonged $t_{1/2}$ conferred by the *CYP2C19*2/*2* genotype.

A recent study of voriconazole in obese patients found that there were no significant differences in AUCs between obese and non-obese patients receiving a fixed oral dose of 200 mg or of 300 mg (Pai MP et al., 50^{th} ICAAC 2010; abstract A1-044). These findings are consistent with voriconazole distributing principally into lean body tissue with some smaller contribution of adipose tissue. Similarly one would predict that if obese patients received voriconazole on a dose per unit weight basis (mg/kg) based upon their total body weight, then the AUCs would be predictably higher.

Severe and potentially life-threatening triazole-vincristine drug interactions may be avoided by withholding the azole before administration of the vinca alkaloid or by substituting with another class of antifungal agents. Based on the estimated $t_{1/2}$ of voriconazole in CYP2C19 homozygous and heterozygous extensive metabolizers, withholding voriconazole for at least 24–48 hours before administration of vincristine should provide for minimal levels of circulating triazole when the vinca alkaloid is administered. However, in homozygous poor metabolizers of CYP2C19, withholding voriconazole for at least 3 days and using therapeutic drug monitoring before the start of vincristine chemotherapy would be warranted. Administration of a non-triazole antifungal agent during the withholding period may be used to prevent progressive fungal infection. A more practical approach is to substitute voriconazole with a non-triazole antifungal agent, such as an echinocandin or a lipid formulation of amphotericin B. Lipid formulations of amphotericin B, caspofungin, or micafungin is recommended for treatment of invasive aspergillosis in patients who are intolerant of voriconazole (Walsh TJ et al., Clin Infect Dis 2008;**46**:327–60). Avoiding a severe drug interaction with vincristine would be consistent with this recommendation. Although reduction of the vincristine dose is another approach (Harnicar S et al., J Oncol Pharm Pract 2009;**15**:175–82), such dosing changes may not be permissible under most cancer chemotherapy protocols. Given the complexities of discontinuation and resumption of an antifungal triazole in patients receiving vincristine-based chemotherapy, the safest approach in many clinical settings may be to use an alternative class of antifungal agents.

In conclusion, therapeutic drug level monitoring and CYP2C19 genotyping may be valuable tools in managing patients receiving voriconazole and vincristine chemotherapy. Voriconazole may require discontinuation several days in advance or replacement by an echinocandin or lipid formulation of amphotericin B to prevent serious vincristine neurotoxicity in patients with delayed clearance.

Acknowledgments

The authors thank Dr. Barry Goldspiel for his thoughtful comments and review of the manuscript. This work was supported in part by the intramural research program of the National Institutes of Health.

Table 1

Voriconazole pharmacokinetic parameters in case patient and in healthy volunteers

Pharmacokinetic Parameter	Voriconazole 405 mg IV every 12h (case patient)*	Voriconazole 325 mg IV every 12h (case patient)+	Voriconazole 4 mg/kg IV every 12h (healthy volunteers) (Purkins L et al., Antimicrob Agents Chemother 2002;46:2546–53)
AUC_{0-12} (ng · h/ml)	77,790	104,245	29,467
Clearance (L/h)	5.01	3.16	¶
Vd (L)	221	101	¶
$t_{1/2}$ (h)	30	24	7.9
trough (mcg/ml)	6.1	6.7	1.7

*infusion time (1.75 h); collection time points from beginning of infusion (2.5, 5.6, 9.5, 11.5 h).

+infusion time (1.5 h); collection time points from beginning of infusion (3.1, 6, 10.2, 12.2 h).

¶not reported.