Boosting of Voriconazole Levels With Omeprazole, A CYP450 2C19 Inhibitor

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Abstract: Children metabolize voriconazole faster than adults and require higher weight-based doses and more frequent administration to achieve therapeutic troughs. We report a case of a 4-year-old girl with disseminated fusariosis with persistently undetectable voriconazole troughs. Omeprazole was added as a CYP2C19-inhibitor to increase voriconazole concentrations. This case highlights the role of omeprazole for voriconazole boosting in a child.

Key Words: fusariosis, voriconazole, therapeutic drug monitoring, omeprazole, CYP450 2C19 inhibitor

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Invasive fusariosis is an uncommon but important opportunistic infection in immunocompromised children with an associated mortality of 75%.[1] Voriconazole has *in vitro* activity against *Fusarium* spp. by selectively inhibiting cytochrome P450 (CYP450)-dependent 14-alpha-sterol demethylase to prevent ergosterol biosynthesis and is recommended first line for the treatment of invasive fusariosis.[2] It is hepatically metabolized primarily by CYP2C19, with minor contributions from CYP2C9 and CYP3A4.[3] Younger children metabolize voriconazole 3 times faster than adults due to higher expression and catalytic efficiency of CYP2C19 as well as a higher contribution of the drug-metabolizing enzyme flavin-containing monooxygenase 3 (FMO_3) toward *N*-oxidation.[3] This results in the need for higher weight-based doses of voriconazole to achieve exposures comparable to adults and metabolism that becomes saturated (nonlinear) at higher doses as compared to adults.[3]

We report a case of a child with invasive fusariosis who successfully achieved therapeutic voriconazole troughs after omeprazole, a known CYP450 2C19 inhibitor, was added as a pharmacokinetic booster. We also review the literature surrounding voriconazole pharmacokinetic boosting with CYP2C19 inhibitors.

CASE REPORT

A 4-year-old girl with relapsed high-risk pre-B cell acute lymphoblastic leukemia, who underwent an allogeneic hematopoietic stem cell transplant approximately 1 year prior, presented to medical care on day 14 of bridging chemotherapy for chimeric antigen receptor T-cell therapy. She presented with neutropenic fever and a left knee abrasion. She scraped her knee while playing outside 6 days before admission and began limping 2 days before admission. Upon presentation, she had a fever of 39.1°C, was normotensive, and otherwise well-appearing. On physical examination, she had tenderness in her left knee and a small abrasion with surrounding edema and minimal erythema. Her absolute neutrophil count was 20 cells/mm^3. Blood cultures were obtained and cefepime and vancomycin were initiated. Within the subsequent 24 hours, the erythema significantly worsened and developed a bluish hue concerning for early necrosis. Magnetic resonance imaging of the lower extremity and joint obtained on hospital day 2 revealed no evidence of fluid collections or bony involvement. A biopsy was obtained on hospital day 3, and liposomal amphotericin B (L-AMB) 5 mg/kg/dose q24h was added to her antimicrobial regimen for suspicion of invasive fungal infection. A serum galactomannan and 1,3-beta-D-glucan obtained on hospital day 3 were both unremarkable (index of 0.05, and <31 pg/mL, respectively). Blood cultures obtained upon admission remained negative.

Histopathology of her left knee lesion obtained from her biopsy indicated dense hyphal forms throughout the dermis and associated vessels indicating angioinvasion. Fungal culture demonstrated the growth of a filamentous organism, which subsequently speciated as *Fusarium solani* complex. Additional debridement of the left knee occurred on hospital days 6 and 8 and heavy growth of *F. solani* was again observed. Extensive imaging was pursued and notable for a 0.6 cm hypoattenuating lesion in the left deltoid muscle, a 0.2 cm pulmonary nodule in the left upper lobe and a 0.8 × 0.9 cm fluid collection in her left elbow. Her L-AMB dose was escalated to 7.5 mg/kg/dose on hospital day 6, and then to 10 mg/kg/dose IV q24h on hospital day 7. Voriconazole was added on hospital day 6 (9 mg/kg/dose IV q12h on day 1, then 8 mg/kg/dose IV q12h thereafter) (Fig. 1).

The *F. solani* isolate had the following minimum inhibitory concentrations (MICs): voriconazole 4 mcg/mL, amphotericin B 8 mcg/mL and both posaconazole and isavuconazole >16 mcg/mL. L-AMB was discontinued once susceptibility results were known. Although *F. solani* is intrinsically resistant to echinocandins,[2] *in vitro* synergy has been reported when used in combination with other antifungals.[4] Therefore, micafungin 4 mg/kg/dose IV q24h[2] was added on hospital day 12 but discontinued on hospital day 21 after synergy testing performed at the University of Texas Health Science Center in San Antonio, TX, did not reveal synergy with the combination of voriconazole and micafungin.

A voriconazole trough goal of 4–6 mcg/mL was selected due to the elevated MIC of 4 mcg/mL for the *F. solani* isolate. Achieving a voriconazole trough/MIC ratio of 2 has been associated with improved rates of successful outcome[3]; however, given that the toxicity threshold for voriconazole is ~6 mcg/mL, targeting a trough of

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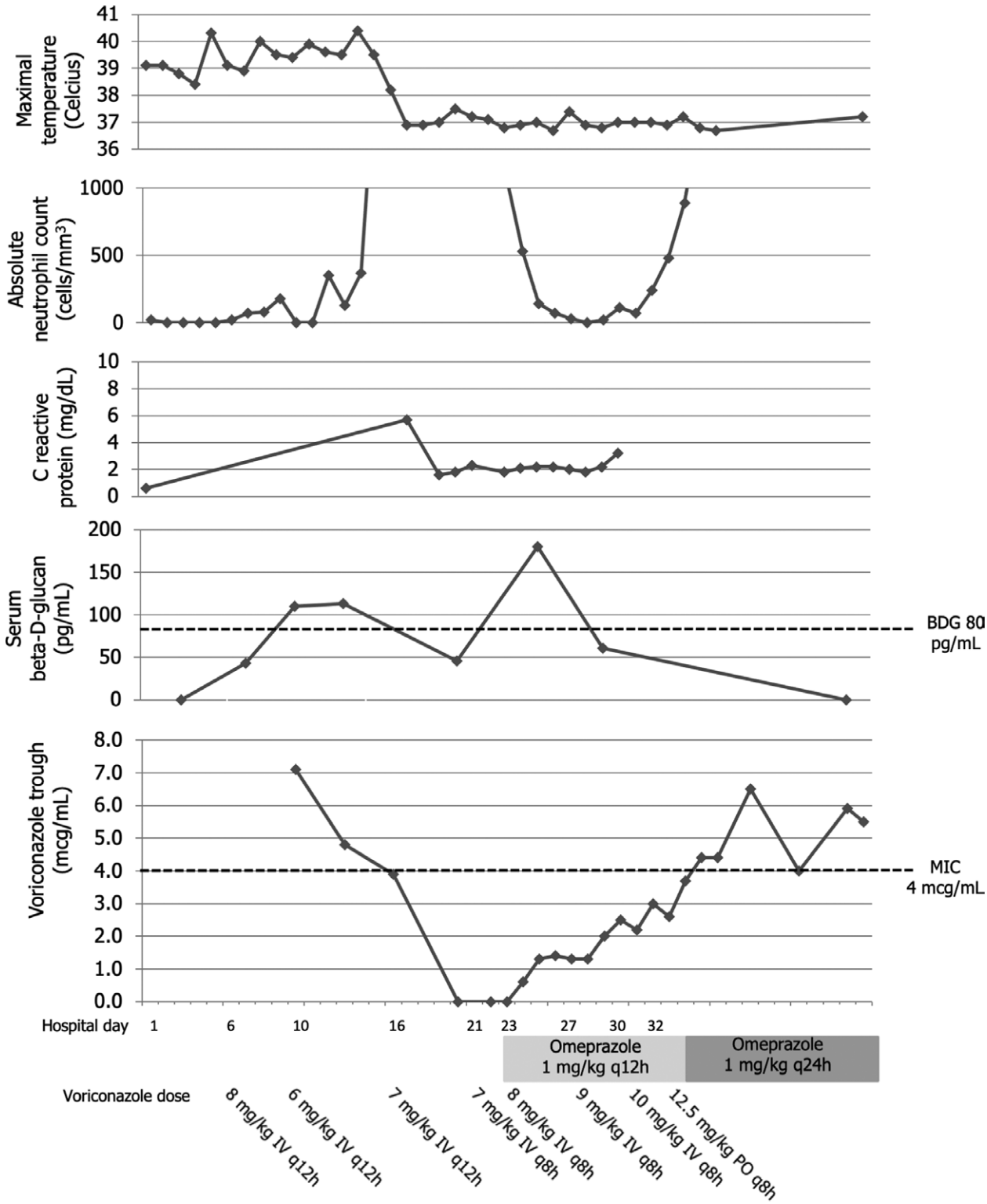

FIGURE 1. Fever curve, absolute neutrophil count, C-reactive protein, serum beta-D-glucan (BDG) levels and voriconazole serum trough concentrations during treatment course for invasive fusariosis in a child with high-risk pre-B cell acute lymphoblastic leukemia; IV, intravenous; PO, oral.

8 mcg/mL would increase the probability of dose-dependent toxicities. Her voriconazole trough was initially supratherapeutic at 7.1 mcg/mL on hospital day 10 after 4 days of standard voriconazole dosing, so her maintenance dose was subsequently decreased to

6 mg/kg/dose IV q12h. A repeat serum beta-D-glucan from hospital day 10 was 110 pg/mL, raising concern for disseminated fusariosis as serum beta-D-glucan is typically elevated in patients with disseminated fusariosis.[5] She remained neutropenic throughout this time, with an absolute neutrophil count of zero on hospital day 10. She underwent a third debridement on hospital day 13.

The patient developed worsening fever, headache and respiratory distress on hospital day 14, which is also when she began to recover her neutrophil count. Imaging revealed new multifocal ground glass opacities in both her upper and lower lung fields and multifocal lesions in her kidneys concerning for new renal abscesses. The voriconazole trough subsequently decreased to 3.9 mcg/mL, therefore her dose was increased to 7 mg/kg/dose IV q12h on day 16. On day 20, her voriconazole trough was undetectable (<0.5 mcg/mL), so her frequency was increased to q8h dosing. A trough was checked early after only 2 days of 7 mg/kg/dose IV q8h and was found to be still undetectable. Considering her worsening disease and persistently undetectable levels, it was decided to increase her dose to 8 mg/kg/dose IV q8h and simultaneously add on a pharmacokinetic booster. Omeprazole, a known CYP2C19 inhibitor, at a dose of 1 mg/kg/dose orally (PO) q12h, was added on day 23 to boost voriconazole levels through its inhibition of CYP2C19-mediated metabolism and voriconazole troughs gradually rose. Her voriconazole dose was escalated several times over the next 10 days and eventually reached a therapeutic trough of 4.4 mcg/mL on a voriconazole dose of ~12.5 mg/kg/dose PO q8h in combination with omeprazole 1 mg/kg/dose PO q24h (Fig. 1).

She became neutropenic again between days 25 and 33, and her serum beta-D-glucan peaked at 180 pg/mL. Between days 35 and 43, she developed signs of worsening *F. solani* infection. Imaging indicated a 2.2 × 0.9 × 2.2 cm fluid collection in her left arm and several new nodules in her thigh, behind her ear, abdominal wall and calf. Tissue samples demonstrated moderate hyphal elements on calcofluor white stain without growth of *F. solani*. She remained afebrile during this time and was continued on voriconazole. She subsequently had a supratherapeutic voriconazole trough of 9.3 mcg/mL as an outpatient on day 60, therefore omeprazole was discontinued and her voriconazole dose was reduced to ~10.7 mg/kg/dose PO q8h. Her troughs remained in the 4–6 mcg/mL range for the next several months on this dose, which she tolerated well without any evidence of voriconazole-related toxicity (eg, hepatotoxicity and neurotoxicity).

Repeat imaging conducted 6 months after the initiation of voriconazole therapy revealed significant interval improvement or resolution of all metastatic sites of proven or suspected infection. No additional fungal growth occurred, and serum beta-D-glucan levels remained undetectable. As she is awaiting enrollment in a humanized chimeric antigen receptor-T cell trial for her underlying pre-B cell acute lymphoblastic leukemia, voriconazole is being continued for the duration of her upcoming treatment.

DISCUSSION

Monitoring of trough concentrations is essential for the optimization of voriconazole therapy.[3] Young children metabolize voriconazole 3 times faster than adults due to higher expression and catalytic efficiency of hepatic enzyme CYP2C19 as well as the significant contribution of the drug-metabolizing enzyme FMO_3 toward *N*-oxidation.[3] This results in a higher capacity for children to eliminate voriconazole on an mg/kg basis.

Generally, voriconazole troughs greater than 1 or greater than 2 mcg/mL are targeted for the treatment of invasive mold infections such as invasive aspergillosis. However, for our patient infected with a *F. solani* complex isolate with a voriconazole MIC of 4 mcg/mL, a higher trough goal range was targeted (4–6 mcg/mL) to ensure drug concentrations remained above the MIC while limiting dose-related toxicity. Our patient's case underscores the importance of speciation and antifungal susceptibility testing for Fusarium isolates as certain species, such as the *F. solani* complex, demonstrate elevated MICs to the most commercially available antifungals. Clinical breakpoints for *Fusarium* spp. have not been established[6] and voriconazole is considered the most active antifungal against *Fusarium* spp., despite exhibiting relatively high MICs (MIC_{50} of 8 mcg/mL[7]).

Our patient experienced supratherapeutic levels of voriconazole initially while receiving the standard dose for a child her age. However, troughs became undetectable (<0.5 mcg/mL) after ~2 weeks of therapy. Sources of potential error with sampling, assay accuracy and pharmacy preparation were investigated and excluded. Repeat levels were sent to an external lab for validation and were also determined to be undetectable. A random voriconazole level was drawn ~2 hours after administration of a newly prepared IV dilution of voriconazole which was detectable at 0.9 mcg/mL. There were no known drug-drug interactions with her other medications that could explain the drop in serum concentrations of voriconazole. Her C-reactive protein was rising and peaked at 5.7 mg/dL when her trough became undetectable, so the potential role of inflammation influencing her voriconazole clearance seemed unlikely. Despite the reported high CYP2C19 activity in children, where enzyme activity is approximately 1.5 to 2-fold higher than in adults during the first few years of life,[3] the acute changes in voriconazole levels described in this case are unlikely due to the age-related CYP2C19 activity differences as the patient initially had supratherapeutic levels follow by a precipitous decline to undetectable levels. Auto-induction of voriconazole metabolism can occur after 1 week of therapy or can appear months later, and the magnitude of the decrease in voriconazole troughs can range from a 1.6 to 12-fold decrease.[3] Because other potential causes were ruled out, we attributed the drastic decrease in voriconazole levels to the auto-induction of metabolism.

Despite several dose escalations, our patient's voriconazole troughs remained undetectable. Proton pump inhibitors are known to inhibit CYP2C19 enzyme activity to varying degrees, with omeprazole, lansoprazole and esomeprazole demonstrating more potent inhibitory effects compared to ilaprazole and pantoprazole.[8] Both adult and pediatric patients receiving voriconazole in combination with omeprazole are more likely to have supratherapeutic voriconazole levels.[8–10] In healthy volunteers, omeprazole 40 mg PO q24h increased voriconazole's maximal serum concentration (C_{max}) and area under the curve (AUC) by 15% and 40%, respectively.[11,12] We conducted a search within PubMed and other databases using keywords such as "voriconazole pharmacokinetic boosting", "CYP2C19 inhibitor", "voriconazole and proton pump inhibitor", etc., to identify if these agents have been intentionally used to increase concentrations of voriconazole. Previous case reports, limited to the adult population, have highlighted the role of using proton pump inhibitors (omeprazole, esomeprazole, lansoprazole or pantoprazole) to pharmacokinetically "boost" the levels of voriconazole in situations where there is difficulty achieving therapeutic troughs either because of an extensive metabolizer CYP2C19 phenotype or because higher than usual troughs were targeted due to elevated MICs (see Table, Supplemental Digital Content 1, http://links.lww.com/INF/E973). Based on the existing published literature, and the known potency of CYP2C19 inhibition, we selected omeprazole as a pharmacokinetic booster for our patient. We anticipated that the onset of the drug-drug interaction would be immediate given that omeprazole is a strong affinity substrate for CYP2C19 and causes immediate competitive inhibition. Given that the drug-drug interaction between omeprazole and voriconazole has been described in both adults and children, the ontogeny

of CYP2C19, where enzyme activity is approximately 1.5 to 2-fold higher than in adults during the first few years of life,[3] does not seem to impact the relevance of this drug-drug interaction. Finally, CYP2C19 polymorphisms do not seem to affect omeprazole's ability to inhibit CYP2C19-mediated voriconazole metabolism.[9] Our patient did not have a baseline CYP2C19 genotype obtained before her stem cell transplant.

In the absence of published experience in children of omeprazole dosing as a pharmacokinetic booster, we determined an omeprazole dose of 2 mg/kg/day was a reasonable starting dose, which is in the middle of the dosing range for children. Voriconazole inhibits CYP2C19 and CYP3A4-mediated metabolism of omeprazole, resulting in an omeprazole C_{max} that is 2 times higher and an AUC that is 4 times higher compared to in the absence of voriconazole co-administration.[11] Therefore, the package labeling recommends the omeprazole dose be reduced by one-half when initiating voriconazole therapy in patients receiving omeprazole doses of 40 mg or greater.[11] Due to her rapidly worsening disease and persistently undetectable levels, it was decided to treat her aggressively by simultaneously increasing her voriconazole dose to 8 mg/kg/dose IV q8h and adding omeprazole 2 mg/kg/day. Because both changes were made at the same time, we were unable to delineate the effect of the addition of the omeprazole alone, which is a limitation of our report. Before discharge, the dose of omeprazole was decreased to 1 mg/kg/day as her troughs were escalating rapidly, probably as a result of reaching the point of saturable metabolism. The combination of omeprazole 1 mg/kg/day and voriconazole 12.5 mg/kg/dose PO q8h resulted in stable voriconazole troughs in the 4–6 mcg/mL range until day 60 when she was found to have a supratherapeutic trough of 9.3 mcg/mL, at which point omeprazole was discontinued and the patient remained therapeutic on a dose of ~10.7 mg/kg/dose PO q8h over the next several months. This case highlights the intra-patient variability in the pharmacokinetics of voriconazole which may result in unexplained changes in clearance over time.

Other CYP2C19 inhibitors have also been reported to be used as pharmacokinetic boosters for voriconazole, most notably cimetidine, a nonspecific inhibitor of CYP1A2, CYP2C19, CYP2D6 and CYP3A4 (see Table, Supplemental Digital Content 2, http://links.lww.com/INF/E973). In healthy subjects, cimetidine 400 mg PO q12h increased voriconazole C_{max} and AUC by 18% and 23%, respectively.[11] However, due to concerns regarding cimetidine toxicity (eg, central nervous system effects and anti-androgenic side effects),[13] we selected omeprazole over cimetidine.

The administration of proton pump inhibitors as pharmacokinetic boosters does not come without risks. Adverse effects associated with proton pump inhibitors include increased risk of *C. difficile* infection and respiratory tract infections.[14] Therefore, the use of these agents as a pharmacokinetic booster should be reserved for situations where aggressive dose escalations fail to achieve desired concentrations of voriconazole.

Despite the elevated voriconazole MIC of 4 mcg/mL for our patient's *F. solani* complex isolate and the persistently undetectable voriconazole troughs initially, our patient was successfully treated for her disseminated fusariosis. Aside from antifungal therapy, surgical debridement[2] and recovery from neutropenia[7] are critical for successful management. Recovery of neutropenia in our patient around day 14 corresponded with defervescence, a decline in her C-reactive protein, and a decline in her serum beta-D-glucan level despite having subtherapeutic voriconazole troughs (Fig. 1). Subsequently, when she became neutropenic again around day 25, her serum beta-D-glucan level increased and peaked at 180 pg/mL. However, despite remaining neutropenic, her serum beta-D-glucan became negative on day 29, which corresponded to when omeprazole was added and when voriconazole troughs were above 1 mcg/mL and rising. Due to the interplay of antifungal therapy and the effect of immune recovery on treatment outcomes, it is not possible to tease out whether her recovery could fully be attributed to the omeprazole boosting of voriconazole concentrations.

CONCLUSION

Employing a CYP2C19 inhibitor, such as omeprazole, appears to be an effective approach to boost voriconazole troughs. This can be particularly helpful in children with enhanced voriconazole clearance or in patients experiencing auto-induction of voriconazole metabolism. We suggest considering the addition of a CYP2C19 inhibitor to boost voriconazole levels if troughs remain or become subtherapeutic even after escalating the mg/kg doses and increasing the frequency of administration to every 8 hours. After achieving therapeutic troughs, weekly trough monitoring is necessary as there is significant intra-patient variability in the pharmacokinetics of voriconazole, which may result in unexplained changes in clearance over time.

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