Voriconazole: Poor Oral Bioavailability and Possible Renal Toxicity in an Infant With Invasive Aspergillosis

Jenny A. Walldorf, MD, MS; Omayma A. Kishk, PharmD; James D. Campbell, MD, MS; and Allison B. Lardieri, PharmD

Voriconazole is the recommended agent of choice for treatment of invasive aspergillosis; however, achieving therapeutic serum concentrations while avoiding toxicity, both with intravenous and oral formulations, is challenging in infants. We report the case of an infant with confirmed invasive aspergillosis who developed renal toxicity possibly associated with IV voriconazole. Renal function improved upon withdrawal of the IV agent and switch to the oral formulation. The infant subsequently required large oral weight-based dosing to achieve therapeutic voriconazole serum concentrations. This case illustrates a rare side effect associated with voriconazole as well as the issues surrounding the pharmacokinetic profile of voriconazole in a pediatric patient.

ABBREVIATIONS BAL, bronchoalveolar lavage; BUN, blood urea nitrogen; CLSI, Clinical and Laboratory Standards Institute; CT, computed tomography; DOL, day-of-life; GT, gastrostomy tube; IV, intravenous; MIC, minimum inhibitory concentration; PA, pulmonary artery; PO, oral; SCr, serum creatinine

KEYWORDS adverse effect; aspergillosis; drug-related side effects; infant; therapeutic drug monitoring; voriconazole

J Pediatr Pharmacol Ther 2018;23(1):54–58

DOI: 10.5863/1551-6776-23.1.54

Introduction

Voriconazole is the recommended agent for treatment of invasive aspergillosis. Achieving therapeutic serum concentrations while avoiding toxicity, both with intravenous (IV) and oral formulations, is challenging in infants.¹ We report the case of an infant with confirmed invasive aspergillosis who developed renal toxicity possibly associated with IV voriconazole. This case illustrates a rare side effect associated with voriconazole as well as the issues surrounding the pharmacokinetic profile of voriconazole in a pediatric patient.

Case Report

The patient was an African American male born at 36 weeks gestation with agenesis of the right pulmonary artery (PA) and posterior urethral valves. On day-of-life (DOL) 16 he had failed unifocalization of the right PA. Necrotic right middle lobe related to air leak or contrast extravasation was resected at that time. Within the first month of life he was treated for *Enterobacter* superficial sternal wound infection and empyema. On the 26th DOL he underwent transurethral fulguration. Routine postsurgical renal ultrasonography on the 56th DOL showed new round calyceal echogenic foci concerning for fungal balls bilaterally. Multiple urine cultures were negative for fungal or bacterial infection and 24-hour urine specimens were negative on cytology and fungal staining. Renal function was within normal limits for age, based on urine output within 1 to

2 mL/kg/hr, blood urea nitrogen within 5 to 18 mg/dL, and serum creatinine (SCr) within 0.2 to 0.4 mg/dL.² Serial serum galactomannan and β -D-glucan were also negative (optical density index < 0.5 and < 60 pg/mL, respectively). When repeated renal ultrasound on DOL 71 showed enlargement and shadowing of the previously seen calyceal foci, oral fluconazole (6 mg/kg daily) was initiated empirically and continued as an outpatient upon discharge.

The infant was readmitted DOL 103 to 113 with respiratory distress diagnosed as pneumonia of unknown etiology, then readmitted on the 117th DOL for respiratory failure and treated for enterococcal and pseudomonas pneumonia. Pulmonary nodules concerning for fungal infection were first identified on a chest computed tomography (CT) scan 2 days later. Despite broad coverage for bacterial pneumonia, fevers persisted, and he remained ventilator-dependent. Fluconazole was discontinued and micafungin was started empirically for broadened fungal coverage. Bronchoalveolar lavage (BAL) and biopsy of renal foci were performed; specimens grew *Aspergillus fumigatus* after 15 and 11 days of incubation, respectively. On DOL 137, IV voriconazole 9 mg/kg/dose every 12 hours (18 mg/kg/day) was added and micafungin discontinued. Voriconazole IV was supplied as VFEND for injection (Pfizer, New York, NY) in a 10 mg/mL concentration, and voriconazole suspension was supplied as VFEND for oral suspension in a 40 mg/mL concentration. Voriconazole therapeutic drug monitoring was based on trough serum concentrations obtained after 5 days of therapy and collected

Figure 1. Renal function over time and concomitant medications with potential to cause renal compromise during hospitalization.

The patient also received medications not shown: corticosteroid pulse treatments throughout hospitalization; courses of ampicillin, clindamycin, linezolid, micafungin; oral sildenafil, bosentan, inhaled nitric oxide and epoprostenol; continuous infusions of fentanyl, nicardipine, hydromorphone, furosemide, bumetanide, milrinone, dexmedetomidine, rocuronium, morphine, and midazolam.

— BUN; ---, --- BUN normal range for age; — Serum Creatinine; ---, --- Serum Creatinine normal range for age
 — Voriconazole IV; --- Voriconazole GT; — Vancomycin; Circulating vancomycin; — Gentamicin; — Piperacillin-Tazobactam GT, gastrostomy tube; IV, intravenous

*Normal range renal function indicators for infants: blood urea nitrogen 5 to 18 mg/dL, serum creatinine 0.2 to 0.4 mg/dL.²

30 minutes before the subsequent dose, with a goal of 1.5 to 5.5 mg/L. Send-out voriconazole concentration results were available within 5 to 7 days. The initial concentration was 1 mg/L and the dose was increased to 11 mg/kg/dose every 12 hours IV (22 mg/kg/day). The subsequent trough concentration was 4.3 mg/L; hence, no dose adjustment was made.

On DOL 148 the patient showed signs of septic shock, fever alternating with hypothermia, and worsening pulmonary hypertension requiring oscillator support and vasopressors. Empiric vancomycin and piperacillin-tazobactam were started with bacterial and fungal blood, sputum, and urine cultures obtained. He remained critically ill over 3 weeks with worsening evidence of renal impairment. Serum creatinine remained within normal range for age until DOL 154 when it rose to 0.6 mg/dL. The initial rise in SCr was concomitant with supratherapeutic vancomycin trough concentrations as high as 39.7 mg/L on DOL 161 (SCr 0.83 mg/L), prompting discontinuation of vancomycin. Subsequent vancomycin concentrations were 29.4 mg/L (SCr 0.97 mg/dL) and 20.5 mg/L (SCr 1.14 mg/dL) at 24 and 48 hours, respectively. Renal failure led to placement of a peritoneal dialysis catheter on DOL 167. However, dialysis was not possible and the peritoneal catheter served instead to drain ascites. Serum creatinine peaked at 2.26 mg/L on DOL 172 even though patient had not

received vancomycin for 9 days (Figure 1). On DOL 179, IV voriconazole was transitioned to oral formulation via gastrostomy tube (GT). Serum creatinine decreased by more than half over 6 days. Repeated voriconazole concentration obtained on DOL 169 was 2.4 mg/mL and the dose was not changed.

A one-to-one dose conversion was used to transition from voriconazole IV 11 mg/kg/dose every 12 hours (22 mg/kg/day) to oral via GT; however, the subsequent trough concentration showed undetectable voriconazole. Feeds were held 30 minutes before and after drug administration and the GT was clamped. The dose was increased to 14.5 mg/kg/dose every 12 hours (29 mg/kg/day) via GT, resulting in troughs between 0.3 and 1.8 mg/L. Subsequently, the dose was increased to 13.3 mg/kg/dose every 8 hours via GT (40 mg/kg/day), then to 15 mg/kg/dose every 8 hours via GT (45 mg/kg/day) with trough concentrations fluctuating between 1.4 and 2.7 mg/L. Ultimately, at 18 mg/kg/dose every 8 hours via GT (54 mg/kg/day) therapeutic trough concentrations were attained and exceeded (3.1–6 mg/L) (Figure 2). Dose changes were made about every 10 days, owing to time elapsed for achievement of steady state and time for the laboratory value to return. During oral therapy, dose escalation to achieve a therapeutic concentration required about 70 days.

A. fumigatus minimum inhibitory concentrations

Figure 2. Voriconazole trough serum concentration by corresponding daily intravenous or oral weight-based dosing regimen.

Serum voriconazole concentrations were obtained after 5 days of therapy and 30 minutes before the subsequent dose, with a goal of 1.5 to 5.5 mg/L.

◆ IV Dosing; ■ PO Q12H Dosing; ▲ PO Q8H Dosing; ---- Trough goal minimum & maximum range
IV, intravenous; PO, orally

(MICs) were reported on DOL 178: voriconazole, micafungin, and amphotericin B MICs were 0.5 mg/L, ≤ 0.015 mg/L, and 2 mg/L, respectively. Based on Clinical and Laboratory Standards Institute (CLSI) susceptibility breakpoints, voriconazole was intermediate, micafungin susceptible, and amphotericin B resistant. Given these findings, accompanied by low voriconazole concentrations, and persistent fever of unknown etiology, micafungin 6 mg/kg/day was added on DOL 193.

Severe pulmonary hypertension and PA stenosis were treated medically with sildenafil, bosentan, inhaled nitric oxide, and inhaled epoprostenol. Daily fevers persisted without proven etiology from 6 months of age. Repeated cultures showed no additional *Aspergillus* or other fungal growth from any source and galactomannans remained below threshold for positivity. Repeated BAL on DOL 193 and 244 revealed *Pseudomonas* and *Enterococcus*, respectively, for which the infant received cefepime and ampicillin, respectively, but remained persistently febrile. Repeated chest CTs showed persistent areas of lung consolidation and some resolution of the suspected fungal nodules. Serial renal ultrasonograms every 1 to 4 weeks showed decreased size but increased number of calyceal foci. Voriconazole was withheld for 3 days to assess for drug fever without defervescence. Evaluations for immune compromise before and after the first 6 months of life were unremarkable.

On DOL 251, he again developed septic shock with increased respiratory and hemodynamic support, and

developed asystole secondary to acidosis and hyperkalemia. The infant expired on DOL 253. Documented cause of death on autopsy was organizing diffuse alveolar damage. Autopsy showed no evidence of *Aspergillus* infection grossly, microscopically, or by culture. In total, the patient received 113 days of voriconazole, of which 72 were oral formulation. An epidemiologic investigation of a cluster of 75 cultures positive for *Aspergillus* spp. had been ongoing within the hospital during this patient's course. Molecular genotyping later revealed that his isolates were closely related to most specimens in the cluster, likely representing a pseudo-outbreak due to culture contamination from construction activity adjacent to the microbiology laboratory.

Discussion

Intravenous voriconazole in our patient was the suspected cause of renal toxicity. We encountered subtherapeutic trough concentrations during IV to oral transition and persistently variable drug concentrations during the chronic oral course. Multiple studies³⁻⁹ document the importance of therapeutic drug monitoring for voriconazole for improved outcomes and to avoid toxicity. Trough concentrations > 1 mg/L are associated with increased rates of successful outcomes while troughs > 6 mg/L are associated with risk of toxicity, mainly neurotoxicity and hepatotoxicity.¹⁰ Factors associated with large interpatient and inpatient vari-

ability of voriconazole exposure in pediatric patients include non-linear saturable pharmacokinetics, poor oral absorption, drug-drug interactions, liver disease, younger patient age, and genetic polymorphisms of cytochrome CYP2C19.¹⁰ Our patient had several of these factors including young age (<2 years), barriers to oral absorption (i.e., chronic gastrointestinal inflammation, drug administration in relation to GT feeds), and potential increased risk of renal toxicity due to concurrent administration of vancomycin and diuretics.

Several studies^{1,11,12} have shown great variability in voriconazole doses required to achieve adequate trough values in immunocompromised pediatric patients, especially in infants and young children. Soler-Palacin and colleagues¹ prospectively studied 30 children receiving IV or oral voriconazole where the median therapeutic dose required for either formulation among children <5 years of age and ≥5 years of age was 38 and 15 mg/kg/day, respectively. There was no significant difference in the dose needed to achieve therapeutic concentrations when comparing IV and oral formulations. A review of 62 pediatric patients¹² found median therapeutic doses of 31.5, 16, and 9.4 mg/kg/day for ages <2, 2 to 12, and >12 years, respectively ($p < 0.034$). Tucker and colleagues¹¹ reviewed 11 cases (0.8–14.8 years) among which 5 individuals ≥2 years of age received voriconazole every 8 hours. The median dose to achieve the first therapeutic trough concentration among all cases was 12 mg/kg/day (range, 6–26.1) versus 20.7 mg/kg/day (range, 10.9–26.1) among the 5 receiving every-8-hour dosing. This was the only study reporting every-8-hour dosing and no individual was in the age range of our patient. Older age was the only variable associated with clinical efficacy.

Our patient's final therapeutic dose (54 mg/kg/day) was large compared to those reported in other published studies among pediatric patients.^{1,11–13} Use of every-8-hour dosing with the oral formulation was deemed necessary after multiple dosage adjustment using every 12 hours failed to overcome rapid hepatic clearance known to occur in infants.

Food interferes with voriconazole gastrointestinal absorption.¹⁴ In our patient, despite holding feeds, fluctuating intestinal inflammation/edema during severe illness may have contributed to persistent variability in absorption. Several authors^{4,15–17} report variable pediatric oral bioavailability, from 45% to 80%. Our patient's final calculated oral bioavailability was 40%. Formal recommendations for transition from IV to oral dosing do not exist, though transition to oral administration using the same IV dose has been suggested owing to unpredictable bioavailability and the risk of toxicities with overdosing.¹⁷ This strategy left our patient underdosed for over a week given send-out laboratory reporting delays.

Our patient developed renal failure during concomitant treatment with vancomycin. He did not have

evidence of renal dysfunction at baseline or during the first 34 days when receiving IV voriconazole. From the Naranjo scale to determine the likelihood of adverse drug reactions,¹⁸ IV voriconazole is a *possible* cause of renal toxicity in this patient, based on a score of 4. Although the voriconazole package insert recommends exercising caution in patients with CrCl < 30 mL/min, renal toxicity in children without underlying insufficiency has not been reported.^{17,19} In adults with underlying renal insufficiency, delayed clearance and toxicity are associated with the IV formulation,²⁰ which contains sulfobutylether beta-cyclodextrin as a solubilizer. Our patient's renal insufficiency may have been related to the use of vancomycin and voriconazole simultaneously, which has also not been previously described. Although elevation in his SCr was not associated with elevated voriconazole concentrations, his function did not return to baseline until after withdrawal of IV voriconazole despite vancomycin concentrations dropping. The oral voriconazole formulation did not seem to have the same effect, as he had at least 1 voriconazole trough concentration while receiving the oral formulation that exceeded the highest serum trough value while on IV without signs of renal insufficiency. During the final 75 days of the patient's life, after the switch to the oral formulation voriconazole, he continued to be critically ill with severe worsening pulmonary hypertension, repetitive fevers without known etiology despite broad-spectrum antibiotics and aggressive workup, yet SCr remained within normal limits for age. Cardiac and pulmonary comorbidities may have contributed to renal underperfusion and associated dysfunction; however, the time course of elevation in SCr and resolution to normal concentrations after withdrawal of IV voriconazole made drug toxicity very concerning and without another clear cause.

During the hospital course, the patient received many concomitant medications; however, voriconazole is the most likely to have caused a drug-drug interaction. He received IV or oral diuretics (furosemide, chlorothiazide, and metolazone) during most of the admission time along with long courses of methylprednisolone and methadone. For the patient's pulmonary hypertension, sildenafil was added prior to the start of voriconazole and was continued throughout the remainder of the patient's life. Bosentan was added during the last 53 days of life. Voriconazole is a strong CYP3A4 inhibitor and can increase serum concentrations of sildenafil, bosentan, methadone, and methylprednisolone. Our patient was never on any medications that have been reported to cause increases or decreases in voriconazole serum concentrations.²¹ From this information, we believe there were no drug-drug interactions that could have resulted in toxic voriconazole concentrations or effects.

Management of our patient was challenging because of multiple comorbidities and uncertainty in the diagnosis of invasive aspergillosis. Aggressive voriconazole

treatment at therapeutic concentrations was necessary given clinical uncertainty. To maximize treatment outcomes and avoid toxicity in future pediatric patients, particularly patients <2 years of age, additional development of proposed modeling algorithms to guide IV to oral dosing is needed. While renal toxicity has not been previously reported in children, our case supports close monitoring, especially with use of the IV formulation and with concomitant nephrotoxic medications during long treatment courses.

ARTICLE INFORMATION

Affiliations Division of Infectious Disease and Tropical Pediatrics, Department of Pediatrics (JAW, JDC), University of Maryland School of Medicine, Baltimore, Maryland; Department of Pharmacy (OAK), University of Maryland Medical Center, Baltimore, Maryland; Food and Drug Administration (ABL), Silver Spring, Maryland

Correspondence Allison B. Lardieri, PharmD;
Allison.Lardieri@fda.hhs.gov

Disclosure The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. The authors had full access to all patient information in this report and take responsibility for the integrity and accuracy of the report.

Accepted March 29, 2017.

Acknowledgments We would like to thank the pediatric intensive care and pediatric infectious diseases clinical teams as well as the pediatric pharmacy group for their contribution in the chronic management of this patient. We would also like to acknowledge the microbiology laboratory led by Dr Jennifer K. Johnson and the hospital infection control group including Dr Surbhi Leekha and Michelle Harris Williams.

Copyright Published by the Pediatric Pharmacy Advocacy Group. All rights reserved.

For permissions, email: matthew.helms@ppag.org

REFERENCES

- Soler-Palacin P, Frick MA, Martin-Nalda A, et al. Voriconazole drug monitoring in the management of invasive fungal infection in immunocompromised children: a prospective study. *J Antimicrob Chemother*. 2012;67(3):700–706.
- Harriet Lane Service (Johns Hopkins Hospital). Blood chemistries and body fluids, table 27-1. In: Branden Engorn JF, ed. *The Harriet Lane Handbook: A Manual for Pediatric House Officers*. 20th ed. Philadelphia, PA: Elsevier; 2015:621.
- Pascual A, Calandra T, Bolay S, et al. Voriconazole therapeutic drug monitoring in patients with invasive mycoses improves efficacy and safety outcomes. *Clin Infect Dis*. 2008;46(2):201–211.
- Neely M, Rushing T, Kovacs A, et al. Voriconazole pharmacokinetics and pharmacodynamics in children. *Clin Infect Dis*. 2010;50(1):27–36.
- Ueda K, Nannya Y, Kumano K, et al. Monitoring trough concentration of voriconazole is important to ensure successful antifungal therapy and to avoid hepatic damage in patients with hematological disorders. *Int J Hematol*. 2009;89(5):592–599.
- Miyakis S, van Hal SJ, Ray J, Marriott D. Voriconazole concentrations and outcome of invasive fungal infections. *Clin Microbiol Infect*. 2010;16(7):927–933.
- Troke PF, Hockey HP, Hope WW. Observational study of the clinical efficacy of voriconazole and its relationship to plasma concentrations in patients. *Antimicrob Agents Chemother*. 2011;55(10):4782–4788.
- Park WB, Kim NH, Kim KH, et al. The effect of therapeutic drug monitoring on safety and efficacy of voriconazole in invasive fungal infections: a randomized controlled trial. *Clin Infect Dis*. 2012;55(8):1080–1087.
- Dolton MJ, Ray JE, Chen SC, et al. Multicenter study of voriconazole pharmacokinetics and therapeutic drug monitoring. *Antimicrob Agents Chemother*. 2012;56(9):4793–4799.
- Owusu Obeng A, Egelund EF, Alsultan A, et al. CYP2C19 polymorphisms and therapeutic drug monitoring of voriconazole: are we ready for clinical implementation of pharmacogenomics? *Pharmacotherapy*. 2014;34(7):703–718.
- Tucker L, Higgins T, Egelund EF, et al. Voriconazole monitoring in children with invasive fungal infections. *J Pediatr Pharmacol Ther*. 2015;20(1):17–23.
- Bartelink IH, Wolfs T, Jonker M, et al. Highly variable plasma concentrations of voriconazole in pediatric hematopoietic stem cell transplantation patients. *Antimicrob Agents Chemother*. 2013;57(1):235–240.
- Boast A, Curtis N, Cranswick N, et al. Voriconazole dosing and therapeutic drug monitoring in children: experience from a paediatric tertiary care centre. *J Antimicrob Chemother*. 2016;71(7):2031–2036.
- Purkins L, Wood N, Kleinermans D, et al. Effect of food on the pharmacokinetics of multiple-dose oral voriconazole. *Br J Clin Pharmacol*. 2003;56(suppl 1):17–23.
- Karlsson MO, Lutsar I, Milligan PA. Population pharmacokinetic analysis of voriconazole plasma concentration data from pediatric studies. *Antimicrob Agents Chemother*. 2009;53(3):935–944.
- Friberg LE, Ravva P, Karlsson MO, Liu P. Integrated population pharmacokinetic analysis of voriconazole in children, adolescents, and adults. *Antimicrob Agents Chemother*. 2012;56(6):3032–3042.
- Walsh TJ, Driscoll T, Milligan PA, et al. Pharmacokinetics, safety, and tolerability of voriconazole in immunocompromised children. *Antimicrob Agents Chemother*. 2010;54(10):4116–4123.
- Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30(2):239–245.
- Lilly CM, Welch VL, Mayer T, et al. Evaluation of intravenous voriconazole in patients with compromised renal function. *BMC Infect Dis*. 2013;13:14.
- Oude Lashof AM, Sobel JD, Ruhnke M, et al. Safety and tolerability of voriconazole in patients with baseline renal insufficiency and candidemia. *Antimicrob Agents Chemother*. 2012;56(6):3133–3137.
- Voriconazole (VFEND) [package insert]. City, State or Country: Novartis; 2002.