Characterization of Therapeutic Drug Monitoring Practices of Voriconazole and Posaconazole at a Pediatric Hospital

Stephanie Duehlmeyer, PharmD, BCPPS; Christopher Klockau, RPH, BCOP; Diana Yu, PharmD, MS, BCPS-AQ ID; and Jamie Rouch, PharmD, BCPPS

OBJECTIVES To characterize the voriconazole and posaconazole serum trough ordering practices in patients receiving prophylactic and treatment antifungal therapy.

METHODS A retrospective chart review over a 6-year period of pediatric patients who received voriconazole and/or posaconazole for >24 hours.

RESULTS A total of 113 patients were included in this study and of these patients, 105 received voriconazole and 16 received posaconazole during the study period. Additionally, 167 trough levels were assessed in this study. Only 50% and 54% of levels were considered within goal recommendations for voriconazole and posaconazole, respectively. The median dose required to achieve goal trough concentration was dependent on drug, indication, and dosage form. Lastly, the most common adverse drug reactions (ADRs) were hepatotoxicity, QTc prolongation, and CNS changes, which were in concordance with ADRs documented in the clinical trials for voriconazole and posaconazole. Approximately 20% of patients receiving either voriconazole or posaconazole died during the study period and the median trough in both groups was subtherapeutic.

CONCLUSIONS Increased monitoring of trough concentrations may be warranted to prevent death or breakthrough invasive fungal infections. Further studies are warranted for assessing the relationship between trough concentrations and treatment outcomes as well as relationship between dosing and achieving goal trough concentrations.

ABBREVIATIONS ADR, adverse drug reaction; CNS, central nervous system; FDA, US Food and Drug Administration; IFI, invasive fungal infection; IV, intravenous; QTc, ECG interval from the QRS complex to the end of the T wave corrected; TDM, therapeutic drug monitoring

KEYWORDS pediatrics; posaconazole; therapeutic drug monitoring; voriconazole

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Introduction

Invasive fungal infections (IFIs) remain an important complication causing considerable morbidity and mortality in patients with cancer.¹ Voriconazole is a triazole that is available for both oral and intravenous administration and has potent activity against IFIs.^{1–4} Voriconazole has also been shown to be efficacious in preventing fungal infections in those who are at high risk, although it does not currently have an FDA indication for prophylaxis.^{1,3} Voriconazole is known to display highly variable, linear pharmacokinetics and is metabolized primarily via CYP2C19, as well as CYP3A4 and CYP2C9.^{1,5} It is well-known that voriconazole has many drug-drug interactions that can alter serum concentrations.¹ Drug-drug interactions are particularly important in the setting of patients with cancer, because voriconazole and many drugs used in cancer chemotherapy are metabolized via the hepatic cytochrome

P450 system.^{2,6} Additionally, genetic polymorphism of the P450 system can alter the metabolism of voriconazole and affect the serum concentration.² There is also evidence that suggests low voriconazole serum concentrations may result in treatment failure, whereas high serum concentrations can result in adverse drug reactions (ADRs) such as hepatotoxicity, visual and/or auditory hallucinations.^{2,7,8} For these reasons, therapeutic drug monitoring (TDM) should be performed to maximize efficacy results and minimize ADRs.

Posaconazole is a second-generation triazole agent with broad activity against many fungi.⁹ Like voriconazole, it also has interindividual and intraindividual variation in bioavailability and drug-drug interactions, requiring TDM.¹⁰ There is an oral suspension along with a delayed-release tablet and intravenous formulation that have been introduced recently, which has increased its use.⁹ The oral suspension has variable bioavailability that

Table 1. Target Trough Recommendations

Medication/Indication	Prior to 2013	After 2014
Voriconazole		
Prophylaxis	≥0.5	≥0.5
Treatment	≥1	≥2
Posaconazole		
Prophylaxis	≥0.5	≥0.7
Treatment	≥0.7	≥1.2

is dependent on food intake, gut motility, gastric acidity, and is dosed 3 to 4 times per day.¹¹ Compared with the oral suspension, the delayed-release tablet showed an improved bioavailability in adult healthy subjects and achieved higher serum concentrations and overall drug exposure with once daily administration. The absorption of the delayed-release tablet is also dependent on concomitant intake of food and gastric acidity, but less so than the oral suspension.¹²

Although there is not a standardized accepted goal for voriconazole TDM, a trough level of 1 to 6 mg/L has been commonly accepted. Voriconazole trough concentrations ≥ 1 mg/L have been associated with improved response to therapy and survival, whereas increased adverse events have been associated with trough concentrations >5 to 6 mg/L.^{2,6,13} When using voriconazole for prophylaxis, it has been suggested that the serum concentration necessary to prevent fungal infections may be lower than that needed to treat an established infection.¹⁴ At our institution, a trough of 2 to 5.5 mg/L is targeted for treatment along with a trough of >0.5 mg/L for prophylaxis. Additionally, goal trough concentration recommendations for posaconazole treatment and prophylaxis have varied over the years. Clinical studies suggest a trough concentration of >1.0 to 1.25 mg/L for treatment and >0.7mg/L for prophylaxis.^{10,15} At our institution, it is recommended to have a goal trough concentration of >1.2 mg/L for treatment and >0.7 mg/L for prophylaxis, which is in accordance with the most recent guidelines.^{16,17}

The FDA states that the safety and effectiveness of voriconazole and posaconazole in pediatric patients below the age of 12 years of age have not been established for either treatment or prophylaxis.^{18,19} Clear guidelines do not exist with detail on when to start monitoring trough levels in patients receiving azoles for either treatment or prophylaxis. At our institution, it has been noticed that there is wide variability in trough level ordering practices in terms of when to get a trough drug level, including at what point in therapy and for what indications.

It has also been noted in the literature that achieving goal trough concentrations after initial dosing in the pediatric population has been difficult to accomplish. Forty percent of patients being therapeutically monitored do not achieve an initial goal voriconazole trough

Table 2. Patient Demographics

Demographic	Result
Total patients, N	113
Sex, n (%), male	62 (55)
Ethnicity, n (%)	
Caucasian	81 (72)
Hispanic	13 (12)
African American	10 (9)
Asian	4 (4)
Other	4 (3)
Underlying diagnosis, n (%)	
Acute lymphoblastic leukemia	33 (29)
Acute myelogenous leukemia	23 (20)
Aplastic anemia	7 (6)
Burkitt's lymphoma	6 (5)
Other	44 (39)
Patient status when trough sampled, n (%)	
Inpatient	115 (69)
Outpatient	51 (31)

concentration.^{4,5} Small studies investigating appropriate dosing and trough monitoring of posaconazole and voriconazole have documented a need for TDM in the pediatric population due to variable bioavailability.^{20,21}

The dosing strategies varied based on provider and patient. In general, treatment dosing of voriconazole was initiated at 9 mg/kg/dose IV every 12 hours for 2 doses followed by 4 to 8 mg/kg/dose IV every 12 hours. Voriconazole prophylaxis was generally 6 mg/kg/dose by mouth or IV every 12 hours for 2 doses followed by 4 mg/kg/dose every 12 hours. Posaconazole dosing was dependent on dosage form, indication, and patient age. Most often, patients <12 years of age received 4 mg/kg/dose 3 times daily of the oral suspension. Patients ≥ 12 years of age were initiated on 200 mg to 300 mg by mouth daily using the extended-release oral tablet. It is evident at our institution that with these recommended starting doses, therapeutic trough levels are often not achieved.

The primary objective of this study is to characterize the voriconazole and posaconazole serum trough ordering practices in patients receiving prophylactic and treatment antifungal therapy. Secondary objectives include the following: characterize the median dosage needed to achieve adequate prophylaxis and treatment trough concentrations of voriconazole and posaconazole, describe the number of patients receiving concomitant medications known to affect voriconazole and posaconazole serum drug concentrations, and to describe the treatment outcomes associated with voriconazole and posaconazole therapy.

Figure 1. Trough ordering practices.

Materials and Methods

Study Design. Children's Mercy is a non-profit pediatric academic hospital with 367 hospital beds. We retrospectively reviewed the records of children < 20 years of age who were treated with voriconazole or posaconazole at Children's Mercy Kansas City over a 6-year period (July 1, 2010 to July 30, 2016). Patients who received voriconazole and/or posaconazole were identified using the electronic medical record. Medical records of those children who received voriconazole and/or posaconazole were reviewed and demographic, clinical, dosing, trough concentrations, concomitant medication, and adverse effect data were collected. The study was approved by the Children's Mercy Institutional Review Board. As this was a retrospective review, consent from patients or guardians was not required and patients were not contacted.

Target Study Population. The study population included patients at Children's Mercy Hospital who had medication orders for voriconazole or posaconazole as well as patients with serum voriconazole or posaconazole trough concentrations between July 1, 2010 and July 30, 2016. Patients were identified to be

included into the study if they had an inpatient order for voriconazole and/or posaconazole. Drug trough levels were assessed for both inpatient and outpatient settings. Patients were excluded if they received the azole for less than 24 hours or if the patient was older than 20 years of age.

Azole TDM. The target trough concentration recommendations evolved over the study period (Table 1). The percentage meeting target troughs was determined by using the recommended trough concentration for each time period of 2010–2013 and 2014–2016. The authors did not assess the appropriateness of the sampling time of the trough concentrations.

Descriptive Statistics. Means, standard deviations, medians, interquartile ranges, and proportions were used to summarize the data. SAS version 9.4 (SAS Institute, Inc, Cary, NC) and SPSS version 23 (IBM Corp, Armonk, NY) were used for all analyses.

Results

Baseline Demographics. A total of 113 patients were included in this study (Table 2). The study population was 55% male, averaging 8 years of age, and was primarily Caucasian. The top underlying diagnoses were acute lymphoblastic leukemia and acute myelogenous

Table 3. Serum Trough Concentrations

	Total Number of Troughs	Trough Concentrations Achieving Goal, n (%)
Voriconazole	N = 127	58 (45.7)
Treatment, n (%)	77 (60.6)	39 (50.7)
Prophylaxis, n (%)	50 (39.4)	19 (38)
Posaconazole	N = 40	27 (67.5)
Treatment, n (%)	28 (70)	15 (53.6)
Prophylaxis, n (%)	12 (30)	12 (100)

Table 4. Median Dose Required to Achieve Goal Trough Concentrations

Group	n	Median Dose (IQR)
Voriconazole treatment		
IV	15	5.7 (5.5–7.4)
Tablet	17	7.5 (4.5–9.6)
Suspension	6	4.6 (3.7–4.7)
Voriconazole prophylaxis		
IV	6	8.1 (6.9–9.7)
Tablet	9	2.8 (2.5–4.3)
Suspension	4	4.6 (3.9–5.9)
Posaconazole treatment		
IV	2	4.5 (3.9–4.9)
Tablet	11	5.0 (3.9–6.9)
Suspension	2	10.0 (6.3–13.8)
Posaconazole prophylaxis		
IV	3	6.6 (3.1–7.1)
Tablet	8	4.2 (3.0–5.3)
Suspension	1	5.2

leukemia, with other underlying diagnoses including oncologic and non-oncologic diseases. The majority of the trough levels assessed were inpatient, although there were 30% outpatient levels included in the study.

Voriconazole and Posaconazole TDM. Of the 113 patients included in this study, 105 received voriconazole and 16 received posaconazole during the study period. Of note, some patients received both drugs throughout the study period. Of the 105 patients receiving voriconazole, 39 were for the treatment indication. Of those 39 patients, 54% had a trough level at some point during therapy. Sixty-six patients received voriconazole for

the prophylaxis indication. Of those 66 patients, 36% had a trough level at some point during therapy. Of the 16 patients receiving posaconazole, 11 were for treatment. Of those 11 patients, 91% had a trough level at some point during therapy. Lastly, 5 patients received posaconazole for prophylaxis and 80% of those patients had a trough level during the study period (Figure 1).

During the study period, 167 trough levels were assessed. Of these levels, the majority (76%) obtained were for voriconazole. Approximately 60% of the troughs drawn for voriconazole were for treatment indication and 40% for prophylaxis. Of the troughs

Table 5. Median Dose (mg/kg/dose) Required to Achieve Goal Trough Concentrations by Age Group

Age, yr	Group	n	Median Dose (IQR)
≤6	Voriconazole treatment	8	6.7 (4.1–8.0)
	Voriconazole prophylaxis	6	8.1 (5.6–9.7)
7–12.9	Voriconazole treatment	8	5.3 (4.5–7.8)
	Voriconazole prophylaxis	5	6.7 (5.1–6.1)
	Posaconazole treatment	5	6.2 (4.9–6.9)
	Posaconazole prophylaxis	1	4.8
≥13	Voriconazole treatment	23	5.7 (4.3–5.3)
	Voriconazole prophylaxis	8	3.3 (2.5–4.1)
	Posaconazole treatment	10	4.8 (3.9–11.5)
	Posaconazole prophylaxis	11	5.2 (3.1–5.5)

Table 6. Adverse Drug Reactions*

ADR, n (%)	Voriconazole (n = 20)	Posaconazole (n = 7)
Hepatotoxicity	8 (40)	1 (14)
QTc prolongation	2 (10)	3 (44)
CNS changes	5 (25)	1 (14)
Visual changes	4 (20)	1 (14)
Allergic reaction	1 (5)	0
Other	0	1 (14)

ADR, adverse drug reaction

* Incidence recorded if Drug Safety Service deemed an ADR was likely due to the azole.

drawn for the treatment indication, only 50% were considered within goal recommendations. Of the troughs drawn for prophylaxis, 38% were within goal recommendations. Alternatively, 70% of the troughs drawn for posaconazole were for treatment and 30% for prophylaxis. Of the troughs drawn for treatment, 54% were considered within goal recommendations, whereas 100% were within goal recommendations for prophylaxis (Table 3).

Median Dose. We investigated the median dose required to achieve goal trough concentrations based on drug, indication, and dosage form (Table 4). There was a wide variability in median dose required to achieve goal trough concentrations depending on drug, indication, and dosage form. Overall, the treatment groups required higher dosing when compared with the prophylaxis groups as expected based on their respective trough goals.

Median Dose by Age Group. The median dose required to achieve goal trough concentrations by age group (Table 5) was investigated as a secondary objective. There are published data that show a wide

variability in pharmacokinetics of azoles amongst different age groups. Age groups of patients 6 years of age or younger, 7 years to 12.9 years, and older than 13 years of age were determined for comparison groups. It was observed that younger patients required higher doses of both azoles when compared with the older adolescent group (Table 5).

Adverse Drug Reactions (ADRs). ADRs to voriconazole and/or posaconazole were collected based on documentation in the electronic medical record. At our institution, there is a Drug Safety Service that thoroughly evaluates each ADR and the strength of its connection to the suspected drug. The ADRs characterized in Table 6 were collected based on the final assessment of the Drug Safety Service. The most common ADRs seen amongst both azole medications were hepatotoxicity, QTc prolongation, and CNS changes. These ADRs are in concordance with what has been documented in clinical trials and the package inserts (Table 6).

Potential Drug Interactions. The following concomitant medications were evaluated due to their known ability to impact serum levels of voriconazole and

Figure 2. Potential drug-drug interactions.

H2RA, Histamine 2 Receptor Antagonist; PPI, Proton Pump Inhibitor

■ Posaconazole; ■ Voriconazole

Table 7. Patient Outcomes*

	Survival	Death
Treatment		
Voriconazole, n (%)	31 (79)	8 (21)
Voriconazole, median trough (range), mg/L	1.7 (0.1–15)	1 (0–27)
Posaconazole, n (%)	9 (82)	2 (18)
Posaconazole, median trough (range), mg/L	1.25 (0.05–5)	0.53 (0.2–2.5)
Breakthrough IFI		
Prophylaxis		
Voriconazole, n (%)		4 (6.1)
Voriconazole, median trough, (range) mg/L		0 (0–0.2)
Posaconazole, n (%)		0

IFI, invasive fungal infection

* At or before the last point of review.

posaconazole: proton pump inhibitors, histamine-2 receptor antagonists, estrogen, chloramphenicol, barbiturates, carbamazepine, dexamethasone, rifampin, and phenytoin. Proton pump inhibitors and histamine-2 receptor antagonists were the most common concomitant medication amongst the subset of interacting drugs during the study period (Figure 2).

Outcomes. Treatment outcomes were assessed by either cure (defined as survival while receiving treatment for IFI during study period) or death (defined as clinical failure determined by IFI-related death). Many of the patients survived the fungal infection. Approximately 20% of patients receiving either posaconazole or voriconazole died during the study period. Of note, the median trough in both groups was subtherapeutic (Table 7). Prophylaxis outcomes were assessed by whether the patient developed a breakthrough fungal infection or not. Only 4 (6%) patients in the voriconazole group developed a breakthrough fungal infection during the study period. Of those 4 patients, 2 (50%) patients received a trough during the study period. These troughs were all subtherapeutic.

Discussion

IFIs are a significant cause for morbidity and mortality in immunocompromised children. Voriconazole and posaconazole are triazoles that are effective against these infections, however data are lacking regarding appropriate dosing for children, increasing the risk for treatment failure or toxicity. The primary objective of this retrospective chart review was to characterize the trough level ordering practices in patients receiving prophylactic and treatment therapy with voriconazole and posaconazole. At our institution, it was observed that voriconazole troughs are ordered in 43% of patient cases and posaconazole troughs are ordered in 88% of cases.

We found that the median dose required to achieve

goal trough concentrations is dependent on indication and dosage form. The drug and dosage form with the widest variability was posaconazole suspension. This is most likely due to its unpredictable absorption and dependence of taking the medication with a meal.¹¹ It has been reported in the literature that children require higher doses of voriconazole and posaconazole to achieve goal trough concentrations.^{4,14} Our findings were similar in that our youngest patient population required higher doses to achieve a goal trough concentration when compared with the older adolescents.

Drug-drug interactions are commonly reported when azoles are used with other medications, particularly when processes involving the CYP450 system exist.²² Further studies are warranted to identify the true relationship between these medications and the effects on the azole serum concentration.

Patient outcomes were also assessed as a secondary objective in this study. The majority of the patients receiving antifungal treatment did not die from an IFI-related event. The patients who died on treatment or had a breakthrough IFI on prophylaxis were noted to have subtherapeutic troughs. These data suggest TDM may have an important role in improving the clinical outcomes of patients on posaconazole and voriconazole.

To our knowledge, this is the first study evaluating the frequency of voriconazole and posaconazole trough monitoring in children. Limitations of our study include the retrospective study design as well as the opportunity for missing outpatient troughs due to patients getting laboratory results at an outside facility. Throughout the study period, there were patients who switched drugs or switched indications, which was hard to fully capture through chart review. Additionally, the authors did not assess the appropriateness of the sampling times of the trough concentrations. Lastly, the small sample size included in this study limits the ability to draw conclusions on outcomes.

Despite these limitations, the data support several conclusions regarding TDM of voriconazole and posaconazole in the pediatric population: 1) increased monitoring of trough concentrations may be warranted to prevent death or breakthrough IFI, 2) the dose necessary to achieve goal trough concentration is dependent on the drug, indication, and dosage form, and 3) further studies are warranted to assess the relationship between dosing and clinical outcomes with target trough concentrations.

Article Information

Affiliations. Department of Pharmacy (SD, CK, DY, JR), Children's Mercy Hospital, Kansas City, MO

Correspondence. Stephanie Duehlmeier, PharmD; srduhlmeier@cmh.edu

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Ethical Approval and Informed Consent. The study was approved by the Children's Mercy Institutional Review Board (IRB). As this was a retrospective review, consent from patients or guardians was not required and patients were not contacted.

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