JPPT | Single Center Retrospective Study

Assessment of the Effective Dose of Isavuconazole, Itraconazole, Posaconazole, and Voriconazole to Achieve Goal Serum Concentrations in Pediatric Patients at a Single Center

KaShena L. Kennedy, PharmD; Elizabeth H. Ristagno, MD, MSc; Linda K. Marshall, PharmD; Kristin C. Mara, MS; Grace Lee, PharmD; and Laura M. Dinnes, PharmD

OBJECTIVE The optimal dose for triazoles in pediatric patients may substantially vary given the dynamic changes in pharmacokinetics and pharmacodynamics, based on disease severity. Therapeutic drug monitoring has been a valuable tool to help guide management and avoid potential toxicities associated with treatment of invasive fungal infections (IFIs). Goal azole serum concentrations are based on specific drug, indication, and minimum inhibitory concentration when known. This study aimed to determine the optimal pediatric azole doses needed to achieve targeted serum concentrations of isavuconazole, itraconazole, posaconazole, and voriconazole.

METHODS This is a single center, retrospective chart review of pediatric patients who received isavuconazole, itraconazole, posaconazole, or voriconazole between January 1, 2011, and August 31, 2021.

RESULTS A total of 273 pediatric patients received isavuconazole, itraconazole, posaconazole, or voriconazole in the inpatient or outpatient setting during the study period. Of the 273 patients, only 122 met criteria for inclusion in the analysis. Eighty-three percent of patients reached a goal serum concentration. Patients younger than 12 years required a higher dose (mg/kg/day) to achieve goal serum concentrations. Patients who received an azole in the form of an oral tablet or intravenously were more likely to reach a goal concentration than those not receiving these formulations. Median time to goal concentration occurred at 20 days for isavuconazole, 34 days for itraconazole, 11 days for posaconazole, and 10 days for voriconazole.

CONCLUSIONS Higher starting azole doses are needed to obtain goal concentrations quickly, especially for children younger than 12 years.

ABBREVIATIONS ALT, alanine transaminase; CYP, Cytochrome P450; HR, hazard ratio; IFIs, invasive fungal infections; IV, intravenous; TDM, therapeutic drug monitoring

KEYWORDS isavuconazole; itraconazole; monitoring; pediatrics; posaconazole; triazole; voriconazole

J Pediatr Pharmacol Ther 2025;30(1):112–122

DOI: 10.5863/1551-6776-30.1.112

Introduction

Prompt initiation of effective triazole doses for invasive fungal infections (IFIs) is of paramount importance to optimize patient clinical outcome owing to the substantial morbidity and mortality associated with IFIs, especially in critically ill and immunocompromised pediatric patients. Thus, the standard of care for most triazole therapy generally includes therapeutic drug monitoring (TDM) to optimize efficacy and limit toxicity. TDM is particularly imperative in the pediatric population because there is substantial inter- and intra-patient variability, resulting in variable responses to antifungal agents. Pediatric patients often require dose adjustments owing to alterations in pharmacokinetics that occur as they develop from a neonate through adolescence.[1,2] Additionally, there are limited data behind current recommended doses, most agents are not fully approved for the pediatric population, and doses are often extrapolated from or compared with the adult population. Currently, there are 5 triazole antifungals used for IFI: isavuconazole, itraconazole, posaconazole, voriconazole, and fluconazole. Of these 5, in the pediatric population TDM is most routinely done for isavuconazole, itraconazole, posaconazole, and voriconazole.

Selecting the best starting dose for pediatric patients is extremely challenging and dependent on a multitude of host and drug factors such as gastrointestinal

absorption, volume of distribution, hepatic and renal clearance, pharmacogenetics, drug formulations, and more.[1,2] Recommended starting doses of triazole antifungals for pediatric patients as described in the literature are summarized in Table 1.

There are limited data in pediatrics that conclusively evaluate the relationship between recommended doses and goal serum concentrations. Thus, the primary outcome of this study was to determine the effective dose needed to reach goal serum concentrations of isavuconazole, itraconazole, posaconazole, and voriconazole in pediatric patients. The secondary aim focuses on identifying the interrelationships between indications and targeted drug concentrations for the 4 azoles. Determining the suitable dose in pediatric patients can help decrease time to attainment of therapeutic serum concentrations and avert adverse effects and toxicities.

Materials and Methods

A single center, retrospective chart review was conducted in pediatric patients from birth through 17 years of age who received isavuconazole, itraconazole, posaconazole, or voriconazole between January 1, 2011, and August 31, 2021. Patients were only included if they had an inpatient or outpatient encounter with at least 1 antifungal drug serum concentration measurement. Drug concentrations for itraconazole, posaconazole, and voriconazole are processed in-house and typically take about 24 hours for results. Drug concentrations for isavuconazole are sent to Eurofins Viracor, LLC, and results are typically available within 5 to 7 days. Patients were excluded if they did not have TDM performed, electronic medical record had incomplete information (i.e., unknown starting azole dose or date), posaconazole immediate-release oral suspension was prescribed, or there was documented refusal of research authorization. Data collected was captured in a secured REDCap (Research Electronic Data; Vanderbilt University, Nashville, TN) database.

Table 1. Summary of Recommended Therapeutic Azole Dose Ranges in the Literature

Azole	<12 yr and/or <30 kg	≥12 yr and/or ≥30 kg
Isavuconazole (isavuconazonium sulfate*)[3–9]	6.5–21 mg/kg/dose PO/IV once daily	Load: 372 mg PO/IV every 8 hr × 6 doses Maintenance: 372 mg PO/IV once daily
Itraconazole[8–11]	2–10 mg/kg/dose PO twice daily	Load: 200 mg PO 3 times daily × 3 days Maintenance: 200 mg PO twice daily
Posaconazole[8–10,12–14]	5–13.5 mg/kg/dose PO/IV once daily	Load: 300 mg PO/IV twice daily × 2 doses Maintenance: 300 mg PO/IV once daily
Voriconazole[8–10,15–18]	8–27 mg/kg/dose PO/IV every 12 hr	Load/maintenance: 200–300 mg PO/IV twice daily

IV, intravenous

* Doses expressed as isavuconazonium sulfate.

Antifungal doses (mg/kg/day) and time (days to first goal concentration) needed to achieve goal serum concentrations of isavuconazole, itraconazole, posaconazole, and voriconazole in pediatric patients were analyzed. The impact of antifungal doses and time to goal concentrations were assessed through documented therapy initiation and acceptable serum trough concentration following the achievement of steady-state concentrations of the medication. We defined steady state as 4 weeks for isavuconazole, 14 days for itraconazole, 7 days for posaconazole, and 5 days for voriconazole. Isavuconazole concentrations were obtained prior to the conversion to maintenance dosing on day 3 (after the 6-dose load) and then again at 14 or 28 days dependent on indication for use, 10 to 14 days for itraconazole, 6 to 7 days for posaconazole, and at 5 days for voriconazole. Concentrations were considered at goal if within the following range for each antifungal: isavuconazole >1 mg/L, itraconazole >1 mg/L (via high-performance liquid chromatography, excluding hydroxy-itraconazole metabolite), posaconazole (prophylaxis) >0.7 mg/L, posaconazole (treatment) >1 mg/L, and voriconazole >1 mg/L or if there was a different concentration noted in the provider's clinical note. Hydroxy-itraconazole is an active metabolite of itraconazole that is reported to have comparable *in vitro* activity.[2] However, recommendations are mixed as to whether the hydroxy-itraconazole component should be used in assessing efficacy; therefore, attainment of targeted range by the parent compound alone was used. Duration of antifungal therapy was calculated as the interval between the first dose given and the dose at the time of a goal concentration (or end-of-study concentration if a goal concentration was not achieved).

Interrelationship between indications and dose required for the different azoles in pediatric patients was examined. Patients were divided into 2 groups. The empiric group included patients who were receiving the antifungal for prophylaxis/prevention or empiric treatment of a fungal infection without microbiologic evidence because goal concentrations would be similar

for prophylaxis and empiric treatment. Patients were included into the targeted therapy group if there was microbiologic evidence of fungal infection.

Baseline and end-of-study monitoring of liver function tests and renal function were also evaluated. End of study was defined as achievement of goal concentration for that antifungal. Liver and renal function were assessed to monitor for any potential toxicity due to drug concentrations or alterations to drug clearance that may have affected drug concentrations. Drug doses were not adjusted on the basis of specific liver or kidney function result but were used as part of full patient assessment and to assist with how therapy could be individualized. For patients who did not meet goal concentration, end of therapy was defined as when antifungal therapy was stopped or as a switch to another agent. Laboratory evaluations included alanine transaminase (ALT), aspartate transaminase, total bilirubin, alkaline phosphate, and serum creatinine. Significant changes were defined as 3 times the upper limit of normal from baseline for hepatic markers and a 50% increase from baseline for serum creatinine. These monitoring laboratory results must have been obtained within 1 week of starting azole therapy and similarly within 1 week of the defined end-of-study period.

Data were summarized by using frequencies and percentages for categorical data and medians and IQRs for continuous data. Comparisons between treatment regimens were made by using chi-square or Fisher exact tests for categorical data and Kruskal-Wallis tests for continuous data. Time-to-therapeutic concentration was assessed by using the Kaplan-Meier method and Cox proportional hazards regression. A spline plot was used to assess the functional form of the relationship between dose and likelihood of achieving a therapeutic concentration. A spline plot and a cut-point analysis were used to determine a dose cutoff where patients were more likely to achieve a therapeutic concentration. Among those who achieved a therapeutic concentration, a scatter plot and linear regression were used to assess the association between starting dose and time needed to reach therapeutic concentration for each treatment regimen. The regression models were also used to assess if there was an interaction between starting dose and indication (i.e., if there are different relationships based on medication indication). All analyses were performed with SAS version 9.4 software (SAS Institute Inc, Cary, NC).

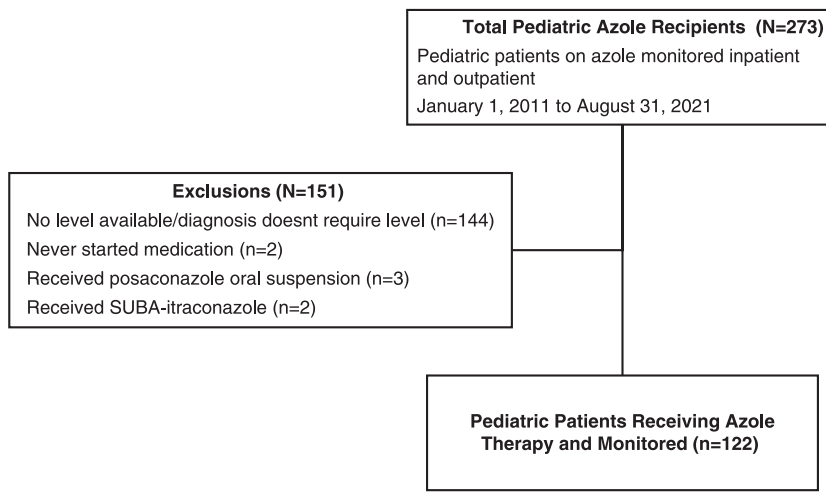
Results

During the 10.5-year study period, 273 patients received isavuconazole, itraconazole, posaconazole, or voriconazole in the inpatient or outpatient setting. One hundred fifty-one patients were excluded, and 122 patients were included in the analysis (Figure 1).

Baseline characteristics are described in Table 2. Median patient age was 13 years (IQR, 8.1–15.9) with 57% aged 12 years or older. Notably, 84% of the population received either itraconazole or voriconazole and most patients (72%) were classified as receiving targeted treatment for an identified fungal organism. Approximately half of the patients in the cohort had a diagnosis of either aspergillosis (32 patients; 26%) or histoplasmosis (32 patients; 26%).

Goal serum concentration was achieved by 101 patients (83%) (Table 3). Approximately 83% of patients who reached a goal concentration received either itraconazole or voriconazole. Median time to goal concentration occurred at 20 days for isavuconazole, 34 days for itraconazole, 11 days for posaconazole, and 10 days for voriconazole. The dosage in mg/kg/dose was higher for patients younger than 12 years for all

Figure 1. Study sample.



SUBA, Super Bio-Availability

Table 2. Baseline Characteristics

	Azole					
	Isavuconazole (n = 4)	**Itraconazole (n = 56)**	**Posaconazole (n = 15)**	**Voriconazole (n = 47)**	**Total (n = 122)**	**p. value***
Age, median (IQR)	13.5 (11.4–14.5)	13.2 (8.4–15.3)	14.2 (12.3–16.2)	10.7 (7.0–16.3)	13.0 (8.1–15.9)	0.32
<12 yr	1 (25%)	23 (41%)	3 (20%)	26 (55%)	53 (43%)	
≥12 yr	3 (75%)	33 (59%)	12 (80%)	21 (45%)	69 (57%)	
Sex						0.081
Female	1 (25%)	34 (61%)	5 (33%)	17 (36%)	57 (47%)	
Male	3 (75%)	22 (39%)	10 (67%)	30 (64%)	65 (53%)	
Weight, median (IQR), kg	37.9 (33.6–42.5)	45.8 (26.3–64.5)	53.7 (44.3–67.5)	35.4 (24.3–62.2)	44.4 (26.5–63.3)	0.15
Height, cm						0.25
n	4	46	12	27	89	
Median (IQR)	150 (139–156)	154 (132–167)	158 (148–161)	131 (117–166)	152 (127–165)	
Total daily dose, median (IQR), mg	372 (372–372)	200 (195–400)	300 (300–300)	400 (300–500)		
Age <12 yr	372	200 (100–300)	300 (100–300)	400 (200–480)		
Age ≥12 yr	372 (372–372)	300 (200–400)	300 (300–300)	460 (400–600)		
Dose, median (IQR), mg/kg/day	9.9 (8.8–11.1)	5.4 (4.1–8.8)	5.6 (4.4–6.8)	10.5 (5.9–16.2)		
Age <12 yr	11.1	8.9 (5.0–10.0)	4.4 (2.4–6.8)	16.3 (13.8–18.1)		
Age ≥12 yr	8.9 (8.7–11.0)	4.4 (3.7–6.6)	5.7 (4.6–6.8)	7.8 (6.4–8.1)		
Monitoring strategy						0.009
Empiric	1 (25%)	8 (14%)	8 (53%)	17 (36%)	34 (28%)	
Targeted	3 (75%)	48 (86%)	7 (47%)	30 (64%)	88 (72%)	
Initial lab tests (1 wk prior to or after initiation)						
Aspartate aminotransferase (U/L)						0.77
n	3	19	9	34	65	
Median (IQR)	26 (15–88)	26 (21–35)	25 (17–51)	31 (23–43)	29 (21–42)	
Alanine transaminase (U/L)						0.42
n	3	21	12	36	72	
Median (IQR)	30 (17–189)	18 (14–28)	21.5 (15.5–93)	26 (15–50)	23 (15–50)	
Total bilirubin (mg/dl)						0.027
n	3	13	8	27	51	
Median (IQR)	0.3 (<0.2 to 0.3)	0.3 (<0.2 to 0.3)	0.4 (0.4–0.5)	0.6 (0.3–1.1)	0.4 (0.3–0.6)	

(Table cont. on page 116)

Table 2. (*cont.*)

	Azole					
	Isavuconazole (n = 4)	**Itraconazole (n = 56)**	**Posaconazole (n = 15)**	**Voriconazole (n = 47)**	**Total (n = 122)**	**p. value***
Alkaline phosphatase (U/L)						0.45
n	4	13	8	25	50	
Median (IQR)	330 (123–734)	108 (68–157)	123 (90–135)	134 (90–182)	133 (86–182)	
Serum creatinine (mg/dL)						0.44
n	4	18	14	41	77	
Median IQR	0.7 (0.6–0.8)	0.6 (0.3–0.8)	0.6 (0.5–0.7)	0.5 (0.3–0.7)	0.5 (0.3–0.8)	

* p value is testing to see if at least one of the groups is different from another.

azoles. This was expected owing to this group's having a lower weight. However, total mg/dose/day was similar for both the <12-year age group and ≥12-year group (Figure 2A and B). For patients younger than 12 years, the median doses that achieved goal concentrations were the following: 11.1 mg/kg/day (372 mg/day) for isavuconazonium sulfate, 10 mg/kg/day (300 mg/day) for itraconazole, 6.8 mg/kg/day (300 mg/day) for posaconazole, and 17.9 mg/kg/day (365 mg/day) for voriconazole. For patients 12 years or older who achieved an appropriate drug concentration, the median dose that was used to achieve the goal was as follows: 5.5 mg/kg/day (186 mg/day) for isavuconazonium sulfate, 6.9 mg/kg/day (400 mg/day) for itraconazole, 6.1 mg/kg/day (300 mg/day) for posaconazole, and 8.5 mg/kg/day (600 mg) for voriconazole. Patients who received higher doses of voriconazole were more likely to reach goal concentration. This is further described in 3 dosing subgroups where differences in total daily dose or mg/kg/day dosing were noted (Figure 2C and D; Table 4).

Table 5 describes the association between baseline characteristics and chances of obtaining goal concentrations. Posaconazole (hazard ratio [HR], 2.67; 95% CI, 1.41–5.05; p = 0.003) and voriconazole (HR, 2.98; 95% CI, 1.89–4.69; p < 0.001) were more likely to reach goal concentrations than itraconazole. There was no significant difference in reaching a goal concentration between participants who were in the empiric group and the targeted treatment group (HR, 1.06; 95% CI, 0.68–1.65; p = 0.80). There was no statistically significant difference in liver function tests or serum creatinine from baseline.

Discussion

To our knowledge, this study is the first to evaluate the dose and time to therapeutic serum concentrations of isavuconazole, itraconazole, posaconazole, and voriconazole and adds to the growing body of literature for azole use in pediatric patients. Understanding the optimal doses to obtain appropriate serum concentrations of these antifungals is increasingly important owing to the major morbidity and mortality consequences that difficult-to-treat IFIs can have. Noting the differences in azole half-life, our study found that the median number of days to reach goal steady-state serum concentrations varied among the azoles, mainly owing to the different frequency at which a concentration is obtained. Additionally, most azoles reached goal concentrations with the second drug assessment after at least 1 dose adjustment. With this observation, initiating azole antifungal therapy at a higher starting dose would lead to achieving goal concentrations sooner. It is important to minimize the time to reach goal serum drug concentrations to hopefully limit antifungal resistance and clinical failures/breakthrough infection associated with extended periods of suboptimal antifungal concentrations. Additional factors that could affect treatment outcomes include route of administration, drug formulations, duration of therapy, renal or hepatic abnormalities, and drug-drug interactions. Some of these factors will be further touched on for each antifungal in the following paragraphs. Renal and hepatic laboratory values are described in Table 2 and Table 3. There were no statistically significant changes in renal or hepatic function tests from baseline.

Isavuconazole. Isavuconazole has been increasingly prescribed in the pediatric population owing to the added advantages over other azoles, such as the lack of QTc prolongation and fewer drug-drug interactions. Despite these benefits of isavuconazole, pediatric dosing and monitoring information are limited. Two of the 4 patients included in the cohort required the adult dose of 372 mg daily to reach a goal concentration of >1 mg/L, which correlated with the 10-mg isavuconazonium sulfate/kg/dose once daily that is recommended in the literature. The other 2 patients

Table 3. Patients Who Reached Goal Serum Azole Concentration (All Measures Are at Time of Goal Concentration)

	Azole					
	Isavuconazole (n = 4)	**Itraconazole (n = 44)**	**Posaconazole (n = 13)**	**Voriconazole (n = 40)**	**Total (n = 101)**	**p value**
Days to goal serum concentration, median (IQR)	20 (4–38)	34 (17–66)	11 (9–14)	10 (6–15)		
Serum drug concentration, median (IQR), mg/L	3.4 (2.9–4.1)	1.3 (1.0–2.1)	1.7 (1.5–2.6)	2.6 (1.8–4.4)		
Total daily dose, median (IQR), mg	279 (186–372)	400 (300–400)	300 (300–300)	400 (300–600)		
Age <12 yr	372	300 (180–400)	300 (200–300)	365 (265–480)		
Age ≥12 yr	186 (186–372)	400 (400–400)	300 (300–300)	600 (400–600)		
Dose, median (IQR), mg/kg/day	11.0 (4.3–11.1)	8.4 (6.3–10.1)	6.3 (5.1–6.8)	14.8 (7.8–18.0)		
Age <12 yr	11.1	10 (9.1–11.3)	6.8 (2.4–8.8)	17.9 (16.2–18.8)		
Age ≥12 yr	5.5 (4.3–8.9)	6.9 (5.8–8.4)	6.1 (5.1–6.7)	8.5 (6.4–10.6)		
Change in dose from baseline, mg/kg/day	−2.2 (−4.9 to 0)	1.0 (0–3.7)	0 (0–0)	0 (0–2.7)		
p value	0.5	<0.001	0.99	0.026		
AST (U/L)						0.80
n	3	17	8	28	56	
Median (IQR)	55 (17–153)	25 (19–42)	35 (19–61)	29 (18–63)	30 (18–56)	
Change in AST from baseline (U/L)						0.36
n	3	8	6	23	40	
Median (IQR)	29 (2 – 65)	–2 (−10 to 6)	–5 (−52 to 26)	2 (−10 to 14)	2 (−10 to 12)	
p-value	0.25	0.57	0.56	0.84	0.80	
ALT (U/L)						0.40
N	4	28	11	27	70	
Median (IQR)	144 (18–380)	24 (15–28)	17 (12–64)	29 (13–105)	25 (14–57)	
Change in ALT from baseline (U/L)						0.65
N	3	15	9	22	49	
Median (IQR)	77 (−9 to 477)	0 (−4 to 7)	0 (−8 to 41)	−1 (−28 to 11)	0 (−9 to 12)	
p-value	0.50	0.75	0.77	0.93	0.59	
Serum creatinine (mg/dL)						0.47
n	4	19	11	33	67	
Median (IQR)	0.8 (0.6–1.0)	0.5 (0.3–0.8)	0.6 (0.3–0.8)	0.5 (0.4–0.7)	0.6 (0.4–0.8)	

(Table cont. on page 118)

Table 3. (*cont.*)

	Azole					
	Isavuconazole (n = 4)	**Itraconazole (n = 44)**	**Posaconazole (n = 13)**	**Voriconazole (n = 40)**	**Total (n = 101)**	**p value**
Change in serum creatinine from baseline (mg/dL)						0.67
n	4	10	11	29	54	
Median (IQR)	0.2 (−0.1 to 0.3)	−0.1 (−0.1 to 0.1)	0.1 (−0.1 to 0.2)	0 (−0.1 to 0.1)	0 (−0.1 to 0.1)	
p value	0.38	0.79	0.52	0.79	0.85	
Total bilirubin (mg/dL)						0.14
n	3	12	8	25	48	
Median (IQR)	0.2 (<0.2 to 0.3)	0.4 (<0.2 to 0.6)	0.6 (0.3–0.8)	0.4 (0.3–0.7)	0.4 (0.2– 0.6)	
Change in total bilirubin from baseline (mg/dL)						0.037
n	3	5	6	19	33	
Median (IQR)	0 (−0.1 to 0)	0.1 (0–0.1)	0.4 (0.1–0.4)	−0.1 (−0.4 to 0.1)	0 (−0.1 to 0.1)	
p value	0.99	0.25	0.063	0.22	0.85	
Alkaline phosphatase (U/L)						0.80
n	3	12	8	27	50	
Median (IQR)	201 (71–874)	105 (89–179)	117 (82–233)	126 (87–192)	124 (87–197)	
Change in alkaline phosphatase from baseline (U/L)						0.19
n	3	6	5	20	34	
Median (IQR)	−115 (−278 to 6)	9 (−9 to 52)	−10 (−61 to 7)	7 (−31 to 44)	6 (−35 to 26)	
p value	0.50	0.44	0.44	0.53	0.99	

ALT, alanine transaminase; AST, aspartate aminotransferase

had to reduce the isavuconazonium sulfate dose from 372 mg to 186 mg (1 capsule) owing to trough concentrations >7 mg/L. The recently published phase 1 clinical trial, NCT03241550, evaluated the pharmacokinetics and pharmacodynamics of isavuconazole in pediatric patients and concluded that a dose of 10-mg isavuconazonium sulfate/kg/dose once daily resulted in goal concentration obtainment for >80% and >76% of simulated pediatric patients following intravenous (IV) and oral administration, respectively.[7] An additional benefit of isavuconazole is the various forms and routes of administration for pediatric patients. Obtaining goal concentrations when opening the capsules and administering via gastrostomy tube when unable to take the capsules whole has been successful.[19,20] One study recently published in the hematology-oncology patient population suggests that TDM may not be warranted owing to limited variability in exposure or stable pharmacokinetics.[21] However, from a safety standpoint, 1 patient in our study did have an elevated ALT concentration of 494 units/L about 1 month after starting isavuconazole. This was a 16-year-old patient who received isavuconazole for ongoing treatment of histoplasmosis after completing amphotericin B therapy owing to the drug-drug interactions between vincristine and itraconazole. The patient was adult sized (>12 years old, >40 kg) and was started on isavuconazonium sulfate 372-mg dose (<10 mg/kg/dose) once daily, which resulted in isavuconazole concentrations of 8.6 mg/L and 9.4 mg/L before dose reduction. Given the TDM concentrations in the setting of elevated ALT, the isavuconazonium sulfate dose was reduced to 186 mg daily. The ALT slowly trended back down to the normal range (7–55 units/L) after dose reduction of isavuconazole. Though there could have been other confounders associated with the elevated ALT that were not recognized, there seemed to be a correlation with improving ALT and the isavuconazole dose decrease. The patient remained on 186 mg daily

Figure 2. Comparing therapeutic levels by azole and age in mg/kg/day and total daily dose.

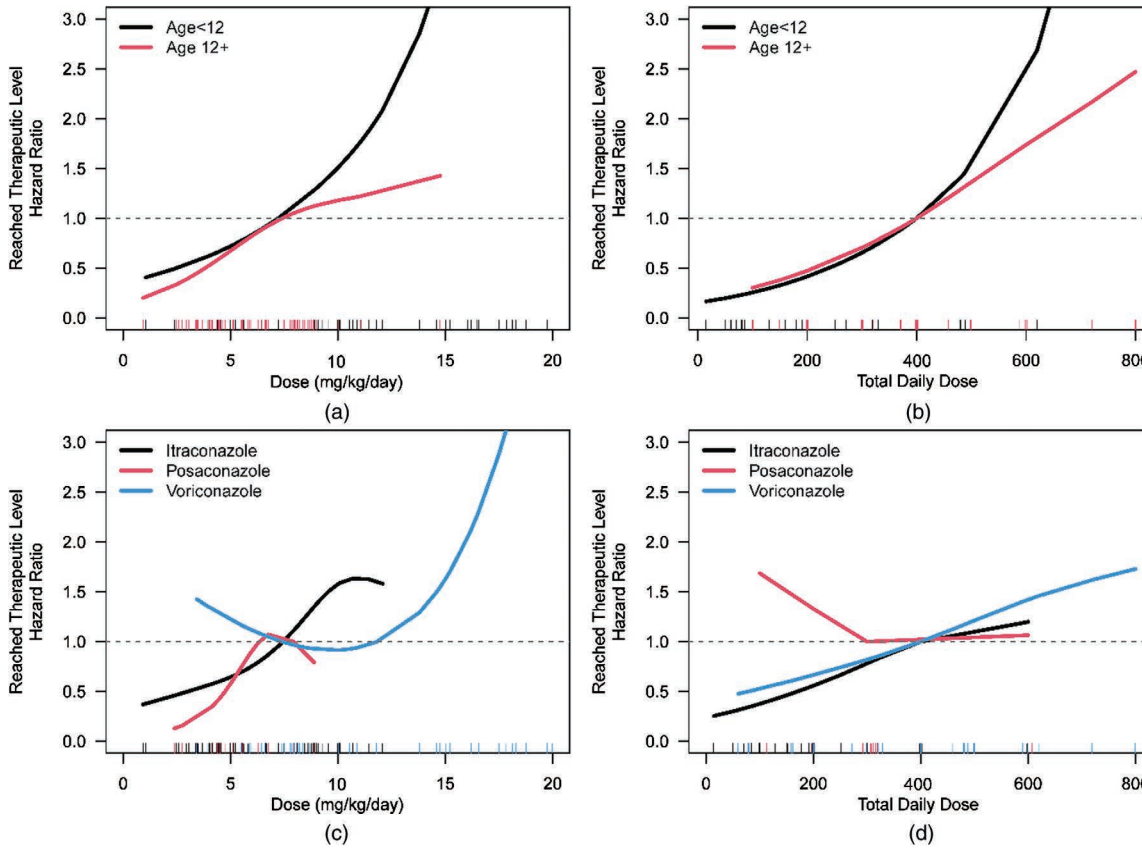


Table 4. Dosing Subgroups*

Azole	Total Daily Dose Subgroup			12-mg/kg/day Subgroup			7.4-mg/kg/day Subgroup		
	Total Daily Dose, mg	Hazard Ratio (95% CI)	p value	Dose, mg/kg/day	Hazard ratio (95% CI)	p value	Dose, mg/kg/day	Hazard ratio (95% CI)	p value
Itraconazole	>400 vs ≤400	1.60 (0.22–11.82)	0.65	>12 vs ≤12	0.73 (0.10–5.35)	0.76	>7.4 vs ≤7.4	3.57 (1.84–6.93)	<0.001
Posaconazole	>400 vs ≤400	1.00 (0.13–7.93)	0.99	>12 vs ≤12			>7.4 vs ≤7.4	1.00 (0.21–4.76)	0.99
Voriconazole	>400 vs ≤400	1.81 (0.94–3.47)	0.077	>12 vs ≤12	2.24 (1.17–4.28)	0.015	>7.4 vs ≤7.4	1.35 (0.62–2.94)	0.45

* Patient subgroup comparison for itraconazole, posaconazole, and voriconazole based on dose: for total daily dose of ≤400 mg and >400 mg, ≤12 mg/kg/day and >12 mg/kg/day, and ≤7.4 mg/kg/day and >7.4 mg/kg/day.

without toxicity, and repeated isavuconazole concentrations were between 2 to 4 mg/L. Although there is not a well-defined concentration that is associated with clinical efficacy or toxicity, isavuconazole TDM may still be beneficial to monitor for possible toxicity and noting when it may be clinically appropriate to adopt the adult-approved dose of 372 mg once daily.

Itraconazole. Itraconazole was the most prescribed triazole included in this study owing to higher incidence of histoplasmosis and blastomycosis seen in

Table 5. Associations Between Achieving a Goal Level and Baseline Characteristics

	Hazard Ratio (95% CI)*	p value
Age, per year	1.00 (0.96–1.04)	0.96
Sex		
Female	0.88 (0.59–1.31)	0.53
Male	Reference	
Weight, per 10 kg	0.99 (0.91–1.07)	0.77
Azole		
Isavuconazole	2.57 (0.91–7.25)	0.074
Itraconazole	Reference	
Posaconazole	2.67 (1.41–5.05)	0.003
Voriconazole	2.98 (1.89–4.69)	<0.001
Monitoring strategy		
Empiric†	1.06 (0.68–1.65)	0.80
Targeted‡	Reference	

* Hazard ratio >1 means more likely to reach a therapeutic level.
† Empiric: Prophylaxis/prevention indication or empiric treatment of a fungal infection without microbiologic evidence.
‡ Targeted: Microbiologic evidence of fungal infection.

our patient population. However, outside of these indications, itraconazole has been generally replaced by voriconazole, posaconazole, or isavuconazole for other indications owing to itraconazole's wide interpatient variability and decreased tolerability (e.g., gastrointestinal intolerance). Disadvantages of itraconazole may be attributed to the unpredictable or decreased absorption (e.g., concomitant use with acid suppressants), and drug-drug interactions with Cytochrome P450 3A4 substrates, inhibitors, or inducers.[1] In light of these results, starting on the higher end of the dosing range with 5 mg/kg/dose is indicated, rather than 2 mg/kg/dose, especially in patients <12 years old.

Posaconazole. Posaconazole is a widely used triazole at our institution because it is the preferred antifungal prophylaxis agent for bone marrow transplant patients. Delayed-release tablets and occasionally IV posaconazole are primarily used at our institution. Immediate-release posaconazole suspension is no longer used because of difficulty obtaining goal concentrations due to highly variable bioavailability; patients who received posaconazole immediate-release suspension were excluded from the study. Although the delayed-release tablet has more predictable bioavailability in adult patients, posaconazole pharmacokinetic data are extremely limited in pediatrics, and the dosing range (mg/kg/day) summarized in literature is quite wide (see Table 1).[2,13] When patients are unable to swallow tablets whole, and alternative azole agents or IV therapy are not preferred, delayed-release tablets are crushed, based on promising results noted in the adult literature.[22] If the crushing method is selected, the patient's dose is often doubled and divided twice daily to try and maintain goal concentrations. Additionally, posaconazole delayed-release tablet can be burdensome and challenging to take because the tablet is only formulated as 100 mg, requiring multiple tablet administrations for each dose. If limited by the patient's ability to take multiple tablets or insurance coverage, attempts were made to divide the once daily dose into twice or thrice daily dosing to enhance exposure before considering an increase in total daily dose. For example, if a patient is unable to achieve goal concentrations with 300 mg daily, patients are instructed to take 100 mg in the morning and 200 mg in the evening. Overall, most pediatric patients required a dose of at least 300 mg daily regardless of their age and weight to achieve a goal concentration.

Voriconazole. Voriconazole is typically used for aspergillosis or as an alternative to posaconazole for antifungal prophylaxis in our pediatric patients. Although both the voriconazole solution and tablet show high bioavailability in the adult population, reported as exceeding 90%, the bioavailability of voriconazole is reported to be lower in pediatric patients. This contributes to the challenge of achieving goal concentrations and transitioning between oral and IV routes. One reason for this difference may be explained by intestinal first-pass metabolism. Additionally, voriconazole displays both linear and nonlinear pharmacokinetics, making dose adjustments challenging.[1,2,8] Published studies have reported needing significantly higher doses, reporting 20 to 50 mg/kg/day to achieve goal drug concentrations.[8–10,15–18] In our cohort, a statistically significant difference of target attainment was detected when patients received >12 mg/kg/day independent of age. Additionally, another important factor that is gaining traction in the literature, which was not evaluated in our study but would be helpful for evaluation in future studies, is the possible relationship between inflammation (i.e., C-reactive protein) and voriconazole serum concentrations.[23] Several studies have reported a correlation between inflammation and voriconazole metabolism that further affects the unpredictable pharmacokinetics of voriconazole (i.e., increased C-reactive protein correlated with increased voriconazole plasma trough concentration); this was not addressed in this study but we have noted an association as part of our practice. Finally, though we have not used thrice daily dosing often, based on growing evidence, it is reasonable to suggest trialing thrice daily dosing especially in patients <12 years old.[17] It is crucial to reach a target of at least 1 mg/L as soon as possible because concentrations ≤0.35 mg/L may be a stronger predictor of mortality while balancing voriconazole's high rate of toxicity even with concentrations within the goal range of 1 to 5 mg/L.[21]

Strengths of this study include a large pediatric sample size during a 10.5-year period with sufficient power to detect statistical differences. Our study adds

to the literature published suggesting the need for higher initial doses with azole antifungal therapy in pediatric patients and the importance of TDM. Future considerations to improve the applicability of this study would include assessing the maintenance of appropriate concentrations and whether continued TDM is needed once a therapeutic target is obtained. A prospective assessment with balanced arm distributions accounting for pharmacokinetics, pharmacodynamic, and pharmacogenomic considerations would help provide confirmatory doses to achieve goal serum concentrations in pediatric patients.

Limitations

This study is not without limitations. The retrospective design prevented the ability to account for any confounders such as patient adherence and appropriate timing and frequency of serum azole concentrations. A new electronic medical record system was implemented in May 2018 at our institution, thus making the data collection prior to that period challenging. Additionally, there was no dedicated pediatric antimicrobial stewardship/infectious diseases pharmacist at our institution prior to 2019. The lack of pharmacist input did affect the frequency and possibly the accuracy of TDM in the beginning of our study cohort. However, TDM concentrations have become standardized in the past few years with a pediatric infectious diseases pharmacist integrated into the multidisciplinary team. Additionally, the study only assessed the first serum concentration within goal range and did not account for dosage form variations and serum concentration fluctuations over the course of the patient's therapy (i.e., auto-induction seen with voriconazole). Therefore, how a patient's dose may change over time was not evaluated. We also were not able to assess underlying conditions and comorbidities that may have affected absorption and overall disposition. Another limitation was the omission of cytochrome P4502C19 (CYP2C19) pharmacogenomic testing assessment and the impact of inflammation on voriconazole concentrations. CYP2C19 testing is available at our institution but not always done as standard of practice. Finally, posaconazole delayed-release oral suspension was not assessed in this study because it was not available during the study time frame.

Table 6. Recommended Azole Starting Doses

Azole	Starting Dose	Timing of Levels
Isavuconazole (isavuconazonium sulfate*)	10 mg isavuconazonium sulfate/kg/dose IV/PO every 8 hr × 6 doses then once daily (max starting dose 372 mg/day)	Day 3 (before starting maintenance dosing), day 14, and day 28
Itraconazole	5 mg/kg/dose PO thrice daily × 3 days, then 5 mg/kg/dose PO twice daily (max starting dose 600 mg/day)	10–14 days
Posaconazole	7 mg/kg/dose PO/IV twice daily × 2 doses then once daily (max starting dose 400 mg/day)	7 days
Voriconazole	<12 yr: 6 mg/kg/dose IV/PO thrice daily or 9 mg/kg/dose IV/PO twice daily (max starting dose 500 mg/day) ≥12 yr: 4–5 mg/kg/dose IV/PO twice daily (max staring dose 600 mg/day)	5 days

IV, intravenous

* Doses expressed as isavuconazonium sulfate.

Conclusions

In summary, higher starting daily doses are generally needed to reach goal concentrations for all azoles evaluated. Dose recommendations based on our findings are summarized in Table 6. These doses are meant to serve as first-dose guidance and are within the range described in the current literature. Individualized dosing should be based on indication and other patient characteristics combined with serum drug concentration monitoring. Higher-than-suggested doses may still be warranted based on the clinical situation especially if the patient is at relatively low risk for toxicity with a more aggressive dosing approach upfront.

Article Information

Affiliations. Department of Pharmacy (KLK), Children's Health Dallas, Dallas, TX; Department of Pharmacy (LKM, GL, LMD), Mayo Clinic, Division of Pediatric Infectious Diseases, Department of Pediatric and Adolescent Medicine (EHR), Mayo Clinic, Department of Quantitative Health Sciences (KCM), Mayo Clinic, Rochester, MN.

Correspondence. Laura M. Dinnes, PharmD; dinnes.laura@mayo.edu

Disclosure. The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript. The authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors attest to meeting the 4 criteria recommended by the ICMJE for authorship of this manuscript.

Ethical Approval and Informed Consent. Given the nature of this study, institutional review board/ethics committee review and informed consent were not required.

Acknowledgment. We would like to acknowledge the tremendous effort and compassionate patient care by our entire team of pediatric infectious diseases physicians, pediatric infectious diseases nurses, and pediatric pharmacists. Preliminary results were presented at PPA Annual Meeting Resident Project Presentations in May 2021.

Submitted. February 6, 2024

Accepted. May 15, 2024

References

1. John J, Loo A, Mazur S, Walsh TJ. Therapeutic drug monitoring of systemic antifungal agents: a pragmatic approach for adult and pediatric patients. *Expert Opin Drug Metab Toxicol*. 2019;15(11):881–895.
2. Bury D, Tissing WJE, Muilwijk EW, et al. Clinical pharmacokinetics of triazoles in pediatric patients. *Clin Pharmacokinet*. 2021;60(9):1103–1147.
3. Ashkenazi-Hoffnung L, Bilavsky E, Levy I, et al. Isavuconazole as successful salvage therapy for mucormycosis in pediatric patients. *Pediatr Infect Dis J*. 2020;39(3): 719–724.
4. Decembrino N, Perruccio K, Zecca M, et al. A case series and literature review of isavuconazole use in pediatric patients with hemato-oncologic diseases and hematopoietic stem cell transplantation. *Antimicrob Agents Chemother*. 2020;64(3): e01783-19.
5. De Leonardis F, Novielli C, Giannico B, et al. Isavuconazole treatment of cerebral and pulmonary aspergillosis in a pediatric patient with acute lymphoblastic leukemia: case report and review of literature. *J Pediatr Hematol Oncol*. 2019;42(6):e469–e471.
6. Martin AM, MacBrayne CE, Heiden A, et al. Isavuconazonium sulfate dosing in pediatric patients using serum therapeutic drug monitoring at a single center: a case series. *J Hematol Oncol Pharm*. 2022;12(5):271–277.
7. Arrieta AC, Neely M, Day JC, et al. Safety, tolerability, and population pharmacokinetics of intravenous and oral isavuconazonium sulfate in pediatric patients. *Antimicrob Agents Chemother*. 2021;65(8):e00290-21.
8. Lexicomp online. In: Post TW, ed. *UpToDate*. Waltham, MA: UptoDate; 2023. Accessed January 24, 2024. uptodate.com
9. American Academy of Pediatrics. Recommended doses of parenteral and oral antifungal drugs. In: Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. *Red Book: 2021 Report of the Committee on Infectious Diseases*. Itasca, IL: American Academy of Pediatrics; 202:913–921.
10. Pana Z, Kougia V, Roilides E. Therapeutic strategies for invasive fungal infections in neonatal and pediatric patients: an update. *Expert Opin Pharmacother*. 2015;16(5):693–710.
11. Leong YH, Boast A, Cranswick N, et al. Itraconazole dosing and drug monitoring at a tertiary children's hospital. *Pediatr Infect Dis J*. 2019;38(1):60–64.
12. Nickless JR, Bridger KE, Vora SB, Brothers AW. Evaluation of intravenous posaconazole dosing and pharmacokinetic target attainment in pediatric patients. *J Pediatr Infect Dis Soc*. 2018;8(4):365–367.
13. Dekkers BGJ, Bakker M, van der Elst KCM, et al. Therapeutic drug monitoring of posaconazole: an update. *Curr Fungal Infect Rep*. 2016;10:51–61.
14. Panagopoulou P, Roilides E. Evaluating posaconazole, its pharmacology, efficacy and safety for the prophylaxis and treatment of fungal infections. *Expert Opin Pharmacother*. 2021;23(2):175–199.
15. Gerin M, Mahlaoui N, Elie C, et al. Therapeutic drug monitoring of voriconazole after intravenous administration in infants and children with primary immunodeficiency. *Ther Drug Monit*. 2011;33(4):464–466.
16. Lempers V, Meuwese E, Mavinkurve-Groothuis AM, et al. Impact of dose adaptations following voriconazole therapeutic drug monitoring in pediatric patients. *Med Mycol*. 2019;57(8):937–943.
17. Barraza M, Torres JP, Coria P, et al. Evaluation dosing IV voriconazole three times a day vs twice daily for the treatment of invasive aspergillosis in immunocompromised children: therapeutic drug monitoring and safety [in Spanish]. *Rev Chilena Infectiol*. 2022;39(1):14–19.
18. Zembles TN, Dasgupta M, Kenkel TJ, et al. Higher weight-based doses are required to achieve and maintain therapeutic voriconazole serum trough concentrations in children. *J Pediatr Pharmacol Ther*. 2023;28(3):247–254.
19. McCreary EK, Nguyen MH, Davis MR, et al. Achievement of clinical isavuconazole blood concntrations in transplant recipients with isavuconazonium suphate capsules administered via enteral feed tube. *J Antimicrob Chemother*. 2020;75(10):3023–3028.
20. Dieringer TD, Schaenman JM, Davis MR. Enteral feeding tube administration with therapeutic drug monitoring of crushed posaconazole tablets and opened isavuconazonium sulfate capsules. *J Antimicrob Chemother*. 2022;77(5):1417–1423.
21. Gatti M, Campoli C, Belotti T, et al. Real-world comparison of isavuconazole and voriconazole in terms of the need for dosage adjustments guided by clinical pharmacological advice during primary prophylaxis of invasive fungal infections in pediatric patients with hemato-oncological malignancies. *Ther Drug Monit*. 2022;44(5):641–650.
22. Stevens RW, O'Connell C, Huang A, et al. Therapeutic drug monitoring following crushed administration of delayed release posaconazole tablets via enteral feeding tubes. *J Antimicrob Chemother*. 2023;78(2):553–555.
23. Li X, Lai F, Jiang Z, et al. Effects of inflammation on voriconazole levels: a systematic review. *Br J Clin Pharmacol*. 2022;88(12):5166–5182.