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ORIGINAL RESEARCH ARTICLE

Therapeutic Drug Monitoring of Voriconazole in Critically Ill Pediatric Patients: A Single-Center Retrospective Study

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Abstract

Background and Objective Voriconazole pharmacokinetics are highly variable in pediatric patients, and the optimal dosage has yet to be determined. The purpose of this study was to describe voriconazole pharmacokinetic and pharmacodynamic targets achieved and evaluate the efficacy and safety of voriconazole for critically ill pediatrics.

Methods This is a single-center retrospective study conducted at a pediatric intensive care unit at a tertiary/quaternary hospital. Pediatrics admitted to the pediatric intensive care unit and who received voriconazole for a proven or suspected fungal infection with at least one measured trough concentration were included. The primary outcomes included the percentage of pediatric patients who achieved the pharmacokinetic and pharmacodynamic targets. Secondary outcomes included assessing the correlation between voriconazole trough concentrations and clinical/microbiological outcomes. All statistical analyses were performed using the R statistical software and Microsoft Excel. Multiple logistic regression was used to assess the predictors of both clinical and microbiologic cures. Multiple linear regression was used to determine significant factors associated with trough concentrations.

Results A total of 129 voriconazole trough concentrations were measured from 71 participants at steady state after at least three doses of voriconazole. The mean (± standard deviation) of the first and second trough concentrations were 2.9 (4.2) and 2.3 (3.3) mg/L, respectively. Among the first trough concentrations, only 33.8% were within the therapeutic range (1–5 mg/L), 46.5% were below the therapeutic range, and 19.7% were above the therapeutic range. A clinical cure occurred in 78% of patients, while a microbiologic cure occurred in 80% of patients.

Conclusions Voriconazole trough concentrations vary widely in critically ill pediatric patients and only a third of the patients achieved therapeutic concentrations with initial doses.

Key Points

A high variability in voriconazole trough concentrations between patients was found.

The initial measured trough concentrations in 71 patients were 33.8% within the therapeutic range, 46.5% below the therapeutic range, and 19.7% above the therapeutic range.

Patient dosing should be individualized by measuring the therapeutic drug concentration of voriconazole.

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1 Introduction

Invasive fungal infections are associated with high morbidity and mortality in immunosuppressed pediatric patients [1]. Patients with prolonged neutropenia, allogeneic hematopoietic stem cell transplant, solid organ transplant, inherited or acquired immunodeficiencies, and corticosteroid use are considered at risk of invasive fungal infections [2]. The incidence of these infections has increased in recent decades [3–5]. For example, the incidence of invasive aspergillosis worldwide has risen lately to > 300,000 cases from the previously reported 200,000 cases, with an associated mortality rate of 30–80% [6]. This is mainly due to the use of immunosuppressive drugs and chemotherapy. Appropriate treatment and dosing with antifungal therapy are essential to improve treatment outcomes and reduce the mortality risk [7, 8].

Voriconazole is a broad-spectrum triazole antifungal agent commonly used for both prophylaxis and the treatment of invasive fungal infections in pediatric patients. Voriconazole has complex pharmacokinetics, the drug has nonlinear pharmacokinetics and high between-subject variability [9]. In addition, voriconazole has a narrow therapeutic window. Therapeutic drug monitoring has been suggested as a tool to improve the treatment of voriconazole and has been shown to improve the efficacy and safety of voriconazole [8, 10], although it is important to note that the package insert for voriconazole does not recommend therapeutic drug monitoring. High voriconazole trough concentrations are associated with toxicities such as hepatotoxicity and visual and/or auditory hallucinations [9, 11, 12]. In contrast, low concentrations can increase the risk of treatment failure [9, 12–14]. The suggested therapeutic range is different from center to center but is in the range of 1–5.5 mg/L. Based on previous studies, approximately 50% of pediatric patients still do not achieve voriconazole therapeutic trough concentrations [3, 8, 15]. Therefore, therapeutic drug monitoring is crucial in determining the efficacy and safety of voriconazole, especially in pediatric patients in pediatric intensive care unit (PICU) settings [16–20].

Voriconazole pharmacokinetics in pediatrics are different than in adults [13]. Because of a higher hepatic clearance and a first-pass effect, pediatric patients need larger weight-based doses or more frequent doses of voriconazole [20]. Additionally, the pediatric population undergoes significant developmental and maturational changes, which may significantly influence the pharmacokinetic variability in this population. Moreover, pediatric patients exhibit different voriconazole pharmacokinetics when compared with adults. One of these differences was evaluated by pharmacokinetic (PK) modeling studies, which showed that pediatric patients demonstrated a three-fold lower area under the concentration–time curve after receiving 4 mg/kg of voriconazole every 12 h when compared with the adult population receiving the same dose [21]. For critically ill pediatric patients, the variability and complexity of pharmacokinetics are expected to be higher. This is because of several factors such as critical diseases, inflammatory status, augmented renal clearance, and therapeutic interventions (e.g., extracorporeal organ support systems or whole-body hypothermia) [22].

To our knowledge, no study has evaluated voriconazole pharmacokinetics and pharmacodynamics in PICUs. Therefore, the purpose of this study was to describe voriconazole PK/pharmacodynamic (PK/PD) targets achieved and to evaluate the efficacy and safety of voriconazole for the pediatric population admitted in the PICU setting.

2 Materials and Methods

2.1 Study Design and Population

This is a single-center retrospective study conducted at the PICU at the King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia. Inclusion criteria included any pediatric patient (1 month to 14 years of age) admitted to the PICU who received voriconazole orally or intravenously for at least 3 days for a proven or probable fungal infection and had at least one measured trough concentration. Following the Hospital Formulary and Drug Therapy Guide for dosing voriconazole, the target initial dose was 9 mg/kg/dose every 12 hfollowed by monitoring of serum trough concentrations to maintain trough concentrations of 2–6 mg/L. Exclusion criteria included patients less than 1 month of age or more than 14 years of age, patients with missing dosing information, or patients without a voriconazole trough concentration during the study time period. The study period was from January 2019 to August 2022. Before July 2020, blood samples of voriconazole concentrations were sent out for assay to the Lab Bioscientia in Germany or Mayo Clinic Laboratories in the USA. Starting from October 2020, blood samples of voriconazole concentrations were assayed in-house at the King Faisal Specialist Hospital and Research Center in Riyadh, Saudi Arabia. For all centers, the assay method was conducted using liquid chromatography-tandem mass spectrometry.

2.2 Data Collection

Data were collected from the hospital's electronic medical records. Data collected consisted of age, gender, height, weight, laboratory values, indication for voriconazole, dose, dosing frequency, trough concentrations, presence

of neutropenia, treatment duration, drugs known to interact with voriconazole (proton pump inhibitors, macrolides, amiodarone, cyclosporine, tacrolimus, nifedipine, sildenafil, phenobarbital, and rifampicin), treatment outcome, dose changes and their timing, time of the level draw, comorbidities, and a description of the fungal infection (proven or probable fungal infections). A proven fungal infection was defined as a fungus detected by the culture of a tissue specimen or by radiographic imaging. A probable fungal infection was defined as clinical documentation of a fungal suspicion based on the clinical presentation and/or radiographic imaging by the attending physician. Neutropenia was defined as an absolute neutrophil count of ≤ 500 cells/mm^3 or < 1000 cells/mm^3 with an anticipated decline to < 500 cells/mm^3 within 48 h, according to the Infectious Diseases Society of America guidelines [23]. The World Health Organization criterion was used for defining obesity in children < 2 years of age, and the Centers for Disease Control and Prevention was used for defining obesity in children ≥ 2 years of age. Children ≥ 2 years of age were classified as obese if the body mass index was $\geq$ 95th percentile, while children $<$ 2 years of age were classified as obese if weight-for-length was $\geq$ 97.7th percentile [24, 25].

2.3 Outcomes

The primary outcomes included describing the percentage of pediatric patients who achieved the PK/PD target in the PICU setting. Secondary outcomes included assessing the correlation between voriconazole trough concentrations and the clinical/microbiological outcomes of pediatric patients in the PICU setting. Additional secondary outcomes focused on describing the voriconazole dosing regimens, adjustments, and safety.

For the primary outcomes, we assessed the percentage of patients who achieved the voriconazole therapeutic target trough concentration. The therapeutic range for voriconazole was defined as having a trough drawn at a minimum of 3 days post-starting treatment between 1 and 5.5 mg/L [9]. We defined a proper dose adjustment as increasing the dose for patients with low trough voriconazole concentrations or decreasing the dose for patients with high voriconazole trough concentrations. We also looked at factors contributing to high or low voriconazole trough concentrations. That included dose, weight, presence of drug interactions, and laboratory values such as alanine transaminase, aspartate transaminase, alkaline phosphatase, C-reactive protein, and albumin levels [26–29]. For drug interactions, interacting drugs were classified as either enzyme inhibitors or inducers.

For the secondary outcomes, we assessed the correlation between voriconazole trough concentrations and clinical or microbiologic outcomes and toxicity. For this analysis, we used the first trough concentration drawn for all patients. The clinical and microbiologic outcomes were evaluated for patients with invasive fungal infections. Invasive fungal infections were classified according to the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium treatment guidelines [30]. Treatment success was defined according to clinical, mycological, or radiologic responses. Complete response indicates the resolution of all clinical signs and symptoms attributable to the infection and radiographic resolution. Treatment failure was defined as a persistent infection $>$ 14 days, or a progressing infection. Microbiological success was defined as the absence of the original pathogen in the culture of the baseline sample as reported in the subsequent cultures. All-cause mortality was defined as death occurring within the study period while the patient was taking voriconazole.

For toxicity, we looked at the relationship between voriconazole trough concentrations and toxicity. That included any documented voriconazole-associated toxicities such as neurological toxicity (e.g., visual disturbance, peripheral neuropathy, or audio or visual hallucinations) and hepatic toxicity.

2.4 Statistical Analysis

The baseline characteristics were analyzed with descriptive statistics. Quantitative variables were summarized as mean (standard deviation). Qualitative variables were summarized as frequencies and percentages. All of the statistical analysis was performed using R statistical software and Microsoft Excel. Multiple logistic regression was used to assess the predictors of both clinical and microbiologic cures. Multiple linear regression was used to determine significant factors associated with trough concentrations. The factors tested in the multiple linear regression model included dose, alanine transaminase, albumin levels, aspartate transaminase, alkaline phosphatase, bilirubin, C-reactive protein, and the presence of cytochrome P450 2C19 enzyme inducers or inhibitors. A p value < 0.05 was considered significant.

3 Results

3.1 Clinical Information

A total of 129 voriconazole trough concentrations were measured from 71 participants. Male individuals constituted 43 patients (60.6%) of the study group. The mean ($\pm$ standard deviation) age (years), weight (kg), and height (cm) were 6.78 ($\pm$ 1.19), 20.19 ($\pm$ 12.07), and 111.97 ($\pm$ 28.14), respectively (Table 1). The average body mass index was 14.93 $\pm$ 2.98. Thirty-three patients (44.5%) were underweight, four patients (5.6 %) were overweight, three patients (4.2%) were obese, and

Table 1 Baseline characteristics of the study population. Data are presented as mean ± SD unless otherwise specified

Characteristic	Value
Age (years)	6.78 ± 1.19
Weight (kg)	20.19 ± 12.07
Height (cm)	111.96 ± 28.14
Body mass index	14.94 ± 2.98
Sex, *n* (%)	
Male	43 (60.6%)
Female	28 (39.4%)
Indication (%)	
Prophylaxis	19.7%
Suspected infection	8.5%
Proven infection	71.8%
Neutropenia based on ANC at the beginning of treatment, *n* (%)	
Yes	32 (45.1%)
No	39 (54.9%)

ANC absolute neutrophil count, *SD* standard deviation

Table 2 Participants laboratory values at baseline

Laboratory results	Mean ± SD
GGT (IU/L)	210.23 ± 237.64
ALT (IU/L)	35.05 ± 36.56
AST (U/L)	39.67 ± 64.73
INR	1.23 ± 0.25
Total bilirubin (umol/L)	13.31 ± 16.75
Alkaline phosphatase (U/L)	164.68 ± 102.44
Plasma albumin (g/L)	31.58 ± 5.09
WBC (10^9/L)	4.47 ± 5.31
ANC (10^9/L)	23.23 ± 33.74
CRP (mg/L)	79.37 ± 78.69
Procalcitonin (ng/mL)	4.63 ± 13.16
Aspergillus galactomannan	0.89 ± 2.91
1,3-β-D-glucan (Fungitell)	129.83 ± 103.29

ALT alanine transaminase, *ANC* absolute neutrophil count, *AST* aspartate transaminase, *CRP* C-reactive protein, *GGT* gamma-glutamyl transferase, *INR* international normalized ratio, *SD* standard deviation, *WBC* white blood cells

31 patients (43.7%) were healthy weight. There were 71.8% of participants who had proven infections, 8.5% of participants had a probable infection, and 19.7% participants had a possible infection. For patients with culture-confirmed fungal infections, the most common isolated organisms were *Aspergillus terreus* and *Aspergillus flavus*. There were 45.1% of participants with neutropenia at the beginning of treatment. The average voriconazole dose was (7.33 ± 3.76) mg/kg. Fifty-nine participants had an appropriate initial dose (defined as 6–9 mg/kg). Conversely, 12 participants had an inappropriate initial dose. Ten out of 12 participants had drug interactions with the following medications (clarithromycin, cyclosporine, rifampin, tacrolimus, acyclovir, and amlodipine) and the second dose was adjusted accordingly if the patient did not have an adequate response, was unable to tolerate the dose, or adequate trough concentrations were not achieved. One of the remaining two participants started with 5.64 mg/kg without justification and the second dose was adjusted to 7.11 mg/kg. No explanation was found for the second patient. Voriconazole doses were given every 12 h. Participants were classified into the following groups according to the possible drug interactions: participants with a drug inducer (1%), participants with a drug inhibitor (66%), participants with each of two inducers and an inhibitor (1%), and participants with no drug interaction (32%). Baseline demographics of the 71 patients are presented in Tables 1 and 2.

3.2 Voriconazole Pharmacokinetics/Pharmacodynamics

The first trough measurement was performed for all patients; however, the second trough measurement was performed for only 58 patients. The mean of the first trough plasma concentrations was 2.90 ± 4.22 mg/L (mean ± standard deviation) and ranged between 0.1 and 22.90 mg/L. The mean of the second trough plasma concentrations was 2.30 ± 3.3 mg/L (mean ± standard deviation) and ranged between 0.26 and 15.96 mg/L. Among the first measured trough concentrations, only 33.80% were within the therapeutic range (1–5 mg/L), 46.48% were below the therapeutic range, and 19.71% were above the therapeutic range. For the second measured trough concentrations, only 34.48% were within the therapeutic range, 53.45% were below the therapeutic range, and 12.07% were above the therapeutic range (Table 3). When assessing the correlation between voriconazole trough concentrations and patients demographics and variables (presence of drug interaction, dose, weight, C-reactive protein, albumin, alanine transaminase, and aspartate transaminase), only the dose was identified as a significant factor ($R^2 = 0.12$, $p < 0.05$). Patients taking enzyme inhibitors had higher trough concentrations (3.14 vs 2.4 mg/L) versus patients not taking enzyme inhibitors. However, results were not statistically significant ($p = 0.3$).

3.3 Clinical and Microbiologic Outcomes

For patients who received voriconazole for treatment, a clinical cure occurred in 73% (41 out of 56) of patients. The average first voriconazole trough concentration was 3.5 mg/L in patients who achieved a clinical cure and 2.4 mg/L in patients who did not achieve a clinical cure; however, the results were not statistically significant ($p = 0.39$). For patients who achieved a clinical cure, 53% had low trough

Table 3 Summary of voriconazole dosing and trough concentrations. Data are presented as mean ± SD unless otherwise specified

Parameter	Value
Dose (mg)	148.01 ± 81.08
Dose (mg/kg)	7.33 ± 3.76
Intravenous route, n (%)	40 (56.34%)
Oral route, n (%)	31 (43.66%)
Trough 1 ($N = 71$)[a]	2.9 ± 4.22 mg/mL
Less than the range (< 1 mg/L)	46.5%
Within the range (1–5 mg/L)	33.8%
More than the range (> 5 mg/L)	19.7%
Trough 2 ($N = 58$)[a]	2.3 ± 3.3 mg/mL
Less than the range (< 1 mg/L)	53.5%
Within the range (1–5 mg/L)	32.8%
More than the range (> 5 mg/L)	12.1%

SD standard deviation

[a]The total number of trough concentrations (including first and second trough concentrations) was 129 from 71 participants

concentrations < 1 mg/L, while for patients who did not achieve a clinical cure, 66% had low trough concentrations < 1 mg/L ($p = 0.38$). A microbiologic assessment was available for 44 patients, a cure occurred in 80% of them. The average first voriconazole trough concentration was 3.7 mg/L in patients who achieved a microbiological cure and 1.6 mg/L in patients who did not achieve a microbiological cure; however, the results were not statistically significant ($p = 0.23$). For patients who did not achieve a clinical cure, 54% had low trough concentrations of < 1 mg/L, while for patients who did not achieve a microbiological cure, 45% had low trough concentrations of < 1 mg/L ($p = 0.6$).

3.4 Toxicity

Suspected voriconazole toxicity occurred in nine patients. We had seven patients with elevations in liver enzymes (three times upper the normal limit) and five of them switched from voriconazole to liposomal amphotericin B. The average voriconazole trough concentrations in patients with elevated liver enzymes was 5.4 mg/L versus 2.6 mg/L in patients who did not have elevations ($p = 0.09$). Three of the seven patients who had elevated liver enzymes had trough concentrations > 5.5 mg/L. The other two toxicities were one patient with QT prolongation and another patient with a type II heart block. Both toxicities occurred in patients who received another drug with cardiac side effects. The patient who developed QT prolongation was taking voriconazole and clarithromycin, while the patient who developed the heart block was taking voriconazole and levofloxacin.

4 Discussion

To our knowledge, this is the first study describing a voriconazole PK/PD target achieved and evaluating the efficacy and safety of voriconazole for the pediatric population admitted in the PICU setting. In our analysis, voriconazole trough concentrations displayed very high variability with a coefficient of variation above 100%. Additionally, only 33% were within the therapeutic range at the first measured trough and 34% at the second measured trough. Similarly, some studies have reported that around 34–36% of pediatric patients achieved the target concentration during the first measured trough [31, 32]. Recent studies have shown a higher percentage (about 55%) of pediatric patients reaching the therapeutic trough concentrations with initial doses [8, 33].

In our study, we noticed patients with lower trough concentrations had a higher treatment failure, and patients with higher troughs had increased voriconazole toxicity. It is important to note that our study's results were not statistically significant. It could be because of the small sample size. Additionally, our patient population was critically ill pediatric patients, a heterogeneous group with high variability. This could have impacted our results. However, several previous studies in adult and pediatric patients have demonstrated this effect [9, 12, 13, 34, 35]. For example, in pediatric patients, the study by Choi et al. demonstrated that patients who experienced a treatment failure at week 6 of voriconazole treatment were more likely to have voriconazole concentrations below 1 mg/L (failure vs success, 42.1% vs 19.7%; $p = 0.012$) [36]. In another study, it was shown that steady-state voriconazole concentrations >3.6 mg/L were associated with an increased risk of hepatoxicity [37].

Given the high variability observed in voriconazole trough concentrations and its narrow therapeutic window, it is important to understand the variables impacting its pharmacokinetics to optimize its dosing. These factors include weight, age, cytochrome P450 2C19 enzyme inhibitors or inducers, genetic polymorphisms in cytochrome P450 2C19, and liver function [9]. In addition to the factors above, critical illness also impacts drugs pharmacokinetics [38]. For instance, several factors can affect drug distribution, such as endothelial dysfunction contributing to increased volume distribution, altered protein binding, fluid resuscitation, organ dysfunction, fluctuating regional blood flow, and cardiac output [39]. Healthcare practitioners need to consider all factors that might influence voriconazole pharmacokinetics for initial dosing. An approach that can handle these complexities to improve voriconazole dosing in pediatrics is model-informed precision dosing. This approach can be used for initial dosing

or to adjust doses when trough concentrations are available using a Bayesian approach. The advantage of this approach is that it can take all variables known to impact voriconazole pharmacokinetics into account to calculate individualized dosing. It can also be used to optimize the monitoring of voriconazole using Bayesian pharmacokinetics [40, 41]. However, limited studies still evaluate the clinical usefulness of using this tool in clinical practice.

Our study has some limitations. First, the nature of the retrospective design may have resulted in some missing or undocumented information. As a result, we could not establish a causal relationship between the outcomes and voriconazole. To account for this, we did employ the use of multiple logistic and linear regression analyses to assess the predictors of both clinical and microbiologic cures and to determine significant factors associated with trough concentrations. Second, this study was conducted at a single center. Therefore, the results may not be generalizable to other institutions. Third, our study included a limited sample size. However, our sample size was comparable to other PK/PD studies [3, 15].

5 Conclusions

We noticed voriconazole trough concentrations vary widely in critically ill pediatric patients and only a third of the patients achieved therapeutic concentrations with initial doses.

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Declarations

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Conflicts of interest/competing interests Khalid W. Taher, Razan Almofada, Sufyan Alomair, Ahmed A. Albassam, and Abdullah Alsultan have no conflicts of interest that are directly relevant to the content of this article.

Ethics approval The study was approved by the King Faisal Specialist Hospital & Research Centre Institutional Review Board (No. 2221242).

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material The King Faisal Specialist Hospital & Research Centre provided the study data; however, there are restrictions on its availability. These data were used under license for the current study and are not available publicly. However, upon reasonable request and with permission from the King Faisal Specialist Hospital & Research Centre, the authors could provide data.

Code availability Not applicable.

Authors' contributions RA and SA worked on the data collection. AAA and AA worked on the data analysis. All authors worked on designing the study, writing the manuscript, and reviewing the final version of the manuscript.

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