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Evaluation of Plasma Concentration and Hepatotoxicity of Voriconazole in Pediatric Patients following Hematopoietic Stem Cell Transplantation

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ABSTRACT

***Background*:** Invasive fungal infection is one of the most important causes of morbidity and mortality in pediatric patients undergoing Hematopoietic Stem Cell Transplantation (HSCT). Voriconazole as a broad-spectrum anti-fungal agent which has been used widely for prevention and treatment of invasive fungal infections in immunocompromised patients. Alteration in voriconazole plasma concentrations may be resulted in lack of efficacy and some adverse effects.

***Methods*:** This observational cohort study assessed the therapeutic plasma concentration of voriconazole and its relationship with hepatotoxic adverse effect in pediatric patients undergoing HSCT. Plasma concentration of voriconazole was measured by High-performance liquid chromatography (HPLC) assay with technique extracted from *Khoschsorur et al*.

***Results*:** Among a total of 14 pediatric patients, 5 patients received voriconazole orally and 9 patients received voriconazole intravenously. The median plasma concentration of voriconazole was 1.8 mcg/ml (range, 0.75-5.54 mcg/ml). There was no correlation between voriconazole dose and plasma concentration of voriconazole (p=0.166). Trough concentration of ≥ 4 mcg/ml was observed in 2 of 3 patients who experienced severe hepatic dysfunction. The plasma concentration of voriconazole did not significantly differ in patients with or without hepatotoxicity (p=0.406).

***Conclusions*:** Our study showed that trough levels of voriconazole were sub-therapeutic in 21.4% of children. Furthermore, hepatic enzyme abnormalities were observed in half of pediatric patients following voriconazole initiation during hospitalization. We didn't find any correlation between plasma concentration of voriconazole and the incidence of hepatotoxicity. We also didn't observe any correlation between voriconazole dose and plasma concentration of voriconazole, but the correlation was linear after exclusion of outlier data.

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Introduction

Invasive fungal infection is one of the most important causes of morbidity and mortality in pediatric patients undergoing Hematopoietic stem cell transplantation (HSCT) (1).

Voriconazole as a broad-spectrum triazole anti-fungal agent has been used widely for prevention and treatment of invasive fungal infections in immunocompromised

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patients including HSCT recipients (2).

Voriconazole is a zero degree antifungal agent with narrow therapeutic window which its plasma reference range is approximately between 0.5 and 5.5 mcg/ml. Some studies have demonstrated that the lower and higher plasma concentrations may be contributed to lack of efficacy and some adverse effects, respectively (3).

Voriconazole may cause some adverse effects, including hepatotoxicity, skin toxicity, neurologic toxicity and vision changes (such as photopsia, photophobia and color changes).Hepatotoxicity is one the major side effects of triazole antifungal agents particularly voriconazole which may be hepatocellular, cholestatic or both. However, there are limited data regarding hepatotoxicity of voriconazole in children (4).

It is also important to know that voriconazole is mainly metabolized by CYP2C19 and in less content by CYP2C9 and CYP3A4, therefore the genetic polymorphism of CYP2C19 may substantially affect the plasma concentration of this drug. In addition, many drugs which influence on these isoenzyme systems may interact with voriconazole and subsequently cause voriconazole plasma concentration alterations. Furthermore, other factors, including age, hepatic function and comorbidities may effect on voriconazole clearance. These multiple factors may cause inter and intra-individual variation in voriconazole plasma levels in children and adults. Several studies have shown that therapeutic drug monitoring (TDM) of voriconazole may be helpful to achieve target reference range and may improve antifungal efficacy and safety (3, 5). In addition, despite the wide use of voriconazole in children, the optimal dose has not been established in this population. It seems reasonable to use greater weight-based dosing in children because of higher hepatic clearance (6).

To our knowledge, monitoring of voriconazole plasma concentration has not been done previously in Iranian pediatric patients receiving voriconazole. According to limited data about the therapeutic plasma concentration of voriconazole and its relationship with hepatotoxic adverse effect, we conducted an observational cohort study in Iranian pediatric HSCT recipients receiving voriconazole.

Methods

Patients and drug administration:

This was an observational cohort study performed from February 2015 through July 2016 at Hematology-Oncology and Stem Cell Transplantation center of Tehran *Shariati* Hospital. A total of 14 Iranian pediatric patients (5 to 12 years of age) undergoing oral or intravenous (IV) voriconazole therapy for prevention or treatment of invasive fungal infection following HSCT enrolled in the study. The patient's age, gender, weight, underlying disease, routes of voriconazole administration, voriconazole doses and hospitalization days after voriconazole initiation were recorded. Oral voriconazole administrated in fasting condition. From Patients received voriconazole orally, nobody had gastrointestinal disorder, diarrhea or unstable hemodynamic condition. Among the 14 patients, nobody had pre-existing liver dysfunction before treatment initiation of voriconazole.

Measurement of voriconazole plasma concentration:

Venous blood sample was collected in heparinized tube 4 day and 9 day after initiation of voriconazole before next dose. The blood samples were centrifuged (3000 rpm, 4 °C, 10 min) and the plasma transferred to 2 ml polypropylene micro-tubes. The plasma samples were stored in -70 °C until assay. Plasma concentration of voriconazole was measured by High-performance liquid chromatography (HPLC) assay with technique extracted from *Khoschsorur et al.,*(7).

Monitoring for hepatic dysfunction:

Hepatic laboratory tests (including AST, ALT, ALP and total bilirubin) were collected and recorded in special sheet throughout voriconazole therapy. The severity of voriconazole induced liver dysfunction was graded as described by the National Cancer Institute (NCI) of the National Institutes of Health (version 4.0: CTCAEv4). Grades 3 and 4 were defined as severe hepatic dysfunction (table 1). *Naranjo Scale* was used by 2 independent investigators to determine whether hepatic dysfunction is actually due to voriconazole rather than other factors. Probability in *Naranjo Scale* was categorized as definite, probable, possible and doubtful. Doubtful cases were not considered as voriconazole induced adverse effect.

Statistical analysis

Statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) software (ver. 10; SPSS Inc.). The Mann-Whitney U-test was used for comparison of differences in voriconazole concentration between oral and IV groups. This test was also used for comparison of differences in voriconazole concentration between patients with or without voriconazole-induced hepatotoxicity. The Spearman rank test was used for evaluation of the correlation between voriconazole doses and plasma concentration of voriconazole. P values less than 0.05 were considered significant.

Results

Among 14 patients included in this study, 5 patients received voriconazole orally and 9 patients received voriconazole intravenously. Demographic and clinical characteristics of patients are summarized in table 2. The median hospitalization days after initiation of voriconazole were 13 days (range, 7-22 days). Plasma concentration of voriconazole was measured in steady state (at least 4 days after initiation of voriconazole).The

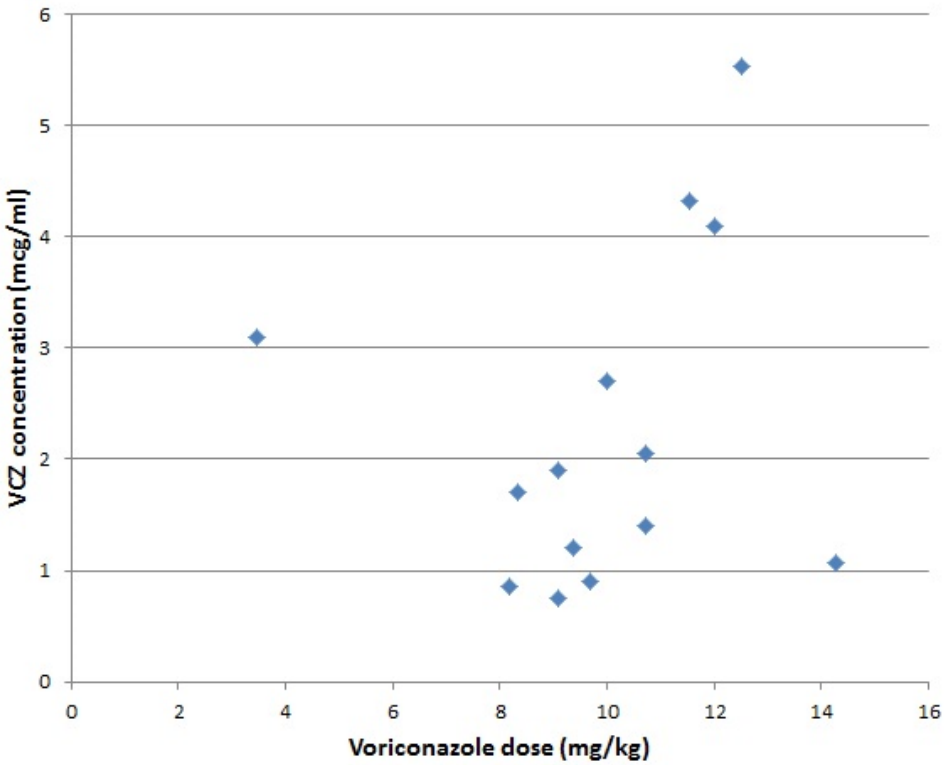

Figure1. correlation between plasma concentration of voriconazole and voriconazole dose. There was no significant correlation (ρ=0.392, p=0.166) VCZ: voriconazole.

median plasma concentration of voriconazole was 1.8 mcg/ml (range, 0.75-5.54 mcg/ml). Trough levels of less than 1 mcg/ml were detected in three patients (21.4%). Trough plasma concentrations of greater than 5 mcg/ml were detected in only one patient (7.14%). The plasma levels of voriconazole didn't differ significantly between oral and IV groups (p=0.739). There was no correlation between voriconazole dose and plasma concentration of voriconazole (p=0.166) (Figure 1).

Among 14 patients, seven patients experienced hepatic dysfunction. Data about voriconazole level and its relationship with hepatotoxicity was shown in table 3. The median time of hepatotoxicity onset after voriconazole initiation was 5 days (range, 4-9 days). Of the seven patients with hepatic dysfunction, severe hepatic dysfunction was observed in 3 patients. Pattern of hepatic dysfunction were hepatocellular (n=4), cholestatic (n=1) or mix (n=2). Trough concentration of ≥ 4 mcg/ml was observed in 2 of 3 patients who experienced severe hepatic dysfunction. Severe hepatic dysfunction didn't occur in patients with voriconazole levels of < 3.1 mcg/ml. All patients without hepatic dysfunction had voriconazole level of ≤ 4.32 mcg/ml. The plasma concentration of voriconazole did not significantly differ in patients with or without hepatotoxicity (p=0.406). Although the difference between plasma concentration of voriconazole in patients who experienced severe hepatic dysfunction and patients without hepatic dysfunction was not statistically significant (p=0.053), the median plasma level of voriconazole in patients with severe hepatic dysfunction (4.10 mcg/ml) was markedly higher than patients without hepatic dysfunction (1.40 mcg/ml) (Figure 2). Voriconazole was discontinued due to hepatotoxicity in all three patients with severe hepatotoxicity.

Our outlier data contributed to the obese child (Wt=58kg, 11 years old) which received 3.45 mg/kg and had plasma concentration of 3.1 mcg/ml.

Discussion

This small study showed that there is significant intra-patient variability of voriconazole plasma concentration in pediatric patients following HSCT. We also found that the incidence of voriconazole induced hepatotoxicity in pediatric patients is as high as 50% during hospitalization. There is controversy about the optimal dose of voriconazole in pediatric patients (8). Neely et al in their study demonstrated that the plasma concentration of voriconazole in 34% of pediatric patients

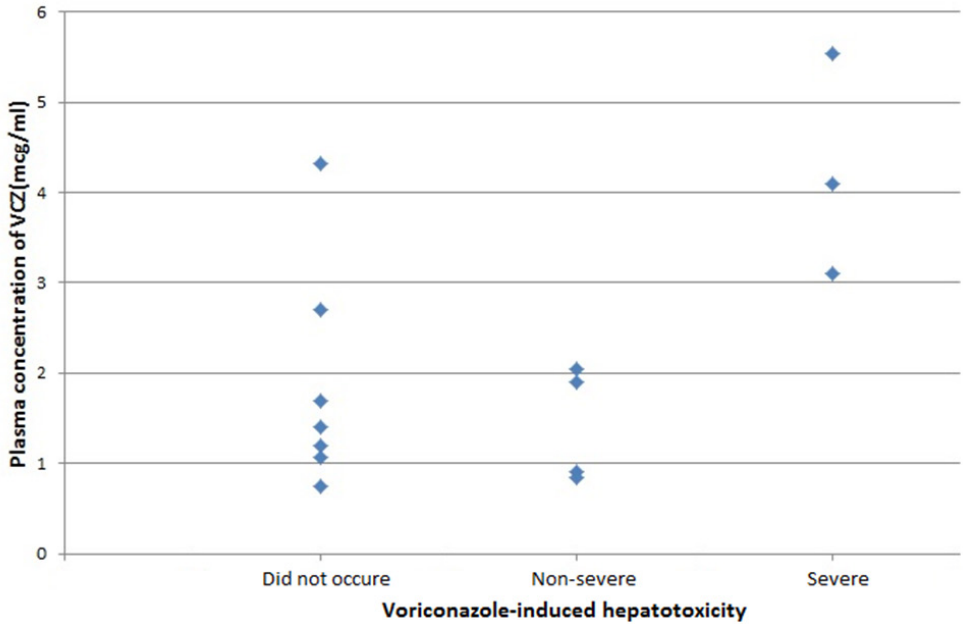

Figure2. Voriconazole-related hepatotoxicity and plasma concentration of voriconazole .VCZ: voriconazole.

>2 years old were less than the therapeutic range (less than 1 mcg/ml) while receiving standard dose (9). Palacin et al also showed children required higher voriconazole dose in comparison with adults to achieve therapeutic plasma concentration. They showed that the median appropriate dose of voriconazole in children <5 years old and children ≥5 years were 38 mg/kg/day and 15 mg/kg/day, respectively which were much higher than the standard adult dose (10). Gerin et al found that doses as high as 20 to 32 mg/kg/day were required to achieve therapeutic range in some immunocompromised pediatric patients receiving voriconazole (11). Our patients were between 5 and 12 years of age and treated with extensive doses of voriconazole (3.45 – 14.28 mg/kg/day). Trough levels of voriconazole were sub-therapeutic in 21.4% of children while receiving doses between 8.19 mg/kg/day and 9.67 mg/kg/day. It seems the higher dose required of voriconazole in children is contributing to a higher rate of clearance in this population. Furthermore bioavailability of oral voriconazole in children is much lower than adults. Initial pharmacokinetic studies in children demonstrated that standard adult weight based dose of voriconazole resulted approximately 3 fold lower plasma concentration in this population (6). We also didn't find any correlation between voriconazole dose and plasma concentration, but the correlation was linear after exclusion of outlier data. Our outlier data contributed to the obese child (wt.=58 kg, 11 years old) which received 3.45 mg/kg and achieved plasma concentration of 3.1 mcg/ml. Similarly, it has been found in the first systematic study that the children voriconazole pharmacokinetic was linear in contrast to adult pharmacokinetic (12).

Hepatotoxicity is one of the most important adverse effects of voriconazole. The incidence of liver enzyme abnormalities following treatment with voriconazole was between 6.3 to 51% in different studies. Discontinuations of voriconazole therapy may be up to 34% due to hepatotoxicity (13). There are conflicting results about the correlation of hepatotoxicity with plasma concentration of voriconazole. Data regarding voriconazole induced hepatotoxicity in children is limited (6). In our study, Hepatic enzyme abnormalities were observed in 50% of pediatric patients following voriconazole initiation during hospitalization. Among patients who received voriconazole, therapy was discontinued in 21.4% of patients due to hepatotoxicity. Therefore, it seems reasonable to monitor liver enzyme tests frequently after initiation of voriconazole. It is important to note that differential diagnosis of voriconazole induced hepatotoxicity from hepatic GVHD is important in HSCT recipients. Presence of liver enzyme abnormalities concomitant with clinical evidence of other organ involvement with GVHD possibly is due to hepatic GVHD. In addition, bilirubin rise is more predominant in hepatic GVHD, but the pattern of voriconazole induced hepatotoxicity usually is hepatocellular (14). In our patients, abnormality in aminotransferase enzymes was observed in 85.71% of hepatotoxic cases. We didn't observe any correlation between plasma concentration of voriconazole and incidence and severity of hepatotoxicitywhich may be due

Table 1. Hepatic dysfunction grades as described by NCI.

FEATURE	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
ALT	Normal	>1.0-2.5	>2.5-5.0	>5.0-20	>20
AST	Normal	>1.0-2.5	>2.5-5.0	>5.0-20	>20
Alkaline Phosphatase	Normal	>1.0-2.5	>2.5-5.0	>5.0-20	>20
GGT	Normal	>1.0-2.5	>2.5-5.0	>5.0-20	>20
Bilirubin	Normal	>1.0-1.5	>1.5-3.0	>3.0-10	>10

The values expressed the multiples of the upper limit of the normal range (ULN). ALT: alanine aminotransferase, AST: aspartate aminotransferase, GGT: gamma-glutamyl transferase, NCI: National Cancer Institute

Table 2. Demographic and clinical characteristics of patients (n=14).

Characteristics	Values
Sex	
Male	6
Female	8
Age (years)	
Median (range)	7.5 (5-12)
Weight (kg)	
Median (range)	21 (13-58)
Underlying disease	
ALL	7
AA	2
FA	2
AML	1
T	2
Route of administration	
IV	9
Oral	5
Voriconazole dose (mg/kg/day)	
Median (Range)	9.83 (3.45-14.28)
Voriconazole concentration (mcg/ml)	
Median (Range)	1.8 (0.75-5.54)

AA:Amyloid A, ALL:acute lymphocytic leukemia, AML:Acute myelogenous leukemia, FA:Fanconi anemia, IV: intravenous

Table 3. Voriconazole concentration and hepatotoxicity.

Voriconazole concentration (mcg/ml)	Voriconazole induced hepatotoxicity (%)	Voriconazole induced severe hepatotoxicity (%)
< 1.5	50 (3/6)	0 (0/6)
1.5 - 4	40 (2/5)	20 (1/5)
> 4	66.67 (2/3)	66.67 (2/3)

to small sample size and/or outlier data. The outlier data have possibly been due to the absence of the equivalent hospitalization period after voriconazole initiation.

This study had some limitations. In addition to the small sample size, CYP2C19 genetic polymorphism as main elimination metabolic pathway of voriconazole was not assessed. It has been demonstrated that CYP2C19 polymorphism can cause significant intra-patient

variability in plasma concentration of voriconazole. Furthermore, as a limitation, all patients didn't receive uniformly equal initial weight based dose.

In conclusion, our study showed that trough levels of voriconazole were sub-therapeutic in 21.4% of children. Furthermore, hepatic enzyme abnormalities were observed in half of pediatric patients following voriconazole initiation during hospitalization. We didn't find any correlation between plasma concentration of voriconazole and the incidence of hepatotoxicity; it may be due to small sample size and/or outlier data. We also didn't observe any correlation between voriconazole dose and plasma concentration, but the correlation was linear after exclusion of outlier data.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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