Original Article

Impact of *CYP2C19* Polymorphisms on Serum Concentration of Voriconazole in Iranian Hematological Patients

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ABSTRACT

Objective: This study aimed to determine the portion of Iranian patients who attain therapeutic serum concentrations of voriconazole (VRCZ) following administration of fixed doses. In addition, the effect of *CYP2C19* polymorphism on serum levels of VRCZ was also investigated. **Methods:** Forty-eight adult patients of Iranian origin with hematologic malignancies, who received VRCZ for treatment of invasive aspergillosis, were recruited into the study. Blood samples were drawn at day 4 of treatment to measure trough drug concentrations and determine genotyping of *CYP2C19* polymorphisms of each patient. High-performance liquid chromatography method was used for measuring VRCZ serum level and *CYP2C19* polymorphisms were conducted by Sanger sequencing. Demographic and clinical characteristics of patients alongside with *CYP2C19* polymorphisms were assessed to determine the effective factor/s on VRCZ serum concentration. **Findings:** Seventy-three percent of patients achieved therapeutic serum concentrations of VRCZ with administration of usual fixed doses in clinical practice. There was no correlation between weight-adjusted dose and serum concentrations of VRCZ. Mean serum levels were significantly different neither in genders nor in routes of administrations. Extensive and ultrarapid metabolizers (URMs) comprised 48.7% and 21.6% study population, respectively. *CYP2C19* polymorphism dramatically influenced the trough levels of VRCZ, so that all patients with subtherapeutic levels expressed URM phenotype. **Conclusion:** With respect to high incidence of URM phenotype in Iranian population, and observed association of this phenotype with sub-therapeutic levels in our study, performing therapeutic drug monitoring is strongly recommended for all patients.

Keywords: *CYP2C19 polymorphism, Iran, therapeutic drug monitoring, Voriconazole*

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Introduction

Invasive fungal infections are increasingly diagnosed as a contributing factor in morbidity and mortality of immunocompromised patients. Voriconazole (VRCZ), a broad spectrum triazole, is widely used for the treatment of these kinds of infections. It is currently considered the first-line treatment of invasive aspergillosis.[1]

Multiple factors including age, immune status of the patient, site of infection, comorbidities, microorganism susceptibility, and proper use of antifungals influence the treatment response.[2] The latter is the only modifiable factor in clinical settings.

VRCZ exhibits nonlinear pharmacokinetics (PK) behavior in adults. A well-documented correlation does exist between trough concentration of VRCZ and its therapeutic or adverse effects. Even though different limits for upper and lower concentrations of

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VRCZ have been recommended, there is a growing consensus on therapeutic range of 1.0–5.5 mg/L.[3-5] Inter- and intra-subject variations in the PK of VRCZ have been reported in previous studies.[2] Age, gender, comedications, route of administration, food, and genetic variation are the most important factors affecting PK of VRCZ. The hepatic metabolic clearance is the predominant elimination pathway of VRCZ and only 2% of the drug is excreted unchanged in the urine. *CYP2C19* plays the major role in the hepatic metabolism of the drug and other enzymes such as 3A4 and 2C9 are involved to a lesser extent.[2]

Polymorphism of *CYP2C19* is the most crucial factor causing intersubject variations in dose-concentration relationship. *CYP2C19*1* homozygotes exhibit extensive metabolizer (EM) phenotype with normal enzyme activity. *CYP2C19*2*2*, *CYP2C19*2*3*, and *CYP2C19*3*3* which contain the defective alleles of *CYP2C19*2* and *CYP2C19*3* are associated with decreased enzyme function. Individuals bearing these genotypes are classified as having the poor metabolizer (PM) phenotype. The novel variant *CYP2C19*17* with corresponding genotypes of *CYP2C19*1*17* and *CYP2C19*17*17* is associated with ultrarapid metabolizer (URM) phenotype. Individuals carrying the *CYP2C19*1*2* or *CYP2C19*1*3* are defined as intermediate metabolizers (IM).[6] Patients bearing nonwild-type alleles may experience supra- or sub-therapeutic drug concentrations following treatment with conventional doses.

Significant dissimilarity was observed in distribution of *CYP2C19* polymorphisms in different racial groups. The incidences of PM phenotype were reported to be 15%–20% in Asian versus 3%–5% in Caucasians.[7] In this regard, pharmacogenetic-pharmacokinetic studies can be helpful in optimization of treatment with narrow therapeutic index drugs such as VRCZ. It has been demonstrated that supra-therapeutic concentrations of VRCZ is associated with increased risk of some adverse effects such as neurotoxicity and hepatotoxicity. On the other hand, sub-therapeutic levels of VRCZ may contribute to treatment failure and increased risk of fungal resistance.[8] Therefore, it seems that therapeutic drug monitoring could be considered to optimize treatment with VRCZ.

This paper attempts to show which portion of Iranian patients achieve therapeutic serum concentrations of VRCZ following administration of usual doses used in clinical practice in hematology-oncology ward. Based on literature review conducted in biomedical databases PubMed, Web of Science, Scopus, and Google Scholar, the present study is the first published research which investigates the impact of *CYP2C19* polymorphisms on VRCZ serum concentrations in Iranian population.

Methods

This cross-sectional study was conducted between May 2015 and Oct 2016 in Hematology-Oncology and Stem Cell Research Center (HOSCRC) of Shariati Hospital affiliated with Tehran University of Medical Sciences (TUMS), Tehran, Iran. The study protocol was approved by the Ethics Committee of TUMS (Ethics Code: IR.TUMS.REC.1394.857).

All patients of Iranian racial origin, older than 18 years of age, who received VRCZ for treatment of invasive fungal infections were recruited. All patients had normal liver function according to Child-Pugh score.[9] The patients were excluded from the study either if they needed treatment with medications known to alter serum levels of VRCZ such as corticosteroids and proton pump inhibitors,[10] or if VRCZ therapy was interrupted within 4 days of initiation. In addition, patients were excluded if they needed switching between dosage forms when they were on the maintenance doses of VRCZ. The patients were explained verbally and written informed consents were obtained from all participants before enrollment. A total of 48 subjects were included in the study.

VRCZ (Pfizer, Illertissen, Germany) 400 mg intravenous (IV) twice daily was administered on the first day and 200 mg twice daily oral PO or IV thereafter. The drug was administered orally if the patient could tolerate oral administration and there was no condition compromising oral absorption such as mucositis, diarrhea, graft-versus-host disease of gastrointestinal (GI) tract, or hemodynamic instability. All patients who received IV VRCZ had creatinine clearance ≥50 ml/min. A clinical pharmacist verified patients' compliance with oral medication. Concomitant medications were recorded daily, and in the case of interactions which led to altered VRCZ concentrations, the patient was excluded. All subjects had 5 ml of blood samples drawn for the measurement of VRCZ blood concentrations at day 4 of treatment when the concentration reached steady state. Samples were taken 30 min before administration of the next dose. Serum concentrations of 1.0–5.5 mg/L were considered as therapeutic range (3–5). A separate blood sample was taken at the same time to detect *CYP2C19* polymorphisms.

To determine *CYP2C19* polymorphisms, 5 ml of venous blood was drawn from each patient, collected in ethylenediaminetetraacetic acid tube, and stored at −20°C. DNA extraction from blood leukocytes was performed using the YT9040 blood DNA extraction kit (Yekta Tajhiz Azma, Iran). Quality and quantity of extracted DNA were evaluated by spectrophotometry using Nanodrop ND-1000 (Nanodrop Technologies,

Wilmington, DE, USA). Samples were stored at −20°C until genotyping and polymerase chain reaction (PCR) running. The genotyping of *CYP2C19*2 (*681G>A), *CYP2C19*3 (*636G>A), and *CYP2C19*17* (-3402C>T) polymorphisms was implemented by Sanger Sequencing assay. PCR was conducted in a thermocycler (Eppendorf, Humburg, Germany) using a method published by Al-Jenoobi *et al*.[11] The PCR amplicons were sequenced on an ABI 3700 sequencer (Kosar Company, Iran). The final analysis was done using the FinchTV program and NCBI website (http://blast.ncbi.nlm.nih.gov/Blast.cgi).

VRCZ serum concentration was determined by high-performance liquid chromatography method. Plasma samples were collected in 5ml heparinized tube and centrifuged at 3000 rpm for 10 min at 4°C. Processed samples were stored at −70°C until assay time. Plasma concentration of VRCZ was measured according to the method developed by Khoschsorur *et al*.[12] Ketoconazole (Merck, Germany), as internal standard, was prepared as 30 mg/L in 70% methanol solution and frozen at −20°C.

Extraction was performed by adding 5 mL of extraction solvent heptane-isoamyl alcohol (90:10 [vol/vol]). The mobile phase consisted of phosphate buffer 0.05 M (pH = 6.0, adjusted with KOH 1 M), acetonitrile, and methanol (35:45:20 [vol/vol/vol]) and was run through C18 column (SB-C18, 250 mm × 4.6 mm, Zorbax, US) by rate of 1.7 ml/min. Detection wavelength was fixed at 255 nm. Retention times for VRCZ and ketoconazole were 2.56 and 4.97 min, respectively. Chromatography was performed using Unicam Crystal 200 (UK).

Normal distribution of data was assessed using Shapiro–Wilk test. Qualitative data were reported as frequency (%) and quantitative data as mean ± standard deviation. The effect of gender and route of administration on serum concentrations of VRCZ was explored by Mann–Whitney test. Spearman rank correlation was used to test correlation between drug dose and serum concentrations. With regard to normal distribution of dose per kg of body weight, comparison of weight-adjusted doses based on categorized concentrations (concentrations <1 vs. ≥1 mg/L) was done using independent samples *t*-test. Kruskall–Wallis test was run to compare VRCZ concentrations in various phenotypes. Analysis was performed using SPSS statistics software (Version 21.0. IBM Corp. Armonk, NY, USA). $P < 0.05$ was considered as significant difference in all the tests.

Results

Forty-eight patients were recruited into the study. Seven subjects were excluded because of VRCZ discontinuation before day 4 of treatment. In addition, three patients were excluded because of switching between routes of administration and one because of interaction with concomitant corticosteroid use. Finally, 37 subjects were included in statistical analysis. Demographic and clinical characteristics of patients are detailed in Table 1.

The mean trough concentration of VRCZ was 2.9 ± 1.7 mg/L in our patients. Serum levels of VRCZ stratified based on gender, route of administration, and phenotype are presented in Table 2.

With the fixed dose that had been administered to all patients, serum levels were in therapeutic range in 73.0% of them. Supra- and sub-therapeutic levels were observed in 10.8% and 16.2% of patients, respectively. All subjects with subtherapeutic levels were URMs. In addition, none of patients with supratherapeutic levels expressed URM

Table 1: Demographic and clinical characteristics of hospitalized patients in hematology-oncology ward (*n*=37)

Variable (unit)	Value
Age (years)	34.6±11.2
Weight (kg)	60.6±13.1
Gender	
Female	18 (48.7)
Male	19 (51.3)
Underlying disorder	
AML	22 (59.5)
HSCT	13 (35.1)
CLL	1 (2.7)
Burkitt lymphoma	1 (2.7)
Administration route	
Oral	17 (46)
Intravenous	20 (54)
Dose (mg/kg/day)	
Total	6.5±0.9
Female	6.8±0.9
Male	6.3±0.8
Oral	6.5±0.9
IV	6.6±0.9
Allele	
*CYP2C19*1*	53 (71.6)
*CYP2C19*2*	13 (17.6)
*CYP2C19*3*	0
*CYP2C19*17*	8 (10.8)
Phenotype/genotype	
EM/*CYP2C19*1*1*	18 (48.7)
URM/*CYP2C19*1*17*	8 (21.6)
IM/*CYP2C19*1*2*	9 (24.3)
PM/*CYP2C19*2*2*	2 (5.4)

Data are presented as mean±SD, or *n* (%), where applicable. SD=Standard deviation, AML=Acute myelogenous leukemia, HSCT=Hematopoietic stem cell transplantation, CLL=Chronic lymphoblastic leukemia, EM=Extensive metabolizer, URM=Ultra-rapid metabolizer, IM=Intermediate metabolizer, PM=Poor metabolizer, IV=Intravenous

phenotype. Three out of 4 patients with supratherapeutic levels exhibited PM or IM phenotypes. Serum levels did not correlate with weight-adjusted dose of VRCZ (P = 0.2, r = −0.2) [Figure 1]. Of note, administered mg/kg dose was not significantly different in patients with subtherapeutic troughs (<1 mg/L) compared to those with higher concentrations (≥1 mg/L) (P = 0.09).

Table 2: Voriconazole dose and serum level at steady state classified based on gender, route of administration, and phenotype of *CYP2C19* in hematology-oncology ward (*n*=37)

Variable	VRCZ serum concentration (mg/L)			*P*
	<1.0	1.0-5.5	>5.5	
Gender				0.6
Female	3 (16.7)	12 (66.6)	3 (16.7)	
Male	3 (15.8)	15 (78.9)	1 (5.3)	
Route of administration				0.3
Oral	3 (17.6)	11 (64.8)	3 (17.6)	
Intravenous	3 (15)	16 (80)	1 (5)	
Phenotype of *CYP2C19*				<0.001
PM	0	1 (50)	1 (50)	
IM	0	7 (77.7)	2 (22.3)	
EM	0	17 (94.4)	1 (5.6)	
URM	6 (75)	2 (25)	0	
Total	6 (16.2)	27 (73.0)	4 (10.8)	

Dose comparison based on gender and route of administration				
			Mean Dose±SD	*P*
Variable	Route	IV	6.6±0.9	0.6
		p.o.	6.5±0.9	
	Gender	Male	6.3±0.8	0.1
		Female	6.8±0.9	

Data are presented as mean±SD, or *n* (%), where applicable. SD=Standard deviation, VRCZ=Voriconazole, EM=Extensive metabolizer, URM=Ultra-rapid Metabolizer, IM=Intermediate metabolizer, PM=Poor metabolizer, IV=Intravenous

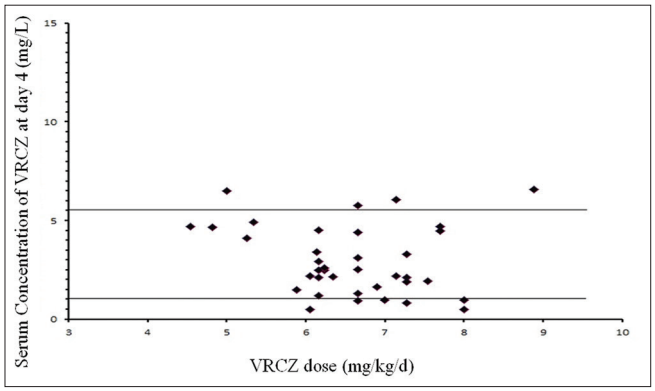

Figure 1: Voriconazole serum concentrations compared to weight-adjusted dose of drug. Values between the two horizontal lines represent concentrations in the therapeutic range (N = 37). Measured serum levels were not correlated with dose of medication based on weight (P = 0.2, r = −0.2)

There was no significant difference in serum concentrations between males and females (P = 0.6). Moreover, serum concentrations were not significantly different in oral versus IV administration (P = 0.3). It should be noted that the mean dose of VRCZ was not significantly different in males/females (6.3 ± 0.8 vs. 6.8 ± 1.0, respectively, P = 0.1) and IV/PO (6.7 ± 0.9 vs. 6.5 ± 0.9, respectively, P = 0.6) administrations when it was adjusted based on body weight.

Mean serum concentrations of VRCZ on the 4th day of treatment were 4.78 ± 0.97, 3.37 ± 1.5, and 2.94 ± 2.13 for IMs, EMs, and URMs, respectively, which indicated a significant difference (P < 0.00001). Pairwise comparisons of phenotypes also revealed significant differences (IM vs. URM, P < 0.0001; IM vs. EM, P < 0.001; URM vs. EM, P < 0.001). Only 2 patients exhibited PM phenotype in our study and were excluded from Kruskall-Wallis analysis. Figure 2 depicts serum levels based on patients' phenotypes.

Discussion

VRCZ, a triazole agent, is recommended as the first line in treatment of aspergillosis.[1] With respect to nonlinear PK and narrow therapeutic index of VRCZ, therapeutic drug monitoring has been recommended to optimize treatment efficacy and prevent adverse drug reactions.[2] Besides various factors affecting pharmacokinetic parameters of the drug, polymorphic variations in *CYP2C19* has been cited as a major contributing factor.[13,14] Therapeutic drug monitoring of VRCZ, although performed vastly in various regions of the world, is not the current standard of practice in Iran. The goal of this study was to determine which portion of patients attain therapeutic ranges following administration of fixed doses currently used in

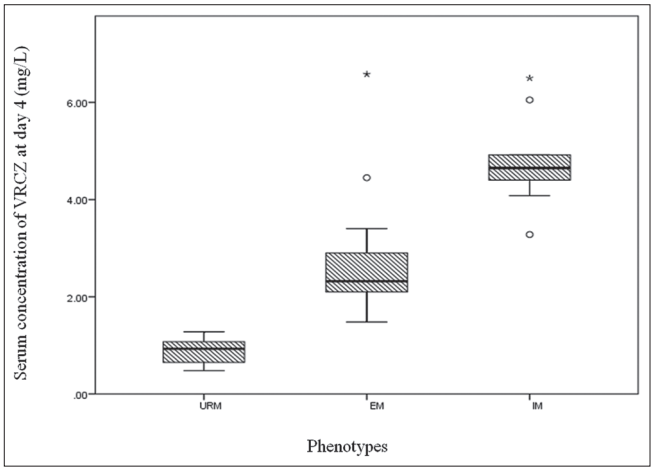

Figure 2: Comparison of serum concentrations of voriconazole in ultra-rapid, extensive, and intermediate metabolizer phenotypes. There was a significant difference in serum levels in different phenotypes (P < 0.00001)

routine practice and also to delineate factors affecting achievement of desired trough concentrations.

In our study, we did not find a correlation between weight-adjusted dose of VRCZ and achieved serum concentrations in the way that administration of higher weight-based doses did not consistently result in higher trough concentrations. The results showed that patients with subtherapeutic levels did not received lower weight-based doses compared to those with higher trough concentrations. Therefore, it seems that trough concentration is disproportionally affected by dose modification. The present findings seem to be consistent with other research which found that 1.7-fold increase in IV VRCZ dose and 2-fold increase in oral dose resulted in 3.1 and 3.9-fold increase in area under the curve (AUC_τ), respectively.[15] Our finding is in agreement with Chu *et al.* who revealed that serum levels were not correlated with dose of VRCZ.[16] On the other hand, in the study by Hope *et al.*, intersubject variations up to 100-fold were observed in immunocompromised pediatric patients receiving the same dose of VRCZ.[17] Therefore, administration of fixed doses or even weight-adjusted doses may result in supra- or sub-therapeutic levels. These findings necessitate individualizing therapy based on trough levels of VRCZ.

The mean concentration of VRCZ was not affected by route of administration in our patients and subtherapeutic levels were equally observed in each route of administration. It could be anticipated with respect to near-complete bioavailability of VRCZ (F = 96%).[2] This result may be explained by the fact that in our study, patients who received oral dosage form were well-selected with no factor compromising oral bioavailability including hemodynamic instability, graft versus host disease of the GI tract, diarrhea, mucositis, and vomiting. This finding is in agreement with Matsumoto *et al*. who showed that there was no correlation between serum levels <1 mg/L or ≥1 mg/L and route of administration.[18] Purkins *et al*. demonstrated that C_{max} of VRCZ after oral administration reduced to 62.7%–89.6% of IV values.[15] Since previous studies have demonstrated that both safety and efficacy of VRCZ are associated with trough concentrations,[2-6] the clinical significance of this finding remains under question. These findings generally suggest that in the absence of factors interfering with oral absorption, oral dosage form could be an acceptable alternative to IV dosage forms without compromising efficacy. This finding is interesting with regard to easier administration and reduced cost of treatment with oral dosage form.

Mean serum concentration of VRCZ did not differ significantly between the two genders. However, far too little attention has been paid to the effect of gender on pharmacokinetic parameters of VRCZ. Up to our knowledge, gender has not been included in model-based simulations for VRCZ which are published to date.[6,19] In the Pfizer VRCZ Advisory Committee Briefing Document, it was claimed that C_{max} and AUC values in young females were 83% and 113% higher than young males, respectively.[20] Based on available evidence to date, the exact role of gender in pharmacokinetic parameters of VRCZ remains unclear.

Another important finding in this study was that polymorphism of *CYP2C19* was the major factor contributing to trough level of VRCZ. As stated above, comparisons also revealed significant difference among the three reported phenotypes. There are similarities between the results obtained in this study and those described by Hassan *et al.* and Wang *et al.*[6,21] All patients with subtherapeutic concentrations in the current study carried *CYP2C19*17* allele which confers URM phenotype. This is comparable with values reported by Hassan *et al*. which showed that 80% of patients with subtherapeutic concentrations expressed this allele.[21] In the model-based simulation by Wang *et al*. in Chinese population, VRCZ dosing based on *CYP2C19* phenotype was recommended for all patients. Their findings suggested that 200 mg VRCZ twice daily PO for PMs and 300 mg PO twice daily for non-PMs would be both safe and effective.[6]

Previous studies reported significant differences in distribution of *CYP2C19* allele variants in various racial groups.[22] Based on the research by Farjadian *et al.*, all ethnic groups in Iran are genetically related to eastern Mediterraneans.[23] The incidence of *CYP2C19*17*, the allele associated with URM phenotype, is higher in this population compared with Asians (15%–25% vs. 0.15%–0.44%).[22,24] With regard to ethnic diversity in Iran, epidemiological studies have been conducted to determine the distribution of *CYP2C19* allele variants in different ethnic groups.[25-27] A recent study by Payan *et al.* revealed that 21.7% of Iranian population were carriers of *CYP2C19*17* and 34.4% of studied population exhibited *CYP2C19*1*17* and *CYP2C19*17*17* genotypes.[22] Considering the high incidence of URM phenotype in Iranian population and considerable effect of this phenotype on serum levels of VRCZ, it is possible that numerous patients face subtherapeutic serum levels with administration of the current recommended doses. Therefore, risk of treatment failure may be unexpectedly high which is associated with increased mortality rate and prolongation of hospital stay with subsequent financial burden. Taking into account all of above-mentioned affecting factors, measurement of VRCZ trough

concentrations seems to be the most practical way to enhance treatment efficacy and prevent failure.

Intrasubject variations with VRCZ treatment have also been reported besides intersubject variations.[5] The current study was unable to analyze intrasubject variations. Since a single measurement of trough concentration may not represent the concentration experienced throughout the treatment period, serial monitoring is mandatory.

In the future investigations, it might be possible to conduct serial level measurements in larger sample size to generate model-based simulations specific to Iranian population. Moreover, it would be interesting to investigate the effects of VRCZ serum concentrations on clinical response and occurrence of adverse effects in Iranian population.

Authors' Contribution

Sholeh Ebrahimpour contributed in study design, sampling, genotyping, analysis, and manuscript preparation. Molouk Hadjibabaie, Soha Namazi, and Mehdi Mohammadi contributed in the study design and manuscript revision. Mohsen Nikbakht performed genotyping and manuscript revision. Ardeshir Ghavamzadeh was involved in sampling and manuscript revision. Hamidreza Taghvaye Masoumi was also involved in the study design and sampling.

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Conflicts of interest

There are no conflicts of interest.

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