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Voriconazole-related severe adverse events: clinical application of therapeutic drug monitoring in Korean patients☆

Si-Hyun Kim [a], Dong-Seok Yim [b], Su-Mi Choi [a], Jae-Cheol Kwon [a], Seunghoon Han [b], Dong-Gun Lee [a,*], Chulmin Park [c], Eun-Young Kwon [c], Sun Hee Park [a], Jung-Hyun Choi [a], Jin-Hong Yoo [a]

[a] Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, South Korea
[b] Department of Pharmacology, College of Medicine, The Catholic University of Korea, Seoul, South Korea
[c] Catholic Research Institutes of Medical Science, College of Medicine, The Catholic University of Korea, Seoul, South Korea

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SUMMARY

Background: Voriconazole is a triazole agent with excellent antifungal activity against *Aspergillus* species. However, despite its potential advantages, the occurrence of unpredictable toxicities might be critical in immunocompromised patients. The aim of this study was to analyze risk factors for voriconazole-related severe adverse events (SAEs).

Methods: This prospective observational study was conducted in Korean patients with hematological malignancies and invasive aspergillosis on intravenous voriconazole therapy between June 2008 and April 2009.

Results: Of the 25 patients enrolled, eight (32%) showed voriconazole-related SAEs, which included hepatotoxicities ($n = 5$), cardiac tachyarrhythmias ($n = 2$), and neurotoxicity ($n = 1$). Sex, age, underlying hematological malignancies, voriconazole dose, the co-administration of a proton pump inhibitor, and CYP2C19 genotype were not found to be related to the occurrence of SAEs. However, trough plasma concentrations of voriconazole were found to be significantly higher in the patients with an SAE: median 6.32 mg/l (interquartile range (IQR) 2.86–9.71 mg/l) vs. median 2.15 mg/l (IQR 0.92–4.00 mg/l); $p = 0.011$. Receiver operating characteristic curve analysis identified a cut-off trough concentration for SAEs of 5.83 mg/l (sensitivity 62.5% and specificity 94.1%). Furthermore, multivariate analysis showed that a trough concentration of ≥5.83 mg/l was the only significant independent risk factor of an SAE.

Conclusions: This study shows that therapeutic drug monitoring is indicated in patients with a voriconazole-related SAE and that dose adjustment is required if the trough concentration of voriconazole exceeds 5.83 mg/l.

1. Introduction

Aspergillus species are the most common filamentous fungal pathogens in febrile neutropenic patients with hematological malignancies and in hematopoietic stem cell transplantation (HSCT) recipients.[1–3] Because invasive aspergillosis is associated with high morbidity and mortality in these patients, physicians require an antifungal agent that is both effective and safe. Voriconazole is currently the drug of choice for the treatment of invasive aspergillosis, because of its excellent in vitro antifungal activity and clinical evidence of its survival benefit.[4–7] As a result, its use has markedly increased in patients with hematological malignancies.

Voriconazole is generally well tolerated and the majority of its adverse events are similar to those of other triazoles.[8] However, anecdotal case reports have described unexpected severe adverse events (SAEs) related to voriconazole, such as hepatic failure and encephalopathy,[9–11] which potentially could result in serious organ damage and negatively impact clinical outcome in patients with hematological malignancies. Accordingly, a means of predicting voriconazole-related SAEs is required, and early intervention is needed to minimize negative impacts on clinical outcome.

This study was performed to investigate voriconazole-related SAEs and identify their risk factors in Korean patients with hematological malignancies treated with intravenous voriconazole for invasive aspergillosis.

☆ This study was presented under the title "Therapeutic drug monitoring of voriconazole in patients with invasive aspergillosis in Korea" at the 47th Annual Meeting of the Infectious Diseases Society of America, Philadelphia, PA, USA, 2009 (Abstract M-1043).

* Corresponding author. Tel.: +82 2 2258 6003; fax: +82 2 535 2494.
E-mail address: symonlee@catholic.ac.kr (D.-G. Lee).

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2. Materials and methods

2.1. Study design and patients

Patients with hematological malignancies being treated with intravenous voriconazole between June 2008 and April 2009 were eligible for this prospective observational study. Pregnant women, patients with an abnormal liver or renal function test (alanine aminotransferase (ALT) or aspartate aminotransferase (AST) more than five times the upper limit of normal; alkaline phosphatase (ALP), γ-glutamyl transpeptidase (GGT), or total bilirubin more than three times the upper limit of normal; or serum creatinine more than two and a half times the upper limit of normal), and patients under 15 years of age were excluded. Voriconazole was intravenously administered for the treatment of probable or proven invasive aspergillosis. Invasive aspergillosis was classified as defined by the European Organization for the Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group Consensus Group.[12] After obtaining written informed consent, demographic data, underlying disease, and clinical characteristics were recorded, and blood samples were drawn for determining voriconazole plasma concentration and the genotype of cytochrome P450 2C19 isoenzyme (CYP2C19). All concomitant medications during voriconazole therapy were reviewed and drugs known to interact with voriconazole were recorded.[13–16] This study was approved by the Institutional Review Board at Yeouido St. Mary's Hospital (SCMC07BR054) and registered at http://www.ClinicalTrials.gov (NCT00673348).

2.2. Safety of voriconazole

During intravenous voriconazole therapy, all adverse events, such as signs and symptoms, laboratory results (including hematology and blood chemistry results; AST, ALT, ALP, GGT, total bilirubin, serum albumin, and creatinine), and radiologic and electrocardiographic findings were recorded, regardless of their causal relationship with voriconazole therapy. Adverse events were categorized and graded as described by the National Cancer Institute, and their severities were recorded as the highest grades achieved after initiating voriconazole therapy.[17] Grades 3 through 5 are referred to as SAEs. Causal relationships between adverse events and voriconazole therapy were assessed using the Naranjo Probability Scale by two independent investigators and classified as definite, probable, possible, or doubtful.[18] Conflicting events were reviewed by a third investigator and discrepancies were resolved by consensus. Doubtful adverse events were not viewed as adverse events during the analysis.

2.3. Voriconazole plasma concentrations

All patients received voriconazole intravenously at a loading dose of 6 mg/kg administered twice on the first day of treatment, and this was followed by 4 mg/kg twice daily whenever possible, according to the manufacturer's recommendations. At least 4 days after starting therapy, paired plasma samples were collected into heparinized tubes (Vacutainer, BD Biosciences, Franklin Lakes, NJ, USA), just before the next dose (trough) and 2 h after the next dose (peak). Samples were centrifuged (3000 rpm, 4 °C, 10 min) immediately after collection, and plasma was stored at −70 °C until assay. Voriconazole concentrations were measured using a high-performance liquid chromatography method based on the report by Khoschsorur et al.[19] Voriconazole was supplied by Pfizer Inc. (USA), and ketoconazole, which was used as internal standard material, was supplied by Sigma (Seoul, Korea). The quality control samples were prepared in 1.5 ml polypropylene tubes with the nominal concentrations of 0.3, 4, and 16 mg/l and stored at −70 °C. The internal standard solution (ketoconazole, 30 mg/l in 70% methanol) was stored at −20 °C. Upon sample analysis, 100 μl of the internal standard solution was added to 500 μl of plasma and then briefly vortexed. For extraction, 5 ml of extraction solvent *n*-heptane–isoamyl alcohol (90:10 (vol/vol)) was added; the tubes were vortexed for 30 s and then centrifuged (3000 rpm, 4 °C, 10 min). The organic layer was transferred into a glass tube and evaporated to dryness at 50 °C under a gentle stream of nitrogen gas (run time: 90 min). The residue was reconstituted with 150 μl of mobile phase, vortexed, transferred into a 1.5-ml polypropylene tube and centrifuged (12 000 rpm, 4 °C, 10 min). The supernatant was finally used for injection. Chromatographic separation was performed on a hydrosphere C18 column (5 μm particle size, 250 × 4.6 mm, Phenomenex, Torrance, CA, USA) maintained at 40 °C. The mobile phase which was composed of 0.05 M phosphate buffer (pH 6.0), acetonitrile, and methanol (35:45:20 (vol/vol/vol)) was supplied at a flow rate of 1.7 ml/min. The detection wavelength was at 255 nm (for both ketoconazole and voriconazole), and the injected volume was 50 μl. The retention times were 2.56 min for voriconazole and 4.97 min for ketoconazole. The range of quantification was 0.1–20 mg/l with the correlation coefficient 0.9989. The intra- and inter-day precision (less than 10% coefficient of variation) and accuracy (95.9–101.9%) were acceptable.

2.4. Genotyping of CYP2C19 alleles

Genomic DNA was extracted from plasma specimens using a QIAamp Blood kit (Qiagen, Chatsworth, CA, USA) as described by Dixon et al.[20] Genotyping of the *CYP2C19*2* and *CYP2C19*3* alleles was performed as described by Goldstein and Blaisdell by *Sma* I restriction fragment length polymorphism (RFLP), and by De Morais et al. by *BamH* I RFLP.[21,22] The presence of *CYP2C19*1* was inferred from the absence of the **2* and **3* alleles.

Polymorphisms of CYP2C19 were classified as follows: extensive metabolizers (EM, *CYP2C19*1/*1*), heterozygous extensive metabolizers (HEM, *CYP2C19*1/*2* or **1/*3*), and poor metabolizers (PM, *CYP2C19*2/*2, *2/*3,* or **3/*3*). The EM genotype was viewed as wild and all other genotypes as mutant.

2.5. Statistical analysis

The Chi-square test or Fisher's exact test was used to compare categorical variables, and the Mann–Whitney *U*-test or Kruskal–Wallis test was used to compare continuous variables. When one of the cells in two-by-two contingency tables was equal to zero, the odds ratio (OR) was estimated via penalized maximum likelihood test.[23] Correlation analysis was performed using the Spearman test. The cut-off value of the trough concentration of voriconazole for SAEs was derived by receiver operating characteristic (ROC) curve analysis. Multivariate logistic regression analysis was performed to identify the risk factors for SAEs. Variables with *p*-values of <0.25 by univariate analysis were entered into the multivariable model.[24] Two-sided *p*-values of <0.05 were considered statistically significant.

3. Results

3.1. Patients

During the study period, 25 adult patients were consecutively enrolled in the study. Demographic and clinical characteristics are summarized in Table 1. Acute leukemia (80%, 20/25), including acute myelogenous and lymphocytic leukemia, was the most

Table 1
Demographic and clinical characteristics of the study subjects ($N = 25$)

Characteristic	n (%) or median (IQR)
Sex, male	12 (48)
Age (years)	45 (38–54)
Underlying hematological malignancies	
Acute myelogenous leukemia	14 (56)
Acute lymphocytic leukemia	6 (24)
Myelodysplastic syndrome	2 (8)
Chronic myelogenous leukemia	2 (8)
Non-Hodgkin's disease	1 (4)
Host factors for invasive aspergillosis	
Neutropenia[a]	20 (80)
Receiving an allogeneic HSCT	2 (8)
Post-allogeneic HSCT with GVHD	3 (12)
Genotype of CYP2C19	
EM	6 (24)
HEM	17 (68)
PM	2 (8)
Voriconazole daily dose (mg/kg/day)	
Loading	12.0 (11.4–12.5)
Maintenance	7.7 (7.1–8.3)
Duration of intravenous voriconazole therapy (days)	8 (7–14)

IQR, interquartile range; HSCT, hematopoietic stem cell transplantation; GVHD, graft-versus-host disease; EM, extensive metabolizer; HEM, heterozygous extensive metabolizer; PM, poor metabolizer.

[a] An absolute neutrophil count of $<0.5 \times 10^9$ cells/l or a count of $<1 \times 10^9$ cells/l with a predicted decrease to $<0.5 \times 10^9$ cells/l.

frequent hematological malignancy. The wild type of CYP2C19 was present in six patients (24%). Mutant types were as follows: *CYP2C19*1/*2* ($n = 9$), **1/*3* ($n = 8$), **2/*2* ($n = 1$), and **3/*3* ($n = 1$). The cytochrome P450 isoenzyme-interacting medications were: proton pump inhibitors ($n = 12$), calcium channel blockers ($n = 11$), benzodiazepines ($n = 9$), methylprednisolone ($n = 6$), oral contraceptives ($n = 4$), and cyclosporine or tacrolimus ($n = 3$). Of these, only the proton pump inhibitors (lansoprazole ($n = 3$) and rabeprazole ($n = 9$)) were capable of altering the voriconazole concentration. No patient had chronic liver disease.

3.2. Adverse events

The most common adverse event was an abnormal liver function test (48%, 12/25), followed by diarrhea (20%, 5/25), rash (16%, 4/25), visual disturbance (12%, 3/25), and vomiting (4%, 1/25). No patient who developed nephrotoxicity had a decrease in glomerular filtration rate of $\geq$25% from baseline or required renal replacement therapy. Voriconazole-related SAEs were observed in eight (32%) of the 25 patients (Table 2), and included hepatotoxicities ($n = 5$), cardiac toxicities ($n = 2$), and neurotoxicity ($n = 1$). The patterns of abnormal liver function tests were cholestatic ($n = 3$), hepatic ($n = 1$), or mixed ($n = 1$). Two patients with an episode of cardiac toxicity had a prolonged QT interval before starting voriconazole therapy (corrected QT interval, 0.48 s and 0.45 s, respectively). However, no increase in QT interval was observed in these patients during voriconazole therapy. These two patients were on a concomitant benzothiazepine calcium channel blocker (verapamil and diltiazem, respectively) to treat hypertension, but did not experience heart failure or any other structural abnormality by transthoracic echocardiography. Toxic encephalopathy developed in one patient who was not taking any drug capable of interacting with voriconazole. Unfortunately, the modification of voriconazole therapy and clinical course of this neurotoxicity was not determined due to discharge from hospital 2 days after the occurrence of neurotoxicity and loss to follow-up. After the occurrence of an SAE, the voriconazole daily dose was reduced in three patients, and two patients switched to oral therapy. Two patients discontinued voriconazole therapy due to SAEs. In one of these two patients (patient 1), supraventricular tachycardia completely resolved the day after discontinuing voriconazole, and the other (patient 7) required discontinuation of voriconazole because of severe hepatotoxicity deemed to be probably related, but finally died from hepatic failure 11 days after discontinuation.

3.3. Therapeutic drug monitoring

The median time from starting voriconazole therapy to the measurement of plasma concentration was 6 days (interquartile range (IQR) 5–7.5 days). Median trough and peak concentrations (IQR) were 2.93 mg/l (1.59–5.82 mg/l) and 4.76 mg/l (2.60–7.80 mg/l), respectively. Trough concentrations of <1 mg/l were detected in four (16%) patients and of $\geq$6 mg/l in five (20%) patients. A strong linear correlation was found between trough and peak concentrations according to the equation: peak levels (mg/l) = 1.378 + 1.00 $\times$ trough levels (mg/l) ($R^2 = 0.958$, $p < 0.001$).

Trough concentrations were not found to depend on CYP2C19 genotype, and median trough concentrations (IQR) were 2.12 mg/l (1.70–5.68 mg/l), 3.76 mg/l (0.92–6.96 mg/l), and 2.75 mg/l (2.55 and 2.94 mg/l) in patients with EM ($n = 6$), HEM ($n = 17$), and PM ($n = 2$), respectively ($p = 0.859$).

3.4. Risk factors for voriconazole-related SAEs

The patients who experienced an SAE had a significantly higher trough concentration (median 6.32 mg/l (IQR 2.86–9.71 mg/l)) than patients who did not (median 2.15 mg/l (IQR 0.92–4.00 mg/l)) ($p = 0.011$). During subgroup analysis, patients with cardiac toxicities ($n = 2$) showed a significantly higher trough concentration (median 9.15 mg/l (8.05 and 10.26 mg/l, respectively) vs. 2.55 mg/l (IQR 1.37–5.63 mg/l); $p = 0.027$). A ROC curve analysis of trough concentrations with respect to the occurrence of an SAE was also performed (Figure 1), and the area under the curve (mean $\pm$ SD) was 0.82 $\pm$ 0.09 (95% confidence interval (CI) 0.63–1.00; $p = 0.012$). Furthermore, a trough concentration cut-off value of 5.83 mg/l was found to have a sensitivity of 62.5% and a specificity of 94.1% for an SAE. No other demographic or clinical parameter was found to be related to an SAE by univariate analysis (Table 3). In addition, the three CYP2C19 genotypes were found to be no different in terms of SAE frequencies. Multivariate logistic regression analysis demonstrated that a trough concentration of $\geq$5.83 mg/l was independently associated with an SAE (adjusted OR 7.745, 95% CI 1.064–93.570; $p = 0.043$) (Table 3).

4. Discussion

In this study, voriconazole-related SAEs and risk factors were evaluated in 25 consecutive Korean patients with hematological malignancies and invasive aspergillosis. Eight patients experienced an SAE: hepatotoxicity in five, cardiac toxicity in two, and neurotoxicity in one patient. A voriconazole trough plasma concentration of $\geq$5.83 mg/l was the only independent risk factor found to be associated with an SAE.

We report the experience with therapeutic drug monitoring of intravenous voriconazole therapy. Voriconazole pharmacokinetics could be affected by changes from intravenous to oral therapy. In one investigation on intravenous-to-oral switchover, maximum plasma concentrations following oral dosing were lower than those obtained following intravenous administration, ranging from 63% to 90%. However, there was no significant difference in pharmacokinetic parameters, including the volume of distribution, clearance of voriconazole, and elimination rate constant, between voriconazole administration routes.[25] These findings suggest that pharmacokinetic data during oral voriconazole therapy could be estimated from that during intravenous therapy.

Table 2
Characteristics and clinical courses of patients who experienced a severe adverse event related to intravenous voriconazole therapy

Patient No.	Age (years)	Sex	Voriconazole daily dose (mg/kg/day)	CYP2C19 genotype	Voriconazole concentration (mg/l)		SAE		Dose adjustment	Clinical assessment at 6 weeks from the start of voriconazole therapy	
					Trough	Peak	Category (severity)	Relation		SAE	Outcome
1[a,b]	58	F	8.6	HEM	8.05	8.62	Cardiac toxicity; supraventricular tachycardia (grade 3)	Probable	Discontinuation	Complete resolution	Survived
2	49	M	6.8	PM	2.55	3.52	Neurotoxicity; toxic encephalopathy (grade 3)	Possible	No adjustment	NA	Loss to follow-up
3	55	F	8.5	EM	1.81	3.55	Hepatotoxicity; elevation of ALT, ALP, GGT (grade 3)	Possible	Switch to oral therapy	Partial resolution	Survived
4[a]	63	M	8.2	HEM	10.26	10.24	Cardiac toxicity; ventricular tachycardia (grade 4)	Possible	Dose reduction	Complete resolution	Survived
5	21	M	7.6	HEM	6.79	8.55	Hepatotoxicity; elevation of GGT (grade 3)	Possible	Dose reduction	Partial resolution	Survived
6[b]	35	F	8.2	HEM	5.84	7.39	Hepatotoxicity; elevation of ALP (grade 3)	Possible	Switch to oral therapy	Complete resolution	Died from refractory leukemia
7[b]	38	M	8.0	HEM	15.62	16.67	Hepatotoxicity; elevation of GGT (grade 5)	Probable	Discontinuation	NA	Died from hepatic failure
8[b]	24	M	6.0	HEM	3.76	5.62	Hepatotoxicity; elevation of AST, ALT (grade 3)	Probable	Dose reduction	Complete resolution	Died from alveolar hemorrhage

SAE, severe adverse event; F, female; M, male; HEM, heterozygous extensive metabolizer; PM, poor metabolizer; EM, extensive metabolizer; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, γ-glutamyl transpeptidase; AST, aspartate aminotransferase; NA, not available.
[a] Concomitant administration of benzothiazepine calcium channel blocker (diltiazem in patient 1 and verapamil in patient 4).
[b] Concomitant administration of proton pump inhibitor (all rabeprazole).

Table 3
Risk factors of severe adverse events related to intravenous voriconazole therapy

	n	SAE (*n* = 8), *n* (%)	OR (95% CI)	*p*-Value	Adjusted OR[a] (95% CI)	*p*-Value
Sex, male	12	5 (42)	2.381 (0.423–13.387)	0.411	-	-
Age ≥55 years	6	3 (50)	2.800 (0.419–18.689)	0.344	-	-
Underlying hematological malignancy, acute leukemia	20	8 (40)	7.480 (0.690–1030.940)	0.108[b]	13.272 (0.719–2578.650)	0.090[b]
Risk for IA, HSCT	5	2 (40)	1.556 (0.205–11.829)	1.000	-	-
Maintenance dose of voriconazole ≥8 mg/kg/day	10	5 (50)	4.000 (0.681–23.512)	0.194	2.557 (0.323–21.150)	0.361[b]
Co-medication, proton pump inhibitor	12	4 (33)	1.125 (0.209–6.046)	1.000	-	-
Genotype of CYP2C19					-	-
HEM or PM (vs. EM)	19	7 (37)	2.917 (0.281–30.298)	0.624	-	-
PM (vs. EM or HEM)	2	1 (50)	2.286 (0.124–41.985)	1.000	-	-
Trough concentration ≥5.83 mg/l	7	5 (71)	12.500 (1.600–97.647)	0.017	7.745 (1.064–93.570)	0.043[b]

SAE, severe adverse event; OR, odds ratio; CI, confidence interval; NA, not available; IA, invasive aspergillosis; HSCT, hematopoietic stem cell transplantation; HEM, heterozygous extensive metabolizer; PM, poor metabolizer; EM, extensive metabolizer.
[a] Binary logistic regression using the enter method (Chi-square = 9.070; $p = 0.028$).
[b] Penalized maximum likelihood test.

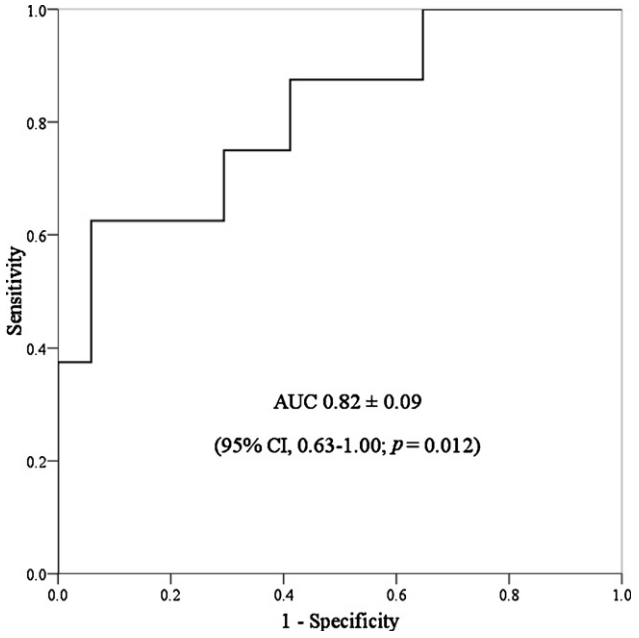

Figure 1. Receiver operating characteristic curve for voriconazole trough concentrations with regard to an occurrence of severe adverse events (AUC, area under the curve).

Previous studies have demonstrated relationships between a high voriconazole plasma concentration and visual disturbance, hepatotoxicity, and neurotoxicity.[10,11,26–29] Cardiac toxicity has been shown to be associated with voriconazole administration in dogs, but human studies on the topic are limited.[30,31] In the present study, two patients developed cardiac tachyarrhythmia. Both had recently received anthracycline-based chemotherapy for acute myelogenous leukemia and had grade 1 hypokalemia when the arrhythmia developed. In addition, they were on concomitant benzothiazepine calcium channel blockers, which may have contributed to cardiac dysrhythmia including PR prolongation, AV block, transient episodes of junctional escape rhythm, AV dissociation, and atrial fibrillation, but not to QT prolongation.[32,33] Voriconazole trough concentrations had extremely high values in these two patients. These findings suggest a significant association between cardiac toxicities and voriconazole plasma concentration, particularly in patients with other factors known to influence cardiac rhythm.

Based on in vitro susceptibility data (minimum inhibitory concentration $(MIC)_{90}$ 0.5–1 mg/l for *Aspergillus* spp.) and a free-circulating fraction of 40–50%, a value of 1 mg/l was chosen as the lower cut-off value for voriconazole trough concentration.[11,34,35] In the present study, SAEs were observed in a significantly higher proportion of patients with a trough concentration of $\geq$5.83 mg/l. Accordingly, we suggest that the optimum therapeutic range of the trough concentration of voriconazole in Korean patients is 1–5.83 mg/l, which is consistent with the results of several studies conducted on the correlation between voriconazole concentration and toxicities and expert opinions on the therapeutic range of voriconazole.[11,14,27,36–38]

The distributions of CYP2C19 genotypes vary in different racial groups. Generally, Asians, including the Japanese and Chinese, have a higher proportion of PM than Caucasians (approximately 14% to 19% in Asians and 2% to 5% in Caucasians).[30] The frequencies of EM and HEM found in the present study (24% and 68%, respectively) were similar to those reported in other Asian populations, but the frequency of PM was relatively low (approximately 8%). Genetic polymorphisms of CYP2C19 result in different rates of voriconazole metabolism, that is, 4- and 2-fold higher voriconazole concentrations are found in patients with PM and HEM, respectively, as compared with patients with EM. However, we found no relationship between CYP2C19 genotypes and voriconazole plasma concentrations or the development of SAEs, which concurs with the findings of Ikeda et al.[39] Too few patients with PM and large inter-individual variability of trough concentration might be responsible for the lack of power. Also, these findings are probably explained by a combination of factors known to impact the pharmacokinetics of voriconazole, such as, age, gender, hepatic function, and the activity of CYP isoenzymes other than CYP2C19.[8,14,15] Furthermore, interactions with other drugs that share the hepatic metabolic pathway of voriconazole might markedly alter voriconazole metabolism in patients with hematological malignancies undergoing intensive chemotherapy or HSCT recipients.

Our study has the limitations of a small sample size and the non-serial monitoring of voriconazole concentration. However, this is the first report to be issued on the risk factors of voriconazole-related toxicity. Furthermore, our findings suggest a therapeutic range for voriconazole trough concentration in Korean patients and a relationship between voriconazole plasma concentration and cardiac toxicity.

We conclude that patients administered voriconazole intravenously require careful monitoring for SAEs, and that such monitoring should include liver function tests, cardiac rhythm, and neurologic changes related to elevated voriconazole plasma concentrations. If a voriconazole-related SAE is suspected, the monitoring of voriconazole plasma trough concentrations may offer a practical means of assessing the appropriate voriconazole dose. A study on the impact of therapeutic dose adjustment on voriconazole plasma concentration and toxicity is required to confirm our findings.

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Conflict of interests: D.-G. Lee has received research grants from Yuhan/Gilead, is a consultant to Astellas, Janssen, MSD, and Pfizer, and has received honoraria from these companies.

Ethical approval: The study was approved by the Institutional Review Board at Yeouido St. Mary's Hospital (SCMC07BR054) and is registered at www.ClinicalTrials.gov (NCT00673348).

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