

# Serum voriconazole level variability in patients with hematological malignancies receiving voriconazole therapy

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**INTRODUCTION:** Voriconazole plasma concentrations have been correlated with oral dosing in healthy subjects, but have been poorly characterized in ill patients with hematological malignancies receiving intensive chemotherapy.

**METHODS:** The relationship between orally administered voriconazole, plasma concentrations and liver toxicity was examined in a cohort of 69 primarily acute leukemia patients undergoing intensive chemotherapy.

**RESULTS:** Oral administration of voriconazole was associated with significant interpatient variability, with voriconazole steady-state concentrations ranging from 0 µg/mL to 16.6 µg/mL. Approximately 20% of patients achieved steady-state concentrations <1 µg/mL. When adjusted for weight, patients receiving higher voriconazole doses tended toward higher plasma concentrations; however, there was no significant relationship between the plasma concentration and genotype, age, sex or use of concomitant proton pump inhibitors. Voriconazole concentrations were correlated with higher serum alkaline phosphatase levels at day 6 to 8, and with higher bilirubin and aspartate aminotransferase levels at day 14 to 16, but not with other liver enzyme levels.

**CONCLUSION:** In ill patients with acute leukemia and related disorders undergoing treatment with oral voriconazole, there is a poor correlation between the voriconazole dose and plasma concentrations, and many patients achieve levels that are considered to be subtherapeutic. The findings support the routine use of therapeutic drug monitoring in these patients.

**Key Words:** Antifungals; Drug levels; Liver toxicity; Voriconazole

Invasive fungal infections (IFI) are a significant source of morbidity and mortality in acute leukemia patients receiving intensive chemotherapy and hematopoietic stem cell transplant (HSCT) (1-4). Voriconazole is a second-generation triazole antifungal that has demonstrated activity in the treatment of a variety of invasive fungal pathogens and has been approved as a first-line treatment for invasive aspergillosis (5-9).

After oral administration, voriconazole readily achieves plasma concentrations above the minimum inhibitory concentration for major pathogens in cancer patients as well as in healthy subjects (10,11). Due

## La variabilité du taux de voriconazole sérique chez les patients atteints d'une hémopathie maligne qui suivent un traitement au voriconazole

**INTRODUCTION :** Les concentrations plasmatiques de voriconazole sont corrélées avec les doses orales chez les sujets en santé, mais sont mal caractérisées chez les patients malades atteints d'une hémopathie maligne sous chimiothérapie intensive.

**MÉTHODOLOGIE :** Les chercheurs ont examiné le lien entre le voriconazole administré par voie orale et la toxicité hépatique dans une cohorte de 69 patients atteints surtout de leucémie aiguë sous chimiothérapie intensive.

**RÉSULTATS :** L'administration de voriconazole par voie orale s'associait à une importante variabilité interpatient, les concentrations à l'état stable oscillant entre 0 µg/mL et 16,6 µg/mL. Environ 20 % des patients ont obtenu des concentrations à l'état stable de moins de 1 µg/mL. Après rajustement selon le poids, les patients qui recevaient des doses plus élevées de voriconazole avaient tendance à présenter des concentrations plasmatiques plus élevées. Cependant, on ne constatait aucun lien significatif entre la concentration plasmatique et le génotype, l'âge, le sexe ou l'utilisation concomitante d'inhibiteurs de la pompe à protons. Les concentrations de voriconazole étaient corrélées avec des taux de phosphatase alcaline sérique plus élevés les jours 6 à 8 et à des taux de bilirubine et d'aspartate aminotransférase plus élevés les jours 14 à 16, mais pas à d'autres taux d'enzymes hépatiques.

**CONCLUSION :** Chez les patients malades atteints d'une leucémie aiguë et de troubles connexes qui suivent un traitement au voriconazole par voie orale, la corrélation entre la dose de voriconazole et les concentrations plasmatiques est faible, et de nombreux patients obtiennent des taux considérés comme subthérapeutiques. Les observations soutiennent une pharmacovigilance systématique chez ces patients.

to the possible association between low voriconazole plasma concentrations and poor patient outcomes, and between elevated levels and hepatic and neurological toxicity, therapeutic drug monitoring (TDM) has been suggested to enhance efficacy and minimize toxicity (3,4,12-18). Previous pharmacokinetic studies have primarily involved healthy volunteers and intravenous dosing in patients. In severely ill patients undergoing intensive chemotherapy or HSCT, and receiving oral voriconazole, several factors may influence levels including treatment-related gastrointestinal and hepatic toxicity, genetic polymorphisms of the cytochrome P450 (CYP) isoenzyme system, altered protein

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binding, drug interactions and variable food intake (19-25). These may lead to large and unpredictable variations in voriconazole plasma concentrations (14,16,23,24).

To shed light on these uncertainties, we prospectively investigated the kinetics of voriconazole levels, as well as the relationship between steady-state levels and hepatotoxicity, in a cohort of severely neutropenic acute leukemia patients receiving oral voriconazole as therapy for suspected IFI.

## METHODS

### Patient population

All adult malignant hematology patients being treated with oral voriconazole from June 2007 to September 2010 were eligible for enrollment. All patients had conditions associated with severe neutropenia and could be at any stage of the treatment regimen including, but not limited to, induction/reinduction chemotherapy, consolidation chemotherapy or supportive care/palliative chemotherapy. Patients with grade  $\geq 2$  liver enzyme or bilirubin elevations at baseline, as defined by Common Terminology Criteria for Adverse Events version 4.03 (26), or those who had received voriconazole in the previous 15 days were excluded. Ethics approval for the present study was obtained from the local institutional review board. All patients provided written informed consent for voriconazole level testing and CYP2C19 isoenzyme genotyping.

All eligible patients were treated with oral voriconazole with doses ranging from 200 mg to 300 mg every 12 h as per the discretion of the treating physician. Patients were advised to take voriconazole on an empty stomach, and doses were administered at 10:00 and 22:00. Some patients received loading doses of voriconazole – either 6 mg/kg intravenously or 400 mg orally – every 12 h for two doses. At the time of patient consent, education/counselling was provided to ensure that patients were receiving voriconazole appropriately. For the determination of toxicity, all patients underwent liver enzyme testing for alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and total bilirubin levels at least once weekly. Liver enzyme data from the day of voriconazole initiation (day 1), day 6 to 8 and day 14 to 16 of therapy were used for correlation analysis but, if not available, the earliest available subsequent liver function test was used.

### Determination of voriconazole level

Voriconazole levels of inpatients were determined at day 2 to 3 (level 1) following initiation of voriconazole, and subsequently at day 4 to 5 (level 2) and day 6 to 8 (level 3). Each level was obtained within 1 h before administration of the next dose. Ambulatory patients had a one-time steady-state level drawn at day 6 to 8 (level 3) in relation to their outpatient clinic visit. If level 3 was not available, level 2 was used for further analysis. As a noninterventional study, the results of the voriconazole levels were not released to the treating physicians and were not used to guide subsequent therapy.

Voriconazole level determination was performed using liquid chromatography tandem mass spectrometry (LC-MS/MS) at the Mass Spectrometry Specialty Laboratory (Laboratory Medicine Program, University Health Network, Toronto, Ontario), similar to previously published work (27-29). LC-MS/MS was chosen over high-performance liquid chromatography with ultraviolet detection or a bioassay due to its greater sensitivity and specificity, and a shorter run time (29).

**Sample preparation:** 50  $\mu$ L aliquots of plasma were mixed with 50  $\mu$ L of d3-voriconazole internal standard. Deuterated isotopic compound was chosen rather than a compound with a similar structure or another antifungal drug because it is a first-choice standard for selective quantification by mass spectrometry (30). After the addition of zinc chloride (0.2 M), voriconazole and internal standard were extracted with ethyl acetate. After centrifugation, the supernatant was evaporated. The residue was then dissolved in 1 mL of methanol solution containing 2 mM ammonium formate with 0.1% of formic acid and analyzed by LC-MS/MS.

**LC-MS/MS system:** This consisted of a High-Pressure Liquid Chromatography 1200 system (Agilent Technologies, USA) coupled to an API 5000 (AB SCIEX, Canada) triple quadrupole mass spectrometer. Chromatographic separation was performed in isocratic elution mode at a flow rate of 0.70 mL/min on a Waters Xterra Phenyl (3.0 mm  $\times$  50 mm, 3.5  $\mu$ m) column. The mobile phase was a mixture of acetonitrile (buffer A) containing 2 mM ammonium acetate and 0.1% formic acid, and methanol (buffer B) containing 2 mM ammonium formate and 0.1% formic acid. The 50:50 ratio of buffers A and B was maintained for 1.5 min. Typical detection time for both voriconazole and d3-voriconazole was 0.48 min.

**Assay specifications:** Precision studies for voriconazole assay showed that coefficients of variation within and between assays ranged from 1.3% to 5.5%. Functional sensitivity was 0.1 mg/L. To evaluate analytical measurement range, a calibration curve was made to cover the therapeutic range (0 mg/L to 6 mg/L) and extended to 20 mg/L. Regression analysis showed that the response was linear within this range of concentrations, with  $R^2 = 0.9968$ . The mean recovery was 99.2% (coefficient of variation = 8.5%). Accuracy of the voriconazole assay was evaluated by participating in the external quality assessment program (31) and also by performing method comparison studies using ultra-performance liquid chromatography with ultraviolet detection and LC-MS/MS methods currently in clinical use at two Canadian hospitals.

### Genotyping

Genomic regions containing CYP2C19 \*2, \*3, \*4, \*5 and \*7 polymorphisms were amplified in a multiplexed polymerase chain reaction as previously described (32). Briefly, the purified polymerase chain reaction products were then used as templates in the SNaPshot reaction (Life Technologies, USA), in which extension primers were designed to be of different lengths and each anneal adjacent to a targeted single-nucleotide polymorphism. The extension primers were extended by one nucleotide using fluorescently labelled dideoxynucleoside triphosphate. The cleaned extended products were separated by capillary electrophoresis on the ABI Prism 3100 Avant Genetic Analyzer (Applied Biosystems, USA) and analyzed using GeneMapper version 4.0 (Life Technologies).

### Statistical analysis

Patients' treatment, baseline characteristics and clinical outcomes were reported using descriptive statistics. Categorical variables, such as patient sex, genotyping, inpatient/outpatient, diagnosis, IFI, loading dose, pretransplant tyrosine kinase inhibitor use, frequency of transplantations in the first chronic phase, matched sibling donor, stem cell source and conditioning regimen, were summarized using counts and percentages. Continuous variables, such as age, voriconazole levels and liver enzyme levels, were summarized using medians and ranges.  $\chi^2$  test/Fisher's exact tests (as appropriate) were used to assess the association between categorical variables. Student's *t* test/Wilcoxon rank-sum test (as appropriate) was used to compare continuous outcome variables for two factors, while ANOVAs/Kruskal-Wallis tests (as appropriate) were used to compare continuous outcomes among categorical covariates having  $>2$  levels. Spearman's correlation coefficient was used to investigate the relationship of voriconazole levels with continuous covariates (33). A two-tailed  $P \leq 0.05$  was considered to be statistically significant. All analyses were performed using SAS version 9.2 (SAS Institute Inc, USA).

## RESULTS

### Patient and treatment characteristics

Sixty-nine patients received 71 courses of voriconazole, with most courses (86%) administered on an inpatient basis. Loading doses were administered during 38% of voriconazole courses, with most patients receiving oral loading. Patients receiving intravenous loading doses were switched to oral voriconazole after 24 h. Most patients received 200 mg twice daily (BID) following loading doses, with a median voriconazole dose of 2.95 mg/kg BID (range 1.7 mg/kg to 5.0 mg/kg) (Table 1).

**TABLE 1**  
**Patient characteristics and voriconazole dosing**

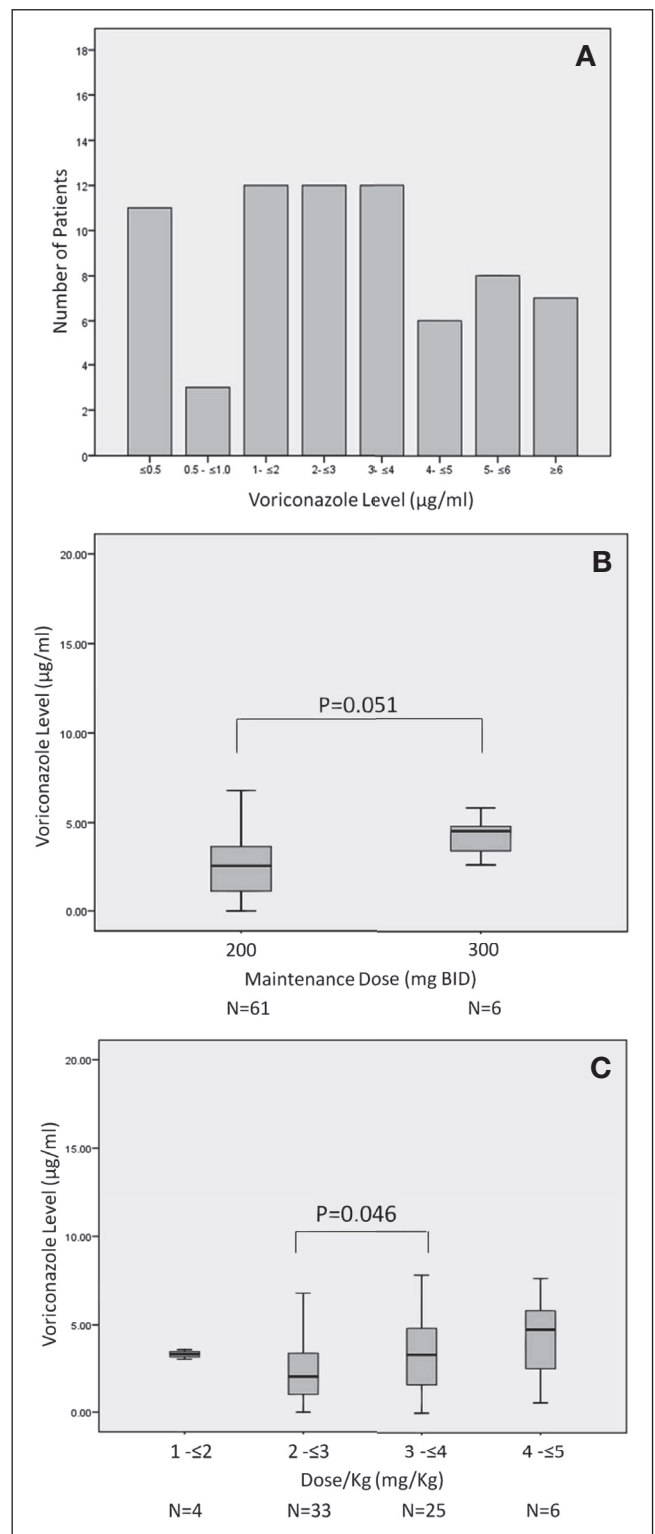
Characteristic	
Patients, n	69
Median age, years (range)	58 (19–80)
Male sex, %	56.5
Voriconazole courses, n	71
Inpatients	61 (85.9)
Outpatients	9 (12.7)
Unknown	1 (1.4)
Diagnosis (% voriconazole courses)	
Acute myeloid leukemia	63 (88.7)
Acute lymphoblastic leukemia	4 (5.6)
Acute promyelocytic leukemia	2 (2.8)
Aplastic anemia	1 (1.4)
Myelodysplasia	1 (1.4)
Invasive fungal infection (% voriconazole courses)	42 (59.2)
Proven	3 (4.2)
Probable	9 (12.7)
Possible	30 (42.3)
<b>Voriconazole dosing</b>	
Loading dose	
Intravenous	2 (2.8)
Oral	25 (35.2)
No loading dose	22 (31)
Unknown	22 (31)
Oral maintenance dose	
200 mg BID	61 (85.9)
250 mg BID	1 (1.4)
300 mg BID	6 (8.5)
Unknown	3 (4.2)
Maintenance dose, mg/kg	
1–≤2	4 (5.9)
2–≤3	33 (48.5)
3–≤4	25 (35.2)
4–≤5	6 (8.8)

Data presented as n (%) unless otherwise indicated. BID Twice per day

### Voriconazole levels

A total of 111 voriconazole levels were measured: 28 at the first time point between day 2 to 3 (median day 2, level 1); 20 at the second time point between day 4 to 5 (median day 4, level 2); and 63 at the third time point between day 5 to 8 (median day 6, level 3). Median voriconazole levels were not significantly different among the three different time points. There was a statistically significant correlation between the voriconazole level at the three different time points ( $P=0.04$ ,  $r=0.598$  comparing levels 1 and 2;  $P=0.001$ ,  $r=0.647$  comparing levels 1 and 3;  $P<0.001$ ,  $r=0.912$  comparing levels 2 and 3). The steady-state level (level 3) was used for subsequent toxicity assessment. However, because there was a very good correlation between voriconazole levels at the level 3 and level 2 time points, the level 2 time point was used in eight cases for which level 3 was not available (Table 2).

There was significant interpatient variability in the steady-state plasma concentration of voriconazole. Patients with a daily voriconazole dose of 200 mg BID had voriconazole levels ranging from 0 µg/mL to 16.6 µg/mL with a coefficient of variation of 89.7%. Fourteen voriconazole courses (19.7%) were associated with a peak steady state level of  $\leq 1.0$  µg/mL. In contrast, levels  $\geq 5$  µg/mL were found during 15 (21.2%) of the voriconazole courses (Figure 1A); all of the latter occurred at the 200 mg BID dose (Table 2). Although patients receiving voriconazole doses of 300 mg BID had a higher median voriconazole level compared with those receiving 200 mg BID, this was not statistically significant (4.5 µg/mL versus 2.5 µg/mL;  $P=0.051$ ,



**Figure 1) A** Distribution of steady-state voriconazole concentrations. **B** Variability between voriconazole maintenance dose and voriconazole steady-state levels. **C** Variability between the voriconazole maintenance dose/kg and voriconazole steady-state levels. BID Twice per day

Figure 1B). As shown in Figure 1C, patients receiving a voriconazole dose of 3 mg/kg to 4 mg/kg had significantly higher median voriconazole levels than those receiving a 2 mg/kg to 3 mg/kg dose (2.0 µg/mL versus 3.3 µg/mL;  $P=0.046$ ). The median voriconazole

**TABLE 2**  
Voriconazole levels at measurement time points as well as in steady state

Time point	Median level (range), µg/mL
Level 1 (day 2–3, n=28)	2.55 (0.10–7.40)
Level 2 (day 4–5, n=20)	2.29 (0.65–8.30)
Level 3 (day 6–8, n=63)	2.61 (0–16.6)
Steady-state level*, µg/mL	n (%)
≤0.5	11 (15.5)
≤1.0	14 (19.7)
≤2.0	26 (36.6)
≥5.0	15 (21.2)

\*Steady state level is defined as level 3

level was also higher among patients receiving a dose of 4 mg/kg to 5 mg/kg compared with those receiving a 3 mg/kg to 4 mg/kg dose, but this difference was not statistically significant ( $P=0.66$ ). Coefficients of variation for patients receiving 1 mg/kg to 2 mg/kg, 2 mg/kg to 3 mg/kg, 3 mg/kg to 4 mg/kg and 4 mg/kg to 5 mg/kg were 6.8%, 79.8%, 88.2% and 57.2%, respectively.

#### Correlative factors for voriconazole levels

There was no correlation between patient age and voriconazole levels measured either as a continuous variable or as a discrete variable using 2 µg/mL as a cut-off ( $P=0.98$ ). There was also no significant association between sex and the likelihood of achieving a steady-state level of >2 µg/mL ( $P=0.094$ ).

Fourteen patients were receiving a concomitant proton pump inhibitor (PPI) during the study period – 10 patients were taking esomeprazole, two patients omeprazole and two patients lansoprazole. There was no significant association between PPI use and achievement of a voriconazole steady-state level of >2 µg/mL ( $P=0.65$ ).

**Correlation with genotype:** CYP2C19 genotyping results were available for 29 patients and characterized as either slow metabolizers (presence of either \*2 or \*3 genotype), rapid metabolizers (\*17 genotype) or neither (\*1/\*1 genotype). As shown in Table 3, there was no significant difference in the median steady state voriconazole levels among different genotypes ( $P=0.2609$ ).

**Correlation with liver enzymes:** At day 6 to 8 of therapy, 69 patients were still on voriconazole; of these, one patient each had bilirubin, AST and ALT levels >3× the upper limit of normal (ULN). Only the ALP was significantly correlated with the voriconazole level ( $P=0.003$ ,  $r=0.37$ ), with bilirubin only trending toward significance ( $P=0.06$ ,  $r=0.242$ ). At day 14 to 16, 49 patients were receiving voriconazole and four had bilirubin levels >3× ULN, while one patient had an elevated AST level (3.2× ULN) and two had an elevated ALP level (3.2× and 4× ULN). Both the bilirubin ( $r=0.436$ ;  $P=0.003$ ) and the AST ( $r=0.337$ ;  $P=0.02$ ) at day 14 to 16 were significantly correlated with the steady-state voriconazole concentration. Relative to patients with a normal bilirubin, those with an abnormal bilirubin (>ULN) had significantly higher median voriconazole levels at both the day 6 to 8 liver enzyme assessment (2.4 µg/mL versus 3.5 µg/mL;  $P=0.03$ ) and the day 14 to 16 liver enzyme assessment (2.1 µg/mL versus 3.5 µg/mL;  $P=0.026$ ). In contrast, there was no significant difference in plasma voriconazole levels for those with an abnormal versus normal AST, ALT or ALP levels (data not shown). Of the 15 patients with steady-state voriconazole levels >5 µg/mL, four had an elevated bilirubin level >ULN at day 6 to 8 and at day 14 to 16.

#### DISCUSSION

Voriconazole TDM has been conducted in both prophylactic and therapeutic settings, with variable results (3,9,12–14,16,17,23,24,34–37). However, many of these studies evaluated intravenous dosing and included a small number of patients. Many patients receive oral voriconazole therapy for practical reasons (eg, ambulatory care therapy) and cost savings. Our study was designed to determine

**TABLE 3**  
Results of CYP2C19 genotyping studies

Genotype	n	Steady-state voriconazole level, median (range), µg/mL
*1/*1	13	3.16 (0.40–7.80)
*1/*2 or *1/*3	8	2.38 (0.00–5.90)
*1/*17	5	1.14 (0.43–3.60)
*2/*17	3	1.10 (1.00–3.00)
P		Not significant

CYP Cytochrome P450

voriconazole levels in the setting of ill patients, primarily with acute leukemia, receiving oral dosing and to evaluate factors associated with the variability in levels.

Because the minimum inhibitory concentration that inhibits the growth of 90% of organisms is ≤1 µg/mL for most organisms targeted by voriconazole and neurological toxicities generally occur at serum levels >5.5 µg/mL, several authors have suggested using a minimal voriconazole target blood concentration of 1 µg/mL to 2 µg/mL and maximal concentrations between 5.0 µg/mL and 6.0 µg/mL (4,12,15,19,38–41). However, attainment of the minimum suggested voriconazole concentration does not ensure therapeutic success, as noted by Pascual et al (4), who observed that two of five IFI associated deaths occurred among those with levels >1.0 µg/mL. Although most patients in our cohort received a maintenance voriconazole dose of 200 mg orally BID, the steady-state concentration showed considerable variability among patients, ranging from 0 µg/mL to 16.6 µg/mL. Therefore, a substantial proportion of patients achieved steady-state levels generally regarded as subtherapeutic – approximately 20% of patients achieved levels <1.0 µg/mL and 37% <2.0 µg/mL; conversely, 15% had levels >5.0 µg/mL (3,4,15,21). Such variability has been previously described. In a study of voriconazole for the treatment of invasive aspergillosis, plasma voriconazole levels ranged from <0.1 µg/mL to 9.7 µg/mL, while Trifilio et al (16) noted the dose of those with voriconazole levels <0.5 µg/mL (2.9 mg/kg to 8.9 mg/kg; median 5.1 mg/kg) was not significantly different from the dose at which levels were higher (2.7 mg/kg to 10.2 mg/kg;  $P=0.35$ ) (3). Miyakis et al (12) noted 32% of patients had levels <0.5 µg/mL, while Racil et al (37) found that, for patients treated with voriconazole 200 mg BID, inter- and inpatient variability coefficients were 81.9% and 50.5%, respectively.

The reasons for the observed variability in levels are likely multifactorial. Lipid-rich foods can decrease the absorption by as much as 20% (34). Chemotherapy-induced gastrointestinal damage, concomitant use of PPIs affecting absorption, and hepatotoxicity due to chemotherapy and other drugs, causing altered metabolism, may affect steady-state levels. Age and sex may also influence drug levels. In a small sample of healthy volunteers receiving voriconazole, the maximum concentration and area under the curve were higher in elderly male subjects and in women compared with younger men (42). However, we were not able to determine any correlation among age, sex or concomitant PPI exposure and steady-state levels in our cohort.

Polymorphisms in the CYP2C19 enzyme involved in the metabolism of voriconazole may also contribute to the variability in voriconazole levels. Poor metabolizers, characterized by \*2 or \*3 alleles, are most commonly observed among non-Indian Asians; these subjects may have voriconazole serum concentrations up to four times higher than those observed in extensive metabolizers (21,43). Voriconazole is both a substrate and an inhibitor of CYP2C19, CYP2C9 and CYP3A4. In contrast, heterozygous ultrarapid metabolizer alleles (CYP2C19\*17), have been reported with a frequency of 18% in both Swedes and Ethiopians, and a low rate of 4% in Chinese individuals (44). Our inability to detect any correlation between genotype and steady-state voriconazole levels may be related to the small sample size, but could also indicate that other clinical factors may override the influence of genotype.



Despite the lack of predictors, our data indicate that patients receiving a higher dose (300 mg BID) or higher dose per kilogram tend to have higher voriconazole levels. This suggests that using either a higher fixed dose, or weight-based dosing, would be preferable in the absence of TDM. However, the majority of patients achieved adequate serum levels with 200 mg BID, suggesting that TDM may reduce the risk of overdoing with higher doses. Patients with subtherapeutic levels could then be dose-escalated. Our data also demonstrated that voriconazole levels measured as early as day 2 to 3 could provide a useful indicator of this because levels were not significantly different among the three time points tested. This would permit early dose escalation as needed.

Abnormal liver function test results have been reported in 1% to 10% of patients receiving voriconazole (10,45). Pascual et al (4) found no correlation between voriconazole levels and ALP or gamma glutamyltransferase levels, and logistic regression analysis failed to demonstrate a significant association between voriconazole levels and hepatotoxicity. Both Racil et al (37) and Miyakis et al (12) further suggest that there is no statistical association between hepatotoxicity and any particular voriconazole concentration. In contrast, a group of Japanese researchers reported that eight of 11 (74%) hematology patients developed hepatic damage with threshold serum concentrations >6 µg/mL (46). Denning et al (3) noted deterioration in liver function in six of 22 patients with plasma concentrations >6 µg/mL, and Trifilio et al (16) found that increases in AST and ALP levels, but not ALT or bilirubin levels, correlated with voriconazole levels in adult patients undergoing HSCT. Within our cohort, while the AST, ALT and ALP levels showed no consistent relationship with voriconazole levels, the ALP level at day 6 to 8, and both the AST and total bilirubin levels at day 14 to 16, were significantly associated with steady-state voriconazole levels. However, other enzymes were not correlated, and elevated liver enzyme and bilirubin levels were observed in patients with voriconazole levels in the optimal range. It is unclear whether the abnormal liver tests resulted from voriconazole administration, or whether the higher voriconazole levels were a result of chemotherapy-induced hepatic toxicity resulting in abnormal voriconazole metabolism (47). Nevertheless, based on our data, the value of TDM as a predictor of liver toxicity appears weak.

Our study had several limitations. It was conducted at a single centre with a limited number of patients, and our study design did not include assessment of chemotherapy-induced gastrointestinal damage, which may affect daily nutritional intake and, subsequently, voriconazole plasma concentrations. Additionally, the majority of our patients were treated as inpatients and received additional medications concurrently with voriconazole including cardiac medications, antibiotics, PPIs and antiemetics. We were unable to fully evaluate the effects of concomitant medications because a limited number of patients received each medication. Furthermore, most concurrent medications

were administered only intermittently. Although both inpatients and outpatients received extensive education regarding the necessity of taking voriconazole on an empty stomach and at designated times, we did not formally evaluate patient compliance, particularly in the case of outpatients.

In contrast to several other studies, we evaluated CYP2C19 polymorphisms; however, these were conducted after marrow reconstitution following induction, reinduction or consolidation chemotherapy. Unfortunately, some patients were not available for genetic testing during this period. Thus, results of CYP2C19 polymorphism genetic testing were available for a limited number of patients (28 of 69 [41%]). Additionally, because metropolitan Toronto is ethnically diverse, the number of patients within each subcategory (ie, slow metabolizers, intermediate metabolizers and rapid metabolizers) was further reduced. This may partially explain our findings of no significant relationship between voriconazole plasma concentrations and genotype. We found no consistent relationship between day 14 to 16 liver enzyme abnormalities and steady-state voriconazole concentrations. Because our hepatotoxicity analysis was conducted approximately one week following voriconazole steady-state measurements, it is possible that further variations in levels may have occurred in the interim. An additional limitation to our study was that we could not reliably evaluate the clinical efficacy of treatment because most infections were only considered to be possible IFIs; confirmatory cultures were not generally available and galactomannan testing was not being routinely performed. Finally, although our population consisted primarily of acute leukemia patients receiving chemotherapy, some patients with myelodysplasia and aplastic anemia were also included; however, due to the small number of these patients, we were unable to evaluate the influence of the underlying condition on plasma voriconazole concentrations.

## CONCLUSION

Our study demonstrates that, in ill patients with acute leukemia and related disorders undergoing treatment with oral voriconazole, there is substantial interpatient variability in voriconazole concentrations, with poor correlations between the administered dose, clinical predictive factors, genotype and serum levels. A substantial proportion of patients receiving doses of 200 mg orally BID had steady-state levels which many consider suboptimal in treating invasive aspergillosis. The unpredictability of these levels supports the argument in favour of routine voriconazole TDM in these ill patients.

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