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Initial voriconazole trough blood levels and clinical outcomes of invasive aspergillosis in patients with hematologic malignancies

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There are limited data on the relationship between voriconazole levels and clinical outcomes relative to invasive aspergillosis (IA). We therefore analyzed the association between initial voriconazole trough blood levels and clinical responses of IA in patients with hematologic malignancies. All adult patients treated with voriconazole in a tertiary care hospital in Seoul, South Korea, between August 2009 and April 2011 were identified from pharmacy records. Initial voriconazole trough levels were routinely measured 1 week after therapy and patient responses were classified as success (complete or partial response) or failure (stable response, progression of disease, or death) at 2 weeks post-therapy. Fifty-two patients, involving 2 (4%) proven, 29 (56%) probable, and 21 (40%) possible IA infections, were included. Of these, 11 (21%) had initial voriconazole levels of ≤ 2 mg/l and the remaining 41 (79%) had > 2 mg/l. There were slightly fewer successful responses (45%, 5/11) in the patients with initial voriconazole levels ≤ 2 mg/l than in those with voriconazole levels > 2 mg/l (51%, 21/41), but the difference was not statistically significant ($P = 0.73$). Neutropenia (OR 0.1, $P = 0.008$) and immunosuppression (OR 0.1, $P = 0.004$) were independently associated with 2-week successful response after voriconazole therapy. In conclusion, initial voriconazole trough levels may not significantly affect clinical outcomes of IA at 2 weeks after voriconazole therapy in patients with hematologic malignancies. Further studies of prospective design are needed to establish the optimal procedure for voriconazole drug monitoring.

Keywords voriconazole, invasive aspergillosis, initial trough blood level, clinical response

Introduction

Invasive aspergillosis (IA) is one of the most common and life-threatening complications in patients with hematologic malignancies, and recipients of hematopoietic stem cell transplants. In these patients, IA continues to be associated with a mortality rate exceeding 50% [1]. Voriconazole is currently the first choice therapy for IA and it is a new treatment option for candidiasis and other emerging invasive fungal infections such as those caused by *Fusarium* spp., as well as refractory to treatment [2,3].

Voriconazole is primarily cleared from the plasma by hepatic metabolism, which is mostly mediated by the cytochrome P450 (CYP) 2C19 isozyme [4]. This CYP2C19 non-wild (mutant) isozyme is generally found in 60–70% of Asian individuals but in only 30% of white and black Americans [5]. Voriconazole concentrations can be as much as 2–4 times higher in individuals with the non-wild isozyme than in those with the wild-type isozyme [4].

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However, multiple factors are associated with the large variation in voriconazole exposure following standard dose administration, such as nonlinear saturable pharmacokinetics, drug-drug interactions, liver disease, patient age, and genetic polymorphism of CYP2C19 [6]. Recently, Pascual *et al.* reported that treatment failure was more common in patients with voriconazole blood levels ≤ 1 mg/l (6/13 or 46%) than in those with levels > 1 mg/l (5/39 or 12%, $P = 0.02$) [6]. However, data on the relationship between voriconazole blood levels and clinical outcomes in different populations, including Asians are limited. The present study was undertaken to investigate the association between initial voriconazole trough blood levels and clinical responses in Korean patients with invasive aspergillosis.

Materials and methods

Study population

Therapeutic drug monitoring (TDM) in patients with hematologic malignancies who were given voriconazole was carried out in the Department of Hematology, Asan Medical Center, Seoul, Korea, between August 2009 and April 2011. The patients received voriconazole for more than 7 days and had one or more TDM episodes for this antifungal. We retrospectively reviewed the medical records of the patients. Invasive fungal infections were classified as proven, probable, or possible, according to the revised consensus definitions of the Invasive Fungal Infection Group of the European Organization for Research and Treatment of Cancer and Mycosis Study Group (EORTC/MSG) [7]. Proven IA was defined as histopathologic evidence of tissue invasion, including the presence of septated, acutely branching filamentous fungi, together with positive culture. Probable IA was defined as the presence of a host factor together with clinical criteria, such as dense, well-circumscribed lesions with or without halo signs, air-crescent signs, or cavities on computed tomography, and mycologic evidence of fungal infection (by culture or cytologic analysis of BAL fluid for *Aspergillus* species, or galactomannan (GM) assays of serum or BAL). Possible IA was defined as the presence of a host factor and either mycologic evidence or clinical criteria including IA.

Voriconazole administration

Voriconazole was administered orally or intravenously for at least 7 days. The administration route and dose were based on the recommendations of the package inserts and adjusted per TDM results [8]. Voriconazole was administered via IV infusion at a dose of 6 mg/kg every 12 h for 2 doses, followed by a maintenance dose of 4 mg/kg every 12 h, or orally at 400 mg every 12 h as a loading dose, followed by 200 mg every 12 h as a maintenance dose.

Measurements of voriconazole blood concentrations

Initial voriconazole trough blood concentrations were routinely measured one week after voriconazole therapy to adjust doses to the target range of 2–6 mg/l. Voriconazole trough blood levels were analyzed by tandem mass spectrometry. Blood was sampled just before the next voriconazole dose. Voriconazole TDM was repeated when treatment failure, breakthrough fungal infection, or adverse events was suspected. Analysis was based on initial voriconazole trough concentrations at steady state.

Clinical response evaluation

Responses to voriconazole therapy were classified as success (complete or partial response) or failure (stable response, progression of disease, or death) at 2, 4, 8, and 12 weeks after voriconazole treatment [9]. Each patient was comprehensively assessed on the basis of clinical (fever, signs and symptoms of infection, and inflammatory markers), radiological (CT or MRI findings) and mycologic outcomes.

Statistical analysis

All statistical analyses were conducted using the SPSS software package (version 12.0) for Windows. Statistical significance was defined as a two-sided P value < 0.05. Categorical variables were compared by the Chi-square test or Fisher's exact test, as appropriate. Continuous variables were compared by Student's t-test or the Mann-Whitney U test, as appropriate. The Spearman method was used to study correlations between pairs of continuous variables. Factors for clinical outcome were identified by backward stepwise logistic regression analysis.

Results

Patient characteristics

Fifty-two patients were identified which included two (4%) with proven, 29 (56%) probable, and 21 (40%) possible IA. The demographics of these eligible patients are presented in Table 1. The most frequent underlying hematologic disease was acute myeloid leukemia (60%, 31/52). Of the 52 patients, 25 (48%) were neutropenic and 24 (46%) concurrently received immunosuppressive agents. Reasons for voriconazole therapy were failure of initial antifungal therapy (79%), intolerance to initial therapy (17%), and switch from intravenous amphotericin B to oral

Table 1 Baseline clinical characteristics of patients with initial voriconazole level ≤ 2 mg/L and > 2 mg/l.

Variables	≤ 2 mg/l ($n = 11$)	> 2 mg/l ($n = 41$)	P
Age, median years (range)	51 (21–67)	53 (16–81)	0.54
Male gender	9 (82)	24 (59)	0.29
Underlying disease			0.44
Acute myeloid leukemia	6 (55)	25 (61)	
Acute lymphocytic leukemia	1 (9)	6 (15)	
Myelodysplastic syndrome	2 (18)	3 (7)	
Others[a]	2 (18)	7 (17)	
Neutropenia at enrollment	3 (27)	22 (54)	0.12
Immunosuppression[b]	6 (55)	18 (44)	0.53
Invasive aspergillosis			0.11
Proven	1 (9)	1 (2)	
Probable	4 (36)	25 (61)	
Possible	6 (55)	15 (37)	
Site of infection			0.28
Lung	9 (82)	38 (93)	
Other site[c]	2 (18)	3 (7)	
Reason for voriconazole therapy			0.25
Failure of initial therapy	6 (55)	35 (85)	
Intolerance to initial therapy	4 (36)	5 (12)	
Switch from IV amphotericin B to oral therapy	1 (9)	1 (2)	
Initial antifungal agent			0.85
Conventional amphotericin B	7 (64)	31 (76)	
Liposomal amphotericin B	3 (27)	2 (5)	
Itraconazole	1 (9)	5 (12)	
Caspofungin	–	3 (7)	
Route of administration			0.03
Intravenous	6 (55)	36 (88)	
Oral	5 (45)	5 (12)	
Duration of voriconazole therapy			0.73
Median days (IQR)	61 (24–131)	50 (23–86)	
Daily dose (mg/kg/day), mean ± SD			0.16
Intravenous	8.1 ± 0.4	8.1 ± 0.9	
Oral	7.3 ± 0.6	6.7 ± 0.4	

Data are numbers (%) of patients, unless otherwise indicated.
[a]Lymphoma (2 patients), hemophagocytic lymphohistocytosis (3 patients), and aplastic anemia (4 patients).
[b]Immunosuppression was defined as concomitant use of cyclosporine or tacrolimus for at least 2 weeks from the time of starting voriconazole therapy.
[c] Invasive *Aspergillus* sinusitis, disseminated aspergillosis, and invasive *Aspergillus* tracheobronchitis.

therapy (4%). Most of the patients (73%, 38/52) received conventional amphotericin B as initial antifungal therapy.

Voriconazole therapy and measurement of trough blood concentrations

Most patients (81%) received voriconazole intravenously and only 19% by the oral route (Table 1). Median duration of therapy was 55 days (IQR, 24–85 days), and mean dose (± SD) by the intravenous route was 8.1 ± 0.8 mg/kg/day, and by the oral route 7.0 ± 0.6 mg/kg/day. Initial voriconazole trough levels were measured at a median of 8 days (IQR, 7–12 days) after starting therapy.

During the course of treatment with voriconazole, a total of 164 TDM episodes were performed on the 52 patients (median, two episodes per patients, IQR 1–4). The mean initial voriconazole trough concentration was 5.81 ± 4.68 mg/l (median 4.93 mg/l; IQR, 2.19–8.08 mg/l). There was great intra-dose variability in voriconazole levels (Fig. 1), and there was a weak positive correlation between daily voriconazole dose and observed trough levels ($r^2 = 0.1$). However, the average voriconazole trough level resulting from intravenous administration was two-fold higher than that resulting from oral administration (6.43 mg/l vs. 3.21 mg/l; $P = 0.04$).

Voriconazole trough levels and two-week successful clinical response

Voriconazole trough concentrations were ≤ 2 mg/l in 11 cases (21%) and > 2 mg/l in 41 cases (79%). A higher

Table 2 Comparison of response rates between initial voriconazole level ≤ 2 mg/l and > 2 mg/l depending on the inclusion of possible invasive aspergillosis.

	Inclusion of possible IA			Exclusion of possible IA		
Clinical responses	≤ 2 mg/l ($n = 11$)	> 2 mg/l ($n = 41$)	P	≤ 2 mg/l ($n = 5$)	> 2 mg/l ($n = 26$)	P
2-week response						
Success	5 (45)	21 (51)	0.73	2 (40)	14 (54)	0.65
Failure	6 (55)	20 (49)		3 (60)	12 (46)	
4-week response						
Success	5 (45)	26 (63)	0.32	2 (40)	15 (58)	0.64
Failure	6 (55)	15 (37)		3 (60)	11 (42)	
8-week response						
Success	5 (45)	25 (61)	0.50	2 (40)	16 (62)	0.63
Failure	6 (55)	16 (39)		3 (60)	10 (38)	
12-week response						
Success	5 (45)	22 (54)	0.63	2 (40)	14 (54)	0.65
Failure	6 (55)	19 (46)		3 (60)	12 (46)	

Data are numbers (%) of patients, unless otherwise indicated. IA, invasive aspergillosis.

proportion of the patients with > 2 mg/l received intravenous voriconazole ($P = 0.03$). The patients with initial voriconazole level ≤ 2 mg/l had slightly fewer successful responses (45%, 5/11) than those with voriconazole level > 2 mg/l (51%, 21/41), but the difference was not statistically significant ($P = 0.73$, Table 2). In the subgroup consisting of 41 patients who received voriconazole due to failure of initial antifungal agents, those with initial voriconazole levels ≤ 2 mg/l had slightly fewer successful responses (33%, 2/6) than those with voriconazole level > 2 mg/l (46%, 16/35), but again there was no statistically significant difference ($P = 0.68$). We performed additional analyses including different cut-off values of initial voriconazole level such as 0.5, 1, 3, and 4 mg/l (Table 3).

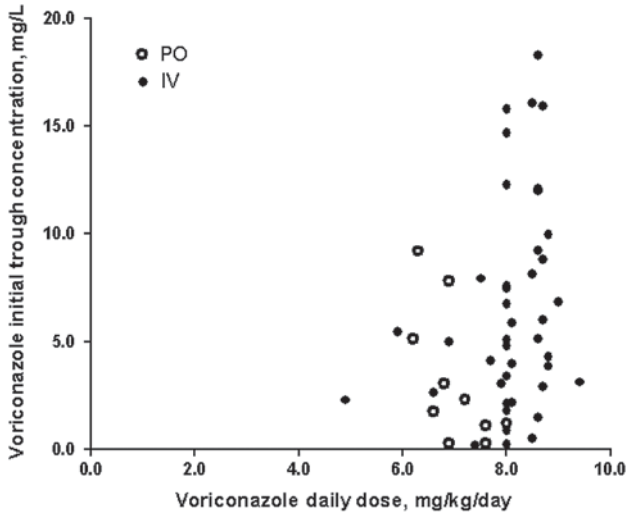

Fig. 1 Initial voriconazole trough concentrations according to daily dose ($r^2 = 0.1$).

Factors associated with two-week successful clinical response

We analyzed the factors associated with two-week successful clinical response after voriconazole therapy (Table 4). In univariate analysis, neutropenia (OR 0.2, $P = 0.01$), concomitant use of immunosuppressants (OR 0.2, $P = 0.005$), use of conventional amphotericin B as initial antifungal agent (OR 3.4, $P = 0.04$), and intravenous administration of voriconazole (OR 0.1, $P = 0.005$) were significantly associated with two-week successful clinical response after voriconazole therapy. Multivariate analysis revealed that only neutropenia (OR 0.1, $P = 0.008$) and immunosuppression (OR 0.1, $P = 0.004$) were independently associated with two-week successful response after voriconazole therapy.

Discussion

Voriconazole retains the excellent oral bioavailability of its parent drug but undergoes extensive, saturable hepatic metabolism, resulting in a nonlinear pharmacokinetic profile in adults [4]. In fact, it has become increasingly evident that intra-patient and inter-patient pharmacokinetic variability of the mold-active triazoles can contribute to therapeutic failure in patients with invasive mycoses [10]. Trifilio and colleagues found that 18 ~ 27% of adult allogeneic hematopoietic stem cell transplant recipients who receive standard oral voriconazole doses may have had subtherapeutic drug exposures [11,12]. However, in the present work, we did not find that initial voriconazole trough levels were associated with successful responses. These various findings suggest that single time point measurements of one-week trough levels of voriconazole may not reflect the exact concentration in patients because

Table 3 Comparison of response rates depending on different cut-off values of initial voriconazole level.

Clinical responses	≤0.5 mg/l >0.5 mg/l			≤1 mg/l >1 mg/l			≤2 mg/l >2 mg/l			≤3 mg/l >3 mg/l			≤4 mg/l >4 mg/l		
	(*n* = 5)	(*n* = 47)	*P*	(*n* = 6)	(*n* = 46)	*P*	(*n* = 11)	(*n* = 41)	*P*	(*n* = 17)	(*n* = 35)	*P*	(*n* = 23)	(*n* = 29)	*P*
2-week response															
Success	2 (40)	24 (51)	>0.99	2 (33)	24 (52)	0.67	5 (45)	21 (51)	0.73	10 (59)	16 (46)	0.38	13 (57)	13 (45)	0.40
Failure	3 (60)	23 (49)		4 (67)	22 (48)		6 (55)	20 (49)		7 (41)	19 (54)		10 (43)	16 (55)	
4-week response															
Success	2 (40)	29 (62)	0.38	2 (33)	29 (63)	0.20	5 (45)	26 (63)	0.32	11 (65)	20 (57)	0.60	15 (65)	16 (55)	0.46
Failure	3 (60)	18 (38)		4 (67)	17 (37)		6 (55)	15 (37)		6 (35)	15 (43)		8 (35)	13 (45)	
8-week response															
Success	2 (40)	28 (60)	0.64	2 (33)	28 (61)	0.38	5 (45)	25 (61)	0.50	9 (53)	21 (60)	0.63	13 (57)	17 (59)	0.88
Failure	3 (60)	19 (40)		4 (67)	18 (39)		6 (55)	16 (39)		8 (47)	14 (40)		10 (43)	12 (41)	
12-week response															
Success	2 (40)	25 (53)	0.66	2 (33)	25 (54)	0.41	5 (45)	22 (54)	0.63	7 (41)	20 (57)	0.28	12 (52)	15 (52)	0.97
Failure	3 (60)	22 (47)		4 (67)	21 (46)		6 (55)	19 (46)		10 (59)	15 (43)		11 (48)	14 (48)	

trough levels may differ in successive measurements [12,13].

We observed a large inter- and intra-dose variability in voriconazole trough levels, which is consistent with previous studies [6,14]. Although the bioavailability of voriconazole is estimated to be 96% [8], the blood levels after intravenous administration in our study were two-fold higher than after oral administration. Therefore, therapeutic exposure cannot be predicted on the basis of total daily or weight-based (mg/kg) dose of voriconazole alone. The variability is probably due to unrecognized confounders that influence voriconazole concentrations, e.g., dosing in relation to food, co-medications, renal and liver disease, and genetic polymorphism of cytochrome CYP2C19 [15,16].

Recently, Pascual *et al*. reported that treatment failure was more frequent in patients with voriconazole blood levels ≤ 1 mg/l (6/13, 46%) than in those with voriconazole levels > 1 mg/l (5/39, 12%, $P = 0.02$) [6]. Miyakis *et al.* also found that successful outcomes were more frequent among patients with a median trough voriconazole concentration > 2.2 mg/l [14]. In contrast to these results, initial voriconazole trough levels in our study were not related to successful clinical response. The reasons for this finding are not clear but could possibly be the result of different definitions of clinical response and different times of measurement of voriconazole trough levels. Interestingly, the CYP2C19 non-wild (mutant) type is generally found in 60–70% of Asian individuals but in only 30% of white and black Americans [5]. Intuitively,

Table 4 Factors associated with two-week successful response after voriconazole therapy.

Characteristics	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Invasive aspergillosis				
Proven	–	0.49		
Probable	1.6 (0.5–4.8)	0.4		
Possible	0.9 (0.3–2.6)	0.78		
Neutropenia at enrollment	0.2 (0.1–0.8)	0.01	0.1 (0.0–0.6)	0.008
Immunosuppression[a]	0.2 (0.1–0.6)	0.005	0.1 (0.0–0.5)	0.004
Reason for voriconazole therapy				
Failure of initial therapy	0.3 (0.1–1.3)	0.09		
Intolerance to initial therapy	2.3 (0.5–10.4)	0.47		
Switch from IV amphotericin B to oral therapy	–	0.49		
Initial antifungal agent				
Conventional amphotericin B	3.4 (1.1–13.0)	0.04	4.3 (0.3–58.8)	0.27
Liposomal amphotericin B	0.6 (0.1–4.2)	0.99		
Itraconazole	0.5 (0.1–2.8)	0.67		
Caspofungin	–	0.23		
Intravenous administration of voriconazole	0.1 (0.0–0.7)	0.005	0.2 (0.0–2.1)	0.18
Low initial voriconazole trough level (≤ 2 mg/l)	0.8 (0.2–3.0)	0.73		

[a]Immunosuppression was defined as concomitant use of cyclosporine or tacrolimus at least two weeks at the time of starting voriconazole therapy.

poor metabolizers may have higher levels of voriconazole trough levels and this might result in better clinical response. However, successful response rates in our study were lower (2-week, 4-week, 8-week, and 12-week; 50%, 60%, 58%, and 52% respectively) than in Pascual's study (79%) [6]. Most patients (79%, 41/52) received voriconazole as salvage therapy in our study because voriconazole use as primary therapy in patients with IA was not covered by the Korean National Health Insurance, while most patients (64%, 33/52) received voriconazole as primary therapy in the Pascual study [6]. This low response rate in salvage therapy might dilute favorable factor in Asian patients and make it more difficult to demonstrate a difference between two groups with lower response rates. Two-week response rate is too early to detect true difference between low and high voriconazole trough level. This hypothesis can be explained by a trend toward a better outcome with higher voricnoazole level at 8-week and 12-week response rates, although these differences did not reach the statistical significance. In addition, the inclusion of possible IA which might include non-IA patients could dilute the true difference between the two groups.

This study has several limitations. We did not examine CYP2C19 polymorphism, and so could not measure how many patients with poor metabolisms were included in our study. In addition, we did not analyze the association between CYP2C19 polymorphism and clinical outcomes or voriconazole trough levels. We detected a 6% difference in clinical successful responses between voriconazole trough levels ≤ 2 mg/l and > 2 mg/l, although the difference was not statistically significant. However, it is possible that our sample size was too small to achieve statistical significance. Our study, similar to others in the field [6,11–14,16], included small number of patients and therefore lacked enough power to detect modest effects of voriconazole levels on clinical outcome. Some may argue that the cut-off value of initial voriconazole level is arbitrary. The previous studies suggest that voriconazole trough blood levels should be measured after 1 week of therapy for dose adjustment to target values of 2–6 mg/L [14,17]. So, we used 2 mg/l as the cut-off value of initial trough level in our routine clinical practice. Furthermore, additional analyses using different cut-off values such as 0.5, 1, 3, and 4 mg/l revealed the similar results. Finally, this was an observational study, not one designed to prove causality between voriconazole trough levels and outcome where as a randomized, controlled trial would provide more valid data.

In conclusion, the present study suggests that initial voriconazole trough levels do not significantly affect clinical outcomes of invasive aspergillosis at two weeks after voriconazole therapy in patients with hematologic malignancies. Further studies of prospective design are needed to establish optimal timing and levels for voriconazole drug monitoring.

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