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Original Article

Impact of flavin-containing monooxygenase 3 and CYP2C19 genotypes on plasma disposition and adverse effects of voriconazole administered orally in immunocompromised patients☆

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ABSTRACT

Flavin-containing monooxygenase (FMO) 3 together with cytochrome P450 (CYP) 2C19 play a significant role in voriconazole *N*-oxidation. This study aimed to evaluate the influence of FMO3 and CYP2C19 genotypes on the plasma disposition and adverse effects of voriconazole in immunocompromised patients. Sixty-five Japanese immunocompromised patients receiving oral voriconazole were enrolled. Predose plasma concentrations of voriconazole and *N*-oxide were determined at day 5 or later. The adverse effects of voriconazole and the FMO3 and CYP2C19 genotypes were investigated. The patients with FMO3 E158K/E308G had a lower plasma concentration of voriconazole. The metabolic ratio to *N*-oxide was significantly higher in the FMO3 E158K/E308G group than in the wild group. In contrast, FMO3 V257M was not associated with the plasma concentration of voriconazole. No significant difference was observed in the saturation index, defined as a correlation coefficient of the regression line between the absolute plasma concentration of voriconazole and the inverse value of the metabolic ratio to *N*-oxide, between the FMO3 genotypes. CYP2C19 phenotype did not affect the plasma concentration and metabolic ratio of voriconazole. The saturation index of voriconazole rose in the order of CYP2C19 extensive, intermediate, and then poor metabolizer groups. However, the FMO3 and CYP2C19 genotypes and their associated voriconazole pharmacokinetics did not have an effect on the incidence of adverse effects. In conclusion, FMO3 E158K/E308G decreased the plasma concentration of voriconazole through its higher metabolic activity. The FMO3 genotype altered the plasma exposure of voriconazole, while the CYP2C19 phenotype affected the metabolic capacity in immunocompromised patients.

1. Introduction

Voriconazole, a triazole antifungal agent, is commonly used for the treatment of candidiasis and invasive aspergillosis. Although voriconazole has high therapeutic efficacy, several adverse effects such as hepatic toxicity, visual changes, and photosensitivity are often observed in clinical settings. A good relationship between the successful therapeutic efficacy and plasma concentration of voriconazole were reported in fungal infectious diseases [1–3]. In addition, the plasma disposition of voriconazole was associated with the incidence of adverse effects [3–5]. The pharmacokinetics of voriconazole show a large variability that depends on the clinical dose. This pharmacokinetic variation is caused by drug-drug interactions, inflammation, and genetic polymorphism of drug metabolizing enzymes [6–9].

Voriconazole pharmacokinetics are characterized by high oral bioavailability and high tissue penetration. In humans, voriconazole is primarily metabolized in the liver and the majority of its metabolites are excreted in the urine. Voriconazole *N*-oxide, which accounts for 72% of the circulating metabolites of voriconazole, results from fluoropyrimidine *N*-oxidation via mainly cytochrome P450 (CYP) isozymes [5]. Although the *N*-oxide has minimal antifungal activity compared with voriconazole, it has been found to inhibit the metabolic activity of CYPs *in vitro*. Our previous study demonstrated that metabolic saturation of the *N*-oxidation pathway contributed to the nonlinear pharmacokinetics

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of voriconazole [10]. A nonlinear pharmacokinetic profile of voriconazole was also observed in the clinical dose range.

Voriconazole is mainly metabolized by CYP2C19 and 3A4, and CYP2C19 contributes largely to the significant pharmacokinetic variability. However, most interindividual variation in the function of CYP2C19 can be explained by *CYP2C19*2* and **3* [11–13]. Both mutations decrease the enzyme activity by the quantitative reduction of enzyme protein. Voriconazole clearance in *CYP2C19*2* or **3* carriers has been reported to result in approximately 4-fold higher plasma exposure to voriconazole than *CYP2C19*1* carriers [14]. Being a poor metabolizer (PM) with these mutant alleles could be a risk factor for adverse effects correlating to exposure of voriconazole. In contrast, there were no associations between the CYP2C19 phenotype, hepatotoxicity, and neurotoxicity in meta-analysis [15]. To date, the plasma disposition and metabolic saturation of voriconazole can not be fully explained using only CYP2C19 phenotype [10].

Flavin-containing monooxygenase (FMO), an oxidative drug metabolizing enzyme, has many substrates including trimethylamine and benzydamine. A non-clinical study demonstrated that 25–30% of the human microsomal metabolism of voriconazole can be catalyzed by FMO with the remaining approximately 70% catalyzed by CYPs [16]. An earlier clinical report demonstrated that several FMO3 genetic mutations cause amino acid substitution to alter the affinity for a particular substrate [17]. The contributions of FMO3 and CYP2C19 genotypes to the plasma disposition of and adverse responses to voriconazole remain to be clarified in clinical settings.

The aim of this study was to evaluate the influences of the FMO3 and CYP2C19 genotypes on the plasma disposition and adverse effects of voriconazole in immunocompromised patients.

2. Materials and methods

2.1. Ethics

The study was performed in accordance with the Declaration of Helsinki and its amendments, and the protocol was approved by the Ethics Committee of Hamamatsu University School of Medicine. The patients received information about the scientific aim of the study and each patient provided written informed consent.

2.2. Study population and schedule

The present study was an observation study conducted at Hamamatsu University Hospital. A total of 65 Japanese immunocompromised patients receiving oral voriconazole (Vfend® tablet, Pfizer Japan Inc, Tokyo, Japan) for prophylaxis or treatment of a fungal infection were enrolled between September 2016 and December 2017. Each patient received 100–300 mg voriconazole twice daily for at least 5 days. Exclusion criteria were as follows: patients (1) who were under 16 years of age; (2) who were being co-treated with a strong CYP2C19 or CYP3A4 modifier including rifampicin, ritonavir, or carbamazepine, a long-acting barbiturate, or a macrolide antibiotic; (3) with nephropathy (serum creatinine > 2.0 mg/dL) or who were being treated with hemodialysis or peritoneal dialysis; (4) with hepatopathy (total bilirubin > 2.0 mg/dL); (5) with a chronic active inflammatory disease (C-reactive protein > 5 mg/dL); (6) with bone-marrow transplantation; and (7) with poor compliance with respect to their medications based on electronic medical records. A blood sample (2 mL) was collected for the first time just before dosing on the 5th day after initiation of voriconazole therapy or later. This study was registered in the University Hospital Medical Information Network clinical trial registry system (UMIN-CTR UMIN000023974).

2.3. Determination of plasma voriconazole and its N-oxide

Voriconazole and *N*-oxide were purchased from Toronto Research Chemicals Inc. (Toronto, Ontario, Canada). Plasma was separated by centrifugation of the blood samples at 1670 ×*g* at 4 °C for 10 min. Plasma concentrations of voriconazole and *N*-oxide were simultaneously determined using isocratic high performance liquid chromatography coupled to ultraviolet detection [18]. The plasma concentrations of voriconazole and *N*-oxide were linear ($r > 0.999$) over the range of 0.1–8.0 μg/mL. The intra- and inter-assay accuracies were 99.0–101.3% and 96.2–112.9% for voriconazole and 98.8–109.1% and 98.8–101.7% for *N*-oxide, respectively. The intra- and inter-assay precisions were 2.2–4.8% and 4.6–9.5% for voriconazole and 1.6–2.1% and 2.4–12.6% for *N*-oxide, respectively. The lower limit of quantitation was 0.1 μg/mL for both voriconazole and *N*-oxide.

2.4. Genotyping of FMO3 and CYP2C19

DNA was extracted from peripheral venous whole blood with a DNA Extractor WB Kit (Wako Pure Chemicals, Osaka, Japan). FMO3 genotypes (E158K, V257M, and E308G) were determined using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay previously described [19]. CYP2C19 genotypes (*G636A* and *G681A* on exon 4 and exon 5) were also determined using PCR-RFLP amplification techniques previously described [20], with some modification. *CYP2C19*1* as the wild type was identified if no **2* or **3* genotypes were detected.

2.5. Evaluation of adverse effects

The adverse effects of voriconazole were obtained from the patient medical records. The degree of severity was graded according to the National Cancer Institute Common Terminology Criteria for adverse events (CTCAE v4.0). Serum levels of total bilirubin (>1.3 mg/dL), γ-glutamyl transpeptidase (>50 IU/L), aspartate aminotransferase (>30 IU/L), and alanine aminotransferase (>30 IU/L) were evaluated for diagnosing hepatotoxicity during voriconazole treatment. Elevation of adverse effect grade of CTCAE v4.0 after administration were regarded as the hepatic failure in patients who met the above value before enrollment. Visual changes and photosensitivity were also investigated from medical records.

2.6. Pharmacokinetic analyses

Plasma exposures of voriconazole and *N*-oxide were evaluated as absolute plasma concentration or its dose and body weight-normalized value. Metabolism of voriconazole was estimated by the plasma concentration ratio of *N*-oxide to voriconazole as the metabolic ratio. The saturation index, defined as a correlation coefficient of the regression line between the absolute plasma concentration of voriconazole and the inverse value of the metabolic ratio to *N*-oxide, was evaluated as the degree of *N*-oxidation metabolic saturability of voriconazole.

2.7. Statistical analyses

All statistical analyses were performed using IBM SPSS statistics v22 (IBM Japan Ltd., Tokyo). The patients were classified into the following three groups: wild type group, E158K/E308G genotype group, and V257M genotype group for determining the genotypes of FMO3. With respect to the determination of CYP2C19 phenotype, the patients were classified into the following three groups: extensive metabolizer (EM) group,

*CYP2C19*1/*1*; intermediate metabolizer (IM) group, *CYP2C19*1/*2* and *CYP2C19*1/*3*; and PM group, *CYP2C19*2/*2*, **2/*3*, and **3/*3*. The influences of FMO3 and CYP2C19 genotypes on the plasma disposition parameters of voriconazole were analyzed using the Kruskal-Wallis test and *post-hoc* Mann-Whitney *U* test with the Dunn correction between the genotypes. Differences in the saturation index obtained from each group of FMO3 or CYP2C19 genotype were determined by testing the *t*-value. Stepwise multiple linear regression analysis ($P < 0.05$ to enter and $P > 0.10$ to remove) was performed to assess the dependence between adverse effects including hepatotoxicity or photosensitivity to plasma concentrations of voriconazole and *N*-oxide, FMO3, and CYP2C19 genotypes. All values are expressed as the median and interquartile range (IQR) unless otherwise stated. A $P < 0.05$ was considered to indicate statistical significance.

3. Results

3.1. Patient characteristics

Table 1 shows the patient characteristics in this study population. Underlying diseases were pulmonary aspergillosis (n = 30), acute myelocytic leukemia (n = 13), possible fungus infection (n = 12), lymphoma malignum (n = 9), and candida esophagitis (n = 1). Voriconazole concentration on trough (median and IQR, 2.59 and 1.44–5.0 μg/mL), *N*-oxide concentration on trough (median and IQR, 1.56 and 1.09–1.99 μg/mL). The number of patients with the wild type, E158K, V257M, and E308G genotypes of FMO3 were 27 (41.5%), 20 (30.7%), 18 (27.7%), and 20 (30.7%), respectively. FMO3 genotypes between E158K and E308G were completely linked. No patient had genotypes in both FMO3 E158K/E308G and V257M. There were 22 (33.8%), 33 (50.8%), and 10 (15.4%) patients with CYP2C19 EM, IM, and PM, respectively.

3.2. Influence of FMO3 genotypes on voriconazole pharmacokinetics

The median dose (mg/kg) of voriconazole was 3.85 mg/kg in the FMO3 wild type group, 3.48 mg/kg in the E158K/E308G group, and 3.75 mg/kg in the V257M group. The median plasma concentration of voriconazole was 0.78 μg/mL per mg/kg in the FMO3 wild type group, 0.49 μg/mL per mg/kg in the E158K/E308G group, and 0.58 μg/mL per mg/kg in the V257M group (Fig. 1). The plasma voriconazole concentration in the FMO3 E158K/E308G group was significantly lower than that in the wild type group ($P = 0.021$). In contrast, no significant difference was observed in the plasma concentrations of *N*-oxide between the FMO3 genotypes. The metabolic ratio of voriconazole in FMO3 E158K/E308G was significantly higher than that in the wild type group ($P = 0.024$). The inverse value of the metabolic ratio was strongly correlated with the absolute plasma concentration of voriconazole in each FMO3 genotype group. The saturation indexes in the FMO3 wild type, E158K/E308G, and V257M groups were 0.628 ($r = 0.714$, $P < 0.001$), 0.863 ($r = 0.869$, $P < 0.001$), and 0.723 ($r = 0.487$, $P < 0.001$), respectively (Fig. 2). No significant difference was observed in the saturation index between the FMO3 genotypes.

Table 1
Patient demographics.

Number of patients, male/female	65, 43/22
Dose (mg twice daily)	200 (150–200)
Age (years)	67 (59–73)
Body weight (kg)	51.1 (40.8–56.7)
Serum albumin (g/dL)	2.9 (2.3–3.4)
Total bilirubin (mg/dL)	0.6 (0.4–0.7)
Aspartate aminotransferase (IU/L)	27 (18–41)
Alanine aminotransferase (IU/L)	24 (16–41)
γ-glutamyl transpeptidase (IU/L)	24 (16–41)
Blood urea nitrogen (mg/dL)	13.7 (11.2–19.8)
Estimated glomerular filtration rate (mL/min/1.73 m^2)	70.8 (55.0–94.3)
Serum creatinine (mg/dL)	0.69 (0.54–0.98)
C-reactive protein (mg/dL)	1.66 (0.41–3.37)
White blood cell (counts/μL)	6535 (3475–7615)

Data are expressed as median and interquartile range in parentheses.

3.3. Influence of CYP2C19 phenotypes on voriconazole pharmacokinetics

The median dose (mg/kg) of voriconazole was 3.80 mg/kg in the CYP2C19 EM group, 3.53 mg/kg in the CYP2C19 IM group, and 3.58 mg/kg in the CYP2C19 PM group. The median plasma concentrations of voriconazole were 0.51 μg/mL per mg/kg in the CYP2C19 EM group, 0.78 μg/mL per mg/kg in the CYP2C19 IM group, and 0.53 μg/mL per mg/kg in the CYP2C19 PM group. No significant difference was observed in the plasma concentration of voriconazole between the CYP2C19 phenotypes (Fig. 3). The plasma *N*-oxide concentration in the CYP2C19 PM group was significantly lower than that in the EM group ($P = 0.044$). No significant difference was observed in the metabolic ratio of voriconazole between the CYP2C19 phenotypes. The inverse value of the metabolic ratio was strongly correlated with the absolute plasma concentration of voriconazole in each CYP2C19 group. The saturation indexes in the CYP2C19 EM, IM and PM groups were 0.505 ($r = 0.782$, $P < 0.01$), 0.703 ($r = 0.755$, $P < 0.001$), and 0.923 ($r = 0.939$, $P < 0.001$), respectively (Fig. 4). Significant differences were observed in the saturation index between the CYP2C19 phenotype groups (EM vs IM: $P < 0.01$; EM vs PM: $P < 0.01$; IM vs PM: $P = 0.027$).

3.4. Influence of genotypes on adverse effects

Three patients had total bilirubin elevation, 4 aspartate aminotransferase elevation, 4 alanine aminotransferase elevation, 4 γ-glutamyl transpeptidase aspartate aminotransferase elevation, and 2 visual changes. No patient had photosensitivity in this study population. All observed cases were graded as less than II. The incidence of adverse effects was not associated with the FMO3 ($R^2 = 0.067$, $P = 0.872$) and CYP2C19 ($R^2 = 0.094$, $P = 0.516$) genotypes in multiple regression analysis.

3.5. Relationship between voriconazole pharmacokinetics and adverse effects

The absolute plasma concentration of voriconazole was not correlated with the clinical laboratory values associated with hepatic toxicity including serum total bilirubin, aspartate aminotransferase, alanine aminotransferase, and γ-glutamyl transpeptidase. In contrast, the absolute plasma concentration of *N*-oxide was correlated with the serum level of total bilirubin ($R^2 = 0.095$, $P = 0.043$). The incidences of visual changes and photosensitivity were not associated with the absolute plasma concentration of voriconazole ($R^2 = 0.031$, $P = 0.874$) and *N*-oxide ($R^2 = 0.031$, $P = 0.874$).

4. Discussion

The contribution of FMO3 genotype to voriconazole pharmacokinetics remains to be clarified in clinical settings. The present study evaluated the influence of FMO3 and CYP2C19 genotypes on the plasma disposition and adverse effects of voriconazole in immunocompromised patients. The FMO3 E158K/E308G genotype

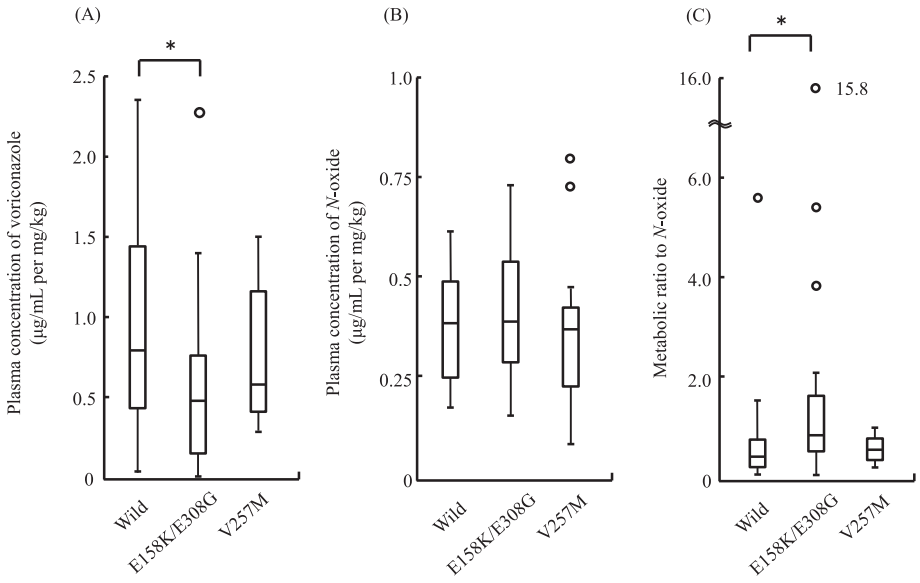

Fig. 1. Influence of FMO3 genotype on dose-normalized plasma concentration of voriconazole (A) and *N*-oxide (B), and their ratio (C) in immunocompromised patients. Box plots represent the medium, 25th, and 75th percentiles. $^{*}P < 0.05$ was considered to indicate statistical significance.

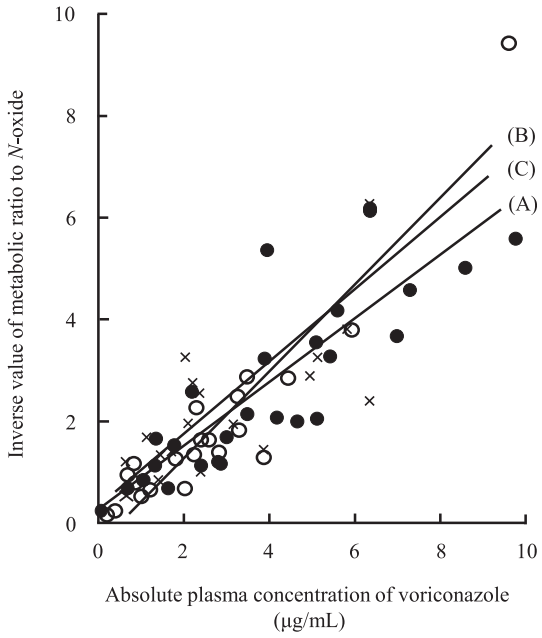

Fig. 2. Correlation between the absolute plasma concentration of voriconazole and inverse value of the metabolic ratio to *N*-oxide in immunocompromised patients. (A) FMO3 wild type (closed circle), (B) E158K/E308G (open circle), and (C) V257M (cross) groups.

decreased the plasma concentration of voriconazole through its higher metabolic activity, while the CYP2C19 phenotypes did not. The CYP2C19 phenotype but not the FMO3 genotype altered the metabolic saturation of voriconazole. However, these genotypes were not directly associated with the incidence of the adverse effects. These data suggest that FMO3 and CYP2C19 genotypes are the factors determining the plasma exposure of and the metabolic capacity of voriconazole, respectively. To the best of our knowledge, this is the first report to evaluate the impact of FMO3 genotype on plasma disposition and adverse effects of voriconazole in clinical settings.

FMO3 E158K/E308G genotype resulted in the lowest plasma concentrations and the highest metabolic ratio of voriconazole. These data indicate that the FMO3 E158K/E308G genotype with higher metabolic activity decreases the plasma concentration of voriconazole. Glucocorticoids administration slightly increase the metabolism of voriconazole, but not alter voriconazole and N-oxide concentrations [21]. Although eleven patients received glucocorticoid therapy in this study, none had E158K/E308G allele. In contrast, the FMO3 V257M genotype did not alter the plasma concentration of voriconazole. The regression line of each FMO3 genotype group between the absolute plasma concentration of voriconazole and the inverse value of the metabolic ratio showed a strong positive correlation from the vicinity of the origin. However, the saturation index was not associated with the FMO3 genotypes. The FMO3 E158K/E308G genotype has been reported to alter the affinity to substrate *in vitro* [22]. With respect to voriconazole, the E158K/E308G genotype increased the voriconazole *N*-oxide metabolism in immunocompromised patients. This result suggests that the FMO3 E158K/E308G genotype is a major factor determining the plasma concentration of voriconazole in humans.

To date, no report has been published on the relationship between the FMO3 genotype including E158K/E308G and voriconazole pharmacokinetics. Twenty-nine percent of the enrolled patients in this study had the FMO3 E158K/E308G genotype. FMO3 is mainly distributed in the adult liver and is involved in *N*- or *S*-oxidation of various drugs [17]. The FMO3 M66I or R492W genotype is responsible for fish-odor syndrome as a result of complete inactivation of the enzyme [22]. However, their genetic frequencies are very low. The frequency of the FMO3 E158K/E308G genotype differs among the races and its frequency is higher in African-Americans than in Asians [23]. The plasma concentrations of voriconazole and *N*-oxide in the present study were similar to the other Japanese report [24]. The clinical impact of FMO3 E158K/E308G on the plasma disposition of voriconazole may differ among the races.

The plasma concentration of *N*-oxide was significantly higher in the CYP2C19 EM groups than in the PM group in this study, while the metabolic ratio to *N*-oxide was slightly lower. Although few reports have evaluated the metabolic ratio of voriconazole for each CYP2C19 phenotype, our results do not contradict the mechanism.

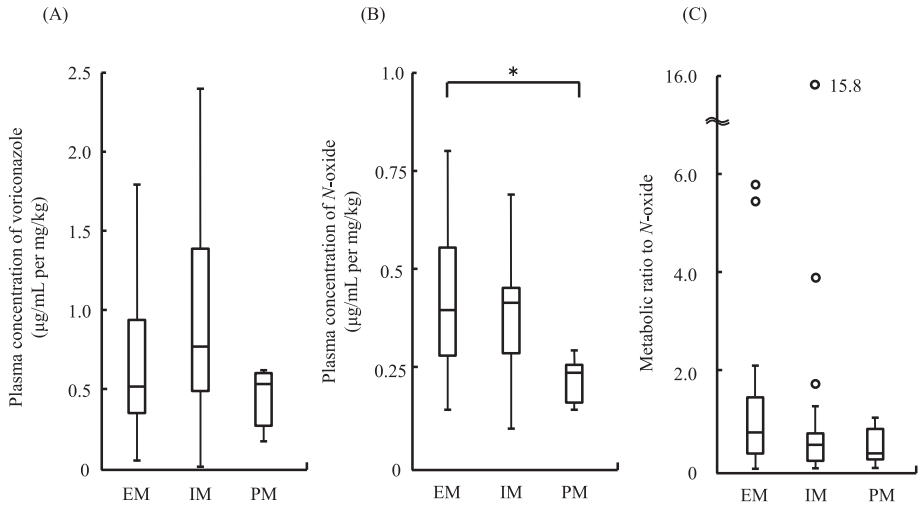

Fig. 3. Influence of CYP2C19 phenotype on dose-normalized plasma concentration of voriconazole (A) and *N*-oxide (B), and their ratio (C) in immunocompromised patients. Box plots represent the medium, 25th, and 75th percentiles. $^{*}P < 0.05$ was considered to indicate statistical significance.

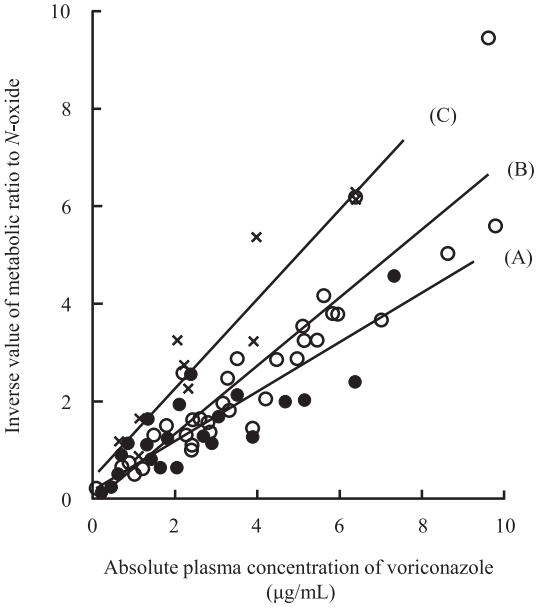

Fig. 4. Correlation between the absolute plasma concentration of voriconazole and inverse value of the metabolic ratio to *N*-oxide in immunocompromised patients. (A) CYP2C19 EM (closed circle), (B) IM (open circle), and (C) PM (cross) groups.

While, median voriconazole concentration was lower in the CYP2C19 PM group compared to the previous report [10]. Although the sample size was limited in the CYP2C19 PM group (n = 10), four patients with FMO3 E158K/E308G showed the decreased voriconazole concentration. It may cause lower median voriconazole concentration in CYP2C19 PM. The influence of CYP2C19 phenotype on voriconazole concentration is still controversial. In several earlier reports, the CYP2C19 phenotype could explain the individual differences in the plasma concentration of voriconazole [25]. However, an inflammatory state also strongly affected the plasma concentration of voriconazole in Japanese patients [21]. Voriconazole concentration was higher in the CYP2C19 IM group compared to the EM group and the PM group. The influence of CYP2C19 phenotype on voriconazole concentration is still controversial. In this study, other confounding factors may affect voriconazole concentration in the PM group, probably due to its small sample size (n = 10). The frequency of CYP2C19 EM is much greater in Caucasians (70–75%) than in Asians (30–40%) [26]. In addition, the frequency of the CYP2C19*17 allele classified as ultrarapid metabolizer in Japanese is 1% [27], while that in Caucasians is 25% [28,29]. The differences in frequency of the CYP2C19 phenotype between the races may be responsible for the impact of the FMO3 genotype on the pharmacokinetic variability of voriconazole.

The saturation index showed a significant difference between the CYP2C19 phenotypes, but not between the FMO3 genotypes. The saturation index is defined as an indicator for capacity of the voriconazole *N*-oxidation pathway [10]. The value of the saturation index is expressed as 1/maximum reaction velocity (V_{max})·time (t) with the conversion formula of the Michaelis-Menten equation. Our data suggest that the CYP2C19 phenotypes but not the FMO3 genotype are associated with the variation in the metabolic capacity of voriconazole. The patients with the FMO3 E158K/E308G genotype may have a smaller Km value than the wild type, indicating that it has high affinity for voriconazole. These results confirm that the FMO3 E158K/E308G genotype is a major factor for determining the plasma concentration of voriconazole.

The FMO3 and CYP2C19 genotypes did not directly have an effect on the incidences of voriconazole adverse effects in this study. A few earlier reports demonstrated the influence of the CYP2C19 phenotypes on the clinical response to voriconazole. Li et al. reported that no association between the CYP2C19 phenotype, hepatotoxicity, and neurotoxicity in a meta-analysis [15]. Few clinical reports have been published on the influence of FMO3 genotype on the incidence of adverse effects of voriconazole. Voriconazole pharmacokinetics are related to the adverse effects [4]. The present study demonstrated that the FMO3 genotype potentially influences the adverse effects of voriconazole through the alteration of plasma exposure. The present study did not enroll patients with acute hepatic toxicity within 5 days after the treatment according to the exclusion criteria. Further study focusing on the relationship between FMO3 genotype and acute hepatic toxicity is needed.

Absolute the plasma concentration of voriconazole was not strongly related to the incidence of hepatic toxicity, the *N*-oxide concentration was positively associated with the serum level of total bilirubin. Veringa et al. also reported a positive correlation between the plasma *N*-oxide concentration and serum total bilirubin [30]. Recent reports have demonstrated that *N*-oxide is the causative substance of photosensitivity [31]. In addition, *N*-oxide,

which acts as a generator of reactive oxygen species, was reported to be a candidate for a skin cancer-inducing substance in an epidemiological survey [31]. In the present study, the patients with CYP2C19 EM had the higher concentration of *N*-oxide. For the CYP2C19 EM population, voriconazole therapy may be carefully observed from the viewpoint of safety. Genotyping of CYP2C19 may be beneficial to patients in the safer use of voriconazole. Further research, including the evaluation of plasma N-oxide, may possibly reveal the factors responsible for development of the hepatotoxicity and phototoxicity associated with voriconazole therapy.

This study has a few limitations that need to be addressed. First, clinical use of the data in the present study is limited to Japanese patients and to immunocompromised patients. Earlier studies demonstrated that inflammation and concomitant drug administration strongly affect voriconazole pharmacokinetics [6,7,21,30]. The present study excluded patients with inflammation and drug-drug interactions according to the exclusion criteria. Analyses including patients with inflammation and drug-drug interactions or other races would confirm the genetic impacts in clinical settings. Second, the incidence of photosensitivity may not have been accurately estimated in this study. This study enrolled only inpatients. Several reports have described that the development of voriconazole photosensitivity induced by sunlight is time dependent [31,32]. For outpatients, a higher incidence of voriconazole-induced photosensitivity may be observed. Third, the study was limited to patients treated with the oral formulation. The influence of intestinal condition on voriconazole bioavailability is so controversial that its intestinal absorption process were not able to assess accurately in our population. The contributions of the FMO3 and CYP2C19 genotypes to the absorption process of voriconazole may be different from that of the liver metabolism process. Our results may not be observed in patients treated with an intravenous formulation.

The clinical implications of FMO3 genotyping on voriconazole therapy have not been clarified in immunocompromised patients. The FMO3 E158K/E308G genotype decreases the plasma concentration of voriconazole through higher metabolic activity. A good relationship between the successful therapeutic efficacy and plasma concentration of voriconazole was reported in fungal infectious diseases [1–3]. Patients with the FMO3 E158K/E308G genotype potentially experience lower antifungal efficacy because of the lowering of the plasma voriconazole concentration. Thus, the genotyping of FMO3 E158K/E308G may contribute to the dose adjustment from the viewpoint of effective antifungal treatment.

In conclusion, the FMO3 E158K/E308G genotype had a decreased plasma concentration of voriconazole through its higher metabolic activity. The FMO3 genotype changed the plasma exposure of voriconazole, while the CYP2C19 phenotype affected the metabolic capacity in immunocompromised patients.

Conflicts of interest

The authors declare there are no conflicts of interest.

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