Published in final edited form as:
Pharmacogenomics. 2014 June ; 15(8): 1065–1078. doi:10.2217/pgs.14.53.

Voriconazole plasma concentrations in immunocompromised pediatric patients vary by *CYP2C19* diplotypes

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Abstract

Aim—Our objective was to describe the association between voriconazole concentrations and *CYP2C19* diplotypes in pediatric cancer patients, including children homozygous for the *CYP2C19*17* gain-of-function allele.

Materials & methods—A linear mixed effect model compared voriconazole dose-corrected trough concentrations (n = 142) among *CYP2C19* diplotypes in 33 patients (aged 1–19 years). Voriconazole pharmacokinetics was described by a two-compartment model with Michaelis −Menten elimination.

Results—Age (p = 0.05) and *CYP2C19* diplotype (p = 0.002) were associated with voriconazole concentrations. *CYP2C19*17* homozygotes never attained therapeutic concentrations, and had lower dose-corrected voriconazole concentrations (median: 0.01 μg/ml/mg/kg; p = 0.02) than *CYP2C19*1* homozygotes (median: 0.07 μg/ml/mg/kg). Modeling indicates that higher doses may produce therapeutic concentrations in younger children and in those with a *CYP2C19*17/*17* diplotype.

Conclusion—Younger age and the presence of *CYP2C19* gain-of-function alleles were associated with subtherapeutic voriconazole concentrations. Starting doses based on age and

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Financial & competing interests disclosure
The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.
No writing assistance was utilized in the production of this manuscript

Ethical conduct of research
The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved

CYP2C19 status could increase the number of patients achieving therapeutic voriconazole exposure.

Keywords

antifungals; CYP2C19; personalized medicine; pharmacogenetics; voriconazole

Background

Pediatric cancer patients who experience prolonged periods of immunosuppression caused by myeloablative hematopoietic stem cell transplantation or myelosuppressive chemotherapy are highly susceptible to invasive fungal infections [1–3] . Voriconazole is a triazole antifungal agent that has potent activity against a broad spectrum of clinically important pathogens, and is recommended as a primary treatment for invasive aspergillosis in immunocompromised patients [4–8]. Because invasive fungal infections are associated with significant morbidity and mortality, promptly attaining therapeutic voriconazole plasma concentrations is imperative for achieving a favorable response [9–11]. An initial low voriconazole plasma concentration, even when therapeutic drug monitoring is subsequently utilized to target a specific concentration, may be a risk factor for increased mortality [12]. However, elevated voriconazole concentrations can result in adverse effects such as neurotoxicity and hepatotoxicity [13–17]. Pediatric patients have large interindividual variation in voriconazole pharmacokinetic parameters, which may contribute to delays in achieving appropriate voriconazole concentrations [3,7,18,19]. Identifying patient characteristics, such as genetic variants in pharmacogenes, that influence voriconazole plasma concentrations will facilitate the individualization of voriconazole dosing, allowing for faster achievement of therapeutic concentrations.

Voriconazole exhibits nonlinear pharmacokinetics, possibly due to saturable metabolism [3,18,20–22]. Children have lower voriconazole plasma concentrations than adults when administered weight-equivalent doses, which may be partially explained by decreased voriconazole oral bioavailability in children [22–24]. The role of gastrointestinal transporters or metabolism in voriconazole absorption is not clear [21]. Age-dependent differences in voriconazole plasma concentrations are also explained by pediatric patients having a higher elimination capacity of voriconazole due to increased voriconazole metabolism [3,7,19,25]. Voriconazole is metabolized by CYP2C19, CYP3A4, and to a lesser extent by CYP2C9, to compounds that have minimal antifungal activity [22,26]. CYP2C19 and FMO3 have been demonstrated to contribute to voriconazole metabolism in human liver microsomes [3,26,27]. *CYP2C19* is a highly polymorphic pharmacogene, and genetic variants in the *CYP2C19* gene locus may alter CYP2C19 substrate metabolism resulting in interindividual phenotypic variability [28–30]. Therefore, *CYP2C19* genetic variants may have a clinically important impact on voriconazole concentrations in pediatric patients [3,31].

Limited data are available describing the correlation between *CYP2C19* genetic variants and voriconazole plasma concentrations in pediatric patients [3,18,19,31]. *CYP2C19* diplotypes predictive of intermediate or poor metabolism have been demonstrated to be associated with elevated voriconazole plasma concentrations when compared with pediatric patients with

normal (extensive) CYP2C19 metabolism [3,31]. However, other studies have suggested that *CYP2C19* polymorphisms may not be predictive of voriconazole plasma concentrations in a clinical setting [18,19]. Previous investigations either did not include patients who carried the *CYP2C19*17* allele, which is responsible for CYP2C19 ultrarapid metabolism, or combined extensive and ultrarapid metabolizers into one category. Therefore, there is a lack of data in pediatric patients to illustrate whether CYP2C19 ultrarapid metabolizers have decreased voriconazole plasma concentrations with standard doses. In this retrospective study focusing on immunocompromised pediatric patients, we present data describing the correlation between voriconazole plasma concentrations and *CYP2C19* diplotypes that are representative of all four phenotypic groups (i.e., ultrarapid, extensive, intermediate and poor metabolizers), including individuals homozygous for the *CYP2C19*17* gain-of-function allele.

Materials & methods

Study design & patient population

This study was designed as a single-center retrospective review focusing on immunocompromised patients with cancer treated at St Jude Children's Research Hospital (TN USA). Patients were prescribed voriconazole for either antifungal prophylaxis or treatment of an invasive fungal infection. Every patient genotyped for *CYP2C19* who was prescribed oral voriconazole prior to 20 March 2013 and had at least one voriconazole plasma trough concentration determined was eligible for study inclusion. Any patient with an ambiguous *CYP2C19* diplotype or any patient carrying a *CYP2C19* allele of uncharacterized enzymatic function was excluded owing to the inability to clearly assign a phenotype. Individual voriconazole plasma trough concentrations were excluded if the concentration was obtained while a patient was on continuous oral feeds, the voriconazole concentration was not a trough, or the voriconazole concentration was not obtained at steady state. To be considered a trough concentration, the blood sample for voriconazole analysis must have been obtained within 2 h of the scheduled trough. Patients were considered to be at steady state after 5 days of voriconazole treatment without a loading dose or after 2 days of treatment following a loading dose [22]. Five individuals received intravenous voriconazole before being switched to an oral formulation; these patients must have been taking oral voriconazole for at least 2 days for the trough concentrations to be considered for analysis. The initial recommended voriconazole maintenance dose in patients 12 years of age and older was 400 mg/day (200 mg administered twice daily) [32–35], and in those less than 12 years of age the initial recommended voriconazole maintenance dose was 14 mg/kg/day (7 mg/kg administered twice daily) [23,32,34,36,37]. Although patients were counseled not to take oral voriconazole within 2 h of food, confirmation of the timing of voriconazole administration in relation to meals was not available. All patients were enrolled on an institutional review board-approved research protocol, Pharmacogenetic Determinants of Treatment Response in Children (PGEN5).

Every voriconazole plasma trough concentration (μg/ml) and the corresponding daily dose (mg/kg) was recorded along with the covariates age, ancestry, gender, and any prescribed drug documented to alter voriconazole plasma concentrations [4,22,38,39]. Ancestry was

determined using DMET Plus (Affymetrix, CA, USA) genotyping results by applying a naive Bayesian classifier to cluster patients into four major groups (i.e., African, Asian, European or Hispanic ancestry) based on population-specific allele frequencies provided by Affymetrix. A particular ancestry group was assigned if the posterior probability was greater than 90%.

Genotyping & phenotype assignment

Genotyping was performed at the Medical College of Wisconsin (WI, USA) in a Clinical Laboratory Improvement Amendments-certified laboratory using the DMET Plus array. Previously, the DMET Plus genotyping results were demonstrated to be concordant with orthogonal genotyping methods [40]. DMET Plus interrogates 18 *CYP2C19* genetic variants, which are translated into 16 possible *CYP2C19* star (*)-alleles using the DMET Console Software (version 1.2; Affymetrix). Four *CYP2C19* star-alleles (*CYP2C19*1, *2A, *2B* and **17*) were observed in the patients meeting inclusion criteria. *CYP2C19*1* is assigned by default when no genetic variants are detected, *CYP2C19*2A* is defined by rs4244285 (c.681G>A), *CYP2C19*2B* is defined by rs4244285 (c.681G>A) and rs17878459 (c.276G>C) and *CYP2C19*17* is defined by rs12248560 (c. −806C>T). Nucleotide coordinates are annotated to GenBank *CYP2C19* mRNA sequence M61854.1[41].

CYP2C19 phenotype assignment was based on Clinical Pharmacogenetics Implementation Consortium guidelines [28,30]. Patients with a *CYP2C19*17/*17* or **1/*17* diplotype are predicted to be ultrarapid metabolizers, *CYP2C19*1/*1* patients are predicted to be extensive metabolizers, patients with either a *CYP2C19*1/*2A* or **1/*2B* diplotype are predicted to be intermediate metabolizers, and patients with a **2A/*2A* diplotype are predicted to be poor metabolizers. Extensive metabolizers are considered to have normal, or wild-type, CYP2C19 metabolic activity.

Analysis of voriconazole plasma concentrations

Except for one sample, voriconazole plasma concentrations were measured at St Jude in a Clinical Laboratory Improvement Amendments-certified laboratory by reverse-phase HPLC with UV detection. Samples underwent liquid–liquid extraction in methyl *tert*-butyl ether and evaporation under nitrogen, followed by reconstitution in a mobile phase consisting of 20 mM sodium acetate (pH 4.88) in acetonitrile at a ratio of 49:51 (v:v). Analytical chromatography was performed by injecting the samples onto a YMC™C8 (YMC America, Inc. PA, USA) reverse phase column (150 mm × 4.6 mm, 3.0 μm particle size) at a flow rate of 1.0 ml/min and a temperature of 35°C using isocratic elution as the mode of separation. Voriconazole concentrations were calculated by comparing the peak height ratio of the drug with the internal standard ketoconazole against a four-point calibration curve. The lower limit of voriconazole detection was 0.025 μg/ml and the upper limit of detection was 30 μg/ml. As part of our validation process, selected patient samples (n = 23) were measured in our laboratory and were also sent to an external reference laboratory (ARUP Laboratories, UT, USA) that used liquid chromatography– tandem mass spectrometry (LC–MS/MS). The median percentage difference between measurements using the two methods was 6% (range: 0.3–21; n = 23). One sample was analyzed outside of St Jude by a reference laboratory that used HPLC for analysis.

Pharmacokinetic analysis

For purposes of estimating doses needed to achieve therapeutic concentrations, a two-compartment nonlinear pharmacokinetic model with Michaelis–Menten elimination was used to describe the pharmacokinetics of voriconazole, as has been used previously [23,36,42,43]. Because only voriconazole plasma trough concentrations were measured in this study, the absorption rate (K_a), bioavailability (f), Michaelis–Menten half-saturation (K_m), volume of distribution of the peripheral compartment (V_p), and intercompartmental clearance (Q) values were obtained from a previously reported voriconazole population pharmacokinetic analysis [23]. The volume of the central compartment (V) and Michaelis–Menten maximum activity (V_{max}) along with interindividual and interoccasion variability were estimated using nonlinear mixed-effects modeling as implemented in Monolix (V4.2). The covariate effects of age and *CYP2C19* diplotype were included in the parameter V_{max}. The model was internally tested to determine how well the *post hoc* estimated pharmacokinetic parameters could predict trough concentrations at higher doses. Specifically, for those patients who had multiple voriconazole trough concentrations reported, we used each patient's *post hoc* estimated pharmaco kinetic parameters determined at each of their lower voriconazole doses to predict the trough concentration at the highest prescribed dose. The predicted trough concentrations were then compared with observed trough concentrations corresponding to the highest prescribed voriconazole dose. Simulation studies using each individual's *post hoc* estimated pharmacokinetic parameters were used to determine a voriconazole dose for each diplotype/age group that increased the percentage of predicted day 5 voriconazole trough concentrations within the goal therapeutic range of 1–6 μg/ml relative to a fixed dose.

Statistical analysis

The χ^2 test was used to compare patient characteristics between age groups. A linear mixed-effects model was used to compare the relationship between *CYPC19* diplotypes and voriconazole trough concentrations corrected for daily voriconazole dose. Linear mixed-effects modeling of all the $\log_2$ transformed voriconazole trough concentrations corrected for daily dose was also used to identify covariates (age, ancestry, gender, *CYP2C19* diplotype and interacting drugs) that may influence voriconazole plasma concentrations, with *CYP2C19* diplotypes treated as an ordinal variable. For pharmacokinetic analysis, the McNemar's χ^2 test was used to compare the number of voriconazole troughs predicted to be within the therapeutic range based on extrapolated doses versus the observed number of voriconazole troughs in the therapeutic range. The significance of covariates that may affect V_{max} was determined using the χ^2 test (to compare the difference in the −2 log-likelihood between the two hierarchical models) and the t-test (to determine if the covariate term was significantly different from zero).

Results

The clinical and demographic characteristics of the 33 patients who qualified for this study are summarized in Table 1. The study population was stratified by age (i.e., <12 years and >12 years) to determine if there was equal representation of younger and older patients among the covariates ancestry, gender and *CYP2C19* diplotypes. There were no significant

differences between the two age groups in any of the covariates. Overall, 58% of patients were 11 years of age and younger and 42% of patients were 12 years or older. The observed allele frequencies for *CYP2C19*1*, **2* and **17* were 59.1, 16.7 and 24.2%, respectively. Based on average allele frequencies observed in European, Hispanic and African ancestry groups, the expected allele frequencies of our patient population for *CYP2C19*1*,**2* and **17* is approximately 64, 15 and 20%, respectively [28].

The voriconazole doses administered ranged from 2.6 to 41.2 mg/kg/day among those aged less than 12 years; doses ranged from 3.6 to 16.1 mg/kg/day for those children aged 12 years or older (Table 2). A total of 142 voriconazole plasma trough concentrations were analyzed, with a median of three voriconazole concentrations per patient (range: 1–15). The relationship between individual voriconazole trough concentrations corrected for the daily voriconazole dose and *CYP2C19* diplotypes is depicted in Figure 1. Patients homozygous for *CYP2C19*17* had lower dose-normalized trough voriconazole concentrations (median: 0.01 μg/ml/mg/kg; range: 0.002–0.05; p = 0.02) and patients with a *CYP2C19*1/*2A, *1/*2B* diplotype (median: 0.14 μg/ml/mg/kg; range: 0.004–1.24; p = 0.04) or *CYP2C19*2A/*2A* diplotype (median: 0.62 μg/ml/mg/kg; range:0.47–0.91; p = 0.04) had higher dose-normalized trough voriconazole concentrations than those with a *CYP2C19*1/*1* diplotype (median: 0.07 μg/ml/mg/kg; range: 0.003–1.47). Patients heterozygous for *CYP2C19*17* did not have significantly lower dose-normalized trough voriconazole concentrations (median: 0.05 μg/ml/mg/kg; range: 0.003–1.26; p = 0.95) than those with a *CYP2C19*1/ *1* diplotype.

Other antifungals (fluconazole and posaconazole), proton pump inhibitors (omeprazole and pantoprazole) and steroids (dexamethasone, hydrocortisone and methylprednisolone) were prescribed to patients included in this study, all of which may alter voriconazole plasma concentrations. For approximately 7% of trough concentrations obtained from *CYP2C19*1/*17* or *CYP2C19*1/*2A, *1/*2B* patients, fluconazole or posaconazole was coadministered with voriconazole; these agents were not concurrently taken with voriconazole in *CYPC19*1/*1* patients. Proton pump inhibitors were coadministered with voriconazole for 58% of the trough concentrations obtained from *CYP2C19*1/*17* patients, 24% of trough concentrations obtained from *CYP2C19*1/*1* patients, and 39% of trough concentrations obtained from *CYP2C19*1/*2A, *1/*2B* patients. Steroids were coadministered with voriconazole for 11% of the trough concentrations obtained from *CYP2C19*1/*17* patients, 8% of trough concentrations obtained from *CYP2C19*1/*1* patients, and 37% of trough concentrations obtained from *CYP2C19*1/*2A, *1/*2B* patients. Although one might predict steroids would induce metabolism of voriconazole (and thus decrease trough levels), those carrying a low function *CYP2C19* allele still tended to have higher trough concentrations despite a slightly higher frequency of steroid use. Those who were either a *CYP2C19*17* homozygote or *CYP2C19*2A* homozygote were not administered any known CYP2C19 inducers or inhibitors. With this small sample size, a multivariate analysis detected no significant effect of these medications, nor ancestry and gender, on voriconazole trough concentrations corrected for daily dose, but *CYP2C19* diplotype and age did have a significant impact (Table 3). Consistent with the previously established relationship between older age and voriconazole plasma concentrations, there

was a correlation between age and higher voriconazole trough concentrations corrected for daily dose (Figure 2) [3,21,24,36].

Voriconazole plasma trough concentrations between 1 and 6 μg/ml were considered to be therapeutic. Therapeutic voriconazole concentrations were not observed in any of the four patients homozygous for *CYP2C19*17* (Figure 3A); however, increasing the voriconazole dose in these patients yielded higher voriconazole concentrations than did lower doses (Figure 3B), suggesting that higher voriconazole doses may overcome ultrarapid metabolism caused by the *CYP2C19*17* allele. Approx- imately 38% of patients heterozygous for *CYP2C19*17* had a mean voriconazole concentration that was sub-therapeutic, and 27% of *CYP2C19*1* homozygotes had a mean concentration that was subtherapeutic. Because only one patient was homozygous for *CYP2C19*2A*, the *CYP2C19*1/*2A*, **1/*2B* and **2A/*2A* diplotype groups were combined for determining the number of patients outside therapeutic voriconazole trough concentrations. None of the patients with these diplotypes had a mean voriconazole concentration that was sub-therapeutic, with one patient having a supratherapeutic concentration (Figure 3A).

The population pharmacokinetic model, using the parameters in Table 4, resulted in a relationship between the observed trough concentrations and the predicted trough concentrations with an $r^2 = 0.97$, $p < 10^{-3}$, and a relative mean absolute error (expressed as a percentage of the predicted concentration) of 19%. Consistent with the observed voriconazole trough concentrations, the population pharmacokinetic parameter V_{max} decreased with age ($p < 1 \times 10{-}^{7}$) and was significantly higher in the *CYP2C19*17/*17* patients ($p = 0.002$; Table 4). Internal testing of our population pharmacokinetic model was performed by using *post hoc* estimated pharmacokinetic parameters determined at lower voriconazole doses to predict trough concentrations at the highest prescribed doses. Comparing predicted voriconazole concentrations to observed concentrations, our population pharmacokinetic model predicted trough concentrations with a median error of −0.3 μg/ml, a 26% error relative to observed concentrations.

Using each individual's *post hoc* estimated pharmacokinetic parameters, a voriconazole daily dose was extrapolated for each *CYP2C19* diplotype/age group to increase the number of voriconazole troughs predicted to be in the therapeutic range. Table 2 shows the median (range) of the predicted trough concentrations based on these extrapolated doses. The proportion of voriconazole troughs within the therapeutic range using extrapolated doses (60%) was predicted to be higher ($p < 0.03$) than the proportion observed to be within the therapeutic range with standard dosing (46.5%), while achieving fewer troughs (28%) below the therapeutic range (compared with 44.4% observed) and maintaining a similar percentage above the therapeutic range (12% compared with 9.2% observed). Considering the *CYP2C19*17/*17* patients, all 11 observed voriconazole troughs were less than 1 μg/ml (median trough: 0.21 μg/ml). However, simulations using extrapolated doses (based on age and diplotype) of 36 mg/kg/day for those less than 12 years of age and 28 mg/kg/day for those 12 years of age or greater predicted that eight of the 11 trough concentrations (73%) in this group would be in the therapeutic range (median trough = 0.88 μg/ml for age <12 years and median trough = 1.76 μg/ml for age ≥12 years; Table 2), with three troughs predicted to be below the therapeutic range.

Based on population pharmacokinetic parameters (Table 4), voriconazole trough concentrations for each *CYP2C19* diplotype/age group were simulated for the initial maintenance voriconazole doses currently used at St Jude (14 mg/kg/day for patients less than 12 years of age and 400 mg/day for patients 12 years of age or greater; Figure 4) and for the extrapolated voriconazole doses based on *CYP2C19* diplotype and age (Figure 5). The diplotype/age-based voriconazole extrapolated doses were predicted to yield a higher percentage of trough concentrations in the therapeutic range than the predictions based on the standard initial St Jude maintenance doses ($p = 1 \times 10^{-10}$).

Discussion

In both adult and pediatric populations, CYP2C19 intermediate and poor metabolizers have been demonstrated to have elevated voriconazole plasma concentrations when compared with extensive metabolizers [3,31,44–47]. However, the clinical importance of CYP2C19 phenotypic variability in relation to voriconazole treatment is controversial. It has been proposed that in a clinical setting, covariates such as comorbidities or concomitant drugs may diminish the influence of *CYP2C19* polymorphisms on voriconazole concentrations [18,19]. In our clinical setting, we were able to detect that *CYP2C19* diplotype was significantly associated with voriconazole plasma concentrations in immunocompromised pediatric patients, even in the presence of covariates such as concomitantly administered drugs. Individuals predicted to be CYP2C19 intermediate or poor metabolizers had higher dose-corrected voriconazole trough concentrations versus extensive metabolizers, which is consistent with a recent study in pediatric patients [31].

There are limited data in adults, and a lack of data in pediatrics, demonstrating that CYP2C19 ultrarapid metabolizers have decreased voriconazole plasma concentrations when compared with extensive metabolizers [46–49]. In a study of healthy Chinese adults, it was shown that even those with only one *CYP2C19*17* allele (*CYP2C19*1/*17*) had approximately 50% lower voriconazole exposure versus *CYP2C19*1* homozygotes [50]. Our data in a pediatric population demonstrates that the *CYP2C19*17* allele is associated with lower dose-corrected voriconazole trough concentrations when compared with *CYP2C19*1* homozygotes, especially in those homozygous for the *CYP2C19*17* allele.

Because nontherapeutic voriconazole plasma concentrations are associated with unfavorable treatment outcomes, we investigated whether *CYP2C19* polymorphisms were correlated with either supratherapeutic or subtherapeutic voriconazole concentrations [9–11,51]. A therapeutic range for voriconazole has not been well defined, but generally trough plasma concentrations less than 1 μg/ml have been associated with treatment failure and concentrations greater than 6 μg/ml have been associated with adverse effects such as neurotoxicity [9,10,14,38,52]. There is increasing evidence to support a minimum therapeutic voriconazole concentration of 2 μg/ml [9,51,53], but for the purpose of our study a trough concentration of 1 μg/ml was considered therapeutic. Only three patients in our study had mean voriconazole concentrations above the therapeutic range, but the group most likely to have supratherapeutic concentrations, CYP2C19 poor metabolizers, was not well represented in this study. The four patients included in our study who were homozygous for *CYP2C19*17* never attained therapeutic voriconazole concentrations at any dosage.

Additionally, every patient homozygous for *CYP2C19*17* had an initial steady-state voriconazole trough concentration that was less than 0.35 μg/ml, which may be a risk factor for increased mortality [12] . Higher voriconazole concentrations were observed in *CYP2C19*17* homozygous patients with increased voriconazole doses (Figure 3B), although doses as high as those predicted to be necessary to yield therapeutic voriconazole concentrations (Table 2) were not used.

All children at least 12 years of age in this study weighed a minimum of 40 kg, therefore the initial recommended voriconazole maintenance dose for our patients 12 years of age and older in this study was 400 mg/day [32–35] with a recommended maximum daily dose of 600 mg/day [34]. In those less than 12 years of age, the initial recommended maintenance dose is less clear with suggested maintenance doses ranging from 8 to 18 mg/kg/day [54,35]. There is evidence to support an initial voriconazole maintenance dose of 14 mg/kg/day in patients less than 12 years of age [23,32,34–36], and this is generally the initial maintenance dose utilized at St Jude. We used pharmacokinetic modeling for the purpose of extrapolating a voriconazole dose predicted to achieve a plasma trough concentration of 1–6 μg/ml in patients stratified by *CYP2C19* diplotype and age (Table 2 & Figure 5) [23,36,42,41,36]. Because initial low voriconazole trough concentrations are associated with unfavorable outcomes, a voriconazole starting dose high enough to achieve therapeutic concentrations may be of benefit [12,51,53,55]. Our predictions suggest that, except for CYP2C19 poor metabolizers, most children <12 years of age should receive starting doses of voriconazole above the recommended dose of 14 mg/kg/day, and for all children, doses based on age and CYP2C19 status should theoretically decrease variability in voriconazole trough concentrations. For patients in our study who were *CYP2C19*17* homozygotes, an extrapolated voriconazole dose that is approximately three-times higher than the initial recommended maintenance dose (14 mg/kg/day for those aged less than 12 years and 400 mg/day for those aged 12 years and older) was predicted to be necessary to yield a steady-state trough concentration of 1–6 μg/ml. The extrapolated voriconazole dose for *CYP2C19*17* homozygotes aged 12 years and older in this study is similar to, though higher than, the dose that was required (800 mg/day) to reach a trough concentration of 1–2 μg/ml in an adolescent cystic fibrosis patient who was homozygous for *CYP2C19*17* [46]. For the purpose of pharmacokinetic modeling, the voriconazole dosage (Table 2) was expressed as mg/kg/day in individuals aged 12 years and older. Because we stratified our patient population by *CYP2C19* diplotype and age we had relatively few patients in each *CYP2C19* diplotype/age group. Other factors that may influence our population pharmacokinetic model include the inability to determine if all patients were in a fasting state. Our patient population ranged from 1 to 19 years of age. Younger individuals may have lower voriconazole bioavailability [22–24], though it is unclear if decreased bioavailability is due to increased CYP2C19 expression, differences in intestinal metabolism or drug transport, or differences in hepatic blood flow [7,23]. Correlation of treatment outcomes or voriconazole-induced adverse events with *CYP2C19* diplotypes was not investigated in this retrospective analysis.

Steroids may upregulate *CYP2C19* expression through a glucocorticoid-response element found in its promoter region, thereby resulting in decreased voriconazole concentrations

[38,49,56], but in our study, steroid use was more common in the diplotypes with higher voriconazole concentrations, suggesting that genotype may have been more important than concurrent drug use in this case. Coadministration of voriconazole with CYP2C19 substrates such as proton pump inhibitors or other antifungals may increase voriconazole plasma concentrations due to competitive inhibition [38]; however, an analysis of over 3300 voriconazole concentrations obtained from 240 patients did not identify proton pump inhibitors as a significant covariate influencing voriconazole metabolism [49]. Although concurrent drugs are likely to interact with voriconazole, we found no evidence of pharmacokinetic interactions in our study, though our study was not powered to detect such differences. Similar to our study, an investigation of 406 voriconazole concentrations obtained from 151 patients found that *CYP2C19* genotype greatly influenced voriconazole pharmacokinetics while proton pump inhibitors or steroids did not significantly influence voriconazole concentrations, though study size hampered covariate analysis [57]. Nonetheless, steroids, proton pump inhibitors or other antifungals were not predictive of voriconazole concentrations, whereas, in agreement with prior studies [3,21,24,36,51], age and CYP2C19 status were.

Conclusion

In this relatively small cohort of immunosuppressed patients exposed to multiple concomitant drugs, we found that *CYP2C19* diplotype was significantly associated with voriconazole trough concentrations in pediatric patients, even when adjusting for age and other clinical covariates. We suggest that tailoring the starting dosage of voriconazole, based on age and *CYP2C19* diplotype, is a reasonable approach to attempt to reach therapeutic voriconazole concentrations, particularly when accompanied by therapeutic drug monitoring of voriconazole plasma concentrations.

Future perspective

There is a growing body of evidence demonstrating that *CYP2C19* genetic variants and age influence voriconazole plasma concentrations. There is substantial evidence for interpatient variability, and for pharmacodynamic associations between response/toxicity and voriconazole concentrations. Future evaluations of whether dosing based on age and CYP2C19 status yields a higher proportion of patients being in the goal range for voriconazole are needed.

Acknowledgments

Supported by NCI grants CA 36401 and CA 21765, NIH/NIGMS Pharmacogenomics Research Network (U01 GM92666), and by the American Lebanese Syrian Associated Charities (ALSAC).

References

Papers of special note have been highlighted as:

• of interest

1. Groll AH, Kurz M, Schneider W, et al. Five-year-survey of invasive aspergillosis in a paediatric cancer centre. Epidemiology, management and long-term survival. Mycoses. 1999; 42:7–8. 431–442. [PubMed: 10865896]
2. Walsh TJ, Gonzalez C, Lyman CA, Chanock SJ, Pizzo PA. Invasive fungal infections in children: recent advances in diagnosis and treatment. Adv. Pediatr. Infect. Dis. 1996; 11:187–290. [PubMed: 8718464]
3. Walsh TJ, Karlsson MO, Driscoll T, et al. Pharmacokinetics and safety of intravenous voriconazole in children after single- or multiple-dose administration. Antimicrob. Agents Chemother. 2004; 48(6):2166–2172. [PubMed: 15155217]
4. Sandherr M, Maschmeyer G. Pharmacology and metabolism of voriconazole and posaconazole in the treatment of invasive aspergillosis: review of the literature. Eur. J. Med. Res. 2011; 16(4):139–144. [PubMed: 21486727]
5. Purkins L, Wood N, Greenhalgh K, Allen MJ, Oliver SD. Voriconazole, a novel wide-spectrum triazole: oral pharmacokinetics and safety. Br. J. Clin. Pharmacol. 2003; 56(Suppl. 1):10–16. [PubMed: 14616408]
6. Walsh TJ, Anaissie EJ, Denning DW, et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. Clin. Infect. Dis. 2008; 46(3):327–360. [PubMed: 18177225]
7. Walsh TJ, Driscoll T, Milligan PA, et al. Pharmacokinetics, safety, and tolerability of voriconazole in immunocompromised children. Antimicrob. Agents Chemother. 2010; 54(10):4116–4123. [PubMed: 20660687]
8. Wingard JR, Carter SL, Walsh TJ, et al. Randomized, double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection after allogeneic hematopoietic cell transplantation. Blood. 2010; 116(24):5111–5118. [PubMed: 20826719]
9. Smith J, Safdar N, Knasinski V, et al. Voriconazole therapeutic drug monitoring. Antimicrob. Agents Chemother. 2006; 50(4):1570–1572. [PubMed: 16569888]
10. Pascual A, Calandra T, Bolay S, Buclin T, Bille J, Marchetti O. Voriconazole therapeutic drug monitoring in patients with invasive mycoses improves efficacy and safety outcomes. Clin. Infect. Dis. 2008; 46(2):201–211. [PubMed: 18171251]
11. Goodwin ML, Drew RH. Antifungal serum concentration monitoring: an update. J. Antimicrob. Chemother. 2008; 61(1):17–25. [PubMed: 17999982]
12. Miyakis S, Van Hal SJ, Ray J, Marriott D. Voriconazole concentrations and outcome of invasive fungal infections. Clin. Microbiol. Infect. 2010; 16(7):927–933. [PubMed: 19845698] • Demonstrates that initial low voriconazole trough concentrations are associated with mortality.
13. Philips JA, Marty FM, Stone RM, Koplan BA, Katz JT, Baden LR. Torsades de pointes associated with voriconazole use. Transpl. Infect. Dis. 2007; 9(1):33–36. [PubMed: 17313469]
14. Fallon RM, Girotto JE. A review of clinical experience with newer antifungals in children. J. Pediatr. Pharmacol. Ther. 2008; 13(3):124–140. [PubMed: 23055874]
15. Alffenaar JW, De Vos T, Uges DR, Daenen SM. High voriconazole trough levels in relation to hepatic function: how to adjust the dosage? Br. J. Clin. Pharmacol. 2009; 67(2):262–263. [PubMed: 19094163]
16. Boyd AE, Modi S, Howard SJ, Moore CB, Keevil BG, Denning DW. Adverse reactions to voriconazole. Clin. Infect. Dis. 2004; 39(8):1241–1244. [PubMed: 15486850]
17. Zonios DI, Gea-Banacloche J, Childs R, Bennett JE. Hallucinations during voriconazole therapy. Clin. Infect. Dis. 2008; 47(1):e7–e10. [PubMed: 18491963]
18. Driscoll TA, Frangoul H, Nemecek ER, et al. Comparison of pharmacokinetics and safety of voriconazole intravenous-to-oral switch in immunocompromised adolescents and healthy adults. Antimicrob. Agents Chemother. 2011; 55(12):5780–5789. [PubMed: 21911570]
19. Driscoll TA, Yu LC, Frangoul H, et al. Comparison of pharmacokinetics and safety of voriconazole intravenous-to-oral switch in immunocompromised children and healthy adults. Antimicrob. Agents Chemother. 2011; 55(12):5770–5779. [PubMed: 21968355]
20. Lazarus HM, Blumer JL, Yanovich S, Schlamm H, Romero A. Safety and pharmacokinetics of oral voriconazole in patients at risk of fungal infection: a dose escalation study. J. Clin. Pharmacol. 2002; 42(4):395–402. [PubMed: 11936564]

21. Leveque D, Nivoix Y, Jehl F, Herbrecht R. Clinical pharmacokinetics of voriconazole. Inter. J. Antimicrob. Agents. 2006; 27(4):274–284.
22. Theuretzbacher U, Ihle F, Derendorf H. Pharmacokinetic/ pharmacodynamic profile of voriconazole. Clin. Pharmacokinet. 2006; 45(7):649–663. [PubMed: 16802848]
23. Karlsson MO, Lutsar I, Milligan PA. Population pharmacokinetic analysis of voriconazole plasma concentration data from pediatric studies. Antimicrob. Agents Chemother. 2009; 53(3):935–944. [PubMed: 19075073] • Describes voriconazole population pharmacokinetic parameters in pediatric patients.
24. Shima H, Miharu M, Osumi T, Takahashi T, Shimada H. Differences in voriconazole trough plasma concentrations per oral dosages between children younger and older than 3 years of age. Pediatr. Blood Cancer. 2010; 54(7):1050–1052. [PubMed: 20146339]
25. Michael C, Bierbach U, Frenzel K, et al. Voriconazole pharmacokinetics and safety in immunocompromised children compared to adult patients. Antimicrob. Agents Chemother. 2010; 54(8):3225–3232. [PubMed: 20547816]
26. Hyland R, Jones BC, Smith DA. Identification of the cytochrome P450 enzymes involved in the *N*-oxidation of voriconazole. Drug Metab. Dispos. 2003; 31(5):540–547. [PubMed: 12695341]
27. Yanni SB, Annaert PP, Augustijns P, Ibrahim JG, Benjamin DK Jr, Thakker DR. *In vitro* hepatic metabolism explains higher clearance of voriconazole in children versus adults: role of CYP2C19 and flavin-containing monooxygenase 3. Drug Metab. Dispos. 2010; 38(1):25–31. [PubMed: 19841059]
28. Scott SA, Sangkuhl K, Gardner EE, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450-2C19 (*CYP2C19*) genotype and clopidogrel therapy. Clin. Pharmacol. Ther. 2011; 90(2):328–332. [PubMed: 21716271]
29. Scott SA, Sangkuhl K, Shuldiner AR, et al. PharmGKB summary: very important pharmacogene information for cytochrome P450, family 2, subfamily C, polypeptide 19. Pharmacogenet. Genomics. 2012; 22(2):159–165. [PubMed: 22027650]
30. Hicks JK, Swen JJ, Thorn CF, et al. Clinical Pharmacogenetics Implementation Consortium guideline for *CYP2D6 and CYP2C19* genotypes and dosing of tricyclic antidepressants. Clin. Pharmacol. Ther. 2013; 93(5):402–408. [PubMed: 23486447]
31. Narita A, Muramatsu H, Sakaguchi H, et al. Correlation of CYP2C19 phenotype with voriconazole plasma concentration in children. J. Pediatr. Hematol. Oncol. 2013; 35(5):e219–e223. [PubMed: 23588332] • Demonstrates that intermediate and poor metabolizers have elevated voriconazole trough concentrations in a pediatric population.
32. Pieper S, Kolve H, Gumbinger HG, Goletz G, Wurthwein G, Groll AH. Monitoring of voriconazole plasma concentrations in immunocompromised paediatric patients. J. Antimicrob. Chemother. 2012; 67(11):2717–2724. [PubMed: 22796890]
33. Geist MJ, Egerer G, Burhenne J, Riedel KD, Weiss J, Mikus G. Steady-state pharmacokinetics and metabolism of voriconazole in patients. J. Antimicrob. Chemother. 2013; 68(11):2592–2299. [PubMed: 23766489]
34. Voriconazole. In. Lexi-Comp Online. Hudson, OH, USA: Lexi-Comp, Inc; www.lexi.com
35. Voriconazole. In. European Medicines Agency Online. Voriconazole Accord: EPAR-Product Information. www.ema.europa.eu/ema
36. Neely M, Rushing T, Kovacs A, Jelliffe R, Hoffman J. Voriconazole pharmacokinetics and pharmacodynamics in children. Clin. Infect. Dis. 2010; 50(1):27–36. [PubMed: 19951112]
37. Prasad PA, Coffin SE, Leckerman KH, Walsh TJ, Zaoutis TE. Pediatric antifungal utilization: new drugs, new trends. Pediatr. Infect. Dis. J. 2008; 27(12):1083–1088. [PubMed: 18989239]
38. Dolton MJ, Ray JE, Chen SC, Ng K, Pont LG, McLachlan AJ. Multicenter study of voriconazole pharmacokinetics and therapeutic drug monitoring. Antimicrob. Agents Chemother. 2012; 56(9): 4793–4799. [PubMed: 22751544]
39. Purkins L, Wood N, Ghahramani P, Love ER, Eve MD, Fielding A. Coadministration of voriconazole and phenytoin: pharmacokinetic interaction, safety, and toleration. Br. J. Clin. Pharmacol. 2003; 56(Suppl. 1):37–44. [PubMed: 14616412]

40. Fernandez CA, Smith C, Yang W, et al. Concordance of DMET plus genotyping results with those of orthogonal genotyping methods. Clin. Pharmacol. Ther. 2012; 92(3):360–365. [PubMed: 22871999]
41. *CYP2C19* allele nomenclature. www.cypalleles.ki.se/cyp2c19.htm
42. Hope WW. Population pharmacokinetics of voriconazole in adults. Antimicrob. Agents Chemother. 2012; 56(1):526–531. [PubMed: 22064545]
43. Friberg LE, Ravva P, Karlsson MO, Liu P. Integrated population pharmacokinetic analysis of voriconazole in children, adolescents, and adults. Antimicrob. Agents Chemother. 2012; 56(6): 3032–3042. [PubMed: 22430956]
44. Scholz I, Oberwittler H, Riedel KD, et al. Pharmacokinetics, metabolism and bioavailability of the triazole antifungal agent voriconazole in relation to *CYP2C19* genotype. Br. J. Clin. Pharmacol. 2009; 68(6):906–915. [PubMed: 20002085]
45. Ikeda Y, Umemura K, Kondo K, Sekiguchi K, Miyoshi S, Nakashima M. Pharmacokinetics of voriconazole and cytochrome P450 2C19 genetic status. Clin. Pharmacol. Ther. 2004; 75(6):587–588. [PubMed: 15179414]
46. Berge M, Guillemain R, Tregouet DA, et al. Effect of cytochrome P450 2C19 genotype on voriconazole exposure in cystic fibrosis lung transplant patients. Eur. J. Clin. Pharmacol. 2011; 67(3):253–260. [PubMed: 21038076]
47. Weiss J, Ten Hoevel MM, Burhenne J, et al. *CYP2C19* genotype is a major factor contributing to the highly variable pharmacokinetics of voriconazole. J. Clin. Pharmacol. 2009; 49(2):196–204. [PubMed: 19033450]
48. Malingre MM, Godschalk PC, Klein SK. A case report of voriconazole therapy failure in a homozygous ultrarapid *CYP2C19*17/*17* patient comedicated with carbamazepine. Br. J. Clin. Pharmacol. 2012; 74(1):205–206. [PubMed: 22122271]
49. Dolton MJ, Mikus G, Weiss J, Ray JE, McLachlan AJ. Understanding variability with voriconazole using a population pharmacokinetic approach: implications for optimal dosing. J. Antimicrob. Chemother. 2014 Epub ahead of print.
50. Wang G, Lei HP, Li Z, et al. The *CYP2C19* ultra-rapid metabolizer genotype influences the pharmacokinetics of voriconazole in healthy male volunteers. Eur. J. Clin. Pharmacol. 2009; 65(3):281–285. [PubMed: 18982321]
51. Owusu Obeng A, Egelund EF, Alsultan A, Peloquin CA, Johnson JA. *CYP2C19* polymorphisms and therapeutic drug monitoring of voriconazole: are we ready for clinical implementation of pharmacogenomics? Pharmacotherapy. 2014 Epub ahead of print.
52. Imhof A, Schaer DJ, Schanz U, Schwarz U. Neurological adverse events to voriconazole: evidence for therapeutic drug monitoring. Swiss Med. Wkly. 2006; 136:45–46. 739–742.
53. Andes D, Pascual A, Marchetti O. Antifungal therapeutic drug monitoring: established and emerging indications. Antimicrob. Agents Chemother. 2009; 53(1):24–34. [PubMed: 18955533]
54. Steinbach WJ. Antifungal agents in children. Pediatr. Clin. North Am. 2005; 52(3):895–915. viii. [PubMed: 15925667]
55. Dolton MJ, McLachlan AJ. Clinical importance of the *CYP2C19*17* variant allele for voriconazole. Br. J. Clin. Pharmacol. 2011; 71(1):137–138. [PubMed: 21143511]
56. Chen Y, Ferguson SS, Negishi M, Goldstein JA. Identification of constitutive androstane receptor and glucocorticoid receptor binding sites in the *CYP2C19* promoter. Mol. Pharmacol. 2003; 64(2): 316–324. [PubMed: 12869636]
57. Wang T, Chen S, Sun J, et al. Identification of factors influencing the pharmacokinetics of voriconazole and the optimization of dosage regimens based on Monte Carlo simulation in patients with invasive fungal infections. J. Antimicrob. Chemother. 2014; 69(2):463–470. [PubMed: 24084636]

Executive summary

Background

- Pediatric patients have large interindividual variation in voriconazole pharmacokinetic parameters, which may contribute to delays in achieving therapeutic voriconazole trough concentrations.
- CYP2C19 is one of the main enzymes responsible for the metabolism of voriconazole, and genetic variants in the *CYP2C19* gene locus may alter voriconazole metabolism thus contributing to the observed inter individual variations in voriconazole trough concentrations.

Results

- *CYP2C19*17* homozygotes had lower dose-corrected voriconazole trough concentrations than extensive metabolizers (*CYP2C19*1/*1*) and never attained therapeutic voriconazole trough concentrations
- Increasing the voriconazole dose in *CYP2C19*17/*17* patients yielded higher voriconazole concentrations, suggesting that higher voriconazole doses in these patients may at least partly overcome their pharmacokinetic disadvantage.
- Intermediate and poor metabolizers (*CYP2C19*1/*2A,*1/*2B*) had higher dose-corrected voriconazole trough concentrations than extensive metabolizers.

Conclusion

- *CYP2C19* diplotypes were significantly associated with voriconazole trough concentrations in pediatric patients, even when adjusting for age and other clinical covariates.
- Our data support the utilization of *CYP2C19* genotyping and age to individualize starting doses of voriconazole.

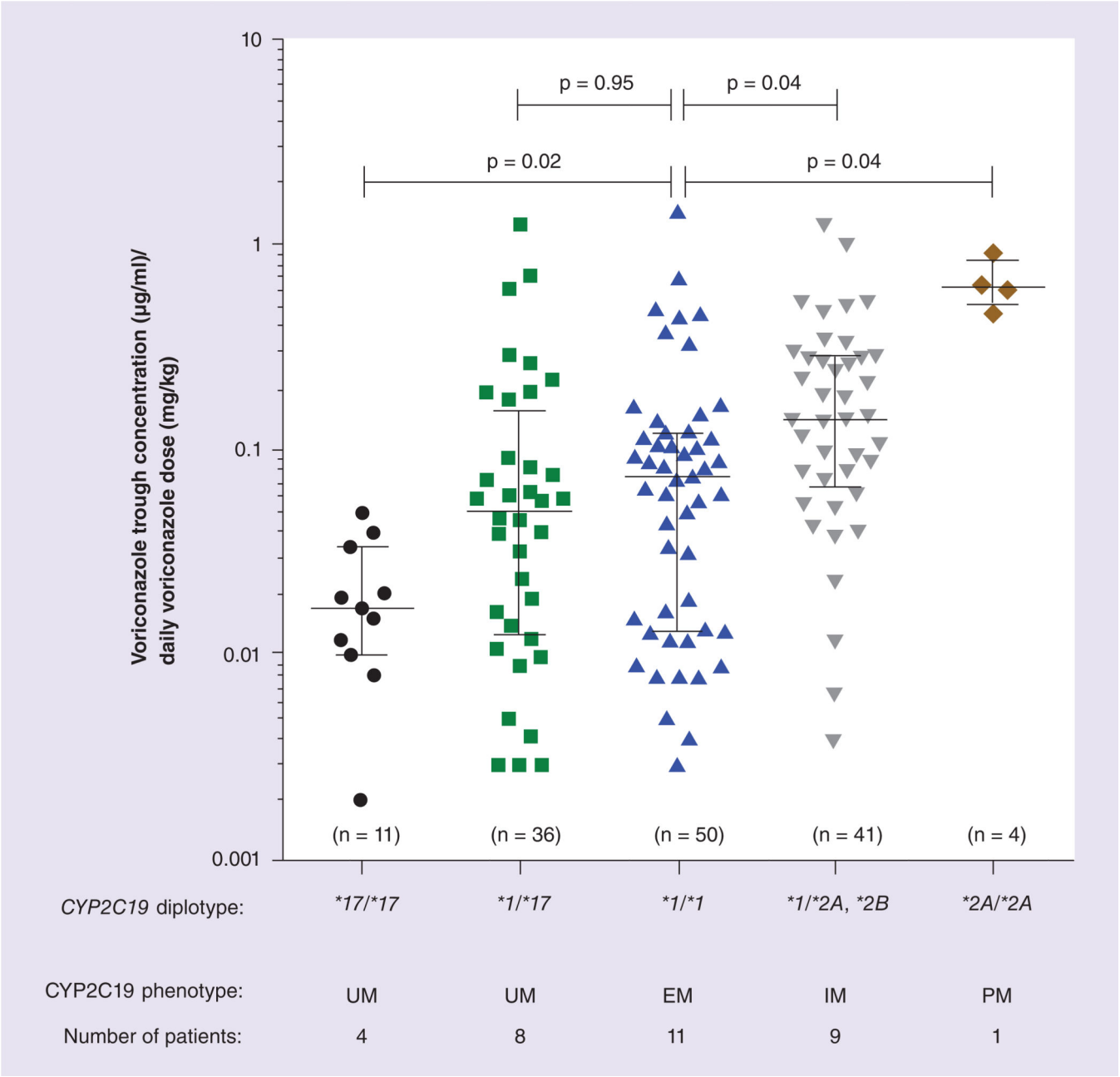

Figure 1. Linear mixed-effects model analysis of the relationship between *CYP2C19* diplotypes and voriconazole trough concentrations corrected for daily voriconazole dose

A total of 142 voriconazole trough concentrations grouped by *CYP2C19* diplotype were measured in 33 children, where (n) is the number of voriconazole concentrations measured in each diplotype group.

EM: Extensive metabolizer; IM: Intermediate metabolizer; PM: Poor metabolizer; UM: Ultrarapid metabolizer.

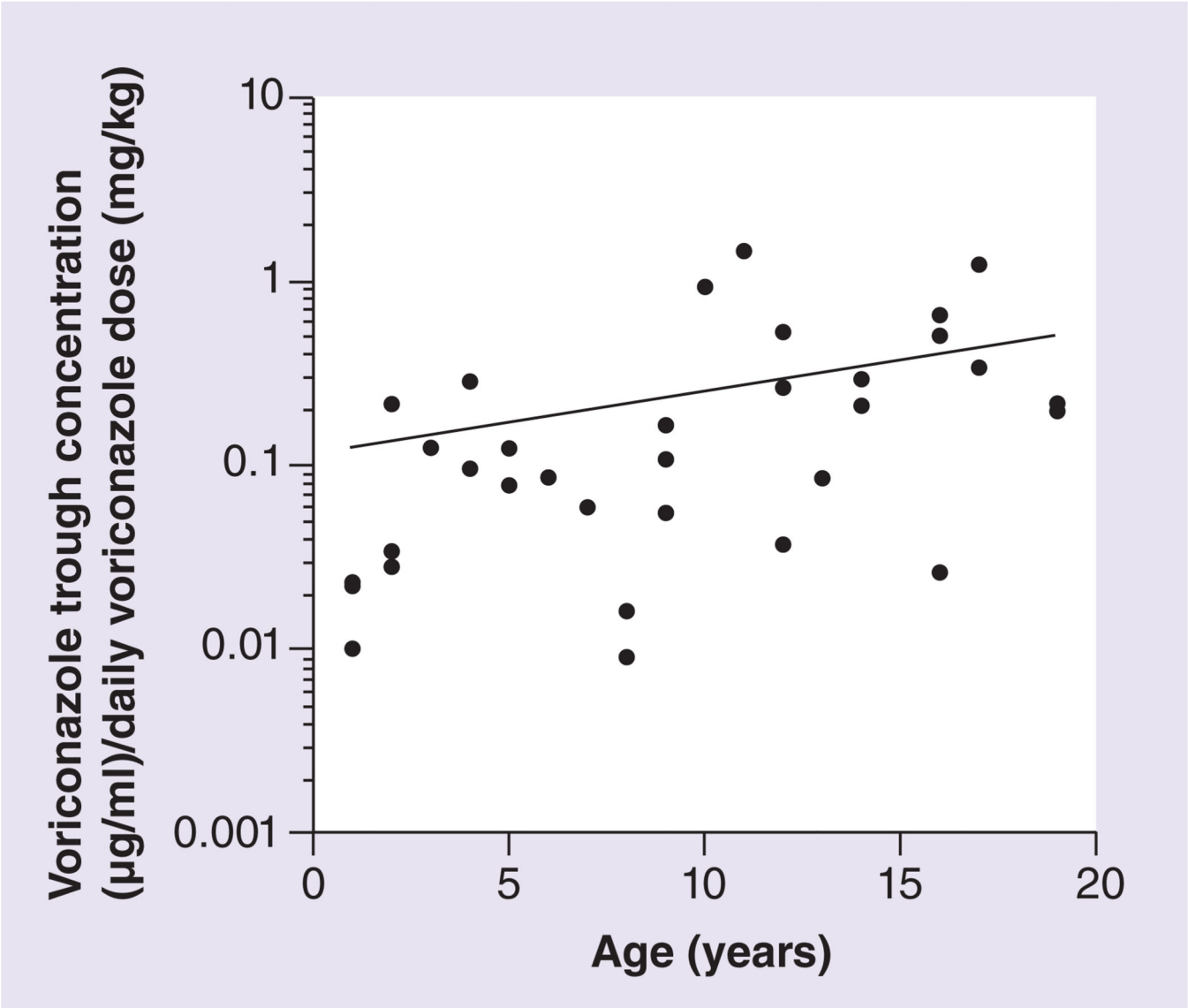

Figure 2.
Correlation of age with voriconazole trough concentrations corrected for daily voriconazole dose ($r^2 = 0.16$; $p < 0.05$).

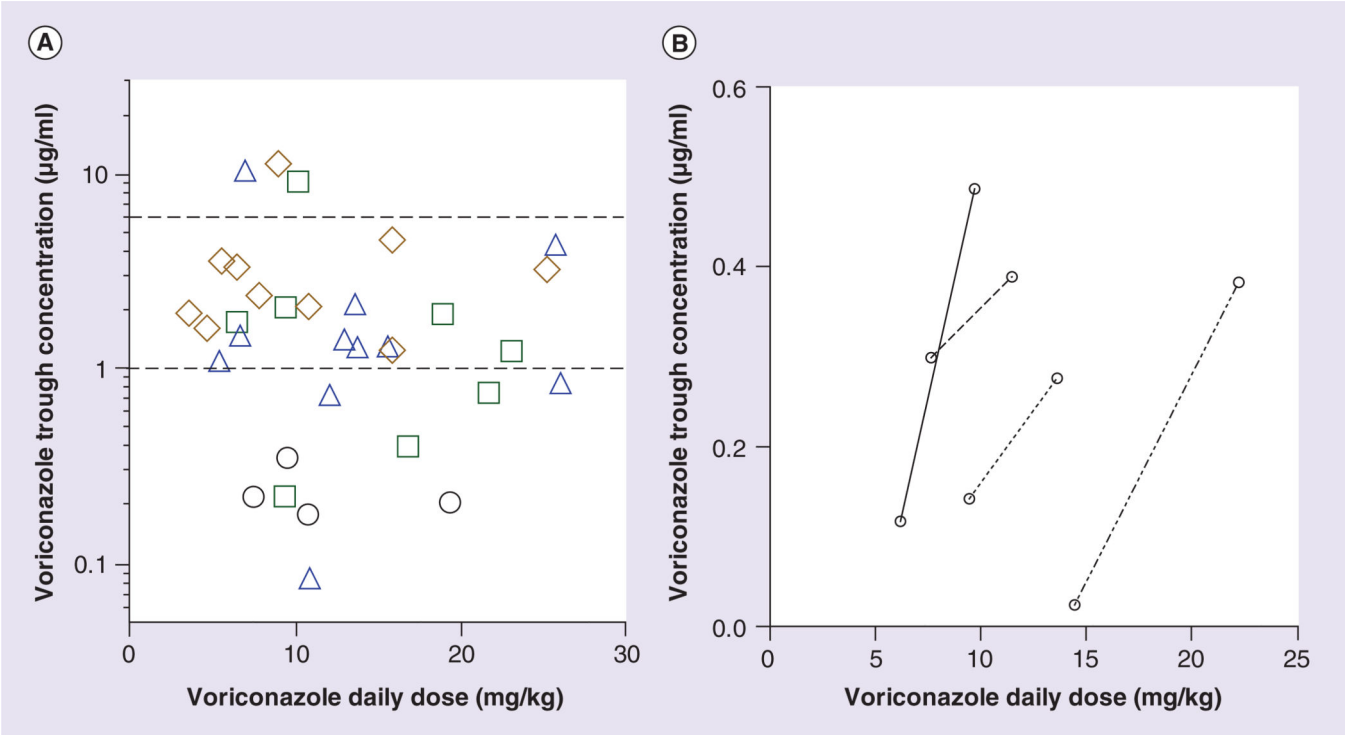

Figure 3. Relationship between *CYP2C19* diplotypes and voriconazole trough concentrations

(A) A scatter plot of the mean voriconazole trough concentration per patient versus the mean voriconazole daily dose. Patients with a *CYP2C19*17/*17* diplotype (predicted ultrarapid metabolizers) are represented by black circles, patients with a *CYP2C19*1/*17* diplotype (predicted ultrarapid metabolizers) are represented by green squares, patients with a *CYP2C19*1/*1* diplotype (predicted extensive metabolizers) are represented by blue triangles, and patients with a *CYP2C19*1/*2A*1/*2B* or **2A/*2A* diplotype (predicted intermediate or poor metabolizers) are represented by brown diamonds. The voriconazole plasma concentrations located between the dotted lines are considered to be therapeutic concentrations. **(B)** A plot of the first initial voriconazole trough concentration and the last measured voriconazole concentration versus daily dose of the four *CYP2C19*17* homozygous patients. Please see color figure at www.futuremedicine.com/doi/pdf/10.2217/pgs.14.53

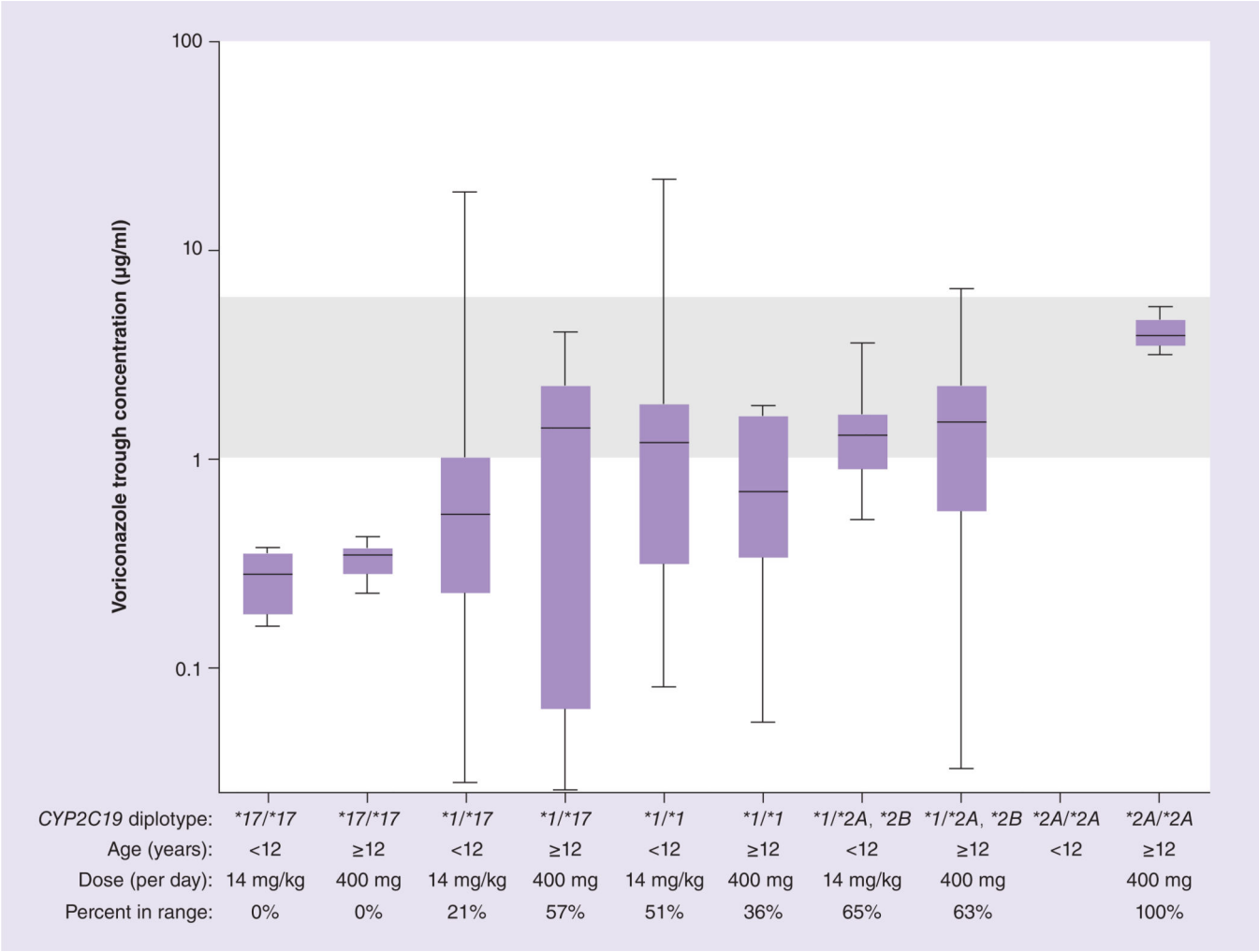

Figure 4. Voriconazole trough concentrations observed for actual voriconazole doses prescribed and percentage of patients in the goal therapeutic range of 1–6 µg/ml (shaded area)

Boxes indicate 25th to 75th percentile, and whiskers indicate the minimum and maximum values.

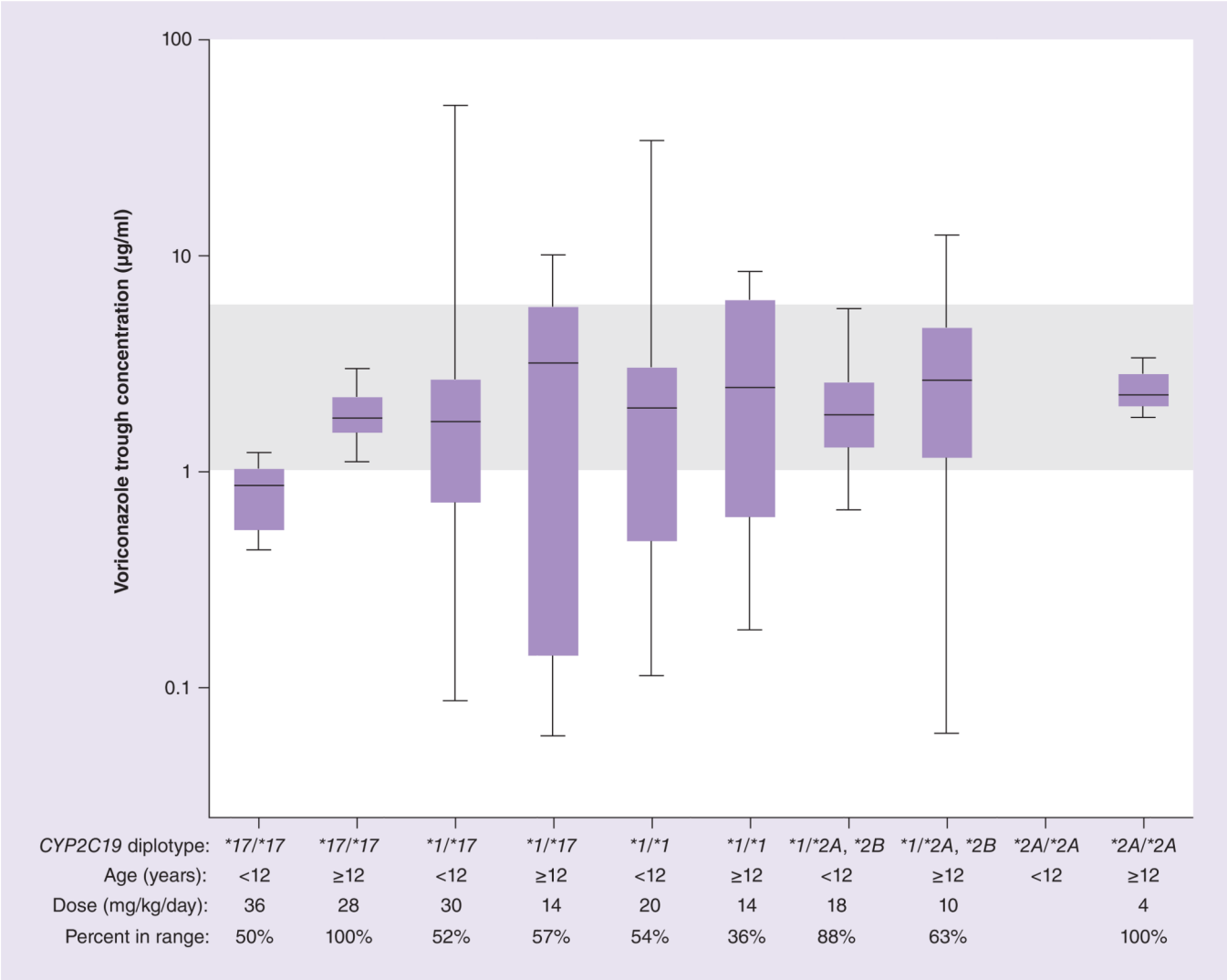

Figure 5. Simulated voriconazole doses based on age and *CYP2C19* diplotype that are predicted to result in trough concentrations in the therapeutic range of 1–6 μg/ml (shaded area)

Variability in each diplotype group is based on actual pharmacokinetic variability observed in patients in each group. Boxes indicate 25th to 75th percentile, and whiskers indicate the minimum and maximum values.

Table 1

Patient characteristics (n = 33).

Characteristic	All patients	<12 years of age	≥ 12 years of age	p-value
Gender, n (%)				
Female	14 (42.4)	9	5	0.72
Male	19 (57.6)	10	9	
Ancestry, n (%)				
African	6 (18.2)	4	2	0.97†
European	23 (69.6)	12	11	
Hispanic	2 (6.1)	2	0	
Multiple race	2 (6.1)	1	1	
***CYP2C19* diplotype, n (%)**				
**17/*17*	4 (12.1)	2	2	0.15‡
**1/*17*	8 (24.3)	6	2	
**1/*1*	11 (33. 3)	8	3	
**1/*2A*1/*2B*	9 (27.3)	3	6	
**2A/*2A*	1 (3.0)	0	1	
Primary diagnosis, n (%)				
Acute lymphoblastic leukemia	12 (36.4)	7	5	0.48§
Acute myeloid leukemia	13 (39.4)	6	7	
Non-Hodgkin lymphoma	3 (9.1)	2	1	
Other¶	5 (15.1)	4	1	
Age, n (%)		19 (57.6)	14 (42.4)	
Median (years)	9.0			
Range (years)	1–19			
Weight				
Median (kg)		19.4	71.6	
Range (kg)		8.6–57.8	4 0 –110	

† Hispanic and multiple race were combined for statistical analysis

‡ *CYP2C19*1/*2A,*1/*2B* and **2A/*2A* diplotype groups were combined for statistical analysis

§ Acute lymphoblastic and myeloid leukemia groups were combined for statistical analysis.

¶ Ganglioglioma, Ewing's sarcoma, germ cell tumor, Hodgkin lymphoma and pineoblastoma

Table 2

Observed median voriconazole dose and corresponding median trough concentration stratified by *CYP2C19* diplotype and age, and extrapolated voriconazole dose predicted to achieve a steady-state trough concentration of 1–6 μg/ml.

***CYP2C19* diplotype**	**Observed median voriconazole dose mg/kg/day (range)**	**Observed median voriconazole trough concentration, μg/ml (range)**	**Extrapolated voriconazole dose to achieve a therapeutic concentration in majority of patients, mg/kg/day**	**Predicted median voriconazole trough concentration based on the extrapolated dose, μg/ml (range)**
Patients <12 years of age				
*CYP2C19*171*17* (n = 2)†	14.05(9.3–22.2)	0.17(0.030.38)	36	0.88(0.44–1.22)
*CYP2C19*1/*17* (n = 6)	19.2(8.6–33.1)	0.90(0.06–10.89)	30	1.72 (0.09–49.65)
*CYP2C19*1/*1* (n = 8)	14.9(2.6–41.2)	0.82 (0.03–20.17)	20	1.89(0.11–34.07)
*CYP2C19*1/*2A,*1/*2B* (n = 3)	23 (15.9–34.6)	2.71 (0.20–8.46)	18	1.82 (0.66–5.70)
*CYP2C19*2A/*2A* (n = 0)	-	-	-	-
Patients ≥12 years of age				
*CYP2C19*17/*17*(n = 2)	7.6(6.2–11.5)	0.30(0.05–0.49)	28	1.76(1.13–3.03)
*CYP2C19*1/*17*(n = 2)	9.5 (6.3–13.6)	1.73(0.03–6.99)	14	3.22(0.06–10.11)
*CYP2C19*1/*1* (n = 3)	8.3(3.9–16.1)	1.39(0.05–3.57)	14	2.21 (0.19–8.10)
*CYP2C19*1/*2A,*1/*2B* (n = 6)	8.3(3.6–16.0)	1.64(0.03–11.21)	10	2.66(0.06–12.41)
*CYP2C19*2A/*2A* (n = 1)	5.9(4.2–6.3)	3.69 (2.97–3.86)	4	2.30(1.80–3.35)

†(n) represents the number of patients per group.

Table 3

Characteristics associated with dose-corrected voriconazole trough concentrations.

Covariate	Coeffcient	p-value†
CYP2C19 diplotype‡	0.85	0.002
Age	0.08	0.05
Ancestry		
Caucasian	–	–
African–American	− 0.18	NS
Hispanic	0.58	NS
Multiple race	1.06	NS
Gender		
Female	–	–
Male	0.22	NS
Antifungals		
Not concomitantly administered	–	–
Concomitantly administered	0.83	NS
Proton pump inhibitors		
Not concomitantly administered	–	–
Concomitantly administered	−0.30	NS
Steroids		
Not concomitantly administered	–	–
Concomitantly administered	0.64	NS

†The p-value indicates if the covariate significantly affected dose-corrected voriconazole plasma concentrations in a linear mixed-effects model.

‡*CYP2C19* diplotypes were treated as an ordinal variable. Increasing numerical ordinal scores are representative of a predicted decrease in CYP2C19 catalytic activity (i.e., *CYP2C19*2A/*2A > CYP2C19*1/*2A,*1/*2B > CYP2C19*1/*1 > CYP2C19*1/*17 > CYP2C19*17/*17*).

NS: Not significant.

Table 4

Population pharmacokinetic parameters.

Parameter	Parameter value	RSE (%)	IIV (%)	IOV (%)	p-value†
Estimated parameters					
V (l/kg)	3.37	43	169	161	–
V_{max} (μg/h/kg)	3.36	27	42	39	–
Effect of covariates on V_{max}‡§					
Age	− 0 .147	18	–	–	$<1 \times 10^{-7}$
*CYP2C19*17/*17*	1.27	32	–	–	0.002
*CYP2C19*1/*17*	− 0 .147	212	–	–	NS
*CYP2C19*1/*2A*1/*2B*	−0.444	70	–	–	NS
*CYP2C19*2A/*2A*	− 0. 419	362	–	–	NS
Fixed parameters					
K_a (l/h)	0.849				
f	0.446				
K_m (μg/ml)	3				
Q (l/h/kg)	0.609				
V_p(l/kg)	2 .17				

†The p-value indicates if the covariate significantly affected V_{max}

‡*CYP2C19*1/*1* reference diplotype.

§Covariate model: $V_{max} = \theta e^{b1 \cdot age + b_i \cdot (CYP2C19_i)}$ where $CYP2C19_i$ = (**17/*17,*1/*17,*1/*2A,*2A/*2A*).

f: Bioavailability; IIV: Interindividual variability; IOV: Interoccasion variability; K_a: Absorption rate; K_m: Michaelis–Menten half-saturation; NS: Not significant; RSE: Relative standard error; Q: Intercompartmental clearance; V_p: Volume of the peripheral compartment; V_{max}: Michaelis–Menten maximum activity.