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Optimization of voriconazole therapy for the treatment of invasive fungal infections in adults

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Abstract

Therapeutic concentrations of voriconazole in invasive fungal infections (IFIs) are ensured using drug monitoring approach, which relies on attainment of steady state pharmacokinetics. For voriconazole, time to reach steady state can vary from 5–7 days, not optimal for critically ill patients. We developed a population pharmacokinetic/pharmacodynamic model-based approach to predict doses which can maximize the net benefit (probability of efficacy – probability of adverse events) and ensure therapeutic concentrations, early on during treatment. Label-recommended 200 mg voriconazole dose resulted in attainment of targeted concentrations in 80% patients in case of *Candida spp.* infections, as compared to only 40–50% patients, with net benefit ranging from 5.8–61.8%, in case of *Aspergillus spp.* infections. Voriconazole doses of 300–600 mg were found to maximize the net benefit up to 51–66.7%, depending on the clinical phenotype (due to CYP2C19 status and pantoprazole use) of the patient and type of *Aspergillus* infection.

Keywords

Invasive fungal infections; Voriconazole; Dose optimization; CYP2C19 polymorphisms; Monte Carlo Simulations

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Introduction

Invasive fungal infections (IFIs) are common in immunocompromised patients, such as those with solid organ transplant or bone marrow transplants (1, 2). Voriconazole is a triazole, anti-fungal agent, used as a first line agent for the treatment for IFIs, mainly caused by *Aspergillus* spp. It is also effective against *Candida* spp. (3, 4), although it is not a first line agent for these fungal pathogens. According to the Infectious Diseases Society of America (IDSA) guidelines (5), voriconazole should be dosed according to the patient's body weight (loading dose of 6 mg/kg intravenous (i.v.) infusion or 400 mg BID orally for 24 hour, followed by a 4 mg/kg i.v. or 200 mg BID oral maintenance dose). In adults, voriconazole is metabolized by CYP450 enzymes (6, 7), mainly by *CYP2C19*. Its CYP-mediated metabolism can be saturated at therapeutic concentrations, which contributes to the large inter-individual variability in voriconazole exposure. To ensure therapeutic concentrations are reached clinically, therapeutic drug monitoring (TDM) is widely used. Using TDM, steady state trough concentrations ($C_{\text{trough,ss}}$) are measured on day 5–7, and doses are adjusted if the $C_{\text{trough,ss}}$ is not within the therapeutic range of voriconazole (2–6 mg/L) (8). However, this waiting period of 5–7 days is particularly problematic in critically ill patients and is associated with high fatality rates (2).

In addition, genetic polymorphisms in *CYP2C19* (9–11), drug-drug interactions, comorbidities, age, and weight affect the pharmacokinetics (PK) of voriconazole and further contribute to the large inter-individual variability in voriconazole exposure (12). *CYP2C19* polymorphisms account for approximately 39% of the variability in clearance in healthy adults (10) following a single dose of voriconazole. We showed in a previous publication (8) that patients with *1/*17 (Rapid metabolizers, RM) or *17/*17 (Ultra-rapid metabolizers, UM) *CYP2C19* genotype have a higher prevalence of sub-therapeutic concentrations compared to other *CYP2C19* genotypes, such as *1/*1 (Normal metabolizers, NM); *1/*2, *2/*17 (Intermediate metabolizers, IM) and *2/*2 (Poor metabolizers, PM), following the same mg/kg maintenance dose.

In isolation, information on voriconazole PK is of limited meaningfulness because it does not consider the susceptibility of the infecting organism towards the drug. Therefore, both the PK of voriconazole and the associated pharmacodynamic (PD) response as well as differences therein (e.g. MIC distributions) need to be taken into consideration when attempting to establish optimal voriconazole dosing regimen. The objective of this study was to establish optimal dosing regimen for voriconazole against *Candida* spp. and *Aspergillus* spp. by accounting for clinically relevant sources of variability including *CYP2C19* polymorphisms, drug-drug interactions, and MIC distributions of the infecting organisms.

Results

Population Pharmacokinetic Analysis

A one-compartment body model with first-order absorption and Michaelis-Menten elimination described the clinical data reasonably well (Figure S1). *CYP2C19* genotype and pantoprazole-use significantly affected the clearance of voriconazole, as highlighted in the exploratory analysis (see methods section). While there was no significant difference in

clearance between NM and IM, maximum metabolic capacity ($V_{\max}$) was approximately 29% higher in RM/UM compared to NMs and IMs (Table S1). The impact of drug-drug interactions was felt in estimated Michaelis-Menten constant (K_m) values, which were approximately 79% higher in the presence of pantoprazole. We consequently decided to categorize our study subjects into 4 groups for further analysis: 1) NM/IM non-pantoprazole, 2) NM/IM pantoprazole, 3) RM/UM non-pantoprazole, and 4) RM/UM pantoprazole. Age, weight, sex, and comorbidities were not identified as significant covariates in our analysis. The estimated value for voriconazole's apparent volume of distribution (V_d/F) of 291 L (Table S1) is consistent with the FDA-reported value of 4 L/kg (12). Additional information on the model's performance and precision of its parameter estimates are provided in the supplementary material.

Population pharmacokinetic-pharmacodynamics analysis

Following a label-recommended dose of 200 mg BID oral voriconazole, both pre-clinical ($\text{fAUC}_{24}/\text{MIC} \geq 25$) (Figure 1a) and clinical ($C_{\text{trough,ss}}/\text{MIC} > 2$) (Figure 1b) PK/PD index of efficacy yielded similar PTA for all the phenotypes of voriconazole. For $\text{MIC} \leq 0.12$ mg/L, all phenotypes showed $\geq 90\%$ PTA, with insignificant differences amongst them (Figure 1b). At $\text{MIC} > 0.12$ mg/L, the PTA is lowest for RM/UM non-Pantoprazole (Figure 1b), while it is highest for NM/IM Pantoprazole. For instance, at a MIC of 1 mg/L, 23.3% RM/UM non-pantoprazole, 39.9% NM/IM non-Pantoprazole, 46.5% RM/UM Pantoprazole and 64.9% NM/IM pantoprazole patients achieved the target (Figure 1b). PTA was lower in RM/UM compared to NM/IM patients in both pantoprazole- and non-pantoprazole- use groups. Pantoprazole improved the PTA by approximately 25%, for both RM/UM and NM/IM patients (Figure 1b). Overall, 43.6% patients achieved the target, following 200 mg voriconazole dose at MIC of 1 mg/L, irrespective of the phenotype (Figure 1b). These probabilities are consistent with those predicted with PK/PD index of $C_{\text{trough,ss}} > 2$ (Table 1).

Susceptibility of *Candida* spp. against voriconazole was higher than *Aspergillus* spp. as evident in MIC distributions (Figure 5d). CFR was $\geq 80\%$ for most of the *Candida* spp., except *C. krusei* (Figure 1d) while it was approximately 40–70% for *Aspergillus* spp. (Figure 1c), following a label-recommended 200 mg oral voriconazole dose. The phenotypic differences were not as pronounced in case of *Candida* spp. (Figure 1d), unlike *Aspergillus* spp. (Figure 1c) where CFR was highest for NM/IM pantoprazole, followed by RM/UM pantoprazole, NM/IM non-pantoprazole and RM/UM non-pantoprazole phenotype.

Figure S2 shows the respective probabilities of efficacy (CFR) and safety (VAE) for all phenotypes and *Aspergillus* spp. with voriconazole dose. For *A. fumigatus*, the most frequent cause of *Aspergillus* spp. infections, 200 mg dose resulted in a net benefit of only 27.8%, 43.5%, 52.9%, and 61.8% for RM/UM non-pantoprazole, NM/IM non-pantoprazole, RM/UM pantoprazole and NM/IM non-pantoprazole phenotypes, respectively (Figure 2). At proposed 500 mg, 400 mg, 400 mg and 300 mg doses (Figure 3), net benefit increases to 61.6%, 63.5%, 66.4% and 66.7% for RM/UM non-pantoprazole, NM/IM non-pantoprazole, RM/UM pantoprazole and NM/IM pantoprazole phenotypes, respectively (Figure 2). For harder to treat *A. terreus* infections, the net benefit increases from 5.8%, 19.7%, 25.2% and 39.9% to 51%, 52.5%, 56.2% and 58.2% at proposed 600 mg, 450 mg, 450 mg and 400 mg

doses for RM/UM non-pantoprazole, NM/IM non-pantoprazole, RM/UM pantoprazole and NM/IM pantoprazole phenotypes, respectively (Figure 2 and Figure 3). Similar trends could be noticed for *A. niger* and *A. flavus* infections (Figure 2 and Figure 3). Additional benefit-risk analysis revealed that the relationship of voriconazole dose with other AEs, such as bilirubin elevation (Figure S3), AST or ALP elevation, was shallow and did not affect dose selection.

Based on our analysis, we have provided dosing recommendations for 2 main clinical scenarios: 1) Reactive dose adjustment for existing/suspected infection (Figure 4a) and (2) Prospective dose optimization for subjects undergoing “high-risk procedures”, such as organ transplant surgery (Figure 4b). In other words, we have distinguished between intend-to-treat and intent-to-prevent scenarios. In scenario 1 (Figure 4a), patients infected with *Candida* spp. and *Aspergillus* spp. infections should be started on a standard loading dose and the susceptibility of fungal isolates to voriconazole be tested. While label-recommended doses can be used prior to the availability of the susceptibility testing results, further dosing regimen should take the pathogen’s susceptibility to voriconazole into consideration. For *Candida* spp. infections, the label-recommended maintenance dose of 200 mg voriconazole should be sufficient for all patients. In contrast, voriconazole doses need to be increased for patients with *Aspergillus* spp. infections. The magnitude of this increase depends on the *CYP2C19* genotype and co-administration of pantoprazole. TDM approach should be adopted when *CYP2C19* genotype or susceptibility of infection is unknown. In scenario 2 (Figure 4b), patients who are at risk for infections, such as those undergoing liver/bone marrow transplantation, should be genotyped for *CYP2C19* *a priori*. If these patients are infected post-transplantation, the results from *CYP2C19* genotyping can then be used to optimize steady state exposure of voriconazole early on, depending on the susceptibility of pathogen.

Discussion

According to the FDA-approved label (4), a maintenance dose of 4 mg/kg i.v or 200 mg oral BID should be sufficient to achieve therapeutic voriconazole exposure. Although the label appreciates that patients with *2, *3 *CYP2C19* allelic variant have 4-fold higher exposure than the ones with wild-type *1 allele, no such information is shown for the patients harboring *17 *CYP2C19* allelic variant. Furthermore, no specific dose adjustment for *CYP2C19* polymorphisms has been proposed. Clinical Pharmacogenomics Implementation Consortium (CPIC) guidelines (13) for voriconazole acknowledge that the PTA at label-recommended voriconazole dose is very small and therapy should be avoided in UM and RM patients. The risk of treatment failure due to sub-therapeutic drug exposure or toxicities associated with elevated drug exposure, is mitigated via TDM in clinical practice (14, 15). However, TDM-based dose optimization approaches are perceived as being reliant on steady state PK measures. Given the long half-life of voriconazole, establishment of PK steady-state typically takes 5–7 days, which can be detrimental to critically ill patients(2), and is in fact unnecessary. One way of addressing this challenge is to complement TDM with model-informed approaches (16–18) in order to maximize the probability of achieving therapeutic steady-state quickly. A major advantage of this combined approach is that it allows for prospective consideration of other clinically-relevant sources of variability, such as

CYP2C19 phenotype, drug-drug interactions, and the infecting organisms' susceptibility to voriconazole compared to retrospective dose adjustment using TDM only.

Our analysis revealed that the label-recommended 200 mg voriconazole dose would be sufficient to achieve the probability of target attainment for all phenotypes against *Candida* spp. infections. For less susceptible *Aspergillus* spp. infections, doses >200 mg were needed to achieve therapeutic concentrations in different clinical phenotypes. Voriconazole dose increase is also significantly associated with transient and reversible adverse events, such as VAE, followed by AST, ALP and bilirubin elevation in patients (19–21). As expected, RM/UM non-pantoprazole patients were at most risk for therapeutic failure of voriconazole. A voriconazole dose of 500 mg BID provided an optimal trade-off between efficacy and safety for RM/UM non-pantoprazole patients, for treatment of *A. fumigatus* infections (Figure 3). However, higher doses of 600, 550 and 600 mg were needed to maximize the net benefit for RM/UM non-pantoprazole patients, suffering from less sensitive infections such as *A. flavus*, *A. niger* and *A. terreus*. For NM/IM non-pantoprazole and RM/UM pantoprazole patients, doses of 400 mg and 450 mg were found to be sufficient for treatment of *A. niger/A. fumigatus* and *A. terreus/A. flavus* infections, respectively. In NM/IM pantoprazole patients, doses ranging from 300–400 mg were predicted to be effective, depending on the type of infection. At proposed doses, probability of bilirubin elevation only increases by 5% compared to the label-recommended 200 mg dose, not found to be critical for dose selection. It is also important to note that voriconazole use is associated with other CNS toxicities besides VAE, such as headache, confusion, hallucination, dizziness, euphoria, amnesia etc. However, the frequency of these adverse events is <2% in patients (4) and not considered dose-limiting (22). Furthermore, projected doses are in line with a retrospective study (23), which found that a 4 mg/kg (280 mg for a 70 kg adult) and 6.75 mg/kg (475 mg for a 70 kg adult) voriconazole dose was required to achieve target concentrations in *CYP2C19* RM and UM phenotypes, respectively. In our study, statistical distinction of RM and UM were not possible, due to very small number of patients in the UM group (N=4). Given the reversible nature of adverse events associated with voriconazole, as opposed to the detrimental effects of treatment failure, benefits associated with dose escalation may outweigh the risks in long term (24).

It should also be acknowledged that the impact of *CYP2C19* RM/UM phenotype on the voriconazole pharmacokinetics (25–27) has not been studied extensively. To the authors' knowledge, this is the first study which has quantified the changes in steady state clearance of voriconazole due to *17 *CYP2C19* genotype as well as pantoprazole use and translated those findings into an optimal dose recommendation. Pantoprazole is based on *in vitro* findings a weak inhibitor of *CYP2C19* compared to other proton pump inhibitors (PPI), such as omeprazole (28). However, *in vivo* studies (29–31) show that pantoprazole use can lead to a significant increase in $C_{trough,ss}$ of voriconazole. Moreover, benefit from TDM of voriconazole were greater in the patients who were co-treated with PPI at dosages 40 mg intravenously (29). Our results are in line with these literature reports and show that pantoprazole use significantly increases the PTA in both NM/IM and RM/UM phenotypes due to increased voriconazole exposure.

Studies have also shown that the PK of voriconazole can be influenced by concomitant administration of CYP3A4 inhibitors (32) or inducers (33). For example, Mikus et al. (32) showed that the coadministration of a potent CYP3A4 inhibitor can lead to a higher and prolonged exposure of voriconazole, which in turn can increase the risk of experiencing adverse drug reactions, particularly in CYP2C19 PMs. The results of our study are inconclusive in this regard because none of the study subjects were taking CYP3A4 inhibitor or inducer during treatment with voriconazole. Furthermore, our clinical study had only 1 CYP2C19 PM patient which was excluded from the modeling analysis as it was not feasible to estimate a covariate effect on clearance using data from only 1 subject. Our current model consequently does not provide dosing recommendations for CYP2C19 PMs but can be readily updated as additional clinical data becomes available.

For voriconazole, different PK/PD indices have been used as predictor of clinical efficacy. In a neutropenic murine model of disseminated candidiasis (34), $fAUC_{24}/MIC$ correlated well with the clinical efficacy of voriconazole. However, the predictive performance of this PK/PD index has not been confirmed in human studies. In clinical practice, $C_{trough,ss}$ provides a more robust and easier to obtain measure than AUC and is consequently used for dose adjustment. Attainment of $C_{trough,ss}$ values as low as 1 mg/L ($C_{trough,ss} > 1$) (35) and as high as 2 mg/L ($C_{trough,ss} > 2$) (36–38) were found to correlate with clinical efficacy. Literature evidence suggests that underexposure is associated with poor outcome. For example, Pascual *et al.* (35) showed that a significantly higher proportion of patients with levels ≤ 1 mg/L received oral voriconazole. Lack of response to therapy was more frequently observed in patients with levels ≤ 1 mg/L (46%) than in those with levels > 1 mg/L (12%; $P = .02$). Evidence from an observational study (39) further suggests that consideration of the pathogen's MIC along with $C_{trough,ss}$ i.e. $C_{trough,ss}/MIC > 2$ correlates well with efficacy and hence been proposed as a suitable PK/PD index of efficacy for voriconazole. Our findings show that both $fAUC_{24}/MIC$ and $C_{trough,ss}/MIC > 2$ result in similar probabilities of target attainment (Figure 1a and Figure 1b). It should be noted, however, that probabilities associated with $C_{trough,ss} > 2$ index (Table 1) will not be identical with those derived from $fAUC_{24}/MIC$ and $C_{trough,ss}/MIC > 2$ indices using MIC values different from 1 mg/L. Dose optimization based on $C_{trough,ss} > 2$ may not be optimal for pathogens with MIC less than or greater than 1, since it does not account for susceptibility of infection. Hence, the choice of using human-data driven and MIC-based PK/PD index i.e. $C_{trough,ss}/MIC > 2$ over animal model-derived index i.e. $fAUC_{24}/MIC$ and non-MIC based index i.e. $C_{trough,ss} > 2$ for dose optimization is well justified.

Our analysis indicates that a label-recommended dose of 200 mg voriconazole would be optimal for all phenotypic groups of patients in case of *Candida* spp. infections, however, dose should be adjusted based on patients' phenotype in case of *Aspergillus* spp. infections. Ideally, the proposed dosing recommendations should be validated in a prospective clinical study by comparing against TDM-based approach. Linkage of developed PK/PD model with clinical outcomes (treatment success or failure) database can also provide valuable insights in the predictive utility of proposed approach. It could also be argued that TDM can provide the same answer, however, with a delay of 5–7 days. With rapid development of point-of-care (PCT) CYP2C19 genotyping assays, the time needed to genotype patients can be reduced and proposed dose adjustments can help in achieving target exposure, much earlier

in the treatment time course. However, CYP2C19 genotyping/susceptibility testing may not be always feasible in all clinical settings. Isavuconazole or posaconazole, which do not undergo metabolism via CYP2C19, can be considered as potential alternatives in those cases (40).

The findings of this study are limited by the lack of MIC data in our patients and comparatively small sample size (n=69). For these two reasons, this study could not delineate an exposure-outcome relationship, also in view of the impact of patient genotype and co-medication(s). To address this limitation and establish an exposure-outcome relationship, MIC data should be collected in future clinical trials.

In conclusion, TDM-directed and genotype-directed are not mutually exclusive dose optimization approaches but rather informative of one another. Our analysis evaluates the advantages and limitations of the two in light of voriconazole's PK, associated variability due to CYP2C19 polymorphisms and comedications, the infecting pathogen's susceptibility as well as the prospective or retrospective use of the drug. It also shows that knowledge on the susceptibility of the infecting organism is key for successful antifungal therapy.

Materials and Methods

Patients and Data Collection

We previously conducted a clinical study (8) to prospectively evaluate the impact of *CYP2C19* polymorphisms on the PK of voriconazole (N=70) in patients receiving weight-based dosing. Respective patient demographics and clinically-relevant patient characteristics are listed in Table 2. The majority of the patients were Caucasians (80.9%) who also received pantoprazole (70.6%). Steady state PK data were available in 68 patients (27 NM, 14 IM, 3 RM and 24 UM), excluding 1 NM patient with unphysiological peak concentration (due to a sample collection error) i.e. $C_{peak,ss}$ (39 mg/L) and 1 poor metabolizer (*2/*2). Exploratory analysis from the previous study (8) highlighted the significant inter-individual variability in $C_{trough,ss}$ (range=0.26–9.53 mg/L), indicating the involvement of potential covariates (Figure 5a). Median $C_{trough,ss}$ were lower in RM/UM group (median=1.9, 90% CI= 0.3–6.6 mg/L) compared to that of NM (median=4.6, 90% CI= 0.5–7.2 mg/L) and IM (median=4.7, 90% CI= 1.7–6.1 mg/L) group at the same mg/kg voriconazole dose (Figure 5b). Interestingly, there was a considerable overlap between the 90% CIs of RM/UM, NM and IM groups, indicating other potential sources of variability. Additionally, patients who were taking pantoprazole had higher median $C_{trough,ss}$ (median=4.5, 90% CI= 0.5–7.2 mg/L) in comparison to patients who were not (median=1.9, 90% CI= 0.3–4.9 mg/L) (Figure 5c). However, the association between genotype and trough concentrations remained after accounting for pantoprazole use. This is consistent with the fact that pantoprazole competitively inhibits *CYP2C19*, resulting in higher voriconazole concentrations.

Population pharmacokinetic analysis

$C_{peak,ss}$ and $C_{trough,ss}$ data obtained from our previous clinical study (8) was characterized using non-linear mixed effect modeling in NONMEM v.7.3. One- and two- compartment models with non-linear elimination were tested as structural models using first-order

conditional estimation method with interaction. Additional details on the structural-, variance-, and covariate model are provided as supplementary material. The model's performance was evaluated based on the goodness of fit plots and non-parametric bootstrapping method (supplementary information).

Population pharmacokinetic-pharmacodynamics analysis

Once developed, the PopPK model was linked to MIC distribution data in NONMEM v.7.3 to perform 2000 Monte Carlo Simulations (MCS) (41) following label-recommended dosing regimen of voriconazole (400 mg BID orally for 24 hours, 200 mg BID orally thereafter). $C_{\text{trough,ss}}$ were determined and the probability of target attainment (PTA) were calculated (details in supplementary) for different pre-clinical and clinical PK/PD indices of efficacy for voriconazole (i) PTA1-Probability of achieving $C_{\text{trough,ss}} > 2$ mg/L (clinical) (8), the most commonly used index (ii) PTA2-Probability of achieving $fAUC_{24}/MIC \geq 25$ (pre-clinical) (34), (iii) PTA3-Probability of achieving $C_{\text{trough,ss}}/MIC > 2$ (clinical) (39).

MCS results were also expressed in terms of Cumulative Fraction of Response (CFR), defined as “the expected population probability of target attainment for a specific drug dose and a specific population of microorganisms” (42) (see equation (9) in supplementary information). Due to the unavailability of MIC data in our previous study (8), we used the MIC distributions for 4 *Aspergillus* spp. (*A. fumigatus*, *A. niger*, *A. terreus*, *A. flavus*) and 11 *Candida* spp. (*C. albicans*, *C. dubliniensis*, *C. famata*, *C. glabrata*, *C. guilliermondii*, *C. kefyr*, *C. krusei*, *C. lusitanae*, *C. parapsilosis*, *C. pintolopesii*, *C. tropicalis*) from European Committee on Antimicrobial Susceptibility Testing (EUCAST) database (43) for our computations (Figure 5d).

PTA and CFR were calculated for the label-recommended maintenance dose of voriconazole (200 mg BID orally) as well as higher maintenance doses of voriconazole i.e. 250, 300, 350, 400, 450, 500, 550 and 600 mg BID orally. In addition, we computed the probabilities of experiencing adverse events, such as visual adverse event (VAE) and hepatotoxicity (aspartate transaminase (AST) elevation, alkaline phosphatase (ALP) elevation and bilirubin elevation) for these dosing regimen using published relationships (19). A benefit-risk analysis was conducted and optimal doses of voriconazole were selected based on the maximal difference (net benefit) between benefit and risk.

$$\text{Net benefit} = \text{Probability of benefit} - \text{Probability of risk (VAE/hepatotoxicity)}$$

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Lin S-J, Schranz J, Teutsch SM. Aspergillosis case-fatality rate: systematic review of the literature. *Clinical Infectious Diseases*. 2001; 32:358–66. [PubMed: 11170942]
2. Singh N, Paterson DL. Aspergillus infections in transplant recipients. *Clinical microbiology reviews*. 2005; 18:44–69. [PubMed: 15653818]
3. Walsh TJ, et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. *Clinical infectious diseases*. 2008; 46:327–60. [PubMed: 18177225]
4. VFEND, P. Package insert. VFEND Tablets/VFEND IV (voriconazole). 2002
5. Patterson TF, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. *Clinical Infectious Diseases*. 2016; 63:e1–e60. [PubMed: 27365388]
6. Theuretzbacher U, Ihle F, Derendorf H. Pharmacokinetic/pharmacodynamic profile of voriconazole. *Clinical pharmacokinetics*. 2006; 45:649–63. [PubMed: 16802848]
7. Hyland R, Jones B, Smith D. Identification of the cytochrome P450 enzymes involved in the N-oxidation of voriconazole. *Drug Metabolism and Disposition*. 2003; 31:540–7. [PubMed: 12695341]
8. Hamadeh IS, et al. Impact of the CYP2C19 genotype on voriconazole exposure in adults with invasive fungal infections. *Pharmacogenetics and genomics*. 2017; 27:190–6. [PubMed: 28306618]
9. Shi H-Y, et al. Effects of erythromycin on voriconazole pharmacokinetics and association with CYP2C19 polymorphism. *European journal of clinical pharmacology*. 2010; 66:1131–6. [PubMed: 20669013]
10. Weiss J, et al. CYP2C19 genotype is a major factor contributing to the highly variable pharmacokinetics of voriconazole. *The Journal of Clinical Pharmacology*. 2009; 49:196–204. [PubMed: 19033450]
11. Mikus G, Scholz IM, Weiss J. Pharmacogenomics of the triazole antifungal agent voriconazole. *Pharmacogenomics*. 2011; 12:861–72. [PubMed: 21692616]
12. Committee, F.A.D.A.. Briefing document for voriconazole (oral and intravenous formulations). Silver Spring MD: US Food and Drug Administration; 2001.
13. Moriyama B, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP2C19 and Voriconazole Therapy. *Clinical Pharmacology & Therapeutics*. 2017
14. Park WB, et al. The effect of therapeutic drug monitoring on safety and efficacy of voriconazole in invasive fungal infections: a randomized controlled trial. *Clinical Infectious Diseases*. 2012; 55:1080–7. [PubMed: 22761409]
15. Moriyama B, Kadri S, Henning SA, Danner RL, Walsh TJ, Penzak SR. Therapeutic drug monitoring and genotypic screening in the clinical use of voriconazole. *Current fungal infection reports*. 2015; 9:74–87. [PubMed: 26918067]
16. Wang T, 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. *Journal of Antimicrobial Chemotherapy*. 2013; 69:463–70. [PubMed: 24084636]
17. Chen L, et al. Optimization of voriconazole dosage regimen to improve the efficacy in patients with invasive fungal disease by pharmacokinetic/pharmacodynamic analysis. *Fundamental & clinical pharmacology*. 2016; 30:459–65. [PubMed: 27341147]
18. Xu G, Zhu L, Ge T, Liao S, Li N, Qi F. Pharmacokinetic/pharmacodynamic analysis of voriconazole against *Candida* spp. and *Aspergillus* spp. in children, adolescents and adults by Monte Carlo simulation. *International journal of antimicrobial agents*. 2016; 47:439–45. [PubMed: 27179818]
19. Tan K, Brayshaw N, Tomaszewski K, Troke P, Wood N. Investigation of the potential relationships between plasma voriconazole concentrations and visual adverse events or liver function test abnormalities. *The Journal of Clinical Pharmacology*. 2006; 46:235–43. [PubMed: 16432276]
20. Walsh TJ, et al. Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. *New England Journal of Medicine*. 1999; 340:764–71. [PubMed: 10072411]

21. Laties AM, et al. Long-term visual safety of voriconazole in adult patients with paracoccidioidomycosis. *Clinical therapeutics*. 2010; 32:2207–17. [PubMed: 21316537]
22. Heo S, Aitken S, Tverdek F, Kontoyiannis D. How common is subsequent central nervous system toxicity in asymptomatic patients with haematologic malignancy and supratherapeutic voriconazole serum levels? *Clinical Microbiology and Infection*. 2017; 23:387–90. [PubMed: 28082193]
23. Lamoureux F, et al. Impact of CYP2C19 genetic polymorphisms on voriconazole dosing and exposure in adult patients with invasive fungal infections. *International journal of antimicrobial agents*. 2016; 47:124–31. [PubMed: 26775563]
24. 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: The Journal of Human Pharmacology and Drug Therapy*. 2014; 34:703–18.
25. Dolton MJ, Mikus G, Weiss J, Ray JE, McLachlan AJ. Understanding variability with voriconazole using a population pharmacokinetic approach: implications for optimal dosing. *Journal of Antimicrobial Chemotherapy*. 2014; 69:1633–41. [PubMed: 24554646]
26. Wang G, et al. The CYP2C19 ultra-rapid metabolizer genotype influences the pharmacokinetics of voriconazole in healthy male volunteers. *European journal of clinical pharmacology*. 2009; 65:281–5. [PubMed: 18982321]
27. Berge M, et al. Effect of cytochrome P450 2C19 genotype on voriconazole exposure in cystic fibrosis lung transplant patients. *European journal of clinical pharmacology*. 2011; 67:253–60. [PubMed: 21038076]
28. Li X-Q, Andersson TB, Ahlström M, Weidolf L. Comparison of inhibitory effects of the proton pump-inhibiting drugs omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole on human cytochrome P450 activities. *Drug metabolism and disposition*. 2004; 32:821–7. [PubMed: 15258107]
29. Cojutti P, et al. Variability of voriconazole trough levels in haematological patients: influence of comedications with cytochrome P450 (CYP) inhibitors and/or with CYP inhibitors plus CYP Inducers. *Basic & clinical pharmacology & toxicology*. 2016; 118:474–9. [PubMed: 26572687]
30. Dolton MJ, Ray JE, Chen SC-A, Ng K, Pont LG, McLachlan AJ. Multicenter study of voriconazole pharmacokinetics and therapeutic drug monitoring. *Antimicrobial agents and chemotherapy*. 2012; 56:4793–9. [PubMed: 22751544]
31. Heinz W, et al. Comparison of plasma trough concentrations of voriconazole in patients with or without comedication of ranitidine or pantoprazole. *Clinical Microbiology & Infection*. 2007; 13:S357.
32. Mikus G, et al. Potent cytochrome P450 2C19 genotype-related interaction between voriconazole and the cytochrome P450 3A4 inhibitor ritonavir. *Clinical Pharmacology & Therapeutics*. 2006; 80:126–35. [PubMed: 16890574]
33. Purkins L, Wood N, Ghahramani P, Love ER, Eve MD, Fielding A. Coadministration of voriconazole and phenytoin: pharmacokinetic interaction, safety, and toleration. *British journal of clinical pharmacology*. 2003; 56:37–44. [PubMed: 14616412]
34. Andes D, Marchillo K, Stamstad T, Conklin R. In vivo pharmacokinetics and pharmacodynamics of a new triazole, voriconazole, in a murine candidiasis model. *Antimicrobial agents and chemotherapy*. 2003; 47:3165–9. [PubMed: 14506026]
35. 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. *Clinical infectious diseases*. 2008; 46:201–11. [PubMed: 18171251]
36. Miyakis S, Van Hal SJ, Ray J, Marriott D. Voriconazole concentrations and outcome of invasive fungal infections. *Clinical Microbiology and Infection*. 2010; 16:927–33. [PubMed: 19845698]
37. Smith J, et al. Voriconazole therapeutic drug monitoring. *Antimicrobial agents and chemotherapy*. 2006; 50:1570–2. [PubMed: 16569888]
38. Ueda K, et al. Monitoring trough concentration of voriconazole is important to ensure successful antifungal therapy and to avoid hepatic damage in patients with hematological disorders. *International journal of hematology*. 2009; 89:592–9. [PubMed: 19340528]

39. Troke PF, Hockey HP, Hope WW. Observational study of the clinical efficacy of voriconazole and its relationship to plasma concentrations in patients. *Antimicrobial agents and chemotherapy*. 2011; 55:4782–8. [PubMed: 21768513]
40. Moriyama B, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP2C19 and Voriconazole Therapy. *Clinical Pharmacology & Therapeutics*. 2017; 102:45–51. [PubMed: 27981572]
41. Drusano G, et al. Use of preclinical data for selection of a phase II/III dose for evernimicin and identification of a preclinical MIC breakpoint. *Antimicrobial agents and chemotherapy*. 2001; 45:13–22. [PubMed: 11120938]
42. Mouton JW, Dudley MN, Cars O, Derendorf H, Drusano GL. Standardization of pharmacokinetic/ pharmacodynamic (PK/PD) terminology for anti-infective drugs. *International journal of antimicrobial agents*. 2002; 19:355–8. [PubMed: 11978507]
43. European Committee on Antimicrobial Susceptibility Testing. <<https://mic.eucast.org/Eucast2/SearchController/search.jsp?action=performSearch&BeginIndex=0&Micdif=mic&NumberIndex=50&Antib=152&Specium=-1>>

Study highlights

What is the current knowledge on the subject?

Voriconazole shows a significant inter-individual variability in clinical response. Therapeutic drug monitoring is used to ensure therapeutic concentrations in clinic.

What question did this study address?

This is the first model-based analysis aimed to optimize voriconazole doses, which can maximize the probability of achieving therapeutic concentrations, either to prior early on during the course of treatment.

What does this study add to our knowledge?

Label-recommended 200 mg voriconazole dose was sufficient for the treatment of *Candida* spp. IFIs. However, voriconazole doses ranging from 300–600 mg were needed for the successful treatment of *Aspergillus* spp. IFIs, depending on the clinical phenotype of the patient and type of *Aspergillus* infection.

How might this change clinical pharmacology or translational science?

Our results can change the way voriconazole is dosed in patients, suffering from invasive fungal infections. Proposed dosing recommendations can help clinicians to determine an optimal treatment strategy for a particular patient based on clinical phenotype and type of infection.

(a)

(b)

(c)

(d)

Figure 1.

Probability of efficacy of voriconazole represented in terms of probability of target attainment (PTA) and Cumulative fraction of response (CFR) against *Candida* spp. and *Aspergillus* spp. following label-recommended dosing regimen of voriconazole (200 mg BID) (a) PTA2-Probability of achieving $fAUC_{24}/MIC \geq 25$ (pre-clinical), (b) PTA3-Probability of achieving $C_{trough,ss}/MIC > 2$ (clinical), (c) CFR against *Aspergillus* spp. and (d) CFR against *Candida* spp. Different colors represent probabilities/CFR for different phenotypes of voriconazole (blue-RM/UM non-pantoprazole; red-NM/IM non-pantoprazole; pink-RM/UM pantoprazole; green-NM/IM pantoprazole; black-overall probability)

Figure 2.

Net benefit by phenotype and *Aspergillus* spp. Different colors represent probabilities for different phenotypes of voriconazole (blue-RM/UM non-pantoprazole; red-NM/IM non-pantoprazole; pink-RM/UM pantoprazole; green-NM/IM pantoprazole). Net benefit is defined as the difference in the Probability of efficacy (CFR %) and probability of visual adverse event.

Figure 3.

Label-recommended and proposed BID maintenance doses of voriconazole for the treatment of invasive fungal infections caused by *Aspergillus* spp. and *Candida* spp. in adults by *CPY2C19* phenotype, pantoprazole use and type of infection. Different colors represent recommended doses for different phenotypes of voriconazole (blue-RM/UM non-pantoprazole; red-NM/IM non-pantoprazole; pink-RM/UM pantoprazole; green-NM/IM pantoprazole).

(a)

(b)

Figure 4.

Clinical recommendations for dosing voriconazole in adults in 2 different scenarios: (a) Intent-to-treat-scenario: Reactive dose adjustment for existing/suspected infections (b) Intent-to-prevent scenario: Prospective dose optimization for high-risk organ transplant patients.

(a)

(b)

(c)

(d)

Figure 5.

Voriconazole pharmacokinetic and clinically relevant sources of variability: (a) Steady state trough concentrations ($C_{\text{trough,ss}}$) in all the patients. (b) $C_{\text{trough,ss}}$, stratified by *CYP2C19* phenotype, (c) $C_{\text{trough,ss}}$, stratified by pantoprazole use. Filled circles and cross symbols represents the $C_{\text{trough,ss}}$ obtained before and after the dose adjustment following TDM, respectively. Dashed blue line indicates the therapeutic range of voriconazole (2–6 mg/L). (d) PD variability in MIC distributions of voriconazole against 4 *Aspergillus* spp. (*A. fumigatus*, *A. niger*, *A. terreus*, *A. flavus*, represented by black lines) and 11 *Candida* spp. (*C. albicans*, *C. dubliniensis*, *C. famata*, *C. glabrata*, *C. guilliermondii*, *C. kefyr*, *C. krusei*, *C.*

lusitaniae, *C. parapsilosis*, *C. pintolopesii*, *C. tropicalis*, represented by grey lines) as obtained from EUCAST database.

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Table 1

Probability of target attainment (PTA1) for different phenotypes of voriconazole determined using $C_{\text{trough,ss}} > 2$ as the PK/PD index of efficacy, following label-recommended dose of 200 mg BID voriconazole.

Phenotype	PTA1 (%)
RM/UM non-pantoprazole	23.2
NM/IM non-pantoprazole	39.9
RM/UM pantoprazole	46.5
NM/IM pantoprazole	64.9
Overall	43.6

Table 2

Demographics and clinical characteristics of patients included in the analysis. Table adapted from Hamadeh *et al.*(8)

Characteristic	Value * (n=68)
Age (years)	53.1 ± 17.9
Weight (kg)	68.9 ± 15
Male sex	41 (60.3)
Race	
Caucasian	55 (80.9)
African American	11 (16.2)
Asian	2 (2.9)
CYP2C19 phenotype	
Normal metabolizers	27 (39.7)
Intermediate metabolizers	14 (20.6)
Rapid Metabolizers	24 (35.3)
Ultra-rapid metabolizers	3 (4.4)
Concomitant medications	
Pantoprazole	48 (70.6)
Comorbidities	
Hematopoietic stem cell transplant	20 (29.4)
Hematologic malignancies	22 (32.4)
Solid organ transplant	12 (17.6)
Other	14 (20.6)

* Mean ± SD or Number (%)