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REVIEW ARTICLE

Interpersonal Factors in the Pharmacokinetics and Pharmacodynamics of Voriconazole: Are CYP2C19 Genotypes Enough for Us to Make a Clinical Decision?

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Abstract: ***Background:*** Invasive mycoses are serious infections with high mortality and increasing incidence. Voriconazole, an important drug to treat invasive mycosis, is metabolized mainly by the cytochrome P450 family 2 subfamily C member 19 enzyme (CYP2C19) and is affected by the genotypes of *CYP2C19*.

Objective: We reviewed studies on how genotypes affect the pharmacokinetics and pharmacodynamics of voriconazole, and attempted to determine a method to decide on dosage adjustments based on genotypes, after which, the main characteristic of voriconazole was clarified in details. The pharmacokinetics of voriconazole are influenced by various inter and intrapersonal factors, and for certain populations, such as geriatric patients and pediatric patients, these influences must be considered. *CYP2C19* genotype represents the main part of the interpersonal variability related to voriconazole blood concentrations. Thus monitoring the concentration of voriconazole is needed in clinical scenarios to minimize the negative influences of inter and intrapersonal factors. Several studies provided evidence on the stable trough concentration range from 1-2 to 4-6 mg/L, which was combined to consider the efficacy and toxicity. However, the therapeutic drug concentration needs to be narrowed down and evaluated by large-scale clinical trials.

Conclusion: Though there is insufficient evidence on the relationship between *CYP2C19* genotypes and clinical outcomes, there is a great potential for the initial voriconazole dose selection to be guided by the *CYP2C19* genotype. Finally, voriconazole therapeutic drug monitoring is essential to provide patient-specific dosing recommendations, leading to more effective anti-fungal regimens to increase clinical efficacy and reduce adverse drug reactions.

Keywords: Voriconazole, pharmacogenomics, pharmacokinetics, CYP2C19 polymorphisms, therapeutic drug monitoring, genotype guided dosing.

1. INTRODUCTION

Precision medicine indicates a model of medical practice that proposes the customization of healthcare, with medical decisions, practices, or products being tailored to the individual patient. In this model, a patient's genetic content is taken into primary consideration to select diagnostic testing and appropriate therapies [1]. Clarifying the genetic background is a future trend of medicine that could guide us to perform highly personalized medical care [2]. Genes encode human hereditary information, which is relatively conserved, usually unique, and rarely changes. Pharmacogenomics aims to clarify how the genetic make-up of an individual affects their response to drugs; *i.e.*, the study of the role of the genome in drug responses. It considers the influence of acquired and inherited genetic variations on the drug response in patients by correlating gene expression or single-nucleotide polymorphisms (SNPs) with pharmacokinetics and pharmacodynamics, including drug absorption, distribution, metabolism, and elimination, as well as drug receptor target effects [3].

Invasive mycoses are serious infections with high mortality and increasing incidence [4, 5]. Voriconazole is a second-generation triazole antifungal agent with a broad spectrum of activity against *Candida* species, *Aspergillus*, *Fusarium*, *Scedosporium*, and *Cryptococcus*. The mechanism of voriconazole's antifungal function is the highly effective blockade of the biosynthesis of ergosterol from lanosterol by inhibiting the fungal 14-alpha-sterol demethylase [6, 7]. It is currently recommended as first-line therapy for acute invasive aspergillosis, as a preventive treatment of agranulocytopenia patients accompanied with fever, and as salvage therapy for infections caused by *Fusarium* and *Scedosporium* [8, 9].

Voriconazole has distinctive nonlinear pharmacokinetics that can be influenced by numerous interpersonal and intrapersonal variables [10]. Adverse reactions to voriconazole include mainly visual anomalies, hepatotoxicity, and neurotoxicity (hallucinations and dizziness), which are related to blood trough concentrations [11, 12]. Therefore, genotype screening and therapeutic drug monitoring (TDM) are helpful in clinical use to increase treatment efficacy and decrease toxicity [13]. TDM of this agent is suggested in major guidelines from the Infectious Diseases Society of America (IDSA), the American Thoracic Society, and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) to improve clinical outcomes and reducing side effects [4, 14-17]. In this article, we review studies on how genotypes affect the pharmacokinetics and pharmacodynamics of voriconazole, and attempted to define a method to decide on dosage adjustment based on genotypes.

2. PHARMACOKINETICS OF VORICONAZOLE

2.1. General Characteristics

Voriconazole is available as both oral and intravenous formulations. The recommended regimen by the manufacturer is two load-

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ing doses of 6 mg/kg given 12 hours apart, followed by 4 mg/kg or 200 mg for patients whose weight exceeds 40 kg, and 150 mg for those weight less than 40 kg, every 12 hours. A steady state concentration could be achieved after 24 hours when loading doses were received, or 6 days later if the patient is only taking maintenance doses twice daily. Voriconazole exhibits high oral bioavailability (~96%), so oral forms are practically equivalent to the intravenous formulations, which allows a convenient switch between these two formulations. In the case of renal failure patients with a glomerular filtration rate less than 50 mL/min, oral forms are given preference because of the patient's limited ability to excrete Sulphobutylether-β-Cyclodextrin (SBECD), the excipient of voriconazole, in cases of unknown adverse events of SBECD accumulation. The average plasma protein-binding rate of voriconazole is 58% and the volume of its distribution is 4.6 L/kg. Voriconazole demonstrates nonlinear pharmacokinetics and saturated metabolism, such that an increased dose would lead to a non-proportional rise in the trough concentration and area under the concentration-time curve (AUC), thus causing an alteration in drug exposure [18].

2.2. Metabolism

Voriconazole is metabolized extensively in the liver by cytochrome CYP450s, comprising CYP2C19, CYP3A, and CYP2C9 enzyme subfamilies [19]. CYP2C19 enzymes are responsible mainly for the conversion of voriconazole into its major inactive metabolite, voriconazole-N-oxide, which accounts for ~72% of plasma metabolites [20, 21]. CYP3A4 plays a relatively minor role in overall voriconazole metabolism, with an affinity for voriconazole that is nearly 50-fold lower than that of CYP2C19 [21, 22]. Nonetheless, a study showed that the presence of the *22 allele of CYP3A4 was associated with a statistically significant increase in the ratio of voriconazole trough concentration/dose (C_{min}/D). A linkage between the existence of CYP3A4*22 allele and elevated initial voriconazole C_{min}/D could be established, regardless of patient's CYP2C19 phenotype [23]. In the poor metabolizers of CYP2C19, the metabolic pathway catalyzed by CYP3A4 comes to the fore, while CYP2C9 is considered to play only a minor role in the biotransformation of voriconazole, because its low level does not alter the pharmacokinetics of the drug [24].

3. INTERPERSONAL AND INTRAPERSONAL FACTORS THAT INFLUENCE VORICONAZOLE PHARMACOKINETICS

Numerous interpersonal and intrapersonal factors influence the pharmacokinetics of voriconazole. Among the interpersonal factors, genetic polymorphisms of the CYP2C19 gene should be considered by many researchers to have the most important effect, which will be discussed thoroughly later. Other factors include age, sex, and severity of the disease. The effect of age on voriconazole pharmacokinetic has not received enough research attention, especially for the elderly. Higher voriconazole concentrations have been reported in patients older than 65 years [19]. A pharmacokinetics analysis using data from ten studies of voriconazole in the treatment of 552 patients showed that the trough blood concentration in elderly patients was about 80-90% higher than that in younger patients, regardless of the formulation. Although higher blood trough concentration does not necessarily indicate a higher risk of adverse reaction, dose adjustment should be considered for this patient type [25]. By contrast, an opposite trend of alteration in serum concentration of this drug seems to apply to the pediatric group, in which the elimination of voriconazole appears to be a more rapid process compared with that in adults. The intravenous maintenance dose of 7 mg/kg every 12 hours in pediatric patients is equivalent to 4 mg/kg every 12 hours in adults, which justifies the consideration of higher weight-based doses [26-29]. Additionally, there is also a discrepancy in drug exposure and elimination between the two genders. A study found that with the same dosing regimens, voriconazole exposures in the majority of adolescents (aged 12 to <17 years) were comparable to those in adults, this was based on the finding that a significant overlap of distribution of AUC_{0-12} could be observed between adolescents and adults; however, if one evaluate voriconazole exposure according to patients' body weight, a trend for increasing voriconazole exposure (AUC_{0-12}) in individuals with higher body weight, moreover, the exposure in young adolescents with low body weight locates generally in the lower end of distribution, which indicates that young adolescents (aged 12 to 14 years old) with low body weight (< 40 kg) were more comparable to children and may need to receive higher doses to match the adult exposures [30]. The C_{max} and AUC of healthy young women (18-45 years) are 83% and 113% higher than those in young men, respectively; however, a convincing explanation has not been proposed [19]. An elevation in voriconazole concentrations noticed in critically ill patients in a study suggested that voriconazole pharmacokinetics may also differ according to the severity of illness and dosage adjustments are recommended in these patients [31].

Discussions of intrapersonal factors primarily focus on drug interactions. Concomitant use of drugs that would either inhibit or increase the activity of cytochrome P450 enzymes could alter voriconazole serum concentrations. A reduction phenomenonwas observed when a drug exhibits the ability to induce CYP450 enzymes is taken concurrently, such as rifampicin, rifabutin, and phenobarbital. Substrates of CYP3A4, such as omeprazole, carbamazepine, glucocorticoids, and erythromycin, are also capable of altering the voriconazole concentration [32]. Interactions between voriconazole and other drugs are diverse and complicated; however, these are not the focus of the present reviewing and discussing in detail. Other intrapersonal factors include food, the inflammatory status of patients, renal function, liver function and other, as-yet-undiscovered factors. Fatty food taken together with the oral form voriconazole reduces the peak plasma concentration (C_{max}) and the AUC by 34% and 24%, respectively, while different stomach pH values do not affect the absorption [33, 34]. To explore how patient's inflammatory status could interfere with the pharmacokinetics of voriconazole, a retrospective data analysis was performed. More than one steady-state voriconazole trough concentrations and C-reactive protein (CRP) levels were measured on the same day during data collection. A linear mixed model was analyzed the repeated voriconazole trough concentrations in relation to CRP concentrations. The results demonstrated that voriconazole trough concentrations are associated significantly with CRP: 0.014 (0.011 to 0.018; $P < 0.001$). This indicated that the inflammatory response, reflected by high CRP levels, appears to play a significant role in the largely unpredictable pharmacokinetics of voriconazole [35]. It has been confirmed that renal impairment does not affect the pharmacokinetics of voriconazole; therefore, no adjustment in the dosage of the oral formulation of voriconazole is necessary for patients with renal dysfunction [36, 37]. Interestingly, the clearance of SBECD, the excipient of voriconazole, is proportional to creatinine clearance. Thus, it is not recommended to administer voriconazole intravenously to patients with creatinine clearance <50 mL/min in case of the unknown adverse events of SBECD accumulation [36]. The accumulation of SBECD in patients treated with intravenous voriconazole and dialysis therapy was observed by Mach and his colleagues; however, no toxic effects were observed [38]. For those undergoing dialysis, the oral form of voriconazole is recommended, although the clinical toxicity of SBECD concentrations resulting from intravenous voriconazole remains unknown [39]. A multiple-dose study showed that patients with Child-Pugh class A and B liver dysfunction receiving a 50% reduced voriconazole maintenance dose achieved an approximate AUC_{24} that was similar to normal subjects [40]. However, studies targeting patients with severe liver diseases are rare.

Over all, the pharmacokinetics of voriconazole are influenced by various factors. For special populations, these influences must be considered:

(1) For geriatric patients, adverse effects should be monitored closely and the dose of voriconazole should be adjusted as needed because of its extremely high blood concentration compared with younger patients, especially for poor metabolizers of CYP2C19;

(2) For pediatric patients, higher weight-based doses (7 mg/kg or more) should be considered because of their higher elimination rate of voriconazole;

(3) For younger adolescents aged less than 14 years old with low body weight (< 40kg), the dose adjustment may refer to pediatric patients;

(4) The oral formulation is recommended for patients with creatinine clearance < 50 mL/min and patients undergoing dialysis.

4. CYP2C19 POLYMORPHISMS AND THEIR INFLUENCE ON VORICONAZOLE PHARMACOKINETICS

4.1. CYP2C19 Polymorphisms

Primarily originating from the presence of gene polymorphisms, the activity of CYP2C19 enzyme shows significant individual diversity [41]. To date, 34 mutations in the CYP2C19 gene have been discovered, at least 10 of which cause altered enzyme activity [13]. Based on the polymorphisms of *CYP2C19*, patients could be classified into four of phenotypes, which are named based on the catalytic ability of CYP2C19 enzyme. The four phenotypes are including(a) homozygous type (*1/*1) expressing normal enzyme activity is often noted as 'extensive metabolizer'(EM); (b) heterozygous type (*1/*2 , *1/*3) shows subnormal activity, and is marked as 'intermediate metabolizer' (IM) or 'heterozygous extensive metabolizer' (HEM) ; (c) the *2/*2, *2/*3, and *3/*3 types show poor activity, are therefore named as 'poor metabolizer'(PM); (d) the *17/*17, having ultra-high activity, is noted as 'ultra-rapid metabolizer'(UM) [42]. However, the classification of the *17 allele remains controversial. While subjects with *1/*17 alleles can be regarded as ultra-extensive metabolizers and the phenotype of those subjects with *2/*17 is difficult to classify [43]. Weiss and his colleagues found that the pharmacokinetic profile of voriconazole in individuals with *2/*17 allelic variants could be perfectly matched with those with *1/*17 [41]. However, Chung and his colleagues hold the opinion that the pharmacokinetic parameters, such as AUC, in patients with *2/*17 were more or less similar to those in the IM group, whilst the AUC in subjects with *1/*17 allelic variant were comparable to those in the EM group [44]. Besides CYP2C19 *2 and *3, other alleles, such as *4 and *8, have also been linked to poor metabolism. The latter two have rather limited influence, when taking their low allelic frequency in various ethnicities into consideration [43].

The distributions of each CYP2C19 phenotype among ethnic groups are distinct. While UMs are relatively common in Caucasians and Africans (31.2% and 33.3%, respectively), it occurs rarely in Asians (0.15-0.44%) [13]. The frequencies of PM in Caucasians, Africans, Hispanics, and Asians are 2.8, 6.7, 0.87, and 14-19%, respectively [45]. When evaluating the possible impact of genetic polymorphisms of CYP2C19 on voriconazole therapy, racial diversity should be taken into consideration.

5. INFLUENCE OF CYP2C19 POLYMORPHISMS ON VORICONAZOLE PHARMACOKINETICS

Voriconazole is metabolized extensively in the liver by CYP2C19; therefore, the CYP2C19 phenotype is thought to be one of the major determinants of voriconazole's pharmacokinetics. Moreover, various lines of evidence support the view that this impact is not limited to only metabolism, but also affects the absorption and clearance of the drug. Many studies have evaluated the effect of CYP2C19 phenotype on the pharmacokinetics of voriconazole.

In a single-center, open-label, two-period crossover study, designed to compare the pharmacokinetics of voriconazole after a single oral dose with intravenous (*i.v.*) administration in healthy individuals, the participants were stratified according to their CYP2C19 phenotype. Included were 20 healthy Caucasian volunteers, who were characterized as EM (n = 8), HEM/IM (n = 8) and PM (n = 4). All participants received one single dose of 400 mg voriconazole orally and one 400 mg voriconazole intravenously in a randomized order. The absolute bioavailability of voriconazole assessed for each CYP2C19 phenotype separately showed that PMs achieved the highest bioavailability [94.4% (95% CI 78.8, 109.9)], while EMs demonstrated the lowest at 75.2% (62.9, 87.4), indicating the impact of different phenotypes on drug absorption. For metabolism, an almost three-fold higher voriconazole exposure in PM participants compared with EM had was reported after oral administration. Both the total (i.v.) and apparent oral clearance showed that PM subjects had three to four times lower clearances compared with EMs. The partial metabolic clearance of voriconazole to its N-oxide and hydroxylated forms was decreased in CYP2C19 PM subjects [20].

A controlled, open-label study aimed to study the pharmacokinetic characteristics of voriconazole in healthy Chinese male volunteers in relation to CYP2C19 phenotype status. This trial included 20 healthy Chinese male volunteers, comprising four UMs, eight EMs, and eight PMs. The study found that after a single 200 mg oral dose of voriconazole, significant differences were noted among EMs, PMs, and UMs groups in terms of $t_{1/2}$, AUC and CL/F values. The $t_{1/2}$ of PMs was much longer than that of UMs, (Ums' value was 51% of the PMs, $p = 0.002$); Peak concentration, $C_{max,}$ in the UMs was higher than that in the EMs and PMs [46].

An open-label single and multiple-dose parallel-group study, which aimed to determine the effect of CYP2C19 polymorphisms on the pharmacokinetics of voriconazole, included 18 healthy Korean male volunteers, with six EMs, six IMs, and six PMs. The study found that mean AUC_{∞} values of IMs and PMs were 1.5 and 3.4 times higher than that the EMs, respectively ($p = 0.002$); the mean trough concentrations were 2.8 times higher in IMs than that in EMs ($p = 0.005$) and 5.1 times higher in PMs than that in EMs ($p = 0.008$) [47].

In summary, genetic polymorphisms of CYP2C19 commonly lead to variations in the pharmacokinetic parameters of voriconazole, including $t_{1/2}$, AUC, CL/F values, and $C_{min.}$ The blood trough concentration (C_{min}) of voriconazole is thought to have the highest relevance to clinical practice, as it is acknowledged associated with the efficacy and toxicity of this drug. In a single-center clinical trial, 144 Chinese patients with fungal infection were enrolled, with phenotypes distribution of 3 UMs, 62 EMs, 62 IMs, and 17 PMs. Two key pharmacokinetic parameters, the C_{min} and the ratio of C_{min} to the concentration of the major metabolite voriconazole-N-oxide (C_{min}/C_N) were analyzed for each of the four phenotypes. The authors concluded that CYP2C19 PMs exhibit both C_{min} and C_{min}/C_N values that are significantly different from those of CYP2C19 EMs and IMs. An obvious discrepancy in C_{min}/C_N, but not the C_{min}, of CYP2C19 EMs and IMs was also observed [48].

To describe the intra- and interindividual variation of voriconazole C_{min} throughout the course of voriconazole therapy and to identify the determinants of this variation, a retrospective study was conducted in France. They collected clinical data, information on medications, and voriconazole C_{min} values of 33 patients with autologous hematopoietic stem cell transplantation (AHSCT). Genotyping was performed on 29 patients. A higher initial voriconazole C_{min}/D in IM compared with UM patients (post hoc test, $P = 0.007$) was observed after oral administration [23].

A recent meta-analysis included ten studies involving 598 patients to evaluate the effect of CYP2C19 polymorphisms on clinical outcomes in patients treated with voriconazole. The results showed

that the PM phenotype had higher trough concentrations than patients with the IM phenotype (mean difference[MD],-0.62 mg/L; 95% CI,-1.05 to -0.19; P = 0.005) and those with EM phenotype (MD, 1.22 mg/L; 95% CI, 0.72 to 1.71; P < 0.0001), patients with the IM phenotype exhibited higher trough concentrations than those with the EM phenotype (MD, 0.61 mg/L; 95% CI, 0.33 to 0.90; P < 0.0001). These findings showed that the voriconazole trough concentrations were influenced strongly by CYP2C19 polymorphisms [49].

The CYP2C19 genotype represents part of the interpersonal variability related to voriconazole blood concentrations. PMs could be at higher risk of experiencing adverse events because of their exposure to higher blood trough concentrations, whereas physicians should consider the possibility of not achieving the optimal therapeutic trough concentrations when treating a PM patient. Therefore, monitoring the drug concentration of voriconazole is needed in clinical settings to minimize the negative influences of inter and intrapersonal factors.

6. THERAPEUTIC DRUG MONITORING

6.1. Why is TDM in Clinical Practice Important?

The metabolism of voriconazole is influenced by multiple factors, including genetic variation, age, sex, dietary factors, comorbidities, polypharmacy, liver function, and renal function. All of these factors eventually lead to the changes in the blood concentration of voriconazole. Previous studies showed that the concentration of voriconazole was related to its efficacy and toxicity in a dose dependent manner. Therefore, TDM of voriconazole is required in clinical practice and is recommended in several guidelines, including the Infectious IDSA, the American Thoracic Society (ATS), Japanese Society of Chemotherapy (JSC), the Japanese Society of Therapeutic Drug Monitoring (JSTDM), and the ESCMID [4,14-17, 32]

6.2. Are the Methods for TDM is Useful?

TDM of voriconazole requires a rapid and simple analytical method to analyze the drug concentrations in plasma. Various analytical methods that measure voriconazole simultaneously in human plasma have been developed, such as liquid chromatography-mass spectrometry (LC-MS) and LC-tandem mass spectrometry (LC-MS/MS) [50, 51]. In recent years, LC-MS/MS has been demonstrated as a powerful technique for the quantitative determination of drugs and metabolites in biological fluids, providing high selectivity and simplification of both sample extraction procedures and chromatography. However, LC-MS/MS systems are not always available in ordinary hospital laboratories because of their expense. Thus, high-performance liquid chromatography (HPLC) has been reported for the simultaneous measurement of voriconazole, which provides a rapid, simple, robust, and reliable method to determine voriconazole in human plasma [52].

For sample preparation, HPLC requires 300 μL of plasma and solid-phase extraction for sample preparation, which is suitable for routine use in ordinary, busy hospital laboratories. Nowadays, HPLC is recommended to measure blood concentrations, without reports of influence factors [32]. When steady-state levels are achieved, usually by the 5^{th} to 7^{th} day after receiving conventional voriconazole administration, blood samples for TDM should be obtained for HPLC analysis. If a loading dose was given, the steady-state trough concentration may reach 24 h later. The high bioavailability of the oral formulation means that TDM can be performed using the same timing in patients receiving the intravenous administration.

7. WHY IS A PROPER BLOOD CONCENTRATION OF VORICONAZOLE NECESSARY WHEN CONSIDERING ITS EFFICACY AND TOXICITY?

According to the recommendation in the guidelines, monitoring voriconazole trough concentration is widely accepted by clinicians; the guidelines still do not recommend an explicit optimum range of trough concentrations. Only the British fungi association recommends control of the blood drug concentrations of voriconazole at 2 to 4-6 mg/L, i to increase clinical efficacy and to reduce adverse reactions [53]. Therefore, questions about the suitable blood trough concentrations of voriconazole remain to be answered. The principle of determining the therapeutic drug concentration of voriconazole is based on two aspects: one is the effective control of the fungal infection, and the other is reducing toxicity. The efficacy and toxicity of voriconazole are dose-dependent, meaning that a high blood concentration exerts a better treatment effect, but also leads more side effects [32, 53, 54]. The adverse reactions of voriconazole mainly include visual anomalies, hepatotoxicity, skin rashes, and neurotoxicity (hallucinations, dizziness, *etc.*). Visual anomalies are common but tend to be mild and reversible, often without a requirement to stop administering the drug [18]. By contrast, hepatotoxicity has become the most common factor that influences treatment. The drug can be continued for grade 1 or 2 hepatotoxicity; whereas, it must be discontinued for grade 3 or 4 hepatotoxicity [44, 55]. The ideal concentration of voriconazole ranges from the upper-end threshold of the treatment concentration to the lower-end threshold of the toxic concentration.

The evaluation of the TDM comprises *in vitro* and *in vivo* experiments. *In vitro* experiments show that the MIC_{90} (minimum inhibitory concentration (MIC) at which 90% of microbes were inhibited) of voriconazole for the majority of *Candida* and *Aspergillus* is 0.5-1 mg/L [56]. An increased drug concentration of voriconazole may lead to adverse effects. *In vitro* studies have found that the blood MIC is related to voriconazole's efficacy; however, clinical research has not confirmed the relationship between the MIC and clinical efficacy. Most *in vivo* studies were performed in Asia. A small scale, single-center observational study from Japan concluded that the therapeutic range for the voriconazole trough concentration should be 2-4 mg/L in Japanese patients [55]. A prospective and observational study from China reported that a voriconazole C_{min} range of 1.5-4 mg/L was approved as the therapeutic target concentration with appropriate clinical efficacy and safety [48]. Another randomized, assessor-blinded, controlled, single center study from Korea assigned patients into two groups: a TDM and non-TDM group. In the TDM group, voriconazole dosage was adjusted based on the target range of 1.0-5.5 mg/L, according to the serum trough level measured on the fourth day after initial of voriconazole; the non-TDM group received a fixed, standard dose. The results showed that treatment success was higher in TDM group compared with the non-TDM group (86% *vs*. 63%, P = 0.036); and the treatment failure was lower in the TDM group compared with the non-TDM group (10% *vs*. 33%, P = 0.046). Voriconazole was discontinued because of adverse events less frequently in the TDM group compared with that in the non-TDM group (4% *vs*. 17%, P = 0.022) [57]. Besides these Asian studies, a multicenter retrospective study in Australia reported that voriconazole concentrations ≥ 1.7 mg/L were associated with treatment success and those ≤ 5 mg/L were associated with fewer neurotoxic adverse events [58]. Recently, a meta-analysis found that only when the C_{min} was < 0.5 mg/L did the clinical curative effect difference have statistical significance. If the blood trough concentration of voriconazole was > 3 mg/L, the hepatotoxicity difference was statistically significant compared with patients receiving ≤ 3 mg/L, with a RR of 0.37, an a 95% CI of 0.16(0.83). The incidence of hepatotoxicity seems to be much higher in Asian patients and also increases significantly at trough concentrations > 4.0, > 5.5 and > 6.0 mg/L. The incidence of neurotoxicity was increased significantly at trough concentrations > 4.0 and > 5.5 mg/L [59].

Several studies provided evidence on the stable trough concentration range from 1-2 and 4-6 mg/L, which was combined to consider efficacy and toxicity; however, the therapeutic drug concentration needs to be narrowed down and evaluated using large-scale clinical trials.

8. THE ROLE OF CYP2C19 GENOTYPE IN GUIDING CLINICAL PRACTICE

8.1. Are CYP2C19 Polymorphisms Related to Clinical Outcomes Directly?

Studies have presented sufficient evidence to confirm the relationship between CYP2C19 genotypes and voriconazole pharmacokinetics; however, there is not enough evidence on the relationship between CYP2C19 genotypes and clinical outcomes. Only a few studies have mentioned the relationship between clinical outcome and CYP2C19 genotypes.

One is a prospective observational study from Korea that aimed to evaluate the role of CYP2C19 genetic polymorphisms in voriconazole therapy. They found that out-of-range initial trough levels were most frequently observed in EMs (46%), followed by IMs (26%) and PMs (0%) ($P = 0.001$); however, the treatment response, all-cause and invasive Aspergillosis-attributable mortality, and the occurrence of voriconazole-related adverse events did not differ significantly among the groups [60]. This research pointed out that the CYP2C19 genetic polymorphisms only affect the therapeutic trough concentration of voriconazole, rather than its therapeutic efficacy and toxicity.

In addition, a meta-analysis assessed the effect of cytochrome CYP2C19 polymorphisms on the clinical outcomes of voriconazole, which showed that the PMs exhibited higher treatment success rates than EMs; however, there were no significant differences in treatment success between IMs and EMs, between IMs and PMs, and between non-PMs and PMs. This finding showed no significant differences for each phenotype comparison group in terms of daily maintenance dose, overall adverse events, hepatotoxicity, and neurotoxicity [49].

8.2. Are CYP2C19 Genotypes Sufficient to Allow Adjustment of the Initial Dose of Treatment?

Although the CYP2C19 genotype has been demonstrated to be associated with voriconazole pharmacokinetic interpersonal variability, there are insufficient data on the genotype-clinical outcomes relationship. What is the role of the CYP2C19 genotype in the clinical use of voriconazole? Perhaps it could be used to guide dose adjustment among different genotypes.

As stated previously, CYP2C19 genotypes, resulting in the UM, EM, IM, and PM phenotypes, contribute to the pharmacokinetic variability observed for voriconazole. According to the current data, patients with the PM phenotype are exposed to significantly higher levels of voriconazole for a fixed dosage regime; therefore, some researchers have tried to determine a proper regime according to the *CYP2C19* genotype. Wang and his colleagues first use a model-based quantitative approach to adjust voriconazole dosage regimens according to *CYP2C19* genetic status in adult patients with invasive fungal infections (IFIs). Patients with the PM phenotype received 200 mg of voriconazole twice daily, orally or intravenously, and non-PM patients received an increased dose of voriconazole of 300 mg twice daily orally [48]. The study revealed that voriconazole gene-adjusted dosing has potential for clinical practice and was proven to be an ideal treatment outcome for treating IFIs. Matsumoto and his colleagues performed a population pharmacokinetic analysis of voriconazole using non-linear mixed effects modeling (NONMEM). They suggested that voriconazole therapy should be initiated with a dose of 7.2-8.9 mg/kg/day for *CYP2C19* wild-type and 4.4-6.5 mg/kg/day for the non-wild-type in Japanese patients to maintain a therapeutic C_{min} range of 2-4 mg/L to balance the efficacy and hepatotoxicity [55].

Although only a few studies have investigated the influence of genotype in initial dose adjustment, they proved that *CYP2C19* genotype data may guide the initial dose of voriconazole, rapidly reaching the therapeutic blood trough concentration, which leads to a better clinical outcome in the treatment of invasive Aspergillosis. The CYP2C19 genotype is reasonable to guide initial voriconazole dose selection to increase the probability of achieving efficacy while avoiding toxicity.

8.3. Are CYP2C19 Genotypes Sufficient to Make Clinical Decisions?

Many factors could influence the blood trough concentration of voriconazole, such as age, sex, weight, liver disease, drug-drug interaction, and genetic polymorphisms of the cytochrome P450 enzymes. Therefore, CYP2C19 genotypes alone are not sufficient to select a maintenance dose of voriconazole, or to guide us to make clinical decisions. Other factors, such as the severity of illness, the MICs for the fungus, and polymorphisms in CYP3A have been considered in the following articles to guide the choice of the right regime of voriconazole. The first is a prospective, observational study in China that used the Monte Carlo simulation to find the optimal dose of voriconazole. They suggested that a 150 or 200 mg intravenous dose twice daily is best suited to achieve the target steady state trough concentration range in critically ill patients with pulmonary disease [31]. Another study used Monte Carlo simulation to simulate 5000 patients by integrating published pharmacokinetic parameters, variability of pharmacokinetic parameters on CYP2C19 genotypes, and microbiological data of different *Aspergillu*s species. The results showed that the standard voriconazole dosage regimen (maintenance dose 200 mg twice daily) was effective for most *Aspergillus* except *A. versicolor* for PMs. For IMs, *A. fumigatus*, *A. terreus* and *A. nidulans* infections could be treated effectively with the standard dosage regimen; however, for EMs, the standard dosage regimen failed to treat all six *Aspergillus* spp. They suggested that the voriconazole dosage must be changed or substituted with other anti-fungal drugs for EMs and IMs [61]. Last, a French study calculated the genotype information for CYP2C19, CYP3A4, and CYP3A5 as a combined genetic score (for details, see the original article). They suggested that the combined genetic score could be used to determine the voriconazole dose individually and underlined the need for longitudinal therapeutic drug monitoring to adapt subsequent doses to maintain the C_{min} within the therapeutic range [23].

CONCLUSION

Many interpersonal factors, especially CYP2C19 genotypes, have been proven to influence voriconazole trough concentrations. Although additional data are still required, there is great potential for initial voriconazole dose selection to be guided by a patient's CYP2C19 genotype. Finally, voriconazole TDM is remains essential to provide patient-specific dosing recommendations, leading to more effective anti-fungal regimens to increase clinical efficacy and reduce adverse drug reactions.

AUTHORS' CONTRIBUTIONS

Yanming Li, Xufeng Zhong and Xunliang Tong contributed to the conception and design and drafted the manuscript. Yang Ju and Xiaoman Du contributed to the revision of the manuscript for important intellectual content. All authors read and approved the final manuscript.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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