



THERAPEUTIC DRUG MONITORING OF BROAD SPECTRUM ANTIFUNGAL, VORICONAZOLE- A REVIEW

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ABSTRACT

Voriconazole is a broad-spectrum antifungal drug. It belongs to triazole group, and is available in market as oral as well as intravenous (IV) forms. It is highly effective against a number of clinically important fungi causing invasive infections. Its pharmacokinetic profile is non-linear with extensive inter-individual and intra-individual variability. Various factors contribute towards this variability including age, race, gender, genotype, hepatic functions, administration with or without food, and concomitant administration of other drugs causing drug interactions. Variability in plasma concentrations of the drug, arising from these factors, may result in variations in efficacy of the drug or may contribute towards potential toxicity. Voriconazole therapeutic drug monitoring is mandatory considering bad prognosis of patients suffering from invasive fungal infections, especially ones who are immunosuppressed, and prolonged period of treatment needed, in order to optimize antifungal treatment and to prevent the adverse events.

Keywords: HPTLC, Orthosiphon stamineus, Sinensetin, Standardization

INTRODUCTION

Most of the drugs show linear pharmacokinetic characteristics. While, the levels of those drugs should be closely monitored, which exhibit non-linear elimination properties together with narrow therapeutic and toxicity window. This particularly implies in the circumstances, where low drug levels can fail to treat potentially life-threatening infections, while high drug levels can cause toxicities. Voriconazole is a broad-spectrum anti-fungal drug, a second-generation triazole, FDA approved to treat many invasive fungal infections like candidiasis, aspergillosis, scedosporiosis and fusariosis (Herbrecht *et al.*, 2002). It particularly has a much superior efficacy against *Aspergillus* species. Voriconazole acts by inhibiting fungal cytochrome P-450 isozyme, leading to inhibition of 14- α -lanosterol de-methylation, which is a crucial step in biosynthesis of fungal ergosterol.

Hence causes inhibition of the fungal cell wall membrane (Saravolatz, Johnson and Kauffman, 2003). It is also used prophylactically in immuno-compromised patients, although not FDA approved for this indication. Dose of Voriconazole is determined by the kind of fungal infection, whether it's invasive or not, and patient's body weight, and patient's overall co-morbid conditions and general health. Usual IV dose is 4 mg/kg body weight, to be infused over 1-2 hours, and to be given every 12 hours, while oral dose is usually 100 mg 12 hourly in patients who are less than 40 kg body weight and 200 mg 12 hourly for patients whose body weight is more than 40 kg, for maintenance purpose. The recommended intravenous loading dose for the first 24 hours of treatment is 6 mg/kg every 12 hours for 2 doses (Walsh *et al.*, 2008). The bioavailability of Voriconazole

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with oral route is approximately 96% when given in the fasting state, however, it decreases by approximately 22% if the drug is taken along with food, that too, if food has high fat contents (Purkins *et al.*, 2003). When in circulation, approximately 58% of the drug is found in protein bound form. The maximum concentration (C_{max}) is achieved at approximately 1-2 hours after administration, but is more delayed when taken with food. So, it is recommended to take Voriconazole empty stomach (Purkins *et al.*, 2003; Purkins *et al.*, 2003).

Metabolism of Voriconazole to its inactive metabolites is done by cytochrome P-450 enzymes, especially CYP2C19, and to a smaller extent by CYP2C9 and CYP3A4 (Purkins, Wood, Greenhalgh, *et al.*, 2003). Voriconazoles interaction with these enzymes contributes to various drug interactions, some of which are listed in **Table 1**. The major enzyme causing metabolism of Voriconazole is CYP2C19, which displays genetic polymorphisms. Patients, who are homozygous extensive metabolizers have up to 4 times lower Voriconazole levels as compared to homozygous poor metabolizers. Whereas, heterozygous extensive metabolizers have up to 2 times lower Voriconazole levels compared to homozygous poor metabolizers (Saravolatz *et al.*, 2003). The number of poor metabolizers is greater among Japanese population. Both C_{max} and area under the curve (AUC) show disproportional rise with higher doses, which shows a saturable metabolism. As the drug is extensively metabolized by liver enzymes, drug should be given with caution in individuals having liver abnormalities.

The drug and its metabolites are primarily excreted by kidneys with 2% being excreted unchanged. The elimination half-life of Voriconazole is nearly 9 hrs. but it rises with higher doses. Presently, there are no recommendations for dose adjustment in renal function compromise, except for the IV form owing to the possible accumulation of the vehicle i.e. cyclodextrin in patients whose creatinine clearance is lesser than 50 ml/min.

When loading dose is not given, the steady state concentration of drug is usually reached in 3-5 days (Purkins *et al.*, 2003). Extensive variability is seen in Voriconazole pharmacokinetics, CYP2C19 genetic polymorphism, non-linear pharmacokinetics, saturable metabolism, concomitant diseases, and drugs and food interactions all play roles in this variability (Pascual *et al.*, 2008; Pascual *et al.*, 2007; Saad, DePestel and Carver 2006). Though the IV formulation has reduced variability in bioavailability, but is still affected by variability in the metabolism of the drug caused by the mentioned factors

In order to prevent breakthrough fungal infections that could result in serious morbidity or mortality, sufficient blood trough levels of the drug are required. While, too high blood trough levels can lead to grave toxicity including neurological side effects such as hallucinations and cognitive impairment; ocular adverse effects such as visual blurring, photophobia, and colour changes; hepatotoxicity including raised liver enzymes; and cardiac toxicity such as QT interval prolongation on ECG and other dysarrhythmias (Walsh *et al.*, 2008).

As per a study comprising 87 bone-marrow transplant recipients, who got a mean daily dose of 400 mg (range 200-800 mg) of Voriconazole as antifungal prophylaxis, 13 (15%) patients had undetectable concentrations, while 11 (12%) had blood trough levels varying between 0.2 to 0.5 mg/L, and 53 (61%) had concentrations between 0.5 to 5 mg/L whereas 10 (11%) had concentrations >5 mg/L (Trifilio *et al.*, 2007). In another prospective trial conducted on 52 immuno-suppressed patients, who were being treated with either IV (8mg/kg/day) or oral (6.5mg/kg/day) Voriconazole for candidiasis, aspergillosis, and other invasive infections, 13 (25%) patients had blood trough levels <1 mg/L and 6 (46%) out of these 13 patients lacked a response. In contrast, 39 patients had blood trough levels >1 mg/L and only 5 (12%) patients out of these 39 lacked a response (Pascual *et al.*, 2008). In the same study, 16 (31%) patients had blood trough levels >5.5 mg/L and 5 (31%) patients out of these 16 later developed encephalopathy while 3 (19%) patients developed cholestatic hepatotoxicity. When this data is compared with the patients with blood trough levels <5.5 mg/L, none developed encephalopathy and 3 (8%) developed cholestatic hepatotoxicity. As per the data of another prospective trial conducted on 25 patients having hematological malignancies who were treated with IV Voriconazole for invasive Aspergillus infection, 8 (32%) had an adverse event with 5 developing hepatotoxicity, 2 had tachyarrhythmia, and 1 developed neurotoxicity. After performing a multivariate analysis, the only significant risk factor associated with adverse events or Voriconazole toxicity was found to be blood trough concentrations of >5.83 mg/L (Kim *et al.*, 2011). Based on the studies that have been performed to date, a therapeutic range of 1 mg/L – 5 mg/L appears to be the most effective at preventing both treatment failure and drug toxicities.

There are three general criteria which are found useful for identifying any drug as appropriate candidate for therapeutic drug monitoring. First, there should be unpredictable population pharmacokinetics or an unpredictable dose-response relationship of the drug. Second, a narrow therapeutic window is desirable. And third, therapeutic range should be clinically defined

(Kontoyiannis, 2012). Voriconazole meets all these criteria and hence, should be therapeutically monitored in the clinical setting.

Figure 1: Drug interactions that affect Voriconazole levels (Hussaini et al., 2011)

Drug	Interaction	Recommendation
Carbamazepine	Decreases voriconazole concentration by affecting CYP3A4 enzyme metabolism (Nivoix et al., 2008)	Co-administration contraindicated
Rifabutin	Decreases voriconazole concentration by increasing metabolism (Hussaini et al., 2011)	Coadministration contraindicated
Ritonavir	Decreases voriconazole concentration by increasing metabolism (Nivoix, Ubeaud-Sequier, Engel, Levêque, & Herbrecht, 2009)	Coadministration contraindicated
St John's wort	Decreases voriconazole concentration by increasing metabolism (Saravolatz et al., 2003)	Coadministration contraindicated
Amiodarone	Both cause QT interval prolongation (Mikus et al., 2006)	Coadministration contraindicated unless benefit outweighs risk
Amobarbital	Decreases voriconazole concentration by increasing metabolism (Rengelshausen et al., 2005)	Coadministration contraindicated unless benefit outweighs risk
Astemizole	Both cause QT interval prolongation (Cronin & Chandrasekar, 2009)	Co-administration contraindicated unless benefit outweighs risk
Phenytoin	Decreases voriconazole concentration by increasing metabolism (Mahata et al.)	Monitor levels of voriconazole
Omeprazole	Increases voriconazole level by affecting hepatic enzyme CYP2C19 (Chandrasekar & Manavathu, 2001)	Monitor for signs of toxicity
Fluoxetine	Increases voriconazole level by affecting hepatic enzyme CYP2C19 (Nivoix et al., 2008)	Monitor closely for signs of toxicity
Hexobarbital	Decreases voriconazole concentration by increasing metabolism (Dolton et al., 2012)	Co-administration contraindicated unless benefit outweighs risk
Ondansterone	Both cause QT interval prolongation (Snyder, Polasek, & Doogue, 2012)	Monitor closely, use alternatives if possible
Efavirenz	Decreases voriconazole level by affecting hepatic enzyme CYP2C19 (Sienkiewicz, Łapiński, & Wiela- Hojeńska, 2016)	Monitor closely, use alternatives if possible

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