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Why is Therapeutic Drug Monitoring for Voriconazole Essential in the Treatment of Fungal Infections

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Introduction

Fungal infections are frequent life-threatening complications in immune compromised patient sand in patients admitted in ICU wards [1]. Voriconazole (VRC) is a second-generation wide-spectrum anti-fungal triazole recommended for the treatment of potentially life-threatening fungal infections including invasive *aspergillosis,* disseminated *candidasies,* and other infections caused by *Fusarium* and *Scedosporium* spp. [2,3]. This compound can be administered as an intravenous infusion and oral formulations. Studies with healthy volunteers demonstrated bioavailability of >90% after oral administration [4]. A steady-state level is achieved in three days with two loading doses of 400 mg for the first day, followed by a maintenance dose of 200 mg every 12 hours thereafter [5]. Investigations have shown both within and between individual's variability in VRC steady-state plasma concentration and non-linear pharmacokinetics due to saturation of its metabolism with respect to dose. This variability was observed with both intravenous and oral formulations [6]. Other pharmacokinetic variability's include decreased absorption of oral VRC with meals, interactions with co-medications, patient's age, hepatic inefficiency and genetic polymorphisms of cytochrome P450 (CYP) iso-enzymes, mainly CYP2C19 enzyme [6,7]. Generally accepted plasma level for VRC is 1-5.5 mg/L. There have been reports that a clear relationship exists between drug concentration and drug response. High levels (>5.5 mg/L) are associated with variant adverse drug reactions. The most frequently side effects of VRC are vomiting , nausea , fever, skin rash, vision color changes, visual disturbances, blurred vision, hepatotoxicity, liver enzyme elevation, encephalopathy, and electrolyte abnormalities. Levels of VRC (<1 mg/L) have been associated with therapeutic failures and breakthrough infection [8]. In addition, using recommended dosing regimens in both adults and pediatrics has shown a significant relationship between VRC plasma levels and clinical efficacy and/or toxicity indicating a need for therapeutic drug monitoring (TDM). TDM may enable clinicians to make a better use of VRC, and is recommended as a tool to individualize VRC doses and may be particularly helpful in the context of preventing drug-related side effects. Therefore, TDM of VRC concentrations is highly recommended to maximize efficacy and minimize adverse events [9].

To perform therapeutic drug monitoring, several available analytic methods enabled quantified the VRC concentration in human plasma or serum. Most of these assays use high-performance liquid chromatography methods with ultra-violet detection (HPLC-UV) or coupled with mass spectrophotometry. Other methods such as bioassays or microbiological assays have also been investigated as a valid alternative to chromatographic methods. Bioassays can determine the total antifungal activity of a drug, conversely, HPLC or ultra-HPLC quantify the concentrations of VRC but cannot assess its activity [10].

In conclusion, *Candida* and *Aspergillus* spp. are the most common causes of invasive fungal infections with high morbidity and mortality in immune compromised patients [1,11,12]. Voriconazole, compared with other antifungal agents, has potent activity against a broader spectrum of clinically significant fungal pathogens, including *Aspergillus, Candida* spp., especially *Candida krusei* and *Candida glabrata* which resist other antifungal agents [13]. Using VRC in combination with TDM can serve as the best method for the survival of patients.

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