What Is the “Therapeutic Range” for Voriconazole?

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(See the article by Pascual et al. on pages 201–11)

Since its introduction in 2002, voriconazole has become a preferred treatment option for invasive aspergillosis and is often considered for prophylaxis in high-risk transplant recipients [1, 2]. Voriconazole is a broad-spectrum derivative of fluconazole that maintains the excellent oral bioavailability of the parent drug but undergoes extensive, saturable hepatic metabolism, resulting in a nonlinear pharmacokinetic profile in adults [1]. Consequently, voriconazole concentrations in serum may vary up to 100-fold from one patient to the next or within an individual patient depending on age, drug dose, concurrent illness, underlying liver function, drug-drug interactions, or genetic polymorphisms affecting cytochrome CYP2C19-mediated metabolism [3, 4]. This pharmacokinetic variability can be unsettling for the prescriber, who is often relying on voriconazole to treat a life-threatening infection.

In fact, it has become increasingly evident that intrapatient and interpatient pharmacokinetic variability of mold-active triazoles (i.e., voriconazole, itraconazole, and posaconazole) can contribute to therapeutic failure in patients with invasive mycoses. In a series of articles from Northwestern Memorial Hospital (Chicago, IL), Trifilio and colleagues found that 18%–27% of adult allogeneic hematopoietic stem cell transplant recipients who receive standard oral voriconazole doses may have subtherapeutic drug exposures [5, 6]. Importantly, the subtherapeutic exposures could not be predicted on the basis of total daily or weight-based (mg/kg) dose of voriconazole alone [6]. These observations were in agreement with previous studies [7–9] suggesting that therapeutic drug monitoring (TDM) of voriconazole, in conjunction with other measures of clinical assessment, could potentially improve the safety and efficacy of the antifungal in patients who are at extremes of drug exposure with currently recommended dosing.

Beyond pharmacokinetic variability, several other questions must be considered when determining whether TDM-guided dosing of mold-active azoles, such as voriconazole, is feasible. First, is a reliable, sensitive, and specific assay available for drug concentration analysis that will yield results quickly and in a cost-effective manner? Second, would it be more practical in most patients to simply increase their drug dose and monitor for toxicity rather than wait for the results of serum concentration monitoring to make dosing adjustments? Finally, how will the results of serum concentration monitoring be interpreted? Do we really know the “therapeutic range” for voriconazole?

Although the idea of a therapeutic range or target concentration is ubiquitous in infectious diseases, it is often misunderstood. The therapeutic range is not an absolute entity; rather, it is a concept of probability. As pointed out by Shumacher [10, p. 7]:

For any drug there are a range of serum concentrations for which the majority of patients will show an effective response with a minimum of side effects and adverse reactions. If the effective and safe range of serum concentrations is very limited, such that reasonable intrapatient and interpatient variations in pharmacokinetics may jeopardize the effectiveness of therapy using standard dosing guidelines, then the concept of therapeutic range and target concentration strategy has meaning. But if the therapeutic range for a drug covers such a wide range of serum concentrations that most patients will be safely and effectively managed within the general dosing guidelines, regardless of reasonable intrapatient and interpatient variations in pharmacokinetics, then the notion of a therapeutic range has no practical significance from a monitoring point of view.

Ideally, the probabilities of response and toxicity over a given range of drug exposures would be extrapolated from large, prospective multicenter trials using clinically relevant end points and sensitive sur-
robrate (diagnostic) markers for drug response. Such data would ensure that target drug concentrations are robust and generalizable to multiple patient populations with different comorbidities, underlying diseases, and possibly different types of fungal infections. Unfortunately, this has not been the case for clinical trials of antifungals. Moreover, the surrogate markers needed for definitive TDM studies analogous to viral RNA and CD4+ cell counts that are used for antiretroviral TDM studies in patients with AIDS are lacking. As a result, the therapeutic range of antifungals has been largely defined by small, retrospective, single-center studies. Therefore, it is not surprising that many clinicians remain unconvinced of the necessity for routine TDM in the treatment of patients with serious fungal infections.

With these caveats in mind, the study by Pascual et al. [11] is a useful step forward towards defining the therapeutic range and potential clinical utility of TDM for voriconazole. The investigators prospectively monitored 52 patients with predominantly hematological malignancies who received voriconazole for proven, probable, or possible fungal infections. Using a provisional therapeutic range of 1–5.5 mg/L, which was based on pathogen susceptibility (MIC90) and adverse event data, the authors proposed an increase in voriconazole daily dose by 50% per day if voriconazole trough concentrations were below the therapeutic range and the patients were not clinically responding. Voriconazole was discontinued if patients developed adverse reactions with a trough concentration >5.5 mg/L. In agreement with previous studies [4–6], the authors found substantial interpatient and intrapatient variability in voriconazole trough concentrations at currently recommended doses; 25% of patients had voriconazole trough concentrations that were <1 mg/L and, 31% of patients had concentrations that surpassed the potentially toxic threshold of 5.5 mg/L at some point during therapy. Lack of therapeutic response to voriconazole was more common among patients with voriconazole trough concentrations ≤1 mg/L, and encephalopathy was observed only in patients with voriconazole serum trough concentrations >5.5 mg/L. Interestingly, suboptimal voriconazole concentrations occurred more frequently among patients receiving oral therapy, suggesting impaired absorption or presystemic metabolism. Also notable was that omeprazole use was more common among patients who developed encephalopathy, including 1 patient who was receiving tacrolimus. Although the pharmacokinetic interactions of these medications with voriconazole have been well-described [12–14], another possibility is that voriconazole could affect the transport or metabolism of omeprazole and tacrolimus (or vice versa) at the blood-brain barrier, predisposing patients to this serious toxicity [15].

Finally, the authors used logistic regression to evaluate the relationship between voriconazole trough concentrations and therapeutic response or toxicity. For every 2-fold increase in the voriconazole trough concentrations, their model predicted a 1.8-fold increase in the odds of treatment success, with a 70% likelihood of treatment response at voriconazole trough concentrations of >1 mg/L. Analysis of neurological toxicities also revealed a concentration-response relationship, but model estimates were less precise because of the small number of patients who developed this serious adverse event.

Like many other single-center TDM studies, the author’s data do have some limitations. First, only 50% of the monitored patients had proven or probable aspergillosis; the most relevant population for this type of study. Response to therapy is more difficult to assess in patients when the diagnosis of the fungal infections is uncertain. Second, the study population consisted only of white patients who were not genotyped for CYP2C19 polymorphisms, which is a major determinant of voriconazole clearance [16, 17]. Unlike in previous studies [18, 19], the investigators did not identify a relationship between voriconazole exposure and markers of hepatic toxicity, which raises the question of why the most common dose-limiting toxicity of this triazole was less evident in their study. Finally, monitored patients were not selected randomly for serum concentration monitoring at fixed time points, which could bias results toward showing a greater impact of TDM than would be expected in a randomized population.

Nevertheless, these limitations should not overshadow the most intriguing finding of the study by Pascual et al. [11]. All 6 patients with persistent or progressive fungal infections and low voriconazole trough concentrations (<1 mg/L) subsequently responded to therapy after their voriconazole daily dose was increased without the addition of a second antifungal to the treatment regimen. Although pharmacokinetic variability is one of the many interrelated factors that can contribute to poor outcome in patients with fungal infection, the data from Pascual et al. [11] suggest that it is eminently correctable.

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References