How Many Steps along the Path Is Too Far?

G. L. Drusano
Ordway Research Institute, Albany, New York

(See the article by Neely et al, on pages 27–36.)

Neely et al [1] have studied the disposition of voriconazole in children suspected or proven to have a fungal infection. Although this is important, and the pharmacokinetic data are most welcome in this difficult-to-study population, the ability to link the drug concentrations observed to outcome is the critical issue for this study.

A number of other investigators have linked measures of voriconazole exposure to outcomes [2–5]. Most of these have linked exposure to some measure of response [2–4]. In this study, voriconazole exposure has been linked to time to death in a Cox proportional hazards model. Because the article also included a table detailing the outcomes for the patients examined and whether they had an actual trough concentration of voriconazole measured (thanks to the authors and the editors), it allowed secondary analyses to be performed. Of the patients examined, 24 had at least 1 trough concentration measured. In a logistic regression analysis, whether the measured voriconazole concentration exceeded 1.0 mg/L had a significant effect on the probability of death (odds ratio, 30.3; 95% confidence interval, 2.637–348.9; \( P = .006 \); McFadden’s \( R^2 = 0.364 \)). Other analyses also show that the number of measurements <1.0 mg/L also had an impact on outcome, but having at least 1 measurement below this threshold was the most important covariate and was all that remained in the final model.

This study was retrospective, as the other studies in the literature that have reported relationships between voriconazole measurements and outcomes have been. Consequently, each alone does not rise to a sufficient level of evidence to make firm recommendations. However, as we see the number of studies of a retrospective nature increase, with essentially the same outcome, the replicability of the findings is another form of evidence indicating that there is, indeed, a relationship between voriconazole concentrations and a measure of clinical outcome. Obviously, it would be better if the studies were prospective, but the mass of evidence at this point is that such a relationship exists.

Is the relationship really between trough voriconazole concentration and outcome (survivorship in this instance)? The answer is probably no. For voriconazole, as well as other triazoles, preclinical data indicate that the area under the curve (AUC) (relative to the minimum inhibitory concentration) is the driver relating exposure to response [6–8]. Indeed, one of the issues with the article, is that there is no microbiological data available for the analysis. Nonetheless, the relationship is strong enough that 2 different statistical approaches (Cox proportion hazards modeling and logistic regression) identified significant relationships between exposure and response. So, we can agree that the measurement of trough concentrations is valid, although inclusion of microbiological data would be welcome. What about the issue of measuring trough drug concentration and not AUC?

If one takes the data of Neely et al [1] for voriconazole parameter estimates and their dispersions and generates a Monte Carlo simulation for a standard voriconazole dose and simulates AUC_{0–12} and trough concentrations, the coefficient of determination between them is \( r^2 = 0.985 \). Obviously then, the trough voriconazole concentration is highly correlated with the AUC, explaining the ability of the trough to “stand in for” the measurement of the AUC. Clinically, measurement of the trough concentration is much more tractable. Consequently, although recognizing that the true linkage to outcome is through AUC, one can recognize that measurement of trough concentration values should be recommended.

Once it is probable that measured trough concentrations provide information regarding the likelihood of a positive outcome (survivorship in this instance), there are other issues that are raised. The most important is the idea that altering the exposure can result in a change in the
probability of a positive outcome. Although a considerable amount of therapeutic drug monitoring is performed in the area of infection (eg, vancomycin and aminoglycosides) and there are preexisting relationships between exposure and response [9–12], there is a paucity of evidence that, once a subtherapeutic exposure is detected, one can alter the exposure and improve the outcome. This is a critical issue. If one sets foot on the path of therapy and the final outcome is determined quickly, what is the use of therapeutic drug monitoring? Recently, Scaglione et al [13] demonstrated in patients with hospital-acquired pneumonia that early alteration of drug dose after identification of inadequate exposure was able to alter the outcome. Indeed, there are hints that outcome can be altered by dose alteration in the articles by Neely et al [1], Pascual et al [3], and Smith et al [4]. This is encouraging evidence for severely ill, fungally infected patients. If one can infer (and it is not completely clear that one can) from this that altering voriconazole exposure can alter the outcome (again, survivorship in this instance), then it is crucial that the effort required be expended to identify patients who could benefit by altering dose to achieve the target exposure. To not do so fails our patients.

This leaves us with a burden. It is now likely that the trough concentration of voriconazole is predictive of clinical outcome. We have little evidence about the time frame in which the dose of drug needs to be altered to have a high likelihood of altering the outcome. Given how seriously ill these patients are, it is imperative that this information be developed. Currently, there are 2 major problems that need to be solved to translate these findings into the routine clinical care of patients. The first is the turnaround time of sample acquisition to drug concentration determination. The second is, in many ways, as important as the first, which is what the physician is supposed to do with the data.

The article by Neely et al [1] states that the turnaround time for sample concentration determination is 7–10 days. This is a huge problem. The data of Scaglione et al [13] were turned around in 2–3 days. Data from Staphylococcus aureus bacteremia show that the window of opportunity to be “correct” in therapy is small and on the order of 2 days [14]. Drawing a blood sample and having the answer in a week is highly unlikely to allow a dose alteration to be optimally effective in altering outcome. It is imperative that turnaround times be decreased. We need to know how many steps can be taken along the path before the outcome is irrevocable! The reality is that if we are to improve outcomes from inadequate drug therapy, then samples need to be assayed on site.

Perhaps an even greater challenge is the question of how the physician should respond to the data. Voriconazole demonstrates clear Michaelis-Menten pharmacokinetics [1, 5, 15, 16]. Consequently, dose alteration is problematic because too great a dose increase will result in a concentration-time profile that will result in a high likelihood of an adverse event (mostly biochemical), as has been previously demonstrated [5]. Consequently, to optimize voriconazole exposure (ie, maximize the probability of a good therapeutic outcome while minimizing the probability of a toxic effect), some form of dose support (a stochastic controller optimally or something as simple as a dosing nomogram) needs to be put into place to support physician dosing responses.

It is important not to throw the baby out with the bath water. Voriconazole is a ground-breaking drug that provides (for the most part) good outcome for the patient without undue toxic effects. Although there are issues to be resolved, it is important to understand that to rationally switch therapy to another agent, one should have the same amount of evidence of therapeutic effect without engendering undue toxic effects (eg, amphotericin B). If we can generate these data and if voriconazole can be assayed locally with the appropriate turnaround time, we can fulfill the promise of modern chemotherapy of optimal response and minimal toxic effects.

Acknowledgments

Potential conflicts of interest. G.L.D.: no conflicts.

References

12. Drusano GL, Ambrose PG, Bhavnani SM, Bertino JS, Nafziger AN, Louie A. Back to the future: using aminoglycosides again and


