How Does a Patient Maximally Benefit from Anti-infective Chemotherapy?

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(See the article by Boyd et al. on pages 1241–4)

Voriconazole is the newest addition to the physician’s armamentarium for the treatment of serious fungal infections. Indeed, therapy with this agent has been demonstrated to have survival advantages relative to amphotericin B deoxycholate therapy for invasive infections due to Aspergillus species [1]. The important issue to address is the optimal way to use this agent so that the patient derives maximal benefit from its administration.

When any drug is administered to a patient, we must explicitly balance the likelihood that we will achieve the goal of therapy—a good microbiological and clinical outcome—without having the patient experience a drug-associated toxicity. To attain this end, it is important to understand the relationship between drug exposure and the probability of a good clinical and/or microbiological response. It is also important to understand the toxicities that are attendant to drug administration.

For the therapy of invasive infections due to Aspergillus species, examination of the extensive clinical trial database did not allow delineation of an exposure-response relationship. Part of the reason for this is the doses selected for administration, which are likely to place many patients at the top end of the exposure-response curve. Part of the reason for this inability to identify a relationship may be that the clinical outcome is dependent on many variables. When during the clinical course the diagnosis was made or suspected and, consequently, when therapy was initiated will likely have a major impact on the likelihood of response. The underlying cause of immunosuppression will also influence the likely outcome, even with optimal chemotherapy. Patients who acquired their infection after therapy for lymphoma will have a different probability of response than patients who have received a bone marrow transplant. Nonetheless, there is a relationship between voriconazole exposure and response, at least in an animal model with Candida as the infecting pathogen, as has been demonstrated by Andes et al. [2].

If we desire optimal outcomes for our patients, we must also minimize the probability that patients will experience a drug-related toxicity. Such toxicities can be either concentration dependent or concentration independent. Examples of concentration-dependent toxicity due to an anti-infective agent are the nephrotoxicity that is sometimes attendant to aminoglycoside administration and the seizures that can be seen in patients administered too high a dose of a β-lactam antibiotic [3, 4]. Conversely, the accelerated allergic reactions seen with administration of penicillin are clearly not concentration dependent.

For concentration-dependent toxicities, there are 2 important pieces of information: first, whether the adverse event exists, and, second, the relationship of the drug concentration to the likelihood of the event’s occurrence. For concentration-independent toxicities, the administration of the drug is the risk factor. The other important piece of information is the frequency with which the event occurs, relative to the number of times the drug is administered.

Voriconazole is mainly eliminated from the body by the cytochrome P450 system. The clearance is mediated by the enzymes CYP 2C19, CYP 2C9, and CYP 3A. A single-nucleotide polymorphism in the gene that codes for CYP 2C19 yields 3 populations of patients: homozygous patients with extensive metabolization of the drug, heterozygous patients, and homozygous patients with poor metabolization. This, in turn, allows a broad range of voriconazole concentrations to be observed after administration of a given dose of the drug to a large number of patients. Further, use of drugs that interact with these enzymes or occurrence of diseases that modify the activity of these enzymes (i.e., acute infections) will also have a major influence.
on the concentration of voriconazole observed. Drugs inducing or activating the enzymes will result in abnormally low concentrations of voriconazole, placing the patient at risk for inadequate therapy (depending on the MIC of the infecting pathogen). Other drugs that inhibit the activity of these enzymes may markedly increase voriconazole concentrations, raising the probability of a concentration-related adverse event. Finally, it is important to recognize that these enzymes are saturable. Once voriconazole concentrations start approaching or exceeding the Michaelis-Menten constant of the enzyme, small increases in the voriconazole dose will result in much larger changes in the drug concentration than the physician might anticipate, markedly enhancing the probability of toxicity.

To do the best job for our patients, it is important to understand the toxicity profile of the drug being considered. Even after the extensive clinical trials program that has been performed for voriconazole, it is unlikely that we fully understand the toxicity profile of this drug with respect to either concentration-related or concentration-independent toxicities.

Part of this lack of clarity involves the patient population in which the drug is used. Patients with fungal infections, particularly if the infecting pathogen is a species of Aspergillus present some of the most complex clinical cases that the infectious diseases clinician sees. These patients are often desperately ill, most frequently immunocompromised, and are likely to be experiencing massive polypharmacy. It is quite understandable that it is extremely difficult to identify with any certainty that the adverse event seen in the patient is tied to the administration of the test agent (voriconazole in this instance) if the patient may be taking 10–20 other medications. This is true for both concentration-related and concentration-independent toxicities.

Boyd and colleagues [5] describe 3 patients taking voriconazole who experienced serious adverse events. They described an episode of acute respiratory distress syndrome, an episode of hallucinations, and a patient with coma. In each instance, randomly acquired blood samples demonstrated very elevated concentrations of voriconazole. The elevated concentrations of drug increase the probability that the adverse events described were related to voriconazole. However, it should be noted that 2 of the 3 patients had a number of other agents coadministered. One should also take the course of the infectious insult into account. Drug-metabolizing enzymes can be inhibited by cytokines, the levels of which are highest at the initiation of illness and decline as the patient improves because of the drug therapy. Further, we have no denominator value to gauge the relatedness of the observed event to the administration of the drug. How many other patients with the observed concentrations would experience such an event? Indeed, to have the highest probability that the observed toxic event was related to the drug and the concentration, the patient would have to go through a set of challenge, dechallenge, and rechallenge evaluations with the drug. Given the serious nature of the clinical picture, it is unlikely that any reasonable physician would subject his or her patient to such a scenario. Consequently, there is uncertainty surrounding the relatedness of the observed adverse events to the administration of the drug.

Focusing on the lack of total certainty misses the importance of the report by Boyd and colleagues [5]. Although we may not be absolutely certain about the relatedness of the events because of the polypharmacy and the clinical picture, the observations are clearly important. Good, careful investigators in clinical trials not only observed the events but also determined some concentration data. This report is a call to the physicians who will be using voriconazole to be vigilant regarding the occurrence of such adverse events. With increasing use of the drug, if physicians are aware of the possible adverse events, an increased number of case reports will be filed, and we can gain greater certitude that the events (e.g., acute respiratory distress syndrome and altered mental state) are related to voriconazole therapy and also may be related to specific voriconazole concentrations. Should this be the case, the use of plasma concentration monitoring will allow patients to obtain the impressive therapeutic benefits of this agent without being encumbered with concentration-related adverse events. Until we have more data, we need to rely upon the infectious diseases community to be cognizant of the possible linkage and to report possible cases, along with concentration-time data. In this way, we can obtain the best care for our seriously ill patients.

References