Voriconazole Therapeutic Drug Monitoring

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We report on 28 patients who underwent voriconazole monitoring because of disease progression or toxicity. A relationship (P < 0.025) between disease progression and drug concentration was detected. Favorable responses were observed in 10/10 patients with concentrations above 2.05 μg/ml, while disease progressed in 44% (n = 18) of patients with concentrations below 2.05 μg/ml.

Most drugs display linear pharmacokinetic profiles. Drugs with nonlinear elimination characteristics that also have narrow therapeutic toxicity widows are candidates for monitoring. This is especially true in the circumstance where low drug exposures are life threatening and high drug exposures result in significant toxicities. Voriconazole is a triazole antifungal with enhanced activity against a broad spectrum of fungal pathogens, including Aspergillus and Candida species (11, 26). We provide a succinct review of voriconazole’s pharmacokinetics (PK) and present new PK-pharmacodynamic (PD) data relating drug concentration to therapeutic response.

The pharmacokinetics of voriconazole in volunteers and patients have shown that voriconazole exhibits a nonlinear pharmacokinetic profile, secondary to saturable clearance (6, 16, 24, 25). Voriconazole is metabolized by the cytochrome P450 system, with less than 2% of the dose excreted unchanged (12, 13, 24, 25). Most voriconazole metabolism is mediated through CYP2C19. Allelic polymorphisms of CYP2C19 have been shown to be the most important determinants of the clearance of voriconazole, resulting in two phenotypes: poor and extensive metabolizers (both homozygous and heterozygous). There is extensive genetic variability in the incidence of poor and extensive metabolizers (5, 10, 18, 28). The proportions of CYP2C19 extensive metabolizers in the U.S. population are estimated to be 2% homozygous extensive and 26% heterozygous extensive. Homozygous extensive metabolizers have a twofold lower exposure than heterozygous extensive metabolizers and fourfold lower drug exposure than poor metabolizers (12, 13).

In 10 trials, the median values for the average and maximum voriconazole plasma concentrations in individual patients (n = 1,121) were 2.51 μg/ml and 3.79 μg/ml, respectively (6, 16, 23, 24, 25). The values for area under the plasma concentration-time curve on day 10 in 200- and 300-mg administration groups were approximately 5.8 and 3.8 times higher, respectively, among the poor metabolizers than among the extensive metabolizers. Trough concentrations also suggested that poor metabolizers were exposed to higher concentrations than were extensive metabolizers. The pharmacokinetics exhibited minimal intrapatient variation but marked interpatient variation, which was postulated to be secondary to genetic factors, enzyme inhibition and induction, old age, and liver disease.

A PK-PD analysis of 6 of the 10 clinical trials (n = 280) did not reveal an association between voriconazole concentration and efficacy (19). This is likely because the antifungal exposure far exceeded the MICs of most pathogens (MIC90, ≤0.5 μg/ml) (26). However, analysis of the clinical trials did suggest a trend towards worse outcome in those patients with voriconazole concentrations of <0.5 μg/ml (http://www.fda.gov).

Despite voriconazole’s efficacy, breakthrough fungal infections have been reported (1, 14, 20, 29). Among the 13 patients described in a report by Imhof et al., pathogen MICs were ≥1 μg/ml for available isolates (14). Unfortunately, data regarding voriconazole serum concentrations in these patients were unavailable.

We retrospectively studied voriconazole monitoring at our institution. Data variables included patient age, gender, voriconazole indication and dose, other potentially interacting pharmaceuticals, voriconazole concentration, reason for the lab request, timing of dose relative to sampling, and outcome. Serum concentrations were determined by a validated high-pressure liquid chromatography method. Progression was defined as an increase in size or number of lesions on follow-up imaging. Survival was defined at time of last follow-up.

A total of 188 patients received voriconazole from 2002 to 2005. The indications for voriconazole were as follows: invasive aspergillosis (82 patients), prophylaxis (13), blastomycosis (3), febrile neutropenia (56), and other fungal infections (34). Twenty-eight patients had at least one drug concentration determination (Table 1). All patients received voriconazole loading and were on 200 mg orally twice daily for at least 2 weeks. Seventeen patients had concentrations determined because of disease progression, while 11 were determined for toxicity. Of those patients who were failing therapy, 15 of 17 patients had a transplant and received voriconazole for aspergillosis. All 17 patients had serum concentrations below the median value from clinical trials (2.51 μg/ml). The voriconazole range, median, mean and standard deviation in this study were <0.2 to 4.8, 1.05, 1.10, and 0.76 μg/ml, respectively. Five patients had duplicate determinations of concentrations prior to dose adjustments (concentrations remained below the median value from the trials until dose adjustment). No concomitant CYP-
Below 2.0 μg/ml prompted an increase in dose in 11 patients, 8 of whom survived the infection. A subsequent concentration, which was available for six patients, was above 2.5 μg/ml in three patients. The mean follow-up period was 13 months after the serum concentration was obtained.

Using data from all 28 patients, PK-PD breakpoints for a clinical response were determined using classification and regression tree-based modeling. A significant ($P < 0.025$) relationship between disease progression and drug concentration was detected. A positive clinical response was observed in 100% (10/10) of patients with random voriconazole concentrations of above 2.05 μg/ml.

Therapeutic drug monitoring is well established when using medicines with narrow therapeutic indices to minimize toxicity (3). Therapeutic drug monitoring is also well established when variable absorption or pharmacokinetics could result in insufficient drug exposures. Drug monitoring is common with a large number of anti-infective agents, including the antifungal agents fluconazole and itraconazole (3, 8, 9, 15, 17, 21, 22). The rationale for monitoring itraconazole concentrations is the erratic oral bioavailability. A relationship between plasma concentrations (0.5 μg/ml) and antifungal efficacy was demonstrated in postmarketing data analyses (9, 15). CYP metabolizer status has been shown to affect clinical responses for other disease states. For example, extensive metabolizers of the proton pump inhibitors have a five-times-lower exposure and experience less effective healing of ulcers (5, 18).

The main limitation of the current report is the small cohort size and the retrospective design. However, the cohort is similar to those utilized in demonstrating the importance of exposure with other anti-infectives. The study most closely related to the current investigation was that which demonstrated the relevance of itraconazole therapeutic drug monitoring (9; A. Glasmacher, C. Hahn, E. Molitor, et al., Abstr. 40th Intersci. Conf. Antimicrob. Agents Chemother., abstr. 700, 2000). There are other examples of cohorts of similar size (five to eight patients with low exposure and failure) which have been used to examine the relationship between drug exposure and outcome with antibacterials (2, 4, 7).

Additionally, we were unable to assess the genotype for this cohort, and we do not have susceptibility data for the fungal isolates. Despite these limitations, this study suggests that clinical failure may be related to subtherapeutic drug exposures. Therapeutic drug monitoring is also well established when variable absorption or pharmacokinetics could result in insufficient drug exposures. Drug monitoring is common with a large number of anti-infective agents, including the antifungal agents fluconazole and itraconazole (3, 8, 9, 15, 17, 21, 22). The rationale for monitoring itraconazole concentrations is the erratic oral bioavailability. A relationship between plasma concentrations (0.5 μg/ml) and antifungal efficacy was demonstrated in postmarketing data analyses (9, 15). CYP metabolizer status has been shown to affect clinical responses for other disease states. For example, extensive metabolizers of the proton pump inhibitors have a five-times-lower exposure and experience less effective healing of ulcers (5, 18).

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REFERENCES


