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Posaconazole Therapeutic Drug Monitoring: a Reference Laboratory Experience▽

We read with great interest the review by Andes et al. (1) describing antifungal therapeutic drug monitoring (TDM). We agree that there are limited data suggesting serum posaconazole concentrations predict the efficacy of prophylaxis or treatment with this agent. Prior studies have reported only mean serum drug levels by patient group (those with breakthrough invasive fungal infections versus those who remained uninfected) or by quartile with an average response rate to therapy (2, 5, 7–9). Serum posaconazole levels have also been repeatedly shown to have a large degree of interpatient variability (4–7). However, it is our experience that undetectable posaconazole levels are commonly encountered despite attempts to maximize absorption.

One of two early posaconazole prophylaxis studies reported mean serum posaconazole levels of 1.470 μg/ml in patients with chronic graft-versus-host disease (GVHD) and 0.958 μg/ml in those with acute GVHD (8) However, the average posaconazole levels were 0.611 μg/ml in patients who developed breakthrough infection and 0.922 μg/ml in those who remained uninfected (5). The other and concurrently published prophylaxis study reported a mean serum posaconazole level of 0.583 ± 381 μg/ml—a mean value below the average of those who experienced breakthrough infection in the aforementioned GVHD prophylaxis study (2). A study evaluating posaconazole as salvage therapy for invasive aspergillosis correlated therapeutic response to serum drug concentrations by quartiles and found those with a mean serum drug level of 0.134 μg/ml had only a 24% response rate (9). Additionally, the FDA briefing document recommends a goal posaconazole average serum drug concentration of >0.700 μg/ml (3).

We retrospectively reviewed 202 consecutive serum posaconazole concentrations obtained between 26 December 2007 and 30 December 2008 by The Fungus Testing Laboratory, San Antonio, TX, a reference laboratory specializing in fungal identification, susceptibility testing, and antifungal drug concentrations. Drug levels were obtained with a validated high-performance liquid chromatography assay (range, 0.125 to 5.0 μg/ml [equipment manufactured by Beckman Coulter, Fullerton, CA]). Levels less than 0.125 μg/ml were reported as undetectable, and levels greater than 5.0 μg/ml were diluted 1:2, reextracted, and reanalyzed.

Our review confirmed the infrequent obtainment of levels suggestive of efficacy as described above. In our series, 158/202 (78.2%) posaconazole levels were <0.92 μg/ml and 135/202

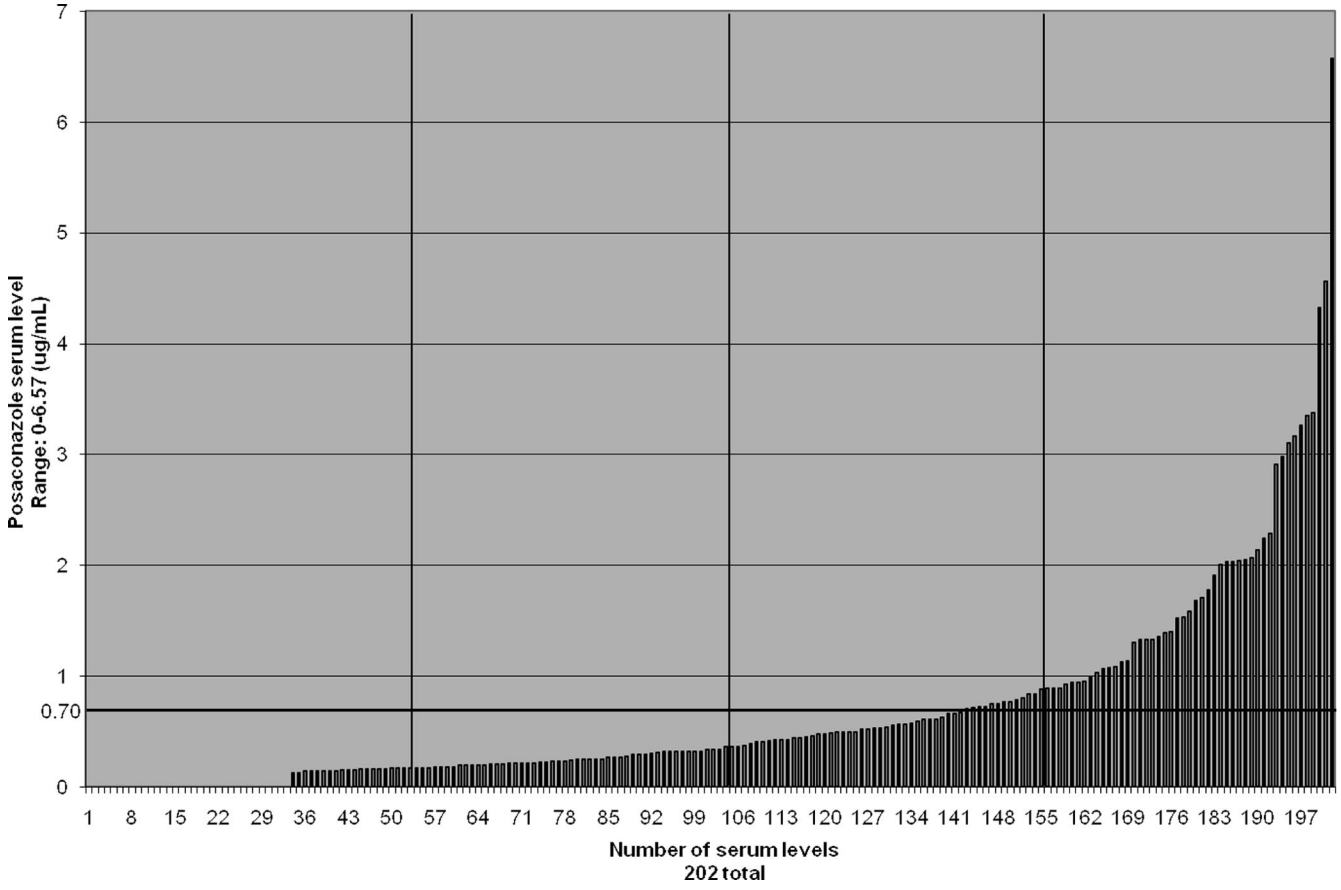

FIG. 1. Distribution of serum posaconazole levels obtained by the Fungus Testing Laboratory, San Antonio, TX, from 26 December 2007 through 30 December 2008.

(66.8%) were <0.611 μg/ml, a value that may represent patients at increased risk of breakthrough infection while receiving posaconazole prophylaxis. Although the exact value known to be therapeutic in the treatment of invasive mycoses has not been determined, it is noteworthy that 33/202 (16.3%) in our series were undetectable (<0.125), 35/202 (17.3%) were <0.134 μg/ml (the value associated with only a 24% response rate in posaconazole use as salvage therapy for invasive aspergillosis), and 142/202 (70.3%) were <0.700 μg/ml (the value cited by the FDA to place patients at increased risk) (Fig. 1).

When drug concentrations thought to be subtherapeutic are observed, attempts at maximizing drug availability/absorption should be undertaken. Strategies proven to maximize posaconazole exposure include administration with or after a high-fat meal, with any meal or nutritional supplement, with an acidic beverage, or in divided doses and with the avoidance of acid suppression drugs (6). However, it is common for low serum posaconzole levels to be found despite these maneuvers, and these differences observed between serum drug levels within clinical trials and "real-world" use may have an important clinical impact on the frequency of TDM and choice of antifungal agent. We thus recommend repeat testing of serum posaconazole levels after the above attempts to maximize absorption. Although previous reports have questioned the need for TDM with posaconazole pending outcome studies based on levels, our data suggest that testing should be performed to ensure that measurable drug is present and therefore has the potential for efficacy.

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