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Relationship of Blood Level and Susceptibility in Voriconazole Treatment of Histoplasmosis▽

Monitoring of voriconazole serum levels has been advocated by Smith et al. as a method of ensuring adequate drug exposure in treating invasive mycoses (9). Voriconazole blood levels may vary considerably between subjects as a consequence of genetic polymorphisms that dictate variable clearance and nonlinear elimination (4, 5, 7, 8, 10). Among patients taking 200 mg twice a day, trough voriconazole concentrations range from below 0.100 μg/ml to nearly 10 μg/ml in several studies (2, 4, 5, 6). Although clinical trial data are lacking, voriconazole is occasionally used to treat *Histoplasma capsulatum* infections. In this report, we determined blood levels in patients treated with voriconazole as a secondary therapy for histoplasmosis, usually because of intolerance of other antifungal therapies, mostly amphotericin B or itraconazole.

Serum specimens from nine patients with disseminated histoplasmosis that had been submitted for antigen testing were later tested for serum levels of voriconazole (3). All nine patients were considered to have improved clinically during secondary oral voriconazole treatment at a dose of 200 mg twice daily. All patients had received voriconazole for at least 2 weeks before blood concentrations were determined, but the exact timing of the blood specimens obtained following the oral administration of voriconazole was not recorded. Specimens had been frozen for up to 4 years prior to the determination of serum drug levels. Our experience with a similar compound, itraconazole, showed no loss of activity after 4 years at −20°C. Furthermore, the levels observed in the patients in this study are consistent with levels obtained in real-time testing of fresh specimens. Isolates of *H. capsulatum* for this patient cohort were unavailable for voriconazole susceptibility testing; therefore, archived *H. capsulatum* isolates from AIDS patients who had either primary or relapsed histoplasmosis were employed for this testing by a modified CLSI (formerly NCCLS) method as described previously (1). A comparison of voriconazole susceptibilities (by MIC measurements) of these archived *H. capsulatum* isolates from patients with both primary and relapsed disease (Fig. 1) was made with the random voriconazole blood levels measured from the nine patients who were being treated with the drug for disseminated histoplasmosis (Fig. 1).

Among 20 samples for the nine patients, voriconazole concentrations ranged from undetectable to 8.00 μg/ml (Fig. 1). Voriconazole blood levels were highly variable and possibly inadequate in several of our patients, with two random blood levels clearly falling below the median MIC for primary (0.015 μg/ml) and relapsed (0.030 μg/ml) isolates. Three other levels fell below the lowest calibrator (0.125 μg/ml) for serum voriconazole levels, and therefore we do not know if they were

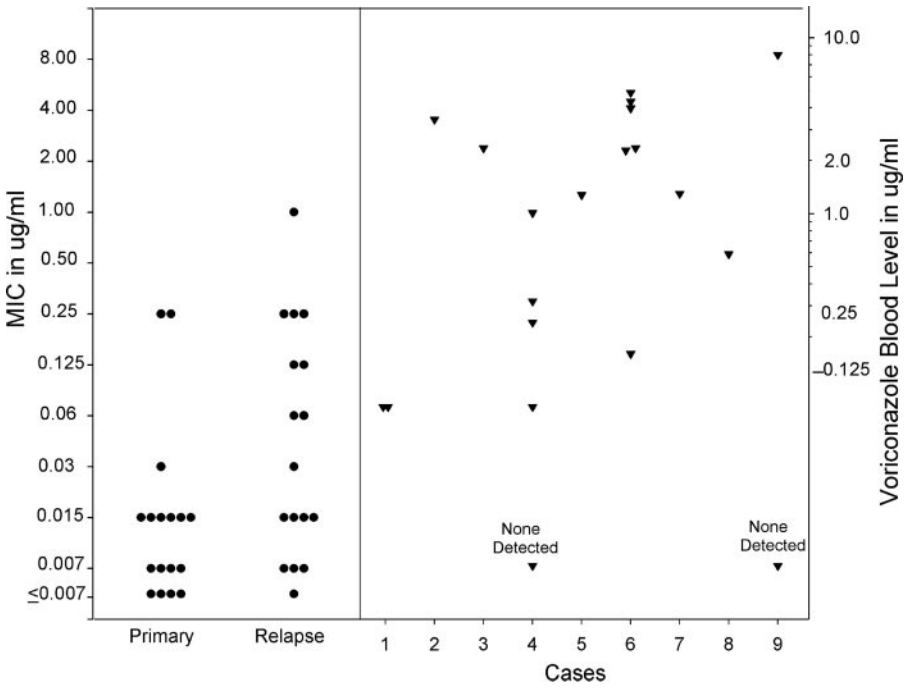

FIG. 1. Comparison of antifungal susceptibilities of primary and relapse isolates of *H. capsulatum* to voriconazole and random voriconazole blood levels in patients receiving voriconazole for the treatment of histoplasmosis. The left-hand axis depicts the MIC scale for the primary and relapse isolates, included in the left-hand section of the figure. The median MIC was 0.015 μg/ml for the primary and 0.030 μg/ml for the relapse isolates. The right-hand axis depicts voriconazole blood levels for the histoplasmosis cases, included in the right-hand section of the figure. The three specimens with blood levels shown below the 0.125-μg/ml voriconazole blood level designation demonstrated a zone of inhibition in the bioassay, which was below the lowest standard. None Detected, no inhibition was observed for the specimen.

below these MIC medians. There were questions about medication compliance in three patients, two of whom had levels of <0.125 μg/ml. Nonetheless, all nine patients had already improved in response to amphotericin B or itraconazole before voriconazole was started, and no patient relapsed while receiving voriconazole, despite the documented low drug levels.

Pascual et al. reported a 90% response for patients with aspergillosis or candidiasis with voriconazole trough levels of >1.0 mg/ml and only a 54% response for patients with lower troughs (6). Smith et al. reported findings for 28 patients with invasive mycoses, mostly aspergillosis, and observed favorable responses for 100% (10/10) of patients with random serum levels, >2.05 μg/ml, compared with unfavorable responses for 44% of patients with lower concentrations (9). Among our nine patients with histoplasmosis, random levels were <2.05 μg/ml in 60%, <1.0 μg/ml in 45%, and <0.125 μg/ml in 30%. Although we cannot establish a "subtherapeutic level" from our cases, since all appear to have responded to the therapies given, we suggest that levels that measure below the calibrator level of 0.125 μg/ml might be considered subtherapeutic. This task is further complicated by the paucity of voriconazole MIC data for histoplasmosis. Given the variability in serum levels in patients receiving voriconazole for histoplasmosis, the relatively high MIC_{90} of voriconazole for *H. capsulatum* noted herein, and the lack of prospective trials establishing the effectiveness of voriconazole for the treatment of histoplasmosis, we suggest that it may be prudent to measure trough concentrations of voriconazole in patients receiving it for treatment of histoplasmosis to ensure detectable drug levels.

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