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ePoster Viewing
Antifungal drug susceptibility and resistance

Determination of susceptibility breakpoints for posaconazole and Aspergillus fumigatus using a pharmacokinetic-pharmacodynamic model

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Objectives: Posaconazole is an antifungal triazole commonly used for prophylaxis and occasionally for treatment of invasive aspergillosis. *A. fumigatus* isolates with reduced *in vitro* susceptibility to posaconazole were associated with distinct mutations in *cyp51a* gene and with clinical failure. The lack of susceptibility breakpoints for posaconazole and *A. fumigatus* hinders the detection of those isolates. Therefore, the aim of the present study was to investigate the pharmacodynamics of posaconazole against *A. fumigatus* isolates with different *cyp51a* mutations and minimal inhibitory concentrations (MIC) and to determine susceptibility breakpoints using an *in vitro* pharmacokinetic-pharmacodynamic (PK-PD) model.

Methods: Four clinical isolates of *A. fumigatus* harboring different *cyp51a* mutations were tested: 1 wild type isolate with no cyp51a mutation and CLSI MIC 0.03 mg/l and 3 isolates each with M220I, TR/L98H and G54W cyp51a mutation with CLSI MIC 0.5, 0.5 and 16 mg/L, respectively. Posaconazole pharmacokinetics of 400mg bid dosage corresponding to maximum concentration 0.851 ± 0.69 mg/l (mean ± standard deviation) and half-life of 12h (Ullmann et al. AAC 2006) were simulated in the *in vitro* PK-PD model. After inoculation with 10^3 CFU/ml, posaconazole was added in the model every 12h for 72h, targeting total maximum concentrations of 0.15, 0.85 and 2.25 mg/l and half life of 12h. Posaconazole concentration was assessed with a bioassay previously described (Rochat et al, AAC 2010) and the % fungal growth was estimated based on the galactomannan production, measured with a sandwich-ELISA (Platelia Aspergillus, Biorad) for each dose and isolate. The AUC_{0-12}/MIC associated with the 50% of fungal growth was calculated with Emax model. Monte Carlo simulation analysis was performed in order to determine the % of target attainment for different MICs.

Results: Posaconazole demonstrated the maximal in vitro activity (<42% growth) against the wild-type isolate and the least activity (>95%) against the isolate harboring the G54W mutation. For the isolates with the same MIC, the in vitro activity of posaconazole was higher against the strain with the TR/L98H mutation compared to the strain with the mutation M220I (15% vs. 79% growth at 2.25 mg/L, respectively). The posaconazole PK/PD relationship followed a sigmoid curve (R^2=0.885) with an AUC/MIC corresponding to 50% of maximal efficacy of 36 (21-59). Monte Carlo analysis showed >70% and <30% target attainment for isolates with MICs ≤0.0625 mg/l and ≥0.5 mg/l.

Conclusions: Posaconazole activity was dependent on the MIC and cyp51A mutation. The PK/PD and Monte Carlo analysis suggests the following susceptibility breakpoints for posaconazole and *A. fumigatus* S≤0.0625, I=0.125-0.25, R=≥0.5 mg/l.