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Abstract (poster session)

Posaconazole pharmacodynamics against azole-resistant Aspergillus fumigatus strains with a novel in vitro pharmacokinetic/pharmacodynamic model

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Objectives: Posaconazole (POS) is an antifungal triazole used for prophylaxis and therapy of invasive aspergillosis. A. fumigatus (AF) isolates with reduced susceptibility to POS have been associated with distinct mutations in the CYP51A gene encoding the target enzyme lanosterol 14Beta-demethylase. However, there are no interpretive susceptibility breakpoints for POS and in vitro pharmacodynamics against isolates with different CYP51A mutations are not well understood. We therefore investigated the in vitro pharmacodynamics (PD) of POS against AF isolates with different CYP51A mutations in an in vitro model simulating POS pharmacokinetics (PK). Methods: Four clinical isolates of AF exhibiting different susceptibility to POS with distinct CYP51A mutations were tested; 1 wild type isolate with no CYP51A mutation and CLSI MIC 0.06 mg/l, 3 isolates each with M220I, TR/L98H and G54W CYP51A mutation with CLSI MIC 0.5, 0.5 and 16 mg/1, respectively. POS dosages were simulated in a novel in vitro PK-PD model in order to obtain area under the plasma concentration-time curves (AUC) of 10, 30 and 100 mg.h/l and an average half-life of 24h as observed in humans after standard dosing with 200 mg tid or 400 bid (median, range AUC: 16, 4-56 mg.h/l). After AF conidia (103 CFU/ml) were inoculated in the model, POS was administered every day for three days. POS concentration in the IC was determined with a bioassay as previously described (Calvo E. et al, AAC 2003). Fungal growth was estimated based on galactomannan production measured with a sandwich-ELISA (Platelia Aspergillus, Biorad) for each dose and the drug free control. The PK/PD parameter AUC/MIC was associated with the % of fungal growth based on the Emax model. Results: POS AUC90, 30 and 10 resulted in 8%, 9% and 30% of growth, respectively for the wild type isolate (MIC 0.06 mg/l) while for the isolates with MIC 0.5 mg/l growth reduction was observed only for POS AUC90 (20% growth for G54W and 75% growth for M220I); no growth inhibition was observed with the isolate with MIC 16 mg/l. The POS PK-PD relationship followed a sigmoid curve (R2=0.91) with an AUC/MIC corresponding to 50% of maximal efficacy of 355 (280-447) mg.h/l attained with standard POS dosages for isolates with MIC 0.06 mg/l. Conclusion: Standard POS dosing may be sufficient for isolates with CLSI MIC of 0.06 mg/l but not against isolates with higher MICs. Different resistance mechanisms may exhibit different in vitro pharmacodynamics despite the same MICs.