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Abstract (oral session)

Determination of azole resistance among Aspergillus fumigatus by studying in vitro pharmacodynamics of voriconazole with a novel pharmacokinetic/pharmacodynamic model

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Objectives: Voriconazole (VCZ) has become the drug of choice for the treatment of invasive aspergillosis. Although strains with reduced in vitro susceptibility to VCZ have been described, clinical breakpoints have not yet been defined. Pharmacokinetic/pharmacodynamic analysis can help to identify VCZ resistant isolates. The aim of our study was to investigate the efficacy of VCZ against Aspergillus fumigatus (AFM) using a novel in vitro pharmacokinetic/pharmacodynamic (PK/PD) model for identifying drug-resistant isolates. Methods: Two clinical isolates of AFM with VCZ CLSI MICs of 0.125 mg/l (wild type strain), and 2 mg/L (CYP51 mutation TR/L98H) were included. standard VCZ dosages 4 mg/kg were simulated in a new in vitro PK simulation system with a half-life of 6h and Cmax of 1.75 mg/l as observed in patients (Purkins et al, AAC 2002). The new system consists of an internal compartment (IC, a 10 ml dialysis tube made out of semi-permeable cellulose membrane allowing the free diffusion of molecules with MW <20kDa) placed inside an external compartment (EC, a 700 ml glass beaker) whose content is diluted with a peristaltic pump at the same rate as the clearance of VCZ in human plasma. Aspergillus conidia (10^3/ml) were inoculated inside the IC and VCZ was added in the IC and EC. Drug levels were determined by microbiological methods and fungal growth by measuring galactomannan concentrations in the IC with a sandwich-ELISA (Biorad). The area under the drug concentration-time curve AUC0-24 (PK parameter) and the area under the galactomannan concentration-time curve AUCGI (PD parameter) were determined for each dose and isolate for 24h. The percent of growth inhibition at each dose was calculated as 1-AUCGI,VOR/AUCGI,GC where AUCGI,VOR is the AUCGI at a certain VCZ dose whereas AUCGI,GC is the AUCGI of the drug free control. Results: The simulated dose 4 mg/kg of VCZ resulted in fAUC0-24 of 10 mg.h/L which corresponds to the lower 95% fAUC0-24 (58% protein binding) observed in patients receiving the standard dose of 4 mg/kg (10-44 mg.h/L, Purkins et al, AAC 2002). By taking into account the population variability of fAUC0-24s in patients, growth inhibition 100% was observed for the isolate with an MIC of 0.125 mg/L, but 0% for the isolate with an MIC of 2 mg/L. Conclusion: PK/PD analysis of VCZ's in vitro activity strongly indicates that AFM isolates with VCZ CLSI MICs>=2 mg/L should be classified as resistant.