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An in vitro pharmakokinetic/pharmakodynamic model predicts in vivo exposure-response relationship of micafungin against Candida albicans

Maria-Ioanna Beredaki*[1], David Andes[2], Johan Mouton[3], Spyros Pournaras[4], Joseph Meletiadis[5]

[1]*"Attikon" University General Hospital; Clinical Microbiology Laboratory*

[2]*University of Wisconsin*

[3]*Erasmus University Medical Center; Department of Medical Microbiology and Infectious Diseases*

[4]*Medical School, University of Athens; Department of Microbiology*

[5]*Clinical Microbiology Laboratory, Attikon University Hospital, Athens, Greece; Department of Medical Microbiology and Infectious Disease, Erasmus MC*

Background: Micafungin is widely used for the treatment of invasive candidiasis. Reduced efficacy against isolates with high MICs and low drug exposures have been observed. In order to optimize micafungin efficacy, it is important to establish the pharmakokinetic/pharmacodynamic- (PK/PD) relationships between micafungin exposure and antifungal activity. Currently there are no *in vitro* dynamic models to explore the PK/PD characteristics of micafungin simulating *in vivo* concentration-time profiles. We studied the efficacy of micafungin using a previously optimized two-compartment *in vitro* PK/PD model to compare with the results obtained in an animal model.

Material/methods: Two clinical *C. albicans* isolates (CA580 and CAK1) with CLSI MICs/MFC 0.008/0.03 and 0.03/2 mg/L, previously used in animal models (Andes et al. *AAC*2008) were tested at an initial inoculum of 10^4CFU/mL. The *in vivo* micafungin dosages of 5, 20 and 80mg/kg/od used in animal model were simulated in a 2-compartment PK-PD dialysis/diffusion model targeting fC_{max} 0.018, 0.076, 0.15 mg/L, respectively, and average half-life of 12h. Micafungin fC_{max} 4 mg/L was also tested in order to attain maximal effects. Micafungin concentrations were determined with a

microbiological assay and log_{10}CFU/mL with quantitative cultures at frequent time points. The $fAUC_{0-24}$/MIC ratio was calculated for each micafungin dose and *C.albicans* isolate. The relationship between $fAUC_{0-24}$/MIC ratio and 72-change in log_{10}CFU/mL from initial inoculum was analyzed by nonlinear regression analysis and the exposure concentration associated with 50% of maximal activity (EC_{50}) was determined. Monte Carlo simulation analysis was performed in order to calculate EC50 target attainment rates for isolates with different CLSI MICs in ICU patients with a mean (interquartile range) micafungin AUC_{0-24} of 78.6 (65.3-94.1)mg.h/L as previously described (Lempers et al. AAC2015). A 99.75% protein binding was taken into account.

Results: The log_{10}CFU/mL in drug free control reached $9log_{10}$ at 72h and progressively reduced to 6-6.6, 4.9-4.8, 1-3.7 and <0.6 log_{10}CFU/mL at doses with fC_{max} 0.018, 0.076, 0.15 and 4mg/L, respectively. The *in vitro* fAUC/MIC–change in log_{10}CFU/mL followed a sigmoid curve similar to that of the animal model (R^2=0.86). The *in vitro* EC50 was 9.4 *f*AUC_{0-24}/MIC (tAUC/MIC=3760), which is close to *the in vivo f*AUC_{0-24}/MIC of 18.9 in mice (Andes et al AAC2010) and the clinical tAUC/MIC of 3000 in patients with invasive candidiasis (Andes et al AAC2011). Attainment rates for fAUC/MIC=9.4 (tAUC/MIC=3760) target were 100%, 93% and 1% for isolates with CLSI MICs ≤0.008, 0.016 and ≥0.032 mg/L, respectively.

Conclusions: An *in vitro* PK/PD model was developed for studying micafungin exposure-response effects simulating in vivo serum concentration-time profiles with comparable results to those observed in animals and clinical studies. The results indicate that drug exposures usually observed in ICU patients may not be sufficient to attain the pharmacodynamic target for isolates with MICs close the current susceptibility breakpoint.