P1698
Poster Session VI
PK/PD of antifungals and miscellaneous antibacterials

PHARMACODYNAMICS OF THE NEW AZOLE ISAVUCONAZOLE IN AN ASPERGILLUS FUMIGATUS MOUSE INFECTION MODEL

S. Seyedmousavi[1], J.F. Meis[2], R.J.M. Bruggemann[3], W.J.G. Melchers[1], P.E. Verweij[1], J.W. Mouton[1]

[1]Medical Microbiology, Radboudumc, Nijmegen, Netherlands ; [2]Medical Microbiology and Infectious Diseases, Canisius Wilhelmina Hospital, Nijmegen, Netherlands ; [3]Pharmacology, Radboudumc, Nijmegen, Netherlands

Objectives
Azole resistance is an emerging problem in *Aspergillus fumigatus* which translates into treatment failure. Alternative treatments with new azoles may improve therapeutic outcome in invasive aspergillosis (IA) even for strains with decreased susceptibility. We determined the efficacy of isavuconazole (ISA) in an immunocompetent *A. fumigatus* murine model.

Methods
The *in vivo* efficacy of 0.25, 1, 4, 16, 64, 128 and 256 mg/kg/day prodrug isavuconazonium sulfate (BAL8557) administered orally once daily was assessed in an immunocompetent murine model of IA against four clinical *A. fumigatus* isolates: a wild-type isolate (AZN 8196, ISA MIC, 0.5 mg/l) and three azole-resistant isolates harboring substitutions in the *cyp51A*-gene: G54W (V 59-73, ISA MIC, 0.5 mg/l), M220I (V28-37, ISA MIC, 4 mg/l) and TR_{34}/L98H (V 52-35, ISA MIC, 8 mg/l). MICs were determined using EUCAST methods. In addition, ISA concentrations in plasma were assayed in a separate pharmacokinetic (PK) study at 10 predefined time points post challenge by a validated UPLC method.

Results
In PK studies, the dose normalized ISA AUC_{0-24} (area under the plasma concentration-time curve from time zero to 24 h post infusion) ratios ranged from 0.24 to 0.84. In efficacy studies, the maximum effect (100% survival) was reached at a dose of 64 mg/kg for the wild-type isolate, 128 mg/kg for the G54W and 256 mg/kg for M220I mutant. A maximal response was not achieved with the TR_{34}/L98H isolates with the highest dose of prodrug isavuconazonium sulfate (256 mg/kg). The Hill equation with a variable slope fitted the data well with a significant relationship between AUC_{0-24}/MIC ratio and 14-days survival (R^2= 0.96) (P <0.05). For a survival of 50%, the effective AUC_{0-24}/MIC ratio for ISA total drug was 24.73 (95% confidence interval, 22.50 to 27.18).

Conclusions
Efficacy of ISA in an *A. fumigatus* murine model of infection was dependent both on the drug exposure and on the ISA MIC of the isolate. The quantitative relationship between exposure and effect (AUC_{0-24}/MIC) can be used to optimize the treatment of human infections by *A.fumigatus*, including strains with decreased susceptibility.