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ePoster Viewing
Pharmacokinetics/pharmacodynamics of antibacterial drugs & therapeutic drug monitoring

Pharmacodynamics of fosfomycin against ESBL producing pathogens

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Background:

The increase of antibiotic resistance in Gram-negative bacteria and unavailability of new antibiotics has increased the interest of the "old" antibiotic fosfomycin in the treatment of systemic infections. However the pharmacodynamics (PD) of this antibiotic are still largely unknown. We therefore determined the PD properties of fosfomycin against extended spectrum beta-lactamase (ESBL) producing *E. coli* and *K. pneumoniae* strains using time-kill assays.

Material/methods:

Time-kill assays of fosfomycin were performed in *E. coli,* n=3 and *K. pneumoniae,* n=3 (MICs of 0.5 – 32 mg/L) at concentrations ranging from 0.125 up to 32 times the MIC at 37 °C. Samples were taken at T0,1,2,3,4,6,8,16,24 and 48h**.** For emergence of resistance, at T0,8,16,24 and 48h samples from 2-8xMIC bottles were plated on agar plates containing 0, 3 and 6xMIC. Mutation frequency was calculated and viable bacterial counts (CFU/ml) were plotted versus time.

In order to assess early-time antibacterial effects, the kill rate (log_{10}CFU/mL x h^{-1}) was determined by linear regression analysis for the time interval of 0-6h. A sigmoidal *Emax* model with variable slope was used to fit the kill rate-drug concentration data. The maximal kill-rate (*Emax*) and the concentration corresponding to 50% of *Emax* (EC50) was determined. Bactericidal activity was defined as >3log_{10}CFU/ml reduction from the initial inoculum.

Results:

The mean growth rates in the drug-free control as determined over the first 6h were similar for all strains (0.59-0.62 log_{10}CFU/ml x h^{-1}). For almost all strains a bactericidal effect within 6-8h was observed for ≥4-8xMIC of fosfomycin concentrations. However, after initial fast killing, regrowth was observed from 6-8h onwards and full growth of resistant subpopulations reaching drug-free control levels were observed at 24-48h for fosfomycin concentrations up to 8-32x the MICs of the strains.

In the *Emax* model some variation in killing curves was observed, although there were no differences in mean max kill-rates between *E.coli* and *K.pneumoniae* (0.52 vs. 0.51). In *E. coli* strain 51 a much higher max killing rate was observed as compared to the other *E. coli* strains (0.68 vs 0.43-0.45 h^{-1}). Alternatively, for *K. pneumoniae* strain 3 a considerable lower kill rate was observed as compared to the other strains (0.30 vs. 0.58 and 0.66 h^{-1}).

The species mean (range) Hill coefficients for *E.coli* and *K. pneumoniae* were 2.18 (0.62-3.02) and 1.29 (0.92-1.70) respectively indicating a stronger concentration dependent early-time antibacterial effect against *K. pneumoniae*.

Conclusions:

Fosfomycin was bactericidal against *E.coli* and *K. pneumoniae* within 8 hours, However emergence of resistance was observed after 8 hours for all strains with growth reaching drug-free control levels. This may limit the use of fosfomycin as a single drug therapy in serious infections. Further optimization of fosfomycin pharmacodynamics is required in order to increase efficacy against ESBL (+) pathogens.