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Paper Poster Session
PK/PD of agents against Gram-negatives

Pharmacodynamics of inhaled amikacin studied in an in vitro pharmacokinetic model of infection

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Background: Inhalation antibiotic therapy for bacterial infection has attractive pharmacodynamic and clinical features. High local concentrations of antibiotic in respiratory secretions may be associated with a rapid decrease in bacterial load, and reduced risk of emergence of resistance. Low systemic concentrations may help avoid adverse events. However, existing clinical breakpoints based on systemic therapy may not be appropriate for inhalational use of drugs. In this study we sought to establish a potential Extracellular Lining Fluid (ELF) clinical breakpoint for amikacin (AMI) to treat Gram-negative pulmonary infection.

Material/methods: An in vitro dilutional pharmacokinetic model was used to simulate ELF AMI concentrations associated with doses of 500mg 12hrly over 5 days. A Cmax of 4,000mg/L - at 35 mins post dose was targeted, declining to 909mg/L 3hr post dose; 136.4mg/L 6hr post dose and 3.6mg/L after 12h. Nine strains of bacteria *E.coli* (n=3) AMI MICs 4-8mg/L; *P.aeruginosa* (n=3) AMI MICs 2-64mg/L and *A.baumannii* (n=3) AMI MICs 2-192mg/L were used. Antibacterial effect was assessed by changes in viable count and emergence of resistance by recovery of isolates able to grow on MICx4 recovery media.

Results: For strains with MICs ≤8mg/L there was rapid and sustained reductions in bacterial load up to 120h. For other strains regrowth occurred after 12hr and after 24hr >10^6CFU/ml bacteria were isolated on MICx4 plates increasing to >10^7CFU/ml by 120h. Log MIC was related to reduction in viable counts at 12, 24, 72 and 120hr using a Sigmoid Emax model (R^2>0.9). Using a bacterial clearance target of -2 log reduction in count by 24hr then strains with MICs of <120mg/L were predicted to achieve antibacterial effect.

Conclusions: Simulated mean ELF concentrations of AMI associated with inhaled therapy were associated with rapid reduction in bacterial load and no resistance for strains with AMI MIC ≤8mg/L. A pharmacodynamic target of -2 log reduction in load by 24hr could be achieved for strains with MIC ≤120mg/L but emergence of resistance was a feature of strains with higher AMI MICs. Combination of inhaled amikacin with systemic therapy should help overcome this risk.