EV0055

ePoster Viewing

Antimicrobials: antimicrobial PK/PD, pharmacogenomics, pharmacoeconomics and general pharmacology, drug interaction studies

Can clinical dosing regimens provide "anti-mutant" fluoroquinolone concentrations? Predictions using *in vitro* dynamic models

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Objectives. *In vitro* studies performed mostly with fluoroquinolone-exposed *Staphylococcus aureus* allowed delineation of concentration-resistance relationships that might provide "anti-mutant" antibiotic dosing. These relationships were reflected in bell-shaped curves that describe AUC/MIC-dependent enrichment of resistant mutants. To explore if similar relationships apply to Gram-negative bacteria, the pharmacodynamics of ciprofloxacin were studied against *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* over a wide range of antibiotic exposures.

Methods. Four strains of *E. coli* (MICs 0.008 - 0.016 mg/L), three strains of *K. pneumoniae* (MICs 0.125 - 2 mg/L) and four strains of *P. aeruginosa* (MICs 0.125 - 0.5 mg/L) were exposed to twice-daily ciprofloxacin for three days over a >100-fold range of AUC/MIC ratios. The enrichment of resistant mutants was monitored by plating on media with 2×, 4×, 8× and 16×MIC of ciprofloxacin. Time courses of resistant mutants were characterized by the area under the bacterial mutant concentration – time curve ($AUBC_M$). Changes in susceptibility were examined by daily MIC determinations.

Results. AUC/MIC relationships with $AUBC_M$ were bell-shaped with each organism. Because of pronounced stratification of individual $AUBC_M$-AUC/MIC curves, "anti-mutant" AUC/MIC ratios at which there was no loss in susceptibility of antibiotic-exposed bacteria were highly variable: 525 to 1070 h (*E. coli*), 560 to 1800 h (*K. pneumoniae*) and 225 to 1100 h (*P. aeruginosa*). These "anti-mutant" AUC/MICs were within clinically achievable values for *E. coli*, but not for *K. pneumoniae* and *P. aeruginosa*. Similarly, mean "anti-mutant" AUC/MIC_{50}s predicted by fitting $AUBC_M$-AUC/MIC combined data for each bacterial species (*r*^2 0.86, 0.50 and 0.75, respectively) were less than clinically achievable AUC/MIC_{50}s only for *E. coli* (650 h versus 1470 h) but not *K. pneumoniae* (470 h versus 730 h) and *P. aeruginosa* (1600 h versus 44 h).

Conclusions. As with *S. aureus*, AUC/MIC-resistance relationships observed with *E. coli*, *K. pneumoniae* and *P. aeruginosa* were bell-shaped. These relationships predict highly variable "anti-mutant" AUC/MIC ratios. These "anti-mutant" ratios can be achieved at clinically attainable AUC/MICs for *E. coli*, but not *K. pneumoniae* and *P. aeruginosa*.