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ePoster Viewing

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

Strain-specific concentration-resistance relationships with ciprofloxacin-exposed *Pseudomonas aeruginosa*: is it possible to predict the enrichment of resistant mutants if the same bacterial species?

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Objectives. To compare the ratios of the 24-hour area under the concentration-time curve (AUC) to the MIC or the mutant prevention concentration (MPC) as predictors of the emergence of bacterial resistance, the pharmacodynamics of ciprofloxacin against *P. aeruginosa* were studied in an *in vitro* model that simulates human pharmacokinetics.

Methods. Pharmacokinetic profiles that mimic b.i.d. ciprofloxacin administration were simulated for three consecutive days. To provide antibiotic concentrations within and out of the mutant selection window, the simulated treatments of each of four ciprofloxacin-susceptible clinical isolates of *P. aeruginosa* (MPC/MIC ratios from 11.2 to 32) were designed over a 100-200-fold range of the AUC/MIC ratio. The amplification 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 *P. aeruginosa* susceptibility were examined by daily MIC determinations.

Results. With each organism, mutants of *P. aeruginosa* resistant to 2× - 16×MIC of ciprofloxacin were enriched in a concentration-dependent pattern: weak or little enrichment at the relatively low and high antibiotic concentrations in contrast to pronounced enrichment that was accompanied by concomitant loss in susceptibility at the intermediate concentrations. Regardless of the level of resistance, both AUC/MIC and AUC/MPC relationships with the $AUBC_M$ were bell-shaped. The respective curves were stratified, more with AUC/MPC than AUC/MIC. Therefore, the “anti-mutant” AUC/MPCs (from 7 to 204 h - a 30-fold difference) appeared to be more variable than “anti-mutant” AUC/MICs (from 223 to 1100 h -a 5-fold difference). Despite more strain-specific AUC/MPC-resistance relationships compared with the respective AUC/MIC relationships, similar correlations between AUC/MPC or AUC/MIC and $AUBC_M$ (*r*^2 0.65 and 0.75, respectively) were established using combined data obtained with all four organisms.

Conclusions. This study suggests a more pronounced strain specificity of the "anti-mutant" AUC/MPC ratio for *P. aeruginosa* compared with AUC/MICs.