

Session: P055 PK/PD in preclinical models

**Category: 5b. Pharmacokinetics/pharmacodynamics of antibacterial drugs & therapeutic drug monitoring**

24 April 2017, 12:30 - 13:30  
P1204

**Concentration-resistance relationships with *Staphylococcus aureus* exposed to linezolid in an in-vitro dynamic model**

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**Background:** Antibiotic concentration relationships with the selection of resistant mutants (RMs) of Gram-positive and Gram-negative pathogens have been shown useful in predicting “anti-mutant” fluoroquinolone dosing. To delineate relationships between the enrichment of linezolid-resistant *S. aureus* and the ratio of 24-hour area under the concentration-time curve (AUC) to the MIC (AUC/MIC), linezolid pharmacokinetics were simulated in an *in vitro* dynamic model. Given the low mutation frequency exhibited by *S. aureus* and, therefore, the possible lack of spontaneous RMs in the starting inoculum, a mixed inoculum of linezolid-susceptible cells and previously selected RMs was used.

**Material/methods:** Three methicillin-resistant *S. aureus* strains susceptible to linezolid (MIC 2 µg/ml) were used in the study: two clinical isolates 479, 688 and a well-characterized strain Mu50 (ATCC 700699). Their RMs (MIC 8 µg/ml) were selected respectively after the 7th (RM7), 23rd (RM23) and 28th (RM28) passage of the parent strains. The elevated linezolid MICs with RM7, RM23 and RM28 were stable after 20 passages on antibiotic-free plates. The presence of RM7, RM23 and RM28 in the mixture with the parent strains (10<sup>2</sup>:10<sup>10</sup>) did not shift the mutant prevention concentrations (MPCs) of linezolid against *S. aureus* 479 (5 µg/ml), *S. aureus* 688 (6 µg/ml) and *S. aureus* ATCC 700699 (10 µg/ml). Mixed inocula at the same ratio of RM to parent strain were used in simulated five-day treatments with twice daily linezolid over a 32-fold range of the AUC/MIC ratio that provided antibiotic concentrations below the MIC, between the MIC and MPC and above the MPC. The amplification of RMs was monitored by plating on media with 2×, 4×, 8×MIC of linezolid. Time courses of resistant mutants were characterized by the area under the RM concentration – time curve (AUBC<sub>M</sub>).

**Results:** With each *S. aureus* strain, mutants resistant to 2×MIC of linezolid were enriched at the AUC/MIC ratios of 30 and 60 h. The selection of mutants resistant to 4× and 8×MIC of linezolid was less pronounced. Minor if any RM enrichment occurred at the lower (7.5 and 15 h) and higher (120 and 240 h) AUC/MIC ratios. AUBC<sub>M</sub> versus AUC/MIC and AUC/MPC curves were bell-shaped and strain-independent ( $r^2$  0.91 and 0.79, respectively). At least with the two clinical *S. aureus* strains (479 and 688) clinically attainable linezolid exposure may be sufficient to restrict the emergence of resistant *S. aureus*.

**Conclusions:** These findings indicate that the amplification of *S. aureus* RMs is AUC/MIC- and AUC/MPC-dependent. Bell-shaped patterns of the AUBC<sub>M</sub>-AUC/MIC or -AUC/MPC relationships support the mutant selection window hypothesis as applied to linezolid-exposed *S. aureus*.