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The Antibacterial Effect (ABE) of Ceftolozane (TOZ)/Tazobactam (TAZ) plus Amikacin (AMI) Against Pseudomonas aeruginosa (PA) Using Simulated Human Dosing

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Background: Combination antimicrobial chemotherapy is widely used as both empiric and definitive therapy to treat PA. Ceftolozane/tazobactam (TOZ/TAZ) has been recently approved for clinical use in Europe and is noteworthy for its potency *in vitro* against PA - including many multi-drug resistant strains. With many anti-pseudomonal antibiotics emergence of resistance (EoR) is a significant issue and the risk may be reduced by use of combination chemotherapy. We used an *in vitro* pharmacokinetic model (IVPKM) to simulate human serum pharmacokinetics of TOL/TAZ plus AMI and measured the effect on three strains of PA over 7 days.

Material/methods: A one compartment IVPKM was used to simulate drug serum concentration associated with 2g TOL/1g TAZ (Cmax 112/32mg/L; TOL t½ 2.5h, TAZ t½) alone and plus AMI 15mg/kg (OD Cmax 50mg/L; BD Cmax 25mg/L, t½ 2.5h). Dosing of TOL/TAZ was q8hly for 7 days and AMI q24hly or q12hly for 7 days. Three strains of PA (x2 AmpC and x1 AmpC plus OprD) were used TOL/TAZ MICs 2-4mg/L, AMI MIC 2-4mg/L. The inoculum was 10^6 CFU/ml and simulations were performed in triplicate. ABE was measured by log change in viable count and area-under-the-bacterial-kill curve (AUBKC) over 168h. EoR was assessed by changes in population analysis profiles on x2, x4 and x8MIC plates 24hly over 7 days.

Results: The MICs to TOL/TAZ (4mg/L) were on the EUCAST clinical breakpoint for 2/3 PA strains tested (strain 3 MIC 2mg/L). For the TOL/TAZ dose simulation viable counts were reduced by >4 log by 4-6h; addition of AMI resulted in >4 log reduction in bacterial load by 2h. Regrowth occurred with TOL/TAZ alone usually by 24-72h (2-4log10); however, addition of AMI resulted in delayed regrowth (2 strains) and less regrowth (1 strain). The TOL/TAZ+AMI, OD or BD dosing regimens had the same ABE. Comparison of $AUBKC_{24}$ and $AUBKC_{168}$ indicated greater ABE for TOL/TAZ+AMI compared to TOL/TAZ alone ($p<0.05$). There was no EoR to TOL/TAZ (growth on MICx4 plates) with any simulation with 2 strains. Growth was noted with one strain with TOL/TAZ + AMI simulations (AMI MIC x2plates, TOL/TAZ and AMI MIC 4mg/L).

Conclusions: TOL/TAZ plus AMI produced more rapid reduction of bacterial load compared to TOL/TAZ alone initially and delayed or reduced regrowth. Overall, ABE was improved by the addition of AMI. EoR was not a major feature with any of the dosing regimens simulated.