Dose Optimization of Antibiotic Combinations Using Fractional Inhibitory Concentration Kinetics in Resistant Bacteria

V. D. Sharma¹, M. Chaudhary²
¹University of Florida, ²Venus Remedies Limited

Purpose
Rising incidence of antibacterial resistance (ABR) against both gram positive (Staphylococcus aureus) and negative (extended spectrum beta lactamases; ESBL producing Escherichia coli) bacteria have resulted in treatment failures and death. The problem is further compounded by limited choices of available antibiotics and limited new antibiotic discoveries. One approach to tackle ABR is the optimized use of antibiotic combinations with careful examination of pharmacokinetics (PK)/pharmacodynamics (PD) and utilization of modeling to understand PK/PD relationships. The present study has evaluated PK/PD drivers of efficacy based on fractional inhibitory concentrations (FICs) kinetics and developed a semi-mechanistic model for dose recommendation.

Methods
The fixed dose combinations (FDCs) of Vancomycin/Ceftriaxone (2/1) and Ceftriaxone/Sulbactam (2/1) were evaluated against Methicillin resistant S. aureus and E. coli ESBL strains respectively. One compartment in-vitro system was used (dose escalation/fractionation studies and dose-response curve [DRC]) and FIC-time curves were analyzed. Changes in bacterial counts were correlated with PK/PD indices (based on FIC–time curve/combined minimum inhibitory concentrations [MICcomb]) including %T>MICcomb, AUCcomb/MICcomb, Cmax/MICcomb, %T>FIC (Figure-1). In-silico PK/PD modeling (adjusted for net bacterial growth during antibiotic exposure) was done for dose optimization using the best PK/PD driver (r² values > 0.9/sigmoidicity factor [γ] <15) of efficacy. Monte-Carlo simulations (n=1000) were also performed to estimates clinical breakpoints of both FDCs using 60-70%>MICcomb (minimum inhibitory concentration) and AUCcomb/MICcomb>400 as a probability-of-target attainment over a range of MICs (1-64 μg/mL).

Results
The PK/PD model incorporating %T>MICcomb (r² > 0.9, γ~2), followed by AUCcomb/MICcomb (r² > 0.9, γ~10) showed good predictability for both FDCs. Using %T>MICcomb as PK/PD driver, the predicted values of bacterial count in dose exposure studies (clinically relevant exposures of 50x and 100x MIC) showed r² > 0.9 and experimental data points were within 95% confidence interval (CI) of the modeled data. The experimental data points in optimized dose fractionation (twice daily, BD) studies were also within 95% CI of modeled data suggesting model robustness. In addition, sigmoidal DRC of optimized BD regimens showed r²> 0.9 allowing predictive dose adjustments for FDCs. Based on the stochastic simulation results, the strains corresponding to the MIC of ≤ 8, 8-16, ≥ 32 μg/mL were susceptible, intermediate and resistant, respectively to the FDC of ceftriaxone/sulbactam (2/1); whereas for ceftriaxone/vancomycin (2/1), the strains corresponding to the MIC of ≤ 4, 8-16, ≥ 32 μg/mL were susceptible, intermediate and resistant, respectively (Figure-2).

Conclusion
The developed semi-mechanistic model based on FIC kinetics might provide initial map for FDC antibiotics dose-optimization.