O583

Abstract (oral session)

Semi-mechanistic pharmacokinetic-pharmacodynamic (PK-PD) modelling of linezolid and vancomycin against Staphylococcus aureus using an in vitro dynamic system

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Objective: Evaluate the ability of semi-mechanistic PK-PD models with growth inhibition for linezolid and death stimulation for vancomycin to describe CFU versus-time profiles using an in vitro dynamic system. Methods: Eight strains of Staphylococcus aureus were tested at 3 initial inocula (5.105, 107and 108) in a Mueller-Hinton broth. The in-vitro dynamic system was set to mimic unbound concentrations versus time profiles of the antibiotics corresponding 4 consecutive dosing of 600mg/12h for linezolid and 1000mg/12h for vancomycin with respective elimination half-lives fixed at 7h and 6h. CFU and antibiotic concentrations were measured over a 48h duration. Experiments were run in duplicate and data were analyzed using non-linear mixed effect model (population approach), the MC-PEM algorithm in the parallelized S-ADAPT software program version (1.57) and the S-ADAPT-TRAN interface. Results: An initial decay of CFU with time followed by re-growth was observed with both antibiotics. Yet the initial decay was more rapid and extensive, and re-growth was observed earlier with vancomycin (< 12h) than with linezolid (>24h). These data were adequately fitted using a model with exponential growth for CFU leading to a plateau in the absence of antibiotics, with the addition of saturable (Emax) bacteria growth inhibition for linezolid or death stimulation for vancomycin. The presence of two sub-populations, one susceptible (S) and one resistant (R) was considered to explain re-growth with time. No inoculum effect was observed. A range of concentrations leading to R bacteria selection could be defined as the model mutant selection window (MMSW), as well as a range of concentrations effective on both S and R subpopulations defined as the model mutant effective eradication window (MMEEW). Conclusion: Semi-mechanistic PK-PD models with two sub-populations were successfully developed to describe the bacteriostatic and bactericidal activities of linezolid and vancomycin, respectively, with re-growth over time observed in vitro, and secondary parameters were derived to facilitate results interpretation.