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Poster Session VI
PK/PD of antibiotics against Gram-positives

SEMI-MECHANISTIC PK/PD MODELLING OF DRUG INTERACTIONS BETWEEN VANCOMYCIN OR LINEZOLID COMBINED WITH MEROPENEM AGAINST STAPHYLOCOCCUS AUREUS.

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Objectives: Drug interactions between antibiotics can be beneficial (addition, synergism) or harmful (antagonism) in nature. We previously studied vancomycin (VAN) or linezolid (LZD) combined with meropenem (MER) against *S. aureus* ATCC 29213 by *in vitro* time-kill curve (TKC) experiments and found an additive/indifferent (VAN-MER) or antagonistic (LZD-MER) interaction. The objective of the present study was to develop a semi-mechanistic PK/PD-model taking into account the different mechanisms of action of VAN, LZD and MER to provide a predictive tool for the development of rational therapeutic regimen of these clinically relevant drugs.

Methods: A simplified bacterial life-cycle (Bulitta et al. 2009) served as the core of the PK/PD model. Three different bacterial states were defined: Growing bacteria 'GRO' transitioned into the replicating state 'REP' in which doubling occurred and subsequently transferred back into 'GRO'. Persistent, drug-unsusceptible bacteria 'PER' were stimulated in 'REP'. Different ways of implementation of the drug effects were assessed (e.g. inhibition of growth, enhancement of death, inhibition of transition from 'GRO' to 'REP' and impaired doubling). Parameter estimation and prediction of the TKCs was performed in 'R' (R™, R Core Team, Vienna, Version 3.0.2). The final PK/PD model was challenged by the prediction of published PD interactions with similar underlying mechanisms.

Results: All parameters were precisely estimated simultaneously. Drug effects were implemented by inhibitory sigmoidal Emax models on the respective turnover rates: MER (EC50(t=0): 0.033 mg/L) and VAN (EC50(t=0): 0.49 mg/L), as cell-wall antibiotics, impaired successful doubling in 'REP' and transition back to 'GRO'. MER fully inhibited successful doubling while VAN only reduced successful doubling by 69.2% (CI: 67.2-71.2%). Furthermore, MER stimulated persistent, drug-unsusceptible bacteria.

LZD (EC50: 0.60 mg/L), as a protein synthesis inhibitor, inhibited transition of the bacteria into the replicating state 'REP'. Thus, bacteria were growth-arrested in 'GRO', and only a basal, replication-independent death of bacteria occurred. When MER was combined with LZD, growth-arrested bacteria were protected from the effect of MER, explaining the observed antagonism between both antibiotics.

Regrowth in TKCs occurring at concentrations of up to 2x MIC (MER) or up to 1.5x MIC (VAN) was successfully dissected into regrowth due to drug degradation (MER) and/or adaption (MER and VAN). Finally, the PK/PD model was evaluated by successfully predicting published TKC studies describing interactions between LZD-VAN, ampicillin-chloramphenicol and penicillin-erythromycin.

Conclusion: Our semi-mechanistic PK/PD model accurately predicted individual drug effects and drug interactions between VAN, LZD and MER. The PK/PD model is applicable to assess time-kill experiments taking into account the mechanism of action of the investigated drugs and to generate hypotheses for further experiments including *in vivo* studies. Extension of the PK/PD model to further drug classes with different mechanisms of action would be desirable.