eP001
ePoster Session
PK/PD to improve treatment of critically ill patients

Population probability of target attainment of colistin at different levels of renal function against *Pseudomonas aeruginosa* and *Acinetobacter baumannii* in Europe

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Objectives: Pharmacodynamic evaluation of anti-infective agents via Monte Carlo simulation (MCS) and organism specific MIC distribution is a useful approach to characterize the target attainment of empiric dosing regimens. The aim of this study was to establish the population probability of target attainment (PTA) of starter Colistin (CST) dosing regimens derived using the Garonzik et al. clinical equations for the treatment of critically ill patients with pulmonary infections in Europe.

Methods: Pharmacokinetic model of CST established in critically ill patients and EUCAST MIC distributions of *Pseudomonas aeruginosa and Acinetobacter baumanii* isolates in Europe were used in this analysis. Free concentrations of CST were calculated using a non-linear protein binding model. Doses up to 300 mg CST base activity per day were evaluated for population PTA with MCS (n=5000) at different levels of renal function for the MIC ranges of 0.0625 to 8 mg/L. Cumulative Fraction of Response (CFR) was calculated for each regimen targeting the $\int$AUC/MIC ratios necessary to achieve a killing of 1 and 2 $\log_{10}$ CFU derived from neutropenic mouse lung infection models.

Results: Empiric dosing regimens suggested by the Garonzik equations are expected to achieve the CFR < 85% for the killing of 1 and the CFR < 60% for the killing of 2 $\log_{10}$ CFU against both organisms at all levels of kidney function from 20 to 120 ml/min. When the CFRs were compared for the two organisms at 20 ml/min renal function intervals, an average of 7.7% and a 23.9% higher success rate was observed against *Acinetobacter baumanii* at the kill targets evaluated. The MCS also showed that these clinical equations based dosing recommendations with the suggested maximum daily dose of 300 mg CST base activity result in a sharp fall of the population PTAs empirically for patients in the normal renal function category. The magnitude of this decline was realized by a difference of up to -32% in CFRs at normal renal function as compared to mild renal impairment.

Conclusion: We conclude that for the treatment of serious *Pseudomonas aeruginosa* and *Acinetobacter baumanii* lung infections to achieve the killing of 1 and 2 $\log_{10}$ CFU, the dosing approaches based on the Garonzik equations provide suboptimal population PTAs, especially in patients with normal renal function. To improve target attainment of CST for the treatment of critically ill patients, the use of alternative dosing approaches allowing for higher daily doses, or applying combination therapy should be considered. A careful evaluation of the balance between the risk of toxicity and expected clinical benefit must be considered before implementation of such alternative dosing strategies.