P1244
Paper Poster Session
PK/PD of agents against Gram-negatives

Emergence of ceftazidime-resistant Pseudomonas aeruginosa during exposure to high concentrations of ceftazidime in vitro and in vivo

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Background: *Pseudomonas aeruginosa* exposed to ceftazidime *in vitro* can survive and become resistant, even when concentrations exceed the MIC during the entire dosing interval (T>MIC=100%). Clinical studies have shown emergence of secondary resistance during ceftazidime treatment, but it is unclear whether this was related to the extent of exposure to ceftazidime. This study aimed to investigate the relationship between exposure to ceftazidime and emergence of resistant *P. aeruginosa* strains during ceftazidime treatment both *in vitro* and in ICU patients.

Material/methods: Development of resistance was followed *in vitro* in chemostat cultures of wild type strain *P. aeruginosa* ATCC27853 subjected to three ceftazidime doses producing concentration-time profiles modelling the 5, 50 and 95 percentiles of plasma concentrations after a 1000mg loading dose, followed by continuous infusion of 3000mg/24h. These profiles were simulated using non-linear mixed effects modelling (NONMEM) based on a published population pharmacokinetic model for ceftazidime in critically ill patients. The chemostat cultures were sampled every 24h for 7 days for cellular parameters and MIC measurements. In parallel, a prospective observational study was conducted in ICU patients treated with ceftazidime. Ceftazidime plasma concentrations were determined and clinical and surveillance cultures positive for *Pseudomonas aeruginosa* were collected for ceftazidime MIC measurement. Plasma concentrations were analyzed by NONMEM to calculate the exposure to ceftazidime, expressed as mean area under the plasma concentration-time curve (AUC_{0-24}) over the period of MIC change and as AUC_{0-72}.

Results: *In vitro*, the bacterial cell density of the culture decreased by a factor 100-10.000 within the first 3 days of simulated treatment and the MIC increased by 5-7 two-fold dilution steps (Figure). The most rapid increase occurred at the median concentration, the lowest concentration yielded a smaller and slower increase in MIC. The cells exposed to the highest concentration were the last to show an increased MIC, but the final MIC values were the highest. Thirty-nine ICU patients were included for the development of the population pharmacokinetic model. Consecutive *P. aeruginosa* isolates, separated by at least 72h, were available from 6 of these patients. From one patient with a relatively

high $AUC_{0\text{-}72}$, isolates showed an increase in MIC from 2 to >256 mg/L. For the other 5 patients, no change in MIC was observed.

Conclusions: *In vitro*, the emergence of resistance to ceftazidime occurred within 3 days irrespective of dose. Although only a limited number of patients showed consecutive *P. aeruginosa* positive cultures, emergence of resistance during therapy was also observed in one patient. Inclusion of patients is still ongoing.