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Paper Poster Session

PK/PD of agents against Gram-negatives

Antibacterial activity of human simulated epithelial lining fluid concentrations of amikacin inhale alone and in combination with meropenem against *Acinetobacter baumannii*

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Background: *Acinetobacter baumannii* (ACBN) is an increasingly frequent, multidrug resistant (MDR) organism causing pneumonia in the critically ill ventilated patients. Due to its MDR profile and reduced penetration of parenteral therapies, this organism has been associated with high mortality. Therefore, alternative delivery techniques to achieve high bronchopulmonary concentrations are of increasing interest. Amikacin Inhale (BAY41-6551), a unique drug–device combination of a specially formulated Amikacin Inhalation Solution and a Pulmonary Drug Delivery System device (AMK-I), which achieves peak epithelial lining fluid (ELF) concentration of ~5000 mg/L with minimal systemic exposure. We aimed to describe the *in vitro* PD profile of human-simulated ELF exposure of AMK-I as monotherapy and as an adjunct to meropenem (MER) against ACBN with increasing AMK MICs.

Material/methods: The efficacy of simulated ELF concentrations of AMK-I 400 mg q12h as monotherapy for 24h and in combination with intravenous MER 2g q8h for 72h was evaluated in an *in vitro* PD model. Five clinical isolates of ACBN with AMK/MER MICs of 2–512/2–64 mg/L were utilized. Efficacy was assessed by comparing the area under bacterial killing curves. Repeated MICs were measured to detect the development of resistance.

Results: The mean \pm SD inoculum 0h bacterial density was $6.6 \pm 0.2 \log_{10}$ CFU/mL. Control groups reached counts of $7.7 \pm 0.4 \log_{10}$ CFU/mL by the end of experiments. MER monotherapy was effective only against ACBN with a MIC of 2 mg/L but not against ACBN with a MIC of 64 mg/L. AMK-I monotherapy rapidly achieved and sustained bactericidal activity below the limit of detection (LOD, $1.7 \log_{10}$ CFU/mL) over 24h for the isolates with AMK MIC 2, 64 and 128, while isolates with MICs of 256 and 512 mg/L demonstrated initial reductions in bacterial density, regrowth was observed at 24h. The combination of AMK-I and MER produced similar rapid and sustainable bactericidal activity against ACBN with AMK MICs of ≤ 128 , meanwhile reducing the initial bacterial counts for MICs of 256 and 512mg/L; however, regrowth with increased MICs was noted over the 48–72h treatment period.

Conclusions: AMK-I monotherapy showed bactericidal activity against isolates with AMK MICs ≤ 128 mg/L, whereas MER was bactericidal only against isolate with a MIC of 2 mg/L. AMK-I plus MER achieved rapid and sustained efficacy for 72h when AMK MICs ≤ 128 , while the combination enhanced the duration of effect over monotherapy for organisms with MICs 256 and 512 mg/L. These data support the development of AMK-I as an adjunct for the treatment of pneumonia caused by ACBN.