Unconventional daptomycin therapy for the treatment of Klebsiella pneumoniae, producing carbapenemase (KPC)

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Background: *Klebsiella pneumoniae* producing carbapenemase (KPC) causes serious infections in debilitated and immunocompromised patients, being associated with prolonged hospital stay and increased mortality rates ranging from 25% to 70%. This scenario is worsening with the identification of KPCs showing discrepancy between genotype and phenotype and limited therapeutic options (colistin and tigecycline), not always effective. Daptomycin (DAP) is a cyclic anionic lipopeptide antibiotic approved by the FDA in 2003 for use in a wide variety of *S. aureus* infections. The mechanism of action of DAP involves the disruption of cytoplasmic membrane function leading to its depolarization and causing cell death

Material/methods: The KPCs strains were obtained from clinical sources; susceptibility testing to DAP and meropenem (MER) were performed by E-test and broth dilution. Identification of KPC was determined by the Hodge Test and PCR. Bactericidal synergy assays for DAP and MER were performed using MH broth with 50 µg/mL Ca2+ DAP and MER alone and in combination. Infection and treatment of *G. mellonella* larvae: worms were infected (inoculated) with the corresponding live KPCs strains (1.5×10^6 CFU), treated at 2, 24 and 48 hours post-inoculation with doses of DAP (10 mg/kg) and/or MER (10mg/kg). PK/PD model was used for simulating one-compartment antibiotic exposures of single MER and combination MER/DAP antibiotic therapy with regimens (i) MER 1000 mg every 8 hours (targeted maximum free drug concentration [fCmax], 110 mg/L; half-life, 1 h) and DAP 10 mg/kg every 24 hours ([fCmax], 11.3 mg/L ; half-life, 8 h)

Results: In-vitro experiments showed that DAP (10 µg/ml) or MER (6 µg/ml) administered alone did not show any demonstrated bactericidal effects. In contrast, when administered together, the combination DAP/MER was synergistic as demonstrated by cell killing at 24 h ≥ 4 log CFU vs. single agents and the initial inoculum. KPC-injected worm groups untreated (PBS) or single-drug treated displayed very low survival rates (≤ 20-10%, days 11-14); DAP/MER combination resulted in survival rates of 90-80% at days 8-9. MER at human simulated doses was evaluated alone and in combination with DAP. MER was highly active in the first 3 doses up to 24h, but failed to suppress significant growth thereafter. Consistently, KPC cultured from the 48h time point with MER alone treatment resulted in a 64-fold less susceptible organism (MER MIC 32 µg/ml versus 0.5 µg/ml prior to the model). MER/DAP combination resulted in a faster time-to-kill to the limit of detection (6 h vs 24 h with MER alone) and significantly lower bacterial burden at the end of treatment (2.5 ± 0.4 vs 6.3 ± 0.2 log CFU/ml, respectively; p=0.007).

Conclusions: These results indicate that DAP/MER combination may have a major impact as an anti-infective alternative by a molecular mechanism under investigation