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

Pharmacodynamics of Cefepime and Tazobactam against carbapenemase positive strains in a neutropenic mouse model

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Background: Cefepime (PM), a so-called fourth generation cephalosporin, retains activity against AmpC producing isolates. However, a growing number of extended-spectrum beta-lactamase (ESBL) and KPC and other carbapenemase producing Enterobacteriaceae compromise the drug. Tazobactam (TZ) is a beta-lactamase inhibitor and has been shown to restore activity of PM in ESBL producing strains. Here we explore the potential of TZ to inhibit KPC and CMY harbouring strains and the exposures required to do so.

Material/methods: *Klebsiella pneumoniae* (no H521 and J124, both harbouring KPC) and *E. coli* M50 (harbouring CMY) isolates with MICs of ≥32mg/L against PM were used in all experiments. MICs in the presence of TZ were determined at various concentrations of TZ. Swiss neutropenic mice were infected 2 h prior to treatment intranasally. Pharmacokinetics of TZ and PM were determined in separate experiments. They were treated q2h with a fixed dose of PM effective against susceptible strains and clinically achievable exposures in combination with TZ for 25h in full dose fractionation experiments (TZ given q2, q4, q6, q12 or q24h in various doses) and cfu counts were subsequently determined. The Hill model with variable slope was fit to the data using Graphpad Prism 6.0 (San Diego, Ca). The static and 1logdrop Pharmacodynamic Indices (PDIs) were determined from the model fit.

Results: MICs of CP/TZ were 16 mg/L or lower in the presence of 8 mg/L TZ. For all three strains significant killing was observed in vivo. The dose-fractionation studies indicated that the effect of TZ was primarily dependent on a time above threshold (%Time>Ct) rather than AUC, Cmax for each of the strains. The more frequent dosing regimen resulted in a superior effect compared to less frequent dosing for the same total daily dose. The value of Ct yielding the best model fit differed by strain from 0.25 to 8 mg/L, but %Time>Ct for stasis decreased significantly with increasing Ct. The mean (range) %Time>C0.25mg/L for stasis was 40.7 (21.9-51.7) and for a 1logdrop was 56.4 (47.0-64.0).

Conclusions: TZ shows significant activity in vivo and results in efficacy of PM in KPC and CMY harbouring strains. Activity of TZ was correlated to %Time>Ct. The %Time>Ct required for a 1log drop was 64 maximum and should be readily achievable in patients with a TZ dose of 1 gr TID as indicated by a recent Phase 1 study in Europe of WCK 4282, a combination of PM + TZ. The exposure-response relationships found here can serve as a basis for establishing the optimal dosing regimen in humans for PM combined with TZ.