P2128 The pharmacodynamic target of cefepime and its reduction at higher MICs

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Background: Cefepime is a cephalosporin belonging to the β-lactam class of antibiotics with activity against a wide range of Gram-negative bacteria, including Enterobacterales and P. aeruginosa. Despite its long term use, surprisingly few preclinical pharmacodynamic data are available. We evaluated the exposure response relationship of cefepime in the neutropenic lung and thigh model.

Materials/methods: A standard neutropenic thigh and lung model was used in CD-1 mice. A total of 29 Enterobacterales (E. coli, K. pneumoniae and E. cloacae; n=17 in the lung- and n=14 in the thigh model) and 10 P. aeruginosa strains (8 lung, 2 thigh) were used, including E.coli ATCC25922 and P. aeruginosa ATCC27853. Strains harboured a variety of beta-lactamase genes :TEM(-1, -84), SHV(-1, -11, -18), OXA-1, CTX-M(-1,-9,-14,-15,-25,-39), VIM, KPC-2, CMY-2, OprD*, Class A*, Class B*, AmpCcon, derepressed AmpC, or chromosomal AmpC. MICs of the strains varied from 0.031-256mg/L. Treatment with cefepime started 2 hours after infection with q2h dosing regimens that continued for 24 hours. Pharmacokinetics of cefepime in mice were determined earlier (AAC2017 61:1). Exposure response curves were constructed for each strain and the static, 1log – and 2log kill %T>MIC determined.

Results: In both the thigh and lung model all exposure-response curves followed a sigmoid pattern, reaching at least stasis. A 1logkill was reached for all except six strains. For Enterobacterales, the mean (range) %T>MIC required for stasis was 7.7 (0-44.6) and 7.4 (0-34.4) in the lung and thigh, respectively. For Pseudomonas this was 10.1 (1.6-26.2) and 20.2 (0-40.4) The low numbers prompted further analysis, and showed that strains with higher MICs required less %T>MIC for stasis and 1logkill and were 0 in some cases. A reasonable correlation was therefore found when 0.25x MIC was plotted against %T>0.25xMIC for all strains (see figure) rather than 1xMIC.

Conclusions: The %T>MIC stasis and 1logkill target of cefepime concurs with that of other cephalosporins for wild type strains. However, much less %T>MIC is required at higher MICs. These findings implicate that strains with elevated MICs due to beta-lactamases could be well treated if higher dosing regimens are used and should be explored for cefepime and other cephalosporins.