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P0256 Efficacy of 48-hour and 24-hour repeat dosing of fosfomycin in a dynamic bladder infection in vitro model

Iain Abbott*[1 2], Rixt Anna Wijma[2], Joseph Meletiadis[2 3], Anton Peleg[1], Johan Mouton[2]

[1]Alfred Hospital and Central Clinical School, Monash University, Department of Infectious Diseases, Melbourne, Australia, *[2]Erasmus Medical Centre, Department Medical Microbiology and Infectious Diseases, Research and Development Unit, Rotterdam, Netherlands*, *[3]Attikon University Hospital, Medical School, National and Kapodistrian University of Athens, Clinical Microbiology Laboratory, Athens, Greece*

Background: Urinary tract infections are a common indication for antibiotics. Oral fosfomycin remains one of the most active antibiotics for MDR-uropathogens. Despite clinical practice of administering repeat oral doses, limited data are available supporting such approaches. We performed pharmacodynamic profiling using a dynamic bladder-infection *in-vitro* model to assess the adequacy of administering a repeat dose (RD) of fosfomycin.

Materials/methods: A bladder-infection *in-vitro* model simulating urinary fosfomycin concentrations after gastrointestinal absorption of repeat 3g dosages was used with Mueller-Hinton broth supplemented with 25mg/L glucose-6-phosphate. Simulated *in-vitro* fosfomycin concentrations were validated by LC-MS/MS measurements. Eight-Enterobacteriaceae isolates that had repeatedly re-grown following a single dose (SD) of fosfomycin were tested (2 *E. coli*, 3 *E. cloacae*, 3 *K. pneumoniae*; baseline MIC 2–64 mg/L). Isolates were exposed to a RD of fosfomycin at 48h and, if re-growth occurred, re-tested with RD given at 24h. Pathogen kill and emergence of resistance was assessed for 72h after RD by quantitative cultures on drug-free and fosfomycin-containing Mueller-Hinton agar (64 mg/L, 512 mg/L).

Results: Observed *in-vitro* fosfomycin concentrations simulated the expected urinary exposures following each dose (average ±SD: T_{max} 3.7 ±0.8h, C_{max} 2565.2 ±375.9mg/L, $AUC_{0\text{-}24}$ 36298.3 ±5960.2mg.h/L)(see figure). *E. coli* isolates were killed following the 48h RD of fosfomycin (baseline MIC 16 and 64mg/L; HLR sub-population 0.0003 and 0.0002% after SD). Six-isolates that re-grew (3 *E. cloacae*, 3 *K. pneumoniae*) were re-tested with RD administered at 24h. Two *K. pneumoniae* isolates were killed (baseline MIC 2 and 4mg/L; HLR subpopulation 0.0001 and 0.0003% after SD). The remaining *K. pneumoniae* isolate (MIC 4mg/L; HLR subpopulation 0.002% after SD) and 3 *E. cloacae* isolates (MIC 32–64mg/L; HLR subpopulation 11.6–100% after SD) re-grew.

Conclusions: Repeat dosing of fosfomycin is most effective in *E. coli* isolates. Reducing the time to the second dose to 24h provided additional kill. The second dose of fosfomycin failed in half of tested isolates. Failure appears to be related to the emergent HLR subpopulation, selected for after the initial dose. These results demonstrate that a single repeat dose will not provide adequate treatment in all cases.

Uropathogen response (PD) and fosfomycin exposure (PK)