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Exposure-response relationships and emergence of resistance of fosfomycin against MDR Enterobacteriaceae in an in-vitro hollow fiber infection model

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Background: Due to declining antibiotic development and the increasing rate of resistance in bacteria, clinicians increasingly deploy old antibiotics to treat infections, such as fosfomycin. However, despite being available for more than 40 years, little information is known with respect to pharmacodynamic characteristics and optimal dosing. We employed the hollow fiber infection model (HFIM) to determine exposure response relationships of fosfomycin, including emergence of resistance

Material/methods: Fosfomycin dosing regimens were simulated *in vitro* using a two-compartment HFIM against 8 Enterobacteriaceae (3 *E.cloacae* (Eb), 2 *K.pneumoniae (*Kp*)*, 2 *E.coli* (Ec) and *1 C.freundii (*Cf*)*) with MICs varying from 1-16 mg/L in Mueller-Hinton broth containing G6P. An inoculum of 6.0 $\log_{10}$ CFU/ml was used and strains exposed to fosfomycin dosing regimens simulating human pharmacokinetics of 1.33gr q24h up to 8gr q8h over 96h. Concentrations of fosfomycin were determined using a bioassay in each experiment for validation. Samples for CFU counting were taken at regular intervals by plating on G6P containing media with and without fosfomycin at a concentration

of 16x MIC. MICs of resistant strains were reconfirmed. The CFU/mL were plotted against pharmacodynamic indices for the susceptible and the resistant subpopulations.

Results: During the first 12h all regimens showed a significant bactericidal effect with > 10E3 decline in CFU for all strains. After 24h of exposure there appeared to be differences in efficacy, that appeared to be correlated to the AUC/MIC ratio. An AUC/MIC ratio of >2200 was required for bactericidal effects of Cf and Ec, and >620 for Eb and no good relationship for Kp. Strains with MIC of >2 mg/L showed significant regrowth after 24h even at the highest dosing regimens. Regrowth was almost completely due to highly resistant (>16x the initial MIC) mutants and resistant strains had almost fully replaced the original strains after 96h. There was no strong correlation between exposure (AUC/MIC or T>MIC) and mutation frequency at 48h, 72h or 96h. There was a weak correlation between AUC/MIC and growth inhibition of the resistant subpopulation

Conclusions: Fosfomycin could be an alternative agent for treatment of infections caused by Enterobacteriaceae; however resistance appeared fast except for the most susceptible strains (1-2 mg/L MICs). Due to the fast emergence of resistance *in vitro* and the achievable concentrations *in vivo,* single drug therapy for systemic infections with fosfomycin is questionable.