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Pharmacodynamics of fosfomycin against extended spectrum beta lactamase and/or carbapenemase producing Enterobacteriaceae

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Background: The increase of antibiotic resistance in Gram-negative bacteria and unavailability of new antibiotics has increased the interest of the “old” antibiotic fosfomycin in the treatment of systemic infections. However the pharmacodynamics (PD) of this antibiotic are still largely unknown. We used time-kill assays (TKC) to assess the PD properties of fosfomycin against a collection of extended spectrum beta-lactamase (ESBL) and/or carbapenemase producing Enterobacteriaceae.

Material/methods: TKC were performed in *E.coli,* n=5, *K.pneumoniae,* n=4, *E.cloacae* n=4, *C.freundii* n=1 (MICs of 0.5 – 64 mg/L) at concentrations ranging from 0.125 up to 32 times the MIC. Samples were taken at T0,1,2,3,4,6,8,16 and 24h. At T0,8,16 and 24 samples from 0, 0.25, 2 and 16x MIC bottles were plated on MH plates containing fosfomycin at a concentration of 0 and 16x the MIC of the strain. Mutation frequency was calculated and viable bacterial counts (CFU/ml) were plotted versus time. The kill rate (log_{10}CFU/mL x h^{-1}) was determined by linear regression analysis for the time

interval of 0 until 6 hours. A sigmoidal *Emax* model with variable slope was used to fit the kill rate drug concentration data using Graphpad Prism 5.0.

Results: The mean log-linear growth rates in the drug-free control as determined over the first 6h were similar (0.51-0.57 log_{10}CFU/ml x h^{-1}), except for *C.freundii* (0.44) were it was a bit lower. In the Emax model no large differences in mean killing rates were observed. Only for *E.cloacae* it was a bit higher (0.66 vs. 0.54-0.56) for the other species. Also for the concentration needed to reach a 50% effect corrected for the MIC(EC50/MIC) the differences were small (0.29-0.44). In addition also the STASIS/MIC ratio was 1.5x higher for *E.coli* and *K.pneumoniae* as compared to *E.cloacae* and C. freundii indicating that a higher concentration is needed to reach a static effect. However the Hill coefficients were respectively 2-3x higher for *E.coli* and *C.freundii* compared to the other species indicating a stronger concentration dependent effect. For all strains a fast bactericidal effect within 6-8h was observed at a concentration of ≥4-8x MIC. Although after initial fast killing, regrowth started to occur from 6-8h onwards and full growth of resistant (sub)populations was observed. The mutation frequency increased with increasing concentrations and was often maximal at 16x the MIC in almost all strains were 80-100 % of the population was irreversibly mutated, with highly increased MIC value's.

Conclusions: Fosfomycin was bactericidal against all strains within 8 hours, However emergence of resistance was observed after 8 hours for all strains with growth reaching drug-free control levels. This limits the use of fosfomycin as a single drug therapy in serious infections. Further optimization of fosfomycin pharmacodynamics is required in order to increase efficacy against ESBL (+) pathogens