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In-vitro pharmacodynamics of fosfomycin against clinical isolates of carbapenem-resistant Klebsiella pneumoniae (CR-KP)

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Background: With the emergence of CR-KP worldwide, there has been renewed interest in once "forgotten" antibiotics, such as polymyxin B and fosfomycin. Intravenous fosfomycin, with doses indicated up to 8g infused over 4 hours given every 8 hour, has shown to be promising against multidrug-resistant (MDR) Gram-negative bacteria, particularly against MDR *Pseudomonas aeruginosa*. To date, there is limited pharmacodynamic data of intravenous fosfomycin against CR-KP. Our study evaluated the *in vitro* pharmacodynamics of fosfomycin against local CR-KP isolates.

Methods: Two molecularly-characterised clinical isolates of CR-KP [KP44 (urine) and KP215 (blood)] and a reference strain (ATCC13883) were tested. Both clinical isolates are extensively drug-resistant, remaining susceptible only to polymyxin B (KP44 and KP215) and tigecycline (KP44). KP44 harboured $bla_{CTXM-15}$, bla_{NDM-1}, with presence of efflux pumps. KP215 harboured $bla_{CTXM-15}$, bla_{CMY-4}, $bla_{OXA-181}$, with OmpK35 porin loss and efflux pumps. Fosfomycin MICs were determined according to CLSI agar dilution methods. *fos* genes were screened using PCR. The possible presence of fosfomycin-resistant subpopulations at baseline of 10^8CFU/mL was determined via population analysis profiles (PAP). 24h time-kill studies (TKS) (baseline inocula of 10^5CFU/mL) were conducted in duplicate to evaluate bacterial killing in relation to escalating fosfomycin concentrations (4-1024mg/L) in the presence of glucose-6-phosphate. The mean killing effect at 24h was characterised by an inhibitory sigmoid Emax model using the ADAPT 5 program.

Results: Fosfomycin MICs of ATCC 13883, KP44 and KP215 were 128mg/L, 16mg/L and 512mg/L respectively. No *fos* genes was detected in KP44 and KP215. In TKS, the majority of fosfomycin concentrations displayed gradual killing up to 8h before regrowth to 10^5-10^9 CFU/mL at 24h. Maximum

killing (≥99.9% reduction from baseline) was observed at 8h for ATCC13883, KP44, and KP215 at fosfomycin concentrations of ≥512mg/L, ≥64mg/L, and ≥512mg/L respectively. From the inhibitory sigmoid Emax model, model fits to the data were satisfactory, r^2 for ATCC13883, KP44 and KP215 were 0.937, 0.983 and 0.974 respectively. Fosfomycin exhibited concentration-independent killing. Baseline PAPs indicated heteroresistance in all isolates tested. Fosfomycin-resistant sub-population colonies grew on fosfomycin impregnated media, with concentrations up to 1024mg/L for ATCC13883, 256mg/L for KP44 and 2048mg/L for KP215; the proportion of bacterial colonies on these fosfomycin-containing plates were $1.5x10^{-5}$, $1.7x10^{-7}$, and $1.4x10^{-5}$ for ATCC13883, KP44 and KP215 respectively. These concentrations exceed the steady-state levels that can be achieved by current recommended maximum intravenous dosing regimens (8g every 8h, infused over 4 hours) (approximately 160mg/L).

Conclusions: The presence of fosfomycin heteroresistance in our tested isolates contributed to regrowth following 24h of fosfomycin exposure in TKS. Our findings suggested that there may be a risk of clinical failure with fosfomycin monotherapy against CR-KP, even those with “low” MICs of 16mg/L. Investigations of fosfomycin combination therapy may be warranted as a viable therapeutic alternative against CR-KP.