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O0727 Population pharmacokinetics and pharmacodynamics of fosfomycin in non-critically ill patients with bacteraemic urinary infections caused by multidrug-resistant Escherichia coli

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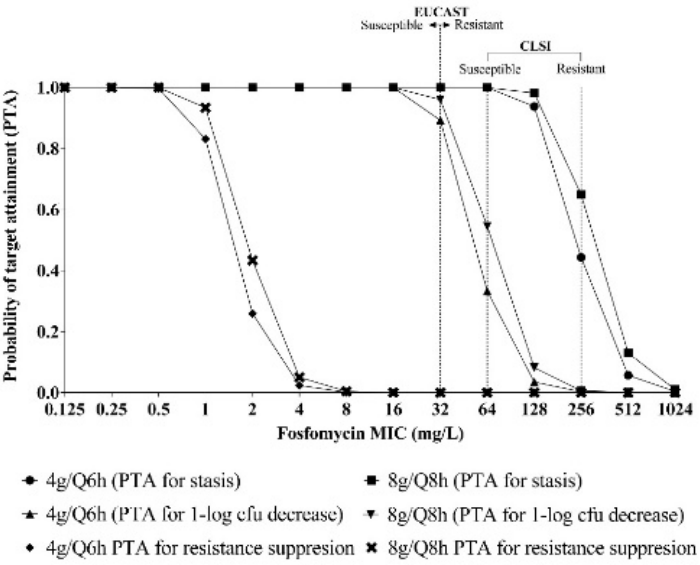
Background: Recent studies have shown that AUC:MIC is the relevant pharmacodynamic index for effect against multidrug-resistant gram-negative bacteria. Optimized dosing of fosfomycin has not yet been explored using these in vivo pharmacodynamic targets. The aim of the present study was to understand the variability of fosfomycin pharmacokinetics in patients with bacteraemic urinary tract infection (B-UTI), to identify optimal regimens that are based on pharmacodynamic targets and to study the adequacy of currently susceptibility breakpoints of CLSI and EUCAST for *Escherchia coli* clinical isolates.

Materials/methods: Sixteen patients with B-UTI due to multidrug-resistant *E. coli,* (FOREST clinical trial) received intravenous fosfomycin (4g/Q6h) and were analysed. Comparisons with previous fosfomycin pharmacokinetic studies were performed. A population two-compartment pharmacokinetic analysis was done, and Monte Carlo simulations (MCS) were performed using 4g/Q6h or 8g/Q8h. The probability of pharmacodynamic target attainment (PTA) was assessed over a range of MICs using as targets for *E. coli*: $AUC_{0\text{-}24}$/MIC of 19.3 for static effect, $AUC_{0\text{-}24}$/MIC of 87.5 for a 1-log drop in bacterial burden, and $AUC_{0\text{-}24}$/MIC of 3136 for resistance suppression.

Results: Fosfomycin concentrations were highly variable and similar to those observed in critically-ill patients (with comparable CrCl). MCS and PTA analysis (figure) did not show improvement by increasing fosfomycin dosing (4g/Q6h vs 8g/Q8h). At these dosages, success for decreasing 1-log bacterial burden was observed in 89-96% (EUCAST breakpoints) and 33-54% (CLSI breakpoints) of patients. No success was observed for bacterial resistance suppression with the current susceptibility breakpoints.

Conclusions: Fosfomycin concentrations are highly variable. Some of the variability is explained by renal impairment. The present work supports the use of 4g/Q6h as an effective regimen for the treatment of non-critically ill patients with bacteremic urinary infection caused by multidrug-resistant *E. coli* as higher dosages might increase toxicity but may not significantly increase efficacy. The current information may suggest the reappraisal of fosfomycin susceptibility breakpoints.


EUCAST
Susceptible
Resistant
CLSI
Susceptible
Resistant
Probability of target attainment (PTA)
1.0
0.8
0.6
0.4
0.2
0.0
0.125
0.25
0.5
1
2
4
8
16
32
64
128
256
512
1024
Fosfomycin MIC (mg/L)
4g/Q6h (PTA for stasis)
8g/Q8h (PTA for stasis)
4g/Q6h (PTA for 1-log cfu decrease)
8g/Q8h (PTA for 1-log cfu decrease)
4g/Q6h PTA for resistance suppresion
8g/Q8h PTA for resistance suppresion