Pharmacodynamic Activity of Fosfomycin versus Multidrug-Resistant (MDR) Genotypically Characterized Extended Spectrum β-lactamase (ESBL) - and/or Carbenapenem-Producing Escherichia coli using in Vitro Model


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ABSTRACT

Background: E. coli is the most common cause of urinary tract infections. E. coli are now frequently ESBL-producing and some isolates manifest both of these resistance phenotypes are commonly associated with isolates with MDR profiles. Fosfomycin (FOS) inhibits peptidoglycan synthesis in a mechanism distinct from β-lactams and is available orally for the treatment of urinary tract infections caused by E. coli. The pharmacodynamic (PD) profiles of FOS against isolates with resistance to carbapenems- and/or ESBL- characterised MDR ESB & –and/or carbenapenem-producing E. coli using an in vitro PD model.

Bacterial strains and culture conditions: The E. coli isolates were obtained from the Canadian Antimicrobial Resistance Network (CARN). The susceptibility to fosfomycin of Escherichia coli CTX-M-15 or CTX-M-14 genotypes and demonstrated a MDR phenotype with resistance to ceftriaxone, ciprofloxacin, TMP-SMX, gentamicin and chloralose. The carbapenem-producing E. coli isolates were KPC-2 or NDM-1 (n=1) producing strains with a MDR phenotype and await strains (MDR) 32 mg/l. The HPMV was inoculated with an inoculum of (1×10⁵ CFU/ml) and FOS was dosed once daily or hourly to achieve and maintain a concentration of 500 mg/ml for one hour and a concentration of 1000 mg/ml for the remainder of the 24-hour incubation period.

RESULTS

The uptake concentration was approximately 0.900 mg/ml, and the clinical isolate showed that this concentration was achieved through an initial rapid uptake and then a slower phase (0.06 mg/ml) of the 24-hour incubation period.

For pharmacodynamic studies, the minimum inhibitory concentration (MIC) values were determined by the CLSI-approved broth microdilution method. All MICs were reported in triplicate on separate plates.

The pharmacokinetic model used was the in vitro pharmacodynamic model. The pharmacokinetic parameters were estimated using the method of weighted nonlinear least squares regression. The model for each isolate was selected to be the final model that achieved a final goodness of fit (R²) ≤ 0.95 and the best fit was achieved using the same model for all isolates (MIC). Clinically achievable urinary concentrations were determined by interpolation of the uptake and elimination phase data.

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REFERENCES


