EFFICACY OF 48 HOUR & 24 HOUR REPEAT DOSING OF FOSFOMYCIN IN A DYNAMIC BLADDER INFECTION *IN VITRO* MODEL

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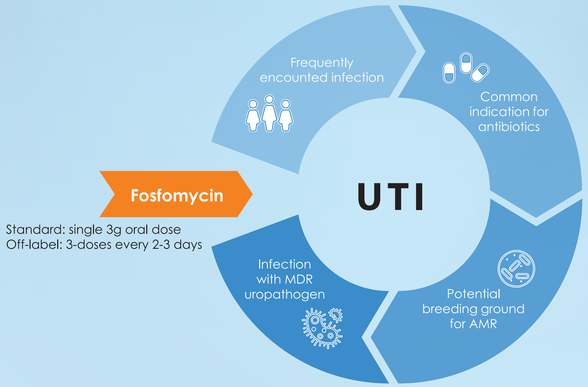
INTRODUCTION

Oral fosfomycin tromethamine remains one of the most active antibiotics for MDR-uropathogens.

Despite the common clinical practice of administering repeat doses of oral fosfomycin, limited data are available supporting such approaches.

We performed pharmacodynamic profiling using a dynamic bladder infection *in vitro* model.



METHODS

Pharmacokinetic simulation

Urinary fosfomycin concentrations were simulated following intestinal absorption, systemic circulation and urinary elimination.

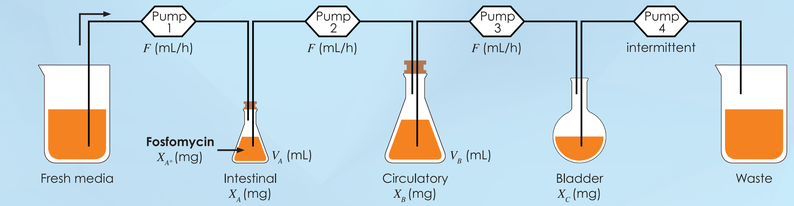
Dosing schedule

Isolates were exposed to a repeat 3g (equiv.) oral dose (RD) at 48h. Where regrowth occurred, isolates were re-tested with a RD given at 24h. The *in vitro* model ran for 72h after the RD.

Micobiological outcome

Pathogen kill and emergence of resistance was determined by quantitative cultures on drug-free and fosfomycin-containing Mueller-Hinton agar (32 mg/L, 512 mg/L).

Schematic diagram of oral fosfomycin distribution



Drug distribution equations

$$X_A = X_{A^*} \cdot e^{-(F/V_A)t} \qquad X_B = \frac{(F/V_A)\cdot X_{A^*}}{F/V_B - F/V_A} \cdot \left(e^{-(F/V_A)t} - e^{-(F/V_B)t}\right) \qquad X_C = X_{A^*} - X_A - X_B$$

Bladder infection *in vitro* model

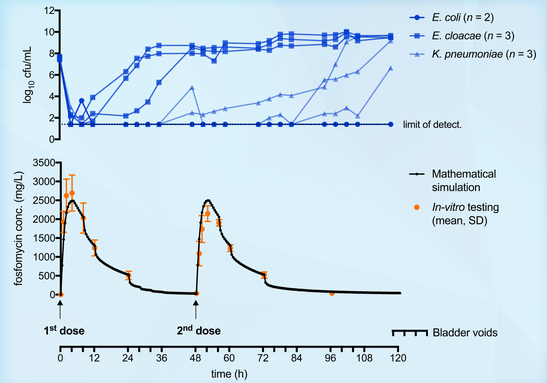
X_{A^*} – initial amount of fosfomycin (mg); X_A – fosfomycin in GI tract (mg); X_B – fosfomycin in systemic circulation (mg); X_C – fosfomycin in bladder (mg); t – time (h); V – volume (mL); F – flow rate (mL/h)

RESULTS

Species	Strain no.	Fosfomycin susceptibility		ESBL	Other oral antibiotic susceptibility (VITEK 2 AST-N344)					Dose response (Change in log10 cfu/mL; HLR %)					
		MIC (mg/L)	Interp.		AMC	CXM	CIP	NIT	SXT	Single dose		Repeat dose at 48h		Repeat dose at 24h	
E. coli	1231	16	S	Yes	R	R	R	R	R	+2.1	0.0004%	Killed		-	
	4757	64	R	Yes	R	R	R	S	S	+2.0	N.D.	Killed		-	
K. pneumoniae	6	4	S	Yes	R	R	R	nr	R	+1.9	0.002%	+1.8	0.0002%	+2.3	0.00004%
	55	4	S	Yes	R	R	S	nr	R	+2.6	0.0004%	+2.2	0.001%	Killed	
	31865	2	S	No	R	R	R	nr	R	+2.1	0.0001%	-0.9	0.003%	Killed	
E. cloacae	9	32	S	Yes	R	R	R	nr	R	+1.9	100%	+1.8	0.02%	+2.0	0.3%
	10	64	R	Yes	R	R	R	nr	R	+2.3	66.7%	+2.0	50.0%	+2.0	100%
	32	32	S	Yes	R	R	S	nr	R	+2.2	0.0008%	+2.0	100%	+1.7	0.01%

Fosfomycin MIC determined by agar dilution. Other oral antibiotic susceptibility testing performed by VITEK 2 (AST-N344, bioMérieux, France). Interpretation of MIC results based on EUCAST clinical breakpoints. ESBL phenotype determined by VITEK 2 advanced expert system. R – resistant; S – susceptible; I – intermediate; nr – not reported; AMC – amoxicillin-clavulanate; CXM – cefuroxime; CIP – ciprofloxacin; NIT – nitrofurantoin; SXT – trimethoprim-sulfamethoxazole; HLR; high-level resistance (fosfomycin MIC ≥ 512 mg/L); N.D. – not detected.

Repeat dose at 48-hours

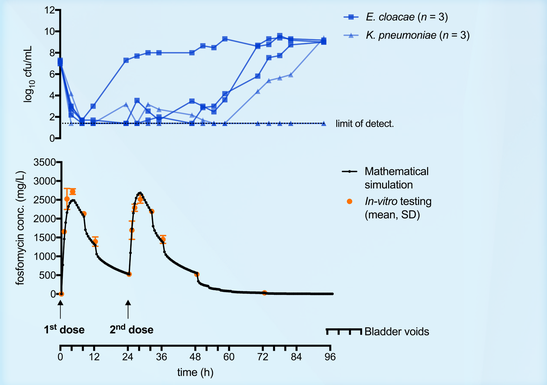


All isolates were exposed to a RD of fosfomycin at 48h.

Both *E. coli* isolates were killed.

Six-isolates re-grew (3 *E. cloacae*, 3 *K. pneumoniae*).

Repeat dose at 24-hours



Six-isolates then re-tested with a RD administered at 24h.

Two *K. pneumoniae* isolates were killed.

The remaining *K. pneumoniae* isolate, and 3 *E. cloacae* isolates all re-grew.

Observed *in vitro* fosfomycin concentrations closely matched the simulated values following each dose; T_{max} 3.7 ± 0.8 h; fC_{max} 2565.2 ± 375.9 mg/L; $fAUC_{0\text{-}24}$ 36298.3 ± 5960.2 mg.h/L

CONCLUSION

Repeat dosing of fosfomycin was most effective in the *E. coli* isolates.

Reducing the time to the second dose to 24h provided additional kill.

Failure appears to be related to the emergent HLR subpopulation, selected for after the initial dose.

Administration of a repeat dose will not provide adequate treatment in all cases.

Acknowledgements

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References

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