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In vivo assessment of pharmacodynamic (PD) effects of fosfomycin trometamol (FT) on beta-lactamase producing Gram-negative uropathogens

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Background: Fosfomycin shows good activity against both Gram-negative and Gram-positive uropathogens, though there are no accurate studies on its pharmacodynamic properties, except for a previous study in which we have demonstrated that fosfomycin trometamol (FT) has high *in vitro* bactericidal activity against Enterobacteriaceae and a long post-antibiotic effect (PAE) with efficacy tending to be concentration dependent (1).

The aim of this study was to further evaluate its PD properties *in vivo* against recently isolated Gram- uropathogens using an experimental model of intraperitoneal (IP) infection in non-neutropenic mice.

Material/methods: FT minimal inhibitory concentration (MIC) of recently isolated β-lactamase producing (βL+) *Escherichia coli*, *Proteus mirabilis and Klebsiella pneumoniae* was determined by broth microdilution, according to CLSI. Swiss Albino mice (25-29 g.) were IP injected with an infective inoculum of 100 to 1,000 median lethal doses. FT (dose range 50 - 800 mg/kg) was administered subcutaneously 1 hour after infection OD or BID on Day 1. FT plasma concentrations in mice were determined microbiologically.

Results: FT peak plasma concentrations ranged from 391 to 15 mg/l and were directly related to the administered dose.

Preliminary data on the antimicrobial efficacy of FT, expressed as mean EC_{25}, EC_{50}, EC_{75} or EC_{90} (mg/l) for animal survival, are shown in the Table.

Strains	MIC (mg/l)	EC_{25} (mg/l)		EC_{50} (mg/l)		EC_{75} (mg/l)		EC_{90} (mg/l)	
		OD	BID	OD	BID	OD	BID	OD	BID
E. coli	16	77.45	135.83	120.7	193.1	188.36	275.42	293.76	391.74
P. mirabilis	32-64	127.94	279.7	164.5	338.9	211.84	410.58	272.27	497.51
K. pneumoniae	8	88.88	196.24	114.1	291.4	146.32	434.21	187.76	647.14

Both EC_{50} and EC_{90} values observed with OD doses were significantly lower than BID doses for all the tested strains.

Conclusions: Mortality rates were higher with FT administered BID than OD. The *in vivo* bactericidal activity of FT was high with EC_{50} values ranging from 5 to 14xMIC and EC_{90} values ranging from 9 to 23xMIC for *P. mirabilis, E. coli and K. pneumoniae* respectively with OD dose. Our data show that an effective bactericidal action is assured by a concentration $\geq$ 8 x MIC, thus confirming the prevalent concentration-dependent activity of fosfomycin in this experimental model.

(1) Mazzei T, Cassetta MI, Fallani S, Arrigucci S, Novelli A. Pharmacokinetic and pharmacodynamic aspects of antimicrobial agents for the treatment of uncomplicated urinary tract infections. Int J Antimicrob Agents. 2006 Aug;28 Suppl 1:S35-41