Evaluation of the Antimicrobial Activity of Fosfomycin When Combined with Selected Antimicrobial Agents and Tested against Bacterial Isolates Using Checkerboard Methods

PR Rhomberg[1], JM Lindley[1], HS Sader[1], K Sweeney[2], EJ Ellis-Grosse[2], RK Flamm[1]

[1]JMI Laboratories, North Liberty, Iowa, USA

[2]Zavante Therapeutics, Inc. San Diego, California, USA

Background: ZTI-01 (fosfomycin; FOS) is an intravenous antibiotic under US development to treat cUTI. Unlike other classes, FOS covalently binds to MurA, a precursor in bacterial cell wall synthesis. FOS has broad *in vitro* activity against Gram-positive and -negative bacteria, including multidrug-resistant (MDR) organisms. Differing MOA antibiotic combinations are frequently employed to treat concerning MDRs. Optimal FOS combinations producing synergy (SYN) and lacking antagonism (ANT) warrant this investigation.

Methods: Forty strains were evaluated: 5 *Staphylococcus aureus* (SA), 5 *Enterococcus faecalis* (EF), 5 *Pseudomonas aeruginosa* (PSA), 5 *Acinetobacter baumannii* (ACB) and 20 enterics, including clinical and ATCC strains. Interaction between FOS (with 25 µg/mL glucose-6-phosphate) and up to 10 combination agents was investigated by checkerboard broth microdilution methods against each species/group from a total of 16 antimicrobial agents. Summary fractional inhibitory concentration (∑FIC) values were calculated for each FOS/agent combination at the minimum, maximum, and mean. ∑FIC was used to classify the combined activity as SYN (≤0.5), indifference (INDIF; >0.5 and <4) or ANT (≥4). Indeterminate (INDET) category was assigned when unable to determine combination effects.

Results: FOS showed no ANT, but showed SYN when combined with multiple agents against isolates from all 5 species/groups. Highest rates of SYN were seen when FOS was combined with piperacillin-tazobactam, cephalosporins, meropenem, or penicillin. Other agents showed SYN rates of 10.0% to 40.0% when combined with FOS. Among INDIF isolates, 17.7% had ∑FIC >1 and <4; 16.8% had ∑FIC =1 (additive); 65.5% had ∑FIC >0.5 and <1 (partial SYN).

Organism (no. tested)	Combination agents	No. of strains by interpretive category (% of total)			
		SYN	INDIF	ANT	INDET
SA (5)	10	18 (36.0)	29 (58.0)	0 (0.0)	3 (6.0)
EF (5)	7	7 (20.0)	27 (77.1)	0 (0.0)	1 (2.9)
PSA (5)	9	7 (15.6)	37 (82.2)	0 (0.0)	1 (2.2)
ACB (5)	8	13 (32.5)	21 (52.5)	0 (0.0)	6 (15.0)
Enteric (20)	10	65 (32.5)	112 (56.0)	0 (0.0)	23 (11.5)
All		110 (29.7)	226 (61.1)	0 (0.0)	34 (9.2)

Conclusions: Nearly 30% of all combinations with FOS were SYN (∑FIC ≤0.5) and 40% demonstrated partial SYN, which indicates combination therapy with FOS may be beneficial. Importantly, no ANT was observed with any of the FOS combinations.

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