Fosfomycin in vitro activity against bacteria with various mechanisms of resistance to other antibacterials from US hospitals

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Background: ZTI-01 (fosfomycin, FOS, for injection) is in US development for complicated urinary tract infections at a dosage of 6 grams every 8 hrs and is the sole member of the epoxide antibiotic class. The unique mode of action acts at an earlier step in cell wall synthesis inhibition compared to other agents. Therefore, FOS is unaffected by common resistance mechanisms found in Gram-negative (GN) and –positive (GP) bacteria.

Methods: Using current CLSI breakpoints for the oral agent (dosed at 3g), we determined FOS susceptibility (S) for recent resistant GN and GP clinical isolates, including vancomycin-resistant *Enterococcus faecium* (VREM) and *E. faecalis* (VREF); methicillin-R *Staphylococcus aureus* (MRSA) and MR coagulase negative staphylococci (MR-CoNS); *Escherichia coli* (EC) and *Klebsiella pneumoniae* (KPN) with an extended spectrum beta-lactamase phenotype (ESBL+) or were carbapenem R (CR); and *Pseudomonas aeruginosa* (PSA) non-S to ceftazidime (CAZ-NS) or to meropenem (MER-NS). The FOS MIC for all isolates was determined by reference agar dilution supplemented with 25 µg/mL glucose-6-phosphate. Isolates were collected from hospitalized patients in the US as part of the SENTRY surveillance program, 2013-2015.

Results:. The MIC range for 81 VREM was 32–>256 µg/mL, 63 isolates had an MIC ≤ 64µg/mL ($MIC_{50/90}$ 64/128 µg/mL). All 101 MRSA had an MIC ≤64 µg/mL ($MIC_{50/90}$ 4/8 µg/mL). Of 153 MR-CoNS, 72 had a MIC ≤64 µg/mL, 76 *S. saprophyticus* had MICs of 128 – >256 µg/mL, 1 *S. capitis* had an MIC=128 µg/mL, and 1 *S. hominis* had an MIC >256 µg/mL. For 49 EC with an ESBL phenotype, the $MIC_{50/90}$ were 0.5/4 µg/mL; 2 isolates had a MIC >256 µg/mL; and remaining isolates had MIC values ≤32 µg/mL. For 11 EC that were CR, 2 had a MIC >256 µg/mL; 9 had an MIC range of 0.5 – 32 µg/mL. Of 50 ESBL+ KPN, 49 had a MIC ≤64 µg/mL and 1 isolate MIC was >256 µg/mL; the $MIC_{50/90}$ were 4/16 µg/mL. For 17 CR-KPN, 16 had a MIC ≤64 µg/mL and 1 isolate had an MIC >256; the $MIC_{50/90}$ were 8/64 µg/mL. For 38 CAZ-NS PSA, 32 had a FOS MIC ≤64 µg/mL, 1 isolate had an MIC >256 µg/mL, and the $MIC_{50/90}$ were 64/128 µg/mL. For 42 MER-NS PSA, 34 had a MIC ≤64 µg/mL, 1 isolate had an MIC of >256 µg/mL, and the $MIC_{50/90}$ were 64/128 µg/mL.

Conclusion: FOS demonstrated potent activity against recent antibiotic R GN and GP isolates and was unaffected by R to other drug classes. Given the bioavailability limits of the current oral formulation, reassessing breakpoints will be warranted by the FDA for the IV formulation. These *in vitro* results indicate that FOS may be useful therapy for infections caused by antibiotic R pathogens.

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