ASM Microbe 2017
Saturday - 61

Fosfomycin *In Vitro* Activity against Bacteria with Various Mechanisms of Resistance to Other Antibacterials from US Hospitals

D SHORTRIDGE[1], RK FLAMM[1], PR RHOMBERG[1], EJ ELLIS-GROSSE[2], HS SADER[1]

[1]JMI Laboratories, North Liberty, Iowa USA

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

Contact Information:
Dee Shortridge, Ph.D.
JMI Laboratories
345 Beaver Kreek Centre, Suite A
North Liberty, IA 52317
Phone: (319) 665-3370
Fax: (319) 665-3371
Email: dee-shortridge@jmilabs.com

Amended Abstract

Background: ZTI-01 (fosfomycin, FOS, for injection) is in US development for complicated urinary tract infections at a dosage of 6 grams every 8 hours 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); *Klebsiella pneumoniae* (KPN) with an extended-spectrum beta-lactamase phenotype (ESBL+) or were carbapenem-R (CR); and *Pseudomonas aeruginosa* (PSA) nonsusceptible 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), and all 3 VREF had MICs = 32 µg/mL. All 101 MRSA had an MIC ≤64 µg/mL ($MIC_{50/90}$ 4/8 µg/mL). Of 153 MR-CoNS, 72 had MICs ≤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 MICs >256 µg/mL; and remaining isolates had MIC values ≤32 µg/mL. For 11 EC that were CR, 2 had MICs >256 µg/mL; 9 had an MIC range of 0.5 – 32 µg/mL. Of 50 ESBL+ KPN, 49 had MICs ≤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 MICs ≤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 FOS MICs ≤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 MICs ≤64 µg/mL, 1 isolate had an MIC >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.

Introduction

- ZTI-01 (fosfomycin, FOS, for injection) is in US development for complicated urinary tract infections at a dosage of 6 grams every 8 hours and is the sole member of the epoxide antibiotic class
  - The current oral dose used in the US is 3g
- The unique mode of action acts at an earlier step in cell wall synthesis inhibition compared to other agents
- Due to its unique mode of action, FOS is unaffected by common resistance mechanisms found in gram-negative (GN) and -positive (GP) bacteria, including methicillin-resistance in staphylococci, vancomycin-resistant enterococci, and ESBL- and carbapenem-resistance in GN
- In this study we evaluated the activity of FOS against recent GN and GP isolates with various resistance mechanisms to other drug classes

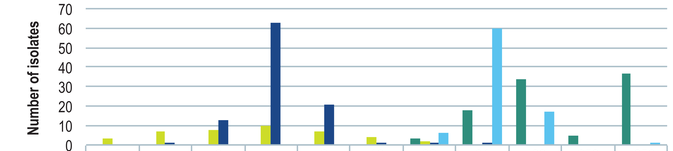
Materials and Methods

- Using current CLSI breakpoints for *Escherichia coli* (EC) and *Enterococcus faecalis* for the oral agent (dosed at 3g) of ≤64 µg/mL susceptible (S) / 128 µg/mL intermediate (I) / ≥256 µg/mL resistant (R), we determined FOS susceptibility for 509 recent GN and GP clinical isolates resistant to various classes of antibiotics
- Isolates were collected from hospitalized patients in the US as part of the SENTRY surveillance program from 2013 through 2015
- Resistant phenotypes according to CLSI breakpoints
  - Gram-positive: vancomycin-resistant *Enterococcus faecium* (VREM) and *E. faecalis* (VREF); methicillin-R *Staphylococcus aureus* (MRSA), and MR coagulase negative staphylococci (MR-CoNS)
  - Gram-negative: EC and *Klebsiella pneumoniae* (KPN) with an extended-spectrum beta-lactamase phenotype (ESBL+) or were carbapenem-R (CR); and *Pseudomonas aeruginosa* (PSA) nonsusceptible (NS) to ceftazidime (CAZ-NS) or to meropenem (MER-NS)
- The FOS MIC for all isolates was determined by CLSI standard reference agar dilution supplemented with 25 µg/mL glucose-6-phosphate

Results

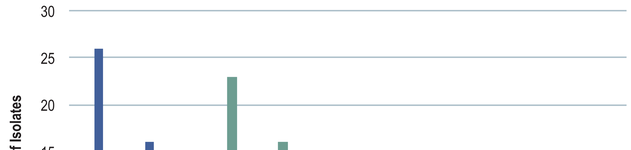
- The MIC range for 81 VREM isolates was 32 – >256 µg/mL and 63 isolates had MICs ≤ 64µg/mL ($MIC_{50/90}$ 64/128 µg/mL), shown in Figure 1
  - 3 VREF had MICs = 32µg/mL
- All 101 MRSA had MICs ≤64 µg/mL ($MIC_{50/90}$ = 4/8 µg/mL) (Figure 1)
- Of 153 MR-CoNS, 72 had MICs ≤64 µg/mL
  - All 41 MR *Staphylococcus epidermidis* (SEPI) were ≤64 µg/mL with MICs ranging from 0.5 – 32 µg/mL (Figure 1)
  - 97 MR *S. saprophyticus* (SSAP) had MICs of 32 – >256 µg/mL (Figure 1)
  - The remaining MR-CoNS isolates had MICs that ranged from 0.5 for 1 *S. cohnii*, to ≥256 µg/mL for 1 *S. hominis* and 2 *S. pettenkoferi*
- For 49 EC with an ESBL phenotype, the $MIC_{50/90}$ were 0.5/4 µg/mL; 47 isolates had MIC values ≤32 µg/mL; the remaining 2 isolates had MICs of >256 µg/mL (Figure 2)
- For 11 EC that were CR, 9 isolates had an MIC range of 0.5 – 32 µg/mL; the remaining 2 isolates had MICs of >256 µg/mL (Figure 2)
- Of 50 ESBL+ KPN, 49 had MICs ≤64 µg/mL and 1 isolate had an MIC of >256 µg/mL; the $MIC_{50/90}$ values were 4/16 µg/mL (Figure 2)
- For 17 CR-KPN, 16 had MICs ≤64 µg/mL and 1 isolate had an MIC of >256; the $MIC_{50/90}$ values were 8/64 µg/mL (Figure 2)
- For 38 CAZ-NS PSA, 32 had FOS MICs ≤64 µg/mL, 1 isolate had an MIC of >256 µg/mL, the 5 remaining isolates had MICs of 128 – 256 µg/mL, and the $MIC_{50/90}$ values were 64/128 µg/mL (Figure 3)
- For 42 MER-NS PSA, 34 had MICs ≤64 µg/mL, 7 isolates had MICs of 128 – 256 µg/mL, 1 isolate had an MIC of >256 µg/mL, and the $MIC_{50/90}$ values were 64/128 µg/mL (Figure 3)

Figure 1 Activity of fosfomycin against recent resistant gram-positive isolates: VRE, MRSA, MR-SSAP, and MR-SEPI



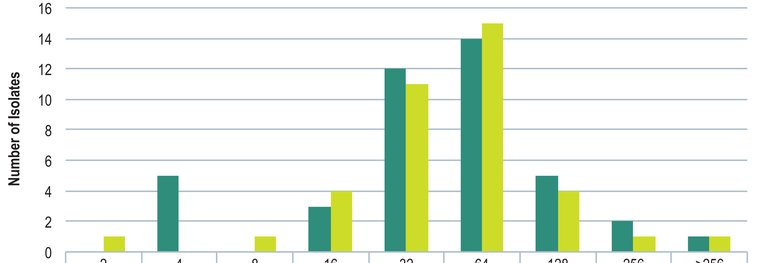
	0.5	1	2	4	8	16	32	64	128	256	>256
MR-SSAP							3	18	34	5	37
MR-SEPI	3	7	8	10	7	4	2				
MRSA		1	13	63	21	1	1	1			
VRE							6	60	17		1

Figure 2 Activity of fosfomycin against recent ESBL-positive or carbapenem-resistant isolates of *K. pneumoniae* or *E. coli*



	0.5	1	2	4	8	16	32	64	128	256	>256
KPN ESBL phenotype			2	23	16	6	1	1			1
KPN CR			1	4	6	4		1			1
EC ESBL phenotype	26	16	2	1			2				2
EC CR	4	3		1			1				2

Figure 3 Activity of fosfomycin against recent meropenem-nonsusceptible or ceftazidime-nonsusceptible *P. aeruginosa* isolates



	2	4	8	16	32	64	128	256	>256
MER-NS PSA		5	0	3	12	14	5	2	1
CAZ-NS PSA	1		1	4	11	15	4	1	1

Conclusions

- FOS demonstrated potent activity against recent antibiotic-R GN and GP isolates and was unaffected by resistance to other drug classes
  - FOS-R isolates were uncommon among drug-R isolates
- All MRSA and MR-SEPI had MICs ≤64 µg/mL, although FOS was less active against SSAP (21/97 were ≤64 µg/mL)
- For VRE, 78% were S by oral CLSI breakpoint (≤64 µg/mL)
- For ESBL+ or CR EC, 95.9% (47/49) were S with MICs ≤64 µg/mL
- For ESBL + or CR KPN, 98.0% (49/50) had MICs ≤64 µg/mL
- For PSA-NS to MER or CAZ, 82.5% (66/80) had MICs ≤64 µg/mL and 93.8% had MICs ≤128 µg/mL
- Given the bioavailability limits of the current oral formulation, reassessing breakpoints will be warranted by the FDA for the IV formulation using a higher dose
- These *in vitro* results indicate that FOS may be useful therapy for infections caused by antibiotic-resistant pathogens

Acknowledgements

This study was sponsored by Zavante Theraputics.

References

Clinical and Laboratory Standards Institute (2017). *M100-S27. Performance standards for antimicrobial susceptibility testing: 27th informational supplement.* Wayne, PA: CLSI.

EUCAST (2017). Breakpoint tables for interpretation of MICs and zone diameters. Version 7.0, January 2017. Available at: http://www.eucast.org/clinical_breakpoints/. Accessed January 2017.

https://www.jmilabs.com/data/posters/ASMMicrobe17-fosfo-vs-R.pdf