Sulopenem Activity against *Enterobacteriaceae* Isolates from Patients with Urinary Tract Infection

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ABSTRACT

Background: Sulopenem is a thiopenem antibiotic with an oral and parenteral formulation being developed for the treatment of urinary tract infection (UTI) and complicated intra-abdominal infection. The activity of sulopenem aligns with the most urgent drug-resistant antimicrobial threats defined by the CDC, including ESBL-producing strains of *Escherichia coli* and *Klebsiella* species. We evaluated the *in vitro* antimicrobial activity of sulopenem against 824 contemporary clinical *Enterobacteriaceae* isolates from patients with an inpatient or community-acquired UTI.

Materials/methods: Sulopenem and other antimicrobial agents were tested for *in vitro* activity against 824 recent (2015-2016) *Enterobacteriaceae* isolates collected through the SENTRY Antimicrobial Surveillance Program from patients in Europe and North America with UTI. Reference broth microdilution susceptibility testing was conducted for sulopenem and ertapenem per Clinical and Laboratory Standards Institute (CLSI) guidelines using cation-adjusted Mueller-Hinton broth; susceptibility data for comparator agents was provided from the SENTRY surveillance database.

Results: The sulopenem $MIC_{50/90}$ values for *Enterobacteriaceae* were 0.06/0.25 µg/mL. For *E. coli*, including those with ESBL-phenotype (N = 32), the $MIC_{50/90}$ results were 0.03/0.06 µg/mL. Carbapenem resistance was not identified among the 207 *E. coli* isolates, whereas 15 (4.9%) of 309 *Klebsiella* species were carbapenem resistant.

Antimicrobial agent	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	MIC Range (µg/mL)	CLSI %S	CLSI %I	CLSI %R
Sulopenem	0.06	0.25	0.015 - >8			
Ertapenem	0.008	0.12	0.004 - >2	95.9	1.2	2.9
Imipenem	≤0.12	1	≤0.12 - >8	91.6	5.5	2.9
Meropenem	0.03	0.06	≤0.015 - >32	98.5	0.2	1.2
Ceftazidime	0.25	32	≤0.015 - >32	84.7	0.7	14.6
Piperacillin-tazobactam	2/4	32/4	≤0.5/4 - >64/4	88.7	5.0	6.3
Amoxicillin-clavulanate (2:1)	4/2	64/32	0.5/0.25 - >64/>32	69.7	8.6	21.7
Nitrofurantoin	32	128	1 - >256	54.9	17.7	27.4
Levofloxacin	0.06	>4	≤0.03 - >4	84.3	1.8	13.9
Trimethoprim-sulfamethoxazole	≤0.5/9.5	>4/76	≤0.5/9.5->4/76	75.6	-	24.4

Conclusions: Sulopenem demonstrated potent *in vitro* activity against organisms commonly implicated in uncomplicated and complicated UTI. These data support the further clinical development of sulopenem for gram-negative infections, including those caused by ESBL-producing *Enterobacteriaceae*.

INTRODUCTION

- Sulopenem is a thiopenem β-lactam antibiotic
  - Oral and parenteral formulation
  - Being developed for the treatment of urinary tract infection (UTI) and complicated intra-abdominal infection
- The activity of sulopenem aligns with the most urgent drug-resistant antimicrobial threats defined by the CDC
  - *Enterobacteriaceae* that encode ESBLs, and
  - AmpC-type β-lactamases that confer resistance to third generation cephalosporins
- We evaluated the *in vitro* antimicrobial activity of sulopenem against 824 contemporary (2015-2016) clinical *Enterobacteriaceae* isolates
  - Organisms acquired from hospitalized patients in North America and Europe
  - Community-acquired or hospital-acquired complicated UTI

METHODS

- Sulopenem and other antimicrobial agents were tested for *in vitro* activity against *Enterobacteriaceae* isolates
  - Collected through the SENTRY Antimicrobial Surveillance Program
  - Patients in Europe and North America with UTI
- Reference broth microdilution susceptibility testing was conducted
  - Clinical and Laboratory Standards Institute (CLSI M07-A10, 2015) guidelines
  - Cation-adjusted Mueller-Hinton broth
- Quality control ranges for bacterial reference strains and interpretive criteria for the comparator compounds tested, as published in CLSI M100-S27 (2017)
- Susceptibility data for additional comparator agents was provided from the SENTRY surveillance database

RESULTS

Table 1: Sulopenem and Comparator Carbapenem Activity Against Key Urinary Pathogens

Antimicrobial Agent	*E. coli* $MIC_{50/90}$ (µg/mL)	*E. coli* MIC Range (µg/mL)	*Klebsiella spp.* $MIC_{50/90}$ (µg/mL)	*Klebsiella spp.* MIC Range (µg/mL)	*P. mirabilis* $MIC_{50/90}$ (µg/mL)	*P. mirabilis* MIC Range (µg/mL)	*Citrobacter spp.* $MIC_{50/90}$ (µg/mL)	*Citrobacter spp.* MIC Range (µg/mL)	*Enterobacter spp.* $MIC_{50/90}$ (µg/mL)	*Enterobacter spp.* MIC Range (µg/mL)
Sulopenem	0.03/ 0.06	0.015 – 0.25	0.06/ 0.12	0.03 – >8	0.25/ 0.5	0.03 – 2	0.06/ 0.12	0.015 - >8	0.12/ 0.5	0.03 – 8
Ertapenem	0.008/ 0.03	0.004 – 0.5	0.008/ 0.12	0.008 - >2	0.015/ 0.03	0.008 – 0.5	0.008/ 0.25	0.004 - >2	0.06/ 1	0.008 - >2
Meropenem	≤0.015/ 0.03	≤0.015 – 0.06	0.03/ 0.03	≤0.015 - >32	0.06/ 0.12	≤0.015 – 0.25	≤0.015/ 0.03	≤0.015 - >32	0.03/ 0.12	≤0.015 – 4

RESULTS

Table 2: Activity of Sulopenem Against Key Urinary Pathogens by Geographic Location

	U.S.				Europe				All			
Organism	N	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	MIC Range (µg/mL)	N	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	MIC Range (µg/mL)	N	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	MIC Range (µg/mL)
*Enterobacteriaceae**	409	0.06	0.25	0.015 - >8	415	0.06	0.25	0.015 - >8	824	0.06	0.25	0.015 - >8
E. coli	103	0.03	0.06	0.03 – 0.25	104	0.03	0.06	0.015 – 0.25	207	0.03	0.06	0.015 – 0.25
E. coli, ESBL +	11	0.03	0.06	0.03 – 0.12	21	0.06	0.06	0.03 – 0.25	32	0.03	0.06	0.03 – 0.25
E. coli, ESBL -	92	0.03	0.06	0.03 – 0.25	83	0.03	0.06	0.015 – 0.25	175	0.03	0.06	0.015 – 0.25
E. coli (w/o CRE)	103	0.03	0.06	0.03 – 0.25	104	0.03	0.06	0.015 – 0.25	207	0.03	0.06	0.015 – 0.25
K. pneumoniae	102	0.06	0.12	0.03 - >8	104	0.06	0.12	0.03 - >8	206	0.06	0.12	0.03 - >8
K. pneumoniae, ESBL +	11	0.12	>8	0.03 - >8	37	0.06	>8	0.03 - >8	48	0.06	>8	0.03 - >8
K. pneumoniae, ESBL -	91	0.06	0.12	0.03 – 0.25	67	0.06	0.06	0.03 – 0.12	158	0.06	0.06	0.03 – 0.25
K. pneumoniae (w/o CRE)	98	0.06	0.12	0.03 – 0.25	93	0.06	0.06	0.03 – 0.12	191	0.06	0.06	0.03 – 0.25
P. mirabilis	51	0.25	0.5	0.03 – 2	52	0.25	0.5	0.03 – 2	103	0.25	0.5	0.03 – 2
P. mirabilis (w/oCRE)	51	0.25	0.5	0.03 - 2	52	0.25	0.5	0.03 - 2	103	0.25	0.5	0.03 - 2
Citrobacter species	51	0.06	0.12	0.015 - >8	52	0.06	0.06	0.015 – 0.25	103	0.06	0.12	0.015 - >8
Citrobacter spp. (w/o CRE)	48	0.03	0.06	0.015 – 0.25	52	0.06	0.06	0.015 – 0.25	100	0.06	0.06	0.015 - 0.25
E. cloacae	51	0.12	0.5	0.03 – 8	51	0.12	1	0.03 – 2	102	0.12	0.5	0.03 - 8
E. cloacae (w/o CRE)	43	0.12	0.25	0.03 – 0.5	43	0.12	0.25	0.03 - 1	86	0.12	0.25	0.03 - 1

*CRE (N; %): *E. coli* (0); *K. pneumoniae* (15; 7%); *Citrobacter* spp. (3; 3%); *E. cloacae* (8; 16%)

Table 3: Activity of Sulopenem and Comparator Antimicrobial Agents Against 824 *Enterobacteriaceae* Isolates

Antimicrobial agent	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	MIC Range (µg/mL)	CLSI %S	CLSI %I	CLSI %R
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CONCLUSIONS

- Sulopenem demonstrated potent in-vitro activity against organisms commonly implicated in urinary tract and intra-abdominal infections.
- Sulopenem may represent a valuable treatment option for Gram-negative infections, including those caused by ESBL-producing or quinolone non-susceptible pathogens.
- These data support the further clinical development of oral and intravenous sulopenem for gram-negative infections, including those caused by drug resistant *Enterobacteriaceae*.