Sulopenem Activity against Enterobacteriaceae Isolates from Patients with Urinary Tract Infection or Intra-Abdominal Infection

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ABSTRACT

Background: Sulopenem is a thiopenem antibacterial with oral and parenteral formulations being developed for the treatment of urinary tract infection (UTI) or complicated intra-abdominal infection (cIAI). The activity of sulopenem aligns with the most urgent drug-resistant antimicrobial threats defined by the Centers for Disease Control (CDC), including ESBL-producing strains of *Escherichia coli* and Klebsiella species. We evaluated the in vitro antibacterial activity of sulopenem against clinical Enterobacteriaceae isolates from patients in North America with UTI or cIAI collected during 2016-2017.

Methods: Sulopenem and other antimicrobial agents were tested for in vitro activity against 1,008 recent (2016-2017) consecutive Enterobacteriaceae isolates collected through the SENTRY Antimicrobial Surveillance Program from patients in North America with UTI (906 isolates) or cIAI (102 isolates). Reference broth microdilution susceptibility testing was conducted using frozen-form panels produced by JMI Laboratories according to CLSI (M07, 2018) guidelines using cation-adjusted Mueller-Hinton broth. Quality control (QC) and interpretation of results were performed in accordance with CLSI M100 (2018) and EUCAST 2018 guidelines.

Results:
Table 1. Activity of sulopenem and comparator antimicrobial agents against 1,008 Enterobacteriaceae North American isolates

Antimicrobial agent	CLSI			MIC_{50} (µg/mL)	MIC_{90} (µg/mL)
	%S	%I	%R		
Sulopenem	--	--	--	0.03	0.25
Meropenem	99.6	0.1	0.3	0.03	0.06
Ertapenem	99.3	0.3	0.4	≤0.008	0.03
Ceftriaxone	87.3	0.6	12.1	≤0.06	>8
Piperacillin-tazobactam	96.3	2.2	1.5	2	8
Amoxicillin-clavulanate (2:1)	75.8	7.7	16.5	4	64
Levofloxacin	82.8	1.8	15.4	0.06	16
Nitrofurantoin	63.8	22.2	14.0	32	128

The sulopenem $MIC_{50/90}$ values for Enterobacteriaceae were 0.03/0.25 µg/mL. For *Escherichia coli*, *Klebsiella* species and *Proteus mirabilis*, the $MIC_{50/90}$ results were 0.03/0.03 µg/mL, 0.03/0.06 µg/mL and 0.12/0.25 µg/mL, respectively.

Conclusions: Sulopenem demonstrated potent *in-vitro* activity against organisms commonly implicated in UTI and cIAI. These data support the further clinical development of sulopenem for gram-negative infections.

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 (cIAI)
- 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 1008 contemporary (2016-2017) clinical *Enterobacteriaceae* isolates
  - Organisms acquired from patients in North America
  - Community-acquired or hospital-acquired complicated UTI and complicated IAI

METHODS

- Sulopenem and other antimicrobial agents were tested for *in vitro* activity against *Enterobacteriaceae* isolates
  - Collected through the SENTRY Antimicrobial Surveillance Program
  - Patients in North America with UTI and cIAI
- 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 Pathogens

Antimicrobial Agent	*E. coli* N=501		*K. pneumoniae* N=201		*P. mirabilis* N=100		*Citrobacter spp.* N=53		*Enterobacter spp.* N=50	
	$MIC_{50/90}$ (µg/mL)	MIC Range (µg/mL)	$MIC_{50/90}$ (µg/mL)	MIC Range (µg/mL)	$MIC_{50/90}$ (µg/mL)	MIC Range (µg/mL)	$MIC_{50/90}$ (µg/mL)	MIC Range (µg/mL)	$MIC_{50/90}$ (µg/mL)	MIC Range (µg/mL)
Sulopenem	0.03/ 0.03	≤0.008 – 0.25	0.03/ 0.06	≤0.008 – >8	0.12/ 0.25	≤0.008 – 1	0.03/ 0.06	0.015 - >8	0.06/ 0.25	0.015 – 1
Ertapenem	≤0.008 / 0.015	≤0.008 – 1	≤0.008 / 0.03	≤0.008 - >8	≤0.008/ 0.015	≤0.008 – 0.06	≤0.008/ 0.12	≤0.008 – 8	0.06/ 0.5	≤0.008 - 1
Meropenem	0.015/ 0.03	≤0.008 – 0.12	0.03/ 0.03	≤0.008 - >8	0.06/ 0.06	0.015 – 0.25	0.03/ 0.03	0.015 - 4	0.03/ 0.06	≤0.008 – 0.25

RESULTS

Table 2: Activity of Sulopenem Against Key cUTI and cIAI Pathogens in North America

Organism	N	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	MIC Range (µg/mL)
*Enterobacteriaceae**	1008	0.03	0.25	≤0.008 - >8
Excluding CRE	1001	0.03	0.25	≤0.008 - 1
E. coli	501	0.03	0.03	≤0.008 – 0.25
ESBL +	62	0.03	0.06	0.015 – 0.25
ESBL -	439	0.03	0.03	≤0.008 – 0.25
Excluding CRE	500	0.03	0.03	≤0.008 – 0.25
K. pneumoniae	201	0.03	0.06	≤0.008 - >8
ESBL +	24	0.06	0.25	0.03 - >8
ESBL -	177	0.03	0.06	≤0.008 – 0.5
Excluding CRE	199	0.03	0.06	≤0.008 – 0.5
P. mirabilis	100	0.12	0.25	≤0.008 – 1
Citrobacter species	53	0.03	0.06	0.015 - >8
Excluding CRE	51	0.03	0.06	0.015 – 0.12
E. cloacae	50	0.06	0.25	0.015 – 1
Excluding CRE	48	0.06	0.25	0.015 – 1
Anaerobes	71	0.06	1	≤0.008 - 4

*Carbapenem Resistant Enterobacteriaceae (CRE) (N; %): *E. coli* (1; 0.2%); *K. pneumoniae* (2; 1%); *Citrobacter* spp. (2; 3.8%); *E. cloacae* (2; 4%)

Table 3: Activity of Sulopenem and Comparator Antimicrobial Agents Against 1008 *Enterobacteriaceae* Isolates

Antimicrobial Agent	CLSI			MIC_{50} (µg/mL)	MIC_{90} (µg/mL)
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CONCLUSIONS

- Sulopenem demonstrated potent *in-vitro* activity against organisms commonly implicated in urinary tract and intra-abdominal infections.
- ESBL production did not have an impact on the *in vitro* activity of sulopenem.
- These data support the further clinical development of oral and intravenous sulopenem for gram-negative infections, including those caused by ESBL-producing or quinolone non-susceptible *Enterobacteriaceae*.

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