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In Vitro Activity of Sulopenem, An Oral Penem, against *Escherichia coli* Isolated from Urine Specimens of Patients Across Canada in 2014-2016

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Abstract

Background: Sulopenem (SULO) is an investigational penem (β-lactam) available in both oral and parenteral dosage forms that is being developed for the treatment of infections caused by multidrug-resistant (MDR) and ESBL-producing Gram-negative bacilli. The current study assessed the *in vitro* activities of SULO and comparator antimicrobial agents against recent (2014-2016) urinary isolates of *E. coli* cultured from patient specimens by Canadian hospital laboratories as participants in the CANWARD study, an ongoing, national, Canadian study assessing antimicrobial resistance patterns of pathogens causing infections in patients receiving care in hospitals across Canada. **Methods:** SULO and comparator agent antimicrobial susceptibility testing was performed centrally by the CANWARD coordinating laboratory using CLSI-defined broth microdilution methodology. MICs were interpreted using CLSI M100, 27th Edition (2017) breakpoints. To date, 153 urinary isolates of *E. coli* from 2014-2016 have been tested, including ESBL-, AmpC-, and KPC-positive isolates. Antimicrobial susceptibility testing is ongoing. **Results:** The table shows MIC_{50}/MIC_{90}/MIC range data for SULO and MIC_{90}/% susceptible data for selected comparator agents for 150 urinary isolates of *E. coli* from the CANWARD study stratified by antimicrobial resistance phenotypes/genotypes. Two additional, previously identified KPC-positive isolates of *E. coli* were also tested and generated SULO MICs of 8->8 µg/mL and meropenem MICs of 4-32 µg/mL. **Conclusion:** The SULO MIC_{90} against urinary isolates of *E. coli* tested to date was 0.06 µg/mL, with a MIC range of 0.015-0.25 µg/mL. The *in vitro* activity of SULO was unaffected by concurrent non-susceptibility to trimethoprim-sulfamethoxazole, ciprofloxacin, the presence of ESBL or AmpC enzymes, or MDR phenotypes (excluding the two additional KPC-positive isolates tested).

E. coli Phenotype/Genotype (n)	MIC_{50}/MIC_{90}/MIC Range (µg/mL) SULO	MIC_{90} (µg/mL)/% Susceptible MERO	CTR	AMC	SXT	NIT	CIP
All isolates (150)	0.03/0.06/0.015-0.25	≤0.03/100	>64/66.0	16/74.0	>8/64.0	16/95.3	>16/58.7
SXT-S (96)	0.03/0.06/0.015-0.12	≤0.03/100	>64/77.1	16/83.3	0.25/100	16/95.8	>16/78.1
SXT-NS (54)	0.03/0.06/0.015-0.25	≤0.03/100	>64/46.3	32/57.4	>8/0	32/94.4	>16/24.1
CIP-S (88)	0.03/0.03/0.015-0.12	≤0.03/100	32/85.2	16/89.8	>8/85.2	16/98.9	0.12/100
CIP-NS (62)	0.03/0.06/0.015-0.25	≤0.03/100	>64/38.7	32/51.6	>8/33.9	32/90.3	>16/0
SXT-NS & CIP-NS (41)	0.03/0.06/0.015-0.25	≤0.03/100	>64/43.9	32/51.2	>8/0	32/95.1	>16/0
ESBL-positive (49)	0.03/0.06/0.03-0.12	≤0.03/100	>64/2.0	32/55.1	>8/42.9	16/93.9	>16/24.5
AmpC-positive (4)	0.03-0.25	≤0.03-0.06	≤0.25->64	32->32	0.25->8	8-32	≤0.06->16
MDR (31)	0.03/0.06/0.03-0.25	≤0.03/100	>64/16.1	32/38.7	>8/6.5	64/87.1	>16/6.5

Abbreviations: S, susceptible; NS, non-susceptible; SULO, sulopenem; MERO, meropenem; CTR, ceftriaxone; AMC, amoxicillin-clavulanate; SXT, trimethoprim-sulfamethoxazole; NIT, nitrofurantoin; CIP, ciprofloxacin; MDR, multidrug-resistant, defined as resistance to ≥3 agents from different antimicrobial classes.

Introduction

Sulopenem, formerly CP-70,429, is an investigational penem β-lactam antimicrobial being developed for the treatment of infections caused by multidrug-resistant and ESBL-producing Gram-negative bacilli. It is available in both parenteral and oral prodrug formulations (1). Unlike imipenem, sulopenem is stable to renal dehydropeptidase I (2).

The purpose of this study was to assess the *in vitro* activities of sulopenem and comparator antimicrobial agents against recent (2014-2016) urinary isolates of *E. coli* collected from patients receiving care in hospitals across Canada.

Materials and Methods

Bacterial Isolates

CANWARD is an ongoing study assessing antimicrobial resistance and pathogen prevalence in Canadian hospitals. Each hospital site was asked to submit clinical isolates (consecutive, one per patient per infection site) from inpatients and outpatients with respiratory, wound, urine and bloodstream infections. Isolates were collected from patients attending hospital clinics, emergency rooms, surgical/medical wards and intensive care units. Isolates were shipped to the coordinating laboratory (Health Sciences Centre, Winnipeg, Canada) where they were subcultured onto appropriate media and stocked in skim milk at -80ºC.

Antimicrobial Susceptibility Testing

539 urinary isolates of *E. coli* from 2014-2016 were tested, including ESBL-, AmpC-, and KPC-positive isolates. Sulopenem and comparator agent antimicrobial susceptibility testing was performed centrally by the CANWARD coordinating laboratory using broth microdilution and CLSI protocols (3). MICs were interpreted using CLSI M100, 28th edition (2018) breakpoints (4). ESBLs were identified and confirmed following CLSI guidelines (4) and multidrug-resistant (MDR) isolates were defined using a published guideline (5).

Results

Table 1. *In vitro* activity of sulopenem and comparator agents against *E. coli* isolated from urine specimens of patients across Canada in 2014-2016

Organism (no. tested) / Antimicrobial Agent	MIC_{50}	MIC_{90}	Range Min	Range Max	%S	%I	%R
All Isolates (539)							
Sulopenem	0.03	0.03	0.015	0.12		NB	
Meropenem	≤ 0.03	≤ 0.03	≤ 0.03	0.12	100	0	0
Ceftriaxone	≤ 0.25	1	≤ 0.25	> 64	90.4	0.1	9.5
Amoxicillin/clavulanate	4	16	0.5	> 32	81.3	14.6	4.1
SXT	≤ 0.12	> 8	≤ 0.12	> 8	75.5	-	24.5
Nitrofurantoin	16	16	≤ 1	256	97.8	1.5	0.7
Ciprofloxacin	≤ 0.06	> 16	≤ 0.06	> 16	76.3	0.1	23.6
SXT-Susceptible (407)							
Sulopenem	0.03	0.03	0.015	0.12		NB	
Meropenem	≤ 0.03	≤ 0.03	≤ 0.03	0.12	100	0	0
Ceftriaxone	≤ 0.25	≤ 0.25	≤ 0.25	> 64	94.3	0	5.7
Amoxicillin/clavulanate	4	16	0.5	> 32	88.0	9.1	2.9
SXT	≤ 0.12	0.25	≤ 0.12	2	100	-	0
Nitrofurantoin	16	16	≤ 1	128	98.3	1.2	0.5
Ciprofloxacin	≤ 0.06	> 16	≤ 0.06	> 16	85.3	0	14.7
SXT Non-Susceptible (132)							
Sulopenem	0.03	0.06	0.015	0.12		NB	
Meropenem	≤ 0.03	≤ 0.03	≤ 0.03	0.06	100	0	0
Ceftriaxone	≤ 0.25	> 64	≤ 0.25	> 64	78.0	0.8	21.2
Amoxicillin/clavulanate	8	16	2	> 32	60.6	31.8	7.6
SXT	> 8	> 8	4	> 8	0	-	100
Nitrofurantoin	16	32	≤ 1	256	96.2	2.3	1.5
Ciprofloxacin	16	> 16	≤ 0.06	> 16	48.5	0.7	50.8
Ciprofloxacin-Susceptible (411)							
Sulopenem	0.03	0.03	0.015	0.12		NB	
Meropenem	≤ 0.03	≤ 0.03	≤ 0.03	0.12	100	0	0
Ceftriaxone	≤ 0.25	≤ 0.25	≤ 0.25	> 64	96.6	0.2	3.2
Amoxicillin/clavulanate	4	16	0.5	> 32	86.9	10.2	2.9
SXT	≤ 0.12	> 8	≤ 0.12	> 8	84.4	-	15.6
Nitrofurantoin	16	16	≤ 1	128	99.8	0	0.2
Ciprofloxacin	≤ 0.06	0.12	≤ 0.06	1	100	0	0

Organism (no. tested) / Antimicrobial Agent	MIC_{50}	MIC_{90}	Range Min	Range Max	%S	%I	%R
Ciprofloxacin Non-Susceptible (128)							
Sulopenem	0.03	0.06	0.015	0.12		NB	
Meropenem	≤ 0.03	≤ 0.03	≤ 0.03	0.06	100	0	0
Ceftriaxone	≤ 0.25	> 64	≤ 0.25	> 64	70.3	0	29.7
Amoxicillin/clavulanate	8	16	1	> 32	63.3	28.9	7.8
SXT	> 8	> 8	≤ 0.12	> 8	46.9	-	53.1
Nitrofurantoin	16	32	≤ 1	256	91.4	6.3	2.3
Ciprofloxacin	> 16	> 16	2	> 16	0	0.8	99.2
SXT and Ciprofloxacin Non-Susceptible (68)							
Sulopenem	0.03	0.06	0.015	0.12		NB	
Meropenem	≤ 0.03	≤ 0.03	≤ 0.03	0.06	100	0	0
Ceftriaxone	≤ 0.25	> 64	≤ 0.25	> 64	66.2	0	33.8
Amoxicillin/clavulanate	8	32	2	> 32	55.9	33.8	10.3
SXT	> 8	> 8	4	> 8	0	-	100
Nitrofurantoin	16	32	≤ 1	256	94.1	4.4	1.5
Ciprofloxacin	> 16	> 16	2	> 16	0	1.5	98.5
ESBL-Positive (49)							
Sulopenem	0.03	0.06	0.03	0.12		NB	
Meropenem	≤ 0.03	≤ 0.03	≤ 0.03	0.06	100	0	0
Ceftriaxone	> 64	> 64	1	> 64	2.0	2.1	95.9
Amoxicillin/clavulanate	8	32	4	> 32	55.1	32.7	12.2
SXT	> 8	> 8	≤ 0.12	> 8	42.9	-	57.1
Nitrofurantoin	16	16	2	256	93.9	2.0	4.1
Ciprofloxacin	> 16	> 16	≤ 0.06	> 16	24.5	0	75.5
Multidrug-Resistant (47)							
Sulopenem	0.03	0.06	0.015	0.12		NB	
Meropenem	≤ 0.03	≤ 0.03	≤ 0.03	0.06	100	0	0
Ceftriaxone	64	> 64	≤ 0.25	> 64	31.9	0	68.1
Amoxicillin/clavulanate	16	32	4	>32	42.6	31.9	25.5
SXT	> 8	> 8	≤ 0.12	> 8	14.9	-	85.1
Nitrofurantoin	8	32	2	256	91.5	2.1	6.4
Ciprofloxacin	> 16	> 16	≤ 0.06	> 16	8.5	0	91.5

Multidrug-resistant (MDR) was defined as non-susceptible to ≥3 agents from different antimicrobial classes (amoxicillin/clavulanate, ceftriaxone, trimethoprim sulfa, ciprofloxacin, gentamicin, nitrofurantoin).
NB, no breakpoints defined for sulopenem; SXT, trimethoprim-sulfamethoxazole.

Table 2. Distribution of sulopenem MICs for *E. coli* isolated from urine specimens of patients across Canada in 2014-2016

	Number of isolates for which the antimicrobial agent MIC (µg/mL) was:										
Antimicrobial agent	**0.002**	**0.004**	**0.008**	**0.015**	**0.03**	**0.06**	**0.12**	**0.25**	**0.5**	**1**	**Total**
Sulopenem				67	425	40	7				539

Sulopenem was highly active against four tested AmpC-producing urinary *E. coli* isolates, with a MIC range of 0.03-0.12 µg/mL. Sulopenem did not demonstrate activity against two tested KPC-positive urinary *E. coli* isolates, with MIC values of ≥ 8 µg/mL.

Conclusions

1. Sulopenem demonstrates potent *in vitro* activity against urinary isolates of *E. coli*. The MIC_{90} against tested isolates was 0.03 µg/mL, with a MIC range of 0.015-0.12 µg/mL.
2. The *in vitro* activity of sulopenem against urinary isolates of *E. coli* was unaffected by concurrent non-susceptibility to trimethoprim-sulfamethoxazole or ciprofloxacin.
3. The *in vitro* activity of sulopenem against urinary isolates of *E. coli* was unaffected by the presence of ESBL or AmpC enzymes or MDR phenotypes (excluding the two additional KPC-positive isolates tested).
4. Sulopenem may represent a valuable treatment option for urinary *E. coli* with various antimicrobial resistance phenotypes, warranting further surveillance and clinical development.

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