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In Vitro Activity of Sulopenem and Comparative Agents against Bacterial Pathogens Isolated from Canadian Patients with Urinary Tract Infections: CANWARD Surveillance Study 2014-2021

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Introduction

Sulopenem (SLP), is an investigational thiopenem (β-lactam) available in both oral (sulopenem etzadroxil + probenecid) and parenteral (sulopenem) dosage forms. It is currently in development for the treatment of uncomplicated and complicated urinary tract infections, including infections caused by extended-spectrum β-lactamase (ESBL)-producing and multidrug-resistant (MDR) Gram-negative bacilli.[1-3] Orally, sulopenem-etzadroxil is combined with probenecid, and has a safety and efficacy profile similar to other penems and β-lactams.[2] Sulopenem is stable to renal dehydropeptidase I, unlike imipenem, and has been reported to be stable against hydrolytic attack by many β-lactamases, including ESBLs and AmpC enzymes which confer resistance to third-generation cephalosporins. The activity of sulopenem addresses several of the most urgent, serious, and concerning drug-resistant antimicrobial threats defined by the CDC, including ESBL-producing *Enterobacterales.*

The current study assessed the *in vitro* activities of sulopenem and comparator antibacterial agents against clinical isolates of Gram-negative and Gram-positive pathogens isolated from urine and submitted by Canadian hospital laboratories to the CANWARD surveillance study[4] from 2014 to 2021.

Materials and Methods

Bacterial Isolates: CANWARD is an ongoing, national, Health Canada partnered study assessing antimicrobial resistance patterns of pathogens causing infections in patients receiving care in hospitals across Canada.[4] Tertiary-care medical centres submitted pathogens from patients attending hospital clinics, emergency rooms, medical and surgical wards, and intensive care units.[4] From January 2014 through October 2021, each study site was asked to submit “clinically significant” isolates (consecutive, one per patient, per infection site) from inpatients and outpatients with respiratory, urine, wound, and bloodstream infections. Isolates were shipped to the coordinating laboratory (Health Sciences Centre, Winnipeg, Canada) where isolate identification was confirmed and minimum inhibitory concentration (MIC) testing was carried out. *Escherichia coli* isolates were from the CANWARD surveillance study from the years 2014 through 2021. All other isolates were from 2016-2021 only. Putative AmpC phenotypes in *E. coli* were defined as an isolate where the ceftriaxone and/or ceftazidime MIC was ≥1 mg/L, the cefoxitin MIC was ≥32 mg/L, and the isolate tested ESBL-negative by the CLSI phenotypic confirmatory disk test.[5]

Antimicrobial Susceptibilities: Following two subcultures from frozen stock, the *in vitro* activity of sulopenem and selected antimicrobials was determined by broth microdilution in accordance with the Clinical and Laboratory Standards Institute (CLSI)[6] and MICs were interpreted using CLSI M100 breakpoints.[5]. Antimicrobial agents were obtained as laboratory grade powders from their respective manufacturers. The MICs were determined using 96-well custom designed microtitre plates.[4] These plates contained doubling antimicrobial dilutions in 100µl/well of cation adjusted Mueller-Hinton broth and inoculated to achieve a final concentration of approximately 5 x 10^5 CFU/mL then incubated in ambient air for 24 hours prior to reading. Colony counts were performed periodically to confirm inocula. Quality control was performed using ATCC QC organisms including: *Streptococcus pneumoniae* 49619, *Staphylococcus aureus* 29213, *Enterococcus faecalis* 29212, *E. coli* 25922, and *Pseudomonas aeruginosa* 27853.

Results

Table 1. *In vitro* activities of sulopenem and comparators versus Gram-negative bacilli

Organism (no. tested) / antimicrobial agent	MIC (µg/mL) 50%	90%	Range	% S	% I	% R
***Escherichia coli* ALL (1248)**						
Sulopenem	0.03	0.06	≤ 0.008-4	NA[a]	NA	NA
Meropenem	≤ 0.03	≤ 0.03	≤ 0.03-1	100	0	0
Ceftriaxone	≤ 0.25	32	≤ 0.25-> 64	88.0	0.2	11.8
Amoxicillin/clavulanate	8	16	0.5-> 32	76.8	16.9	6.4
TMP/SMX	≤ 0.12	> 8	≤ 0.12-> 8	73.7	-	26.3
Ciprofloxacin	≤ 0.06	> 16	≤ 0.06-> 16	74.1	1.0	24.9
Nitrofurantoin	16	16	≤ 0.5-> 512	97.7	1.1	1.2
Gentamicin	≤ 0.5	2	≤ 0.5-> 32	91.0	0.4	8.6
***Escherichia coli* ESBL (133)**						
Sulopenem	0.03	0.06	0.015-0.25	NA	NA	NA
Meropenem	≤ 0.03	0.06	≤ 0.03-0.25	100	0	0
Ceftriaxone	> 64	> 64	1-> 64	0.8	0.7	98.5
Amoxicillin/clavulanate	16	32	4-> 32	44.8	35.4	19.8
TMP/SMX	> 8	> 8	≤ 0.12-> 8	33.8	-	66.2
Ciprofloxacin	> 16	> 16	≤ 0.06-> 16	18.8	0.7	80.5
Nitrofurantoin	16	32	2-512	91.0	3.7	5.3
Gentamicin	≤ 0.5	> 32	≤ 0.5-> 32	72.2	2.2	25.6
***Escherichia coli* AmpC (19)**						
Sulopenem	0.06	0.25	0.015-4	NA	NA	NA
Meropenem	≤ 0.03	0.06	≤ 0.03-1	100	0	0
Ceftriaxone	64	> 64	≤0.25-> 64	42.1	10.5	47.4
Amoxicillin/clavulanate	> 32	> 32	8-> 32	5.9	5.9	88.2
TMP/SMX	≤ 0.12	> 8	≤ 0.12-> 8	68.4	-	31.6
Ciprofloxacin	0.25	> 16	≤ 0.06-> 16	57.9	5.3	36.8
Nitrofurantoin	16	64	8-256	89.5	5.2	5.3
Gentamicin	≤ 0.5	1	≤ 0.5-> 32	94.7	0	5.3
***Escherichia coli* MDR[b] (190)**						
Sulopenem	0.03	0.06	0.015-4	NA	NA	NA
Meropenem	≤ 0.03	0.06	≤ 0.03-1	100	0	0
Ceftriaxone	64	> 64	≤0.25-> 64	38.4	0	61.6
Amoxicillin/clavulanate	16	32	4-> 32	24.1	52.4	23.5
TMP/SMX	> 8	> 8	≤ 0.12-> 8	18.4	-	81.6
Ciprofloxacin	> 16	> 16	≤ 0.06-> 16	13.2	2.1	84.7
Nitrofurantoin	16	64	≤1-512	87.9	5.8	6.3
Gentamicin	1	> 32	≤ 0.5-> 32	56.3	2.1	41.6
***Klebsiella pneumoniae* ALL (200)**						
Sulopenem	0.06	0.12	0.015-1	NA	NA	NA
Meropenem	≤ 0.03	0.06	≤ 0.03-0.5	100	0	0
Ceftriaxone	≤ 0.25	> 64	≤ 0.25-> 64	88.0	0	12.0
Amoxicillin/clavulanate	4	16	1-> 32	85.2	8.8	6.0
TMP/SMX	≤ 0.12	> 8	≤ 0.12-> 8	86.0	-	14.0
Ciprofloxacin	≤ 0.06	2	≤ 0.06-> 16	84.0	3.5	12.5
Nitrofurantoin	64	128	2-> 512	37.5	42.0	20.5
Gentamicin	≤ 0.5	≤ 0.5	≤ 0.5-> 32	97.0	0	3.0
***Klebsiella pneumoniae* ESBL (20)**						
Sulopenem	0.06	0.12	0.03-1	NA	NA	NA
Meropenem	0.06	0.12	≤ 0.03-0.5	100	0	0
Ceftriaxone	> 64	> 64	16-> 64	0	0	100
Amoxicillin/clavulanate	16	32	8-> 32	22.2	38.9	38.9
TMP/SMX	> 8	> 8	≤ 0.12-> 8	15.0	-	85.0
Ciprofloxacin	2	> 16	≤ 0.06-> 16	25.0	10.0	65.0
Nitrofurantoin	64	4	32-512	15.0	55.0	30.0
Gentamicin	≤ 0.5	> 32	≤ 0.5-> 32	80.0	0	20.0
***Enterobacter cloacae* (47)**						
Sulopenem	0.12	0.5	0.03-4	NA	NA	NA
Meropenem	0.06	0.12	≤ 0.03-1	100	0	0
Ceftriaxone	≤ 0.25	> 64	≤ 0.25-> 64	61.7	0	38.3
Amoxicillin/clavulanate	> 32	> 32	8-> 32	2.3	0	97.7
TMP/SMX	≤ 0.12	1	≤ 0.12-> 8	91.5	-	8.5
Ciprofloxacin	≤ 0.06	0.25	≤ 0.06-> 16	91.5	2.1	6.4
Nitrofurantoin	64	128	4-256	27.7	51.1	21.3
Gentamicin	≤ 0.5	1	≤ 0.5-32	95.7	2.1	2.1
***Klebsiella oxytoca* (35)**						
Sulopenem	0.06	0.06	0.03-0.25	NA	NA	NA
Meropenem	≤ 0.03	0.06	≤ 0.03-0.12	100	0	0
Ceftriaxone	≤ 0.25	2	≤ 0.25-32	88.6	2.9	8.6
Amoxicillin/clavulanate	4	8	1-> 32	90.6	3.1	6.3
TMP/SMX	≤ 0.12	1	≤ 0.12-> 8	91.4	-	8.6
Ciprofloxacin	≤ 0.06	0.12	≤ 0.06-1	97.1	0	2.9
Nitrofurantoin	32	64	4-256	82.9	8.6	8.6
Gentamicin	≤ 0.5	1	≤ 0.5-32	97.1	0	2.9

[a] NA – not available.
[b] MDR was defined as nonsusceptible to 3 agents from different antimicrobial classes (ceftriaxone, amoxicillin-clavulanate, TMP/SMX, nitrofurantoin, ciprofloxacin, and gentamicin).

Table 1. *In vitro* activities of sulopenem and comparators versus Gram-negative bacilli (Continued)

Organism (no. tested) / antimicrobial agent	MIC (µg/mL) 50%	90%	Range	% S	% I	% R
***Proteus mirabilis* (88)**						
Sulopenem	0.25	0.5	0.015-1	NA	NA	NA
Meropenem	0.06	0.12	≤ 0.03-0.25	100	0	0
Ceftriaxone	≤ 0.25	≤ 0.25	≤ 0.25-1	100	0	0
Amoxicillin/clavulanate	1	4	0.5-> 32	93.8	2.5	3.8
TMP/SMX	≤ 0.12	> 8	≤ 0.12-> 8	73.9	-	26.1
Ciprofloxacin	≤ 0.06	4	≤ 0.06-> 16	80.7	0	19.3
Nitrofurantoin	128	256	64-256	0	19.3	80.7
Gentamicin	1	8	≤ 0.5-> 32	89.8	1.1	9.1
***Pseudomonas aeruginosa* (75)**						
Sulopenem	> 8	> 8	8-> 8	NA	NA	NA
Meropenem	1	8	≤ 0.03-> 32	84.0	5.3	10.7
Ceftriaxone	64	> 64	4-> 64	NA	NA	NA
Amoxicillin/clavulanate	> 32	> 32	> 32-> 32	NA	NA	NA
TMP/SMX	8	> 8	1-> 8	NA	NA	NA
Ciprofloxacin	0.25	4	≤ 0.06-> 16	82.7	2.7	14.7
Nitrofurantoin	> 512	> 512	> 512-> 512	NA	NA	NA
Gentamicin	1	4	≤ 0.5-> 32	93.3	5.3	1.3

Table 2. *In vitro* activities of sulopenem and comparators versus Gram-positive cocci

Organism (no. tested) / antimicrobial agent	MIC (µg/mL) 50%	90%	Range	% S	% I	% R
***Staphylococcus aureus* - MSSA (29)**						
Sulopenem	0.06	0.25	0.03-0.25	NA[a]	NA	NA
Meropenem	0.12	0.25	0.06-0.5	NA	NA	NA
Ceftriaxone	4	4	1-8	NA	NA	NA
Amoxicillin/clavulanate	0.5	1	0.12-2	NA	NA	NA
TMP/SMX	≤ 0.12	≤ 0.12	≤ 0.12-0.5	100	-	0
Ciprofloxacin	0.5	16	0.12-> 16	86.2	0	13.8
Nitrofurantoin	16	16	4-16	100	0	0
Gentamicin	≤ 0.5	≤ 0.5	≤ 0.5-2	100	0	0
***Enterococcus faecalis* (158)**						
Sulopenem	4	8	1-> 8	NA	NA	NA
Meropenem	4	8	1-> 32	NA	NA	NA
Ceftriaxone	> 64	> 64	2-> 64	NA	NA	NA
Amoxicillin/clavulanate	0.5	1	0.25-> 32	NA	NA	NA
TMP/SMX	≤ 0.12	> 8	≤ 0.12-> 8	NA	NA	NA
Ciprofloxacin	1	> 16	0.12-> 16	62.0	13.9	24.1
Nitrofurantoin	8	16	2-128	98.7	0.6	0.6
Gentamicin	16	> 32	1-> 32	NA	NA	NA

[a] NA – not available

Table 3. Distribution of sulopenem MICs versus Gram-negative organisms

Organism agent	Number of isolates for which the sulopenem MIC (µg/ml) was: ≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	>8
***E. coli* ALL**	284	812	129	16	6				1		
***E. coli* ESBL**	15	66	44	5	3						
***E. coli* AmpC**	4	4	4	5	1				1		
***E. coli* MDR**	29	99	50	8	3				1		
***K. pneumoniae* ALL**	6	81	90	21			2				
***K. pneumoniae* ESBL**		4	11	4			1				
E. cloacae		10	9	11	9	7			1		
K. oxytoca		15	18	1	1						
P. mirabilis	1	3	7	10	33	30	4				
P. aeruginosa										3	72

Table 4. Distribution of sulopenem MICs versus Gram-positive organisms

Organism agent	Number of isolates for which the sulopenem MIC (µg/ml) was: ≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	>8
***S. aureus* (MSSA)**		2	17	7	3						
E. faecalis							2	8	71	64	13

Conclusions

1. Sulopenem demonstrated potent *in vitro* activity against *Enterobacterales* with MIC_{50} and MIC_{90} values ranging from 0.03-0.5 µg/ml for individual species.
2. *Enterobacterales* known to be ESBL-positive, AmpC-positive, as well as MDR demonstrated sulopenem MIC_{90} values of ≤0.25 µg/ml.
3. Sulopenem demonstrated potent *in vitro* activity against MSSA with MIC_{50} and MIC_{90} values of 0.06 and 0.25 µg/ml, respectively.
4. Sulopenem was less active or inactive *in vitro* versus *E. faecalis* and *P. aeruginosa* (MIC_{90}, ≥8 µg/ml).
5. Sulopenem is active versus Gram-negative and Gram-positive pathogens causing urinary tract infections.

Bacterial Isolates Collected
1880 clinical urinary isolates were tested against sulopenem.

- 525 (27.9%) isolates were collected from male patients; 1355 (72.1%) were from female patients.
- 213 (11.3%) isolates were from patients ≤17 years of age; 675 (35.9%) were from patients aged 18-64 years; and 992 (52.8%) were from patients aged ≥65 years.
- 649 (34.5%) isolates were from patients in emergency rooms; 616 (32.8%) from patients in hospital clinics; 486 (25.9%) from patients on medical wards; 87 (4.6%) from patients on surgical wards; and 42 (2.2%) from patients in intensive care units.

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