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Activity of Doripenem and Other Carbapenems against 23,243 Pathogens Isolated from Canadian Hospitals: CANWARD 2007 - 2010

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ABSTRACT

Background: Doripenem (Dori) is a new carbapenem with broad-spectrum activity. As part of CANWARD, a national, annual, ongoing surveillance study assessing antimicrobial resistance in Canadian hospitals, we examined the antimicrobial activities of Dori, meropenem (Mero) and ertapenem (Erta) against isolated pathogens.

Methods: From January 2007 – November 2010, 10-15 sentinel Canadian hospitals submitted pathogens from patients attending hospital clinics, emergency rooms, medical and surgical wards, and intensive care units. Annually, each centre was asked to submit consecutive pathogens from blood, respiratory, urine and wound/IV infections. 7718, 5282, 5375 and 4868 isolates were collected for 2007, 2008, 2009 and 2010, respectively. Susceptibility testing was performed using CLSI broth microdilution methods.

Results: MIC_{50} and MIC_{90} (µg/mL) values for Dori, Mero and Erta are shown below:

Organism (n)	Dori $MIC_{50/90}$	Mero $MIC_{50/90}$	Erta $MIC_{50/90}$
E. coli (4806)	≤0.12/≤0.12	≤0.12/≤0.12	≤0.06/≤0.06
P. aeruginosa (1851)	0.5/4	0.5/8	8/>32
K. pneumoniae (1432)	≤0.12/≤0.12	≤0.12/≤0.12	≤0.06/≤0.06
E. cloacae (533)	≤0.12/0.12	≤0.12/≤0.12	≤0.06/0.5
P. mirabils (368)	0.12/0.25	≤0.12/≤0.12	≤0.06/≤0.06
K. oxytoca (347)	≤0.12/≤0.12	≤0.12/≤0.12	≤0.06/≤0.06
S. marcescens (342)	0.12/0.12	≤0.12/≤0.12	≤0.06/0.06
S. maltophilia (313)	>32/>32	>32/>32	>32/>32
E. aerogenes (132)	≤0.12/0.12	≤0.12/≤0.12	≤0.06/0.25
C. freundii (110)	≤0.12/≤0.12	≤0.12/≤0.12	≤0.06/0.12
A. baumannii (91)	0.25/1	0.5/2	4/16
H. influenzae (815)	≤0.06/0.5	≤0.06/0.12	≤0.03/0.12
MSSA (3526)	≤0.12/≤0.12	0.12/0.12	0.25/0.25
MRSA (1112)	4/32	8/32	8/>32
HA-MRSA (760)	8/32	16/>32	16/>32
CA-MRSA (308)	1/2	2/4	2/8
S. epidermidis (496)	1/16	2/32	4/>32
MSSE (412)	1/8	1/8	2/32
MRSE (76)	16/32	32/32	>32/>32
S. pneumoniae (1610)	≤0.06/0.06	≤0.06/≤0.06	≤0.06/0.12
S. pyogenes (346)	≤0.06/≤0.06	≤0.06/≤0.06	≤0.06/≤0.06
E. faecalis (612)	4/8	4/8	8/16
E. faecium (209)	>32/>32	>32/>32	>32/>32
VRE (46)	>32/>32	>32/>32	>32/>32

MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; HA-MRSA, healthcare-associated MRSA; CA-MRSA, community-associated MRSA; MSSE, methicillin-susceptible *S. epidermidis*; MRSE, methicillin-resistant *S. epidermidis*; VRE, vancomycin-resistant enterococci.

Conclusions: Doripenem displayed similar activity to meropenem, with greater activity versus *P. aeruginosa* and *A. baumannii*.

INTRODUCTION

Doripenem is a new carbapenem which demonstrates the favourable characteristics of other carbapenems including broad-spectrum activity and β-lactamase stability (1,2). It demonstrates in vitro activity against Gram-positive and Gram-negative pathogens including anaerobic bacteria (1). Doripenem has potency against Gram-positive cocci which is most similar to that of imipenem (greater than that of meropenem), and activity against Gram-negative bacteria which is most like that of meropenem (greater than that of imipenem) (1).

The purpose of this study was to assess the activity of doripenem and comparators against Gram-positive and Gram-negative pathogens in Canadian hospitals.

MATERIALS & METHODS

Bacterial Isolates*:* Tertiary-care medical centres (12 in 2007, 10 in 2008, 15 in 2009 and 14 in 2010) representing 8 of 10 provinces across Canada submitted pathogens from patients attending hospital clinics, emergency rooms, medical and surgical wards, and intensive care units. The sites were geographically distributed in a population-based fashion. From January 2007 through December 2010, inclusive, each study site was asked to submit clinical isolates (consecutive, one per patient, per infection site) from inpatients and outpatients with respiratory, urine, wound, and bloodstream infections. The medical centres submitted "clinically significant" isolates from patients with a presumed infectious disease. Surveillance swabs, eye, ear, nose and throat swabs were excluded. We also excluded anaerobic organisms. Isolate identification was performed by the submitting site and confirmed at the reference site as required, based on morphological characteristics and antimicrobial susceptibility patterns. Isolates were shipped on Amies semi-solid transport media to the coordinating laboratory (Health Sciences Centre, Winnipeg, Canada), subcultured onto appropriate media, and stocked in skim milk at -80°C until minimum inhibitory concentration (MIC) testing was carried out. In 2007, 2008, 2009 and 2010, 7881, 5282, 5375 and 4868 isolates were collected, respectively.

Antimicrobial Susceptibilities*:* Following 2 subcultures from frozen stock, the in vitro activity of doripenem and selected antimicrobials was determined by broth microdilution in accordance with the Clinical and Laboratory Standards Institute (CLSI) guidelines (3,4,5). Antimicrobial minimum inhibitory concentration (MIC) interpretive standards were defined according to CLSI breakpoints (5). Susceptibility testing could not be performed with all agents due to lack of space on the susceptibility panels. Antimicrobial agents were obtained as laboratory grade powders from their respective manufacturers. Stock solutions were prepared and dilutions made as described by CLSI (3,4). The MICs of the antimicrobial agents for the isolates were determined using 96-well custom designed microtitre plates. 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; *S. pneumoniae* 49619, *S. aureus* 29213, *E. faecalis* 29212, *E. coli* 25922, and *P. aeruginosa* 27853.

RESULTS

Table 1: Doripenem in vitro activity against aerobic Gram-positive bacteria isolated from patients in Canadian hospitals in 2007-2010

Organism and phenotype (no. of isolates)	Antimicrobial Agent	MIC Range (µg/ml)	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)	% Susceptible
MSSA (3,526)	Cefazolin	≤0.5-32	≤0.5	1	99.9
	Cefepime	≤1-128	4	4	99.9
	Ceftobiprole	0.12-2	0.25	0.5	100
	Ceftriaxone	1-256	4	4	99.7
	Doripenem	≤0.12-1	≤0.12	≤0.12	NA
	Ertapenem	≤0.03-8	0.25	0.25	99.9
	Meropenem	≤0.06-1	≤0.12	≤0.12	100
MRSA (1,112)	Cefazolin	32->128	64	>128	0
	Cefepime	32->256	>256	>256	0
	Ceftobiprole	0.25-4	1	2	100
	Ceftriaxone	>256	>256	>256	0
	Doripenem	4-64	4	32	NA
	Ertapenem	8->32	8	>32	0
	Meropenem	16->32	8	32	0
MSSE (412)	Cefazolin	≤0.5-8	1	4	100
	Cefepime	≤1-16	4	16	100
	Ceftobiprole	≤0.06-2	0.5	1	NA
	Ceftriaxone	≤0.25-128	8	32	69.8
	Doripenem	≤0.06-16	1	8	NA
	Ertapenem	0.12->32	2	32	55
	Meropenem	≤0.06-32	1	8	84
MRSE (76)	Cefazolin	32-128	64	128	0
	Cefepime	32-128	64	128	0
	Ceftobiprole	≤1-4	1	2	NA
	Ceftriaxone	64->256	256	>256	0
	Doripenem	8-32	16	32	NA
	Ertapenem	16->32	>32	>32	0
	Meropenem	8->32	32	>32	0

MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; MSSE, methicillin-susceptible *S. epidermidis*; MRSE, methicillin-resistant *S. epidermidis*.

Organism and phenotype (no. of isolates)	Antimicrobial Agent	MIC Range (µg/ml)	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)	% Susceptible
S. pneumoniae (1,610)	Cefuroxime	≤0.25->16	≤0.25	0.5	94.3
	Ceftobiprole	≤0.06-0.5	≤0.03	≤0.03	NA
	Ceftriaxone	≤0.06-4	≤0.06	0.12	99.4
	Doripenem	≤0.06-2	≤0.06	0.06	NA
	Ertapenem	≤0.06-4	≤0.06	4	99.9
	Meropenem	≤0.06-2	≤0.06	≤0.06	96.4
S. pyogenes (346)	Cefuroxime	≤0.25	≤0.25	≤0.25	NA
	Ceftobiprole	≤0.06-0.12	≤0.06	≤0.06	100
	Ceftriaxone	≤0.06	≤0.06	≤0.06	100
	Doripenem	≤0.06	≤0.06	≤0.06	NA
	Ertapenem	≤0.06-0.12	≤0.06	≤0.06	100
	Meropenem	≤0.06-0.12	≤0.06	≤0.06	100
E. faecalis (612)	Cefazolin	0.5->128	32	64	NA
	Cefepime	≤1->128	128	128	NA
	Ceftobiprole	≤0.06->32	0.5	1	NA
	Ceftriaxone	≤0.25->256	>256	>256	NA
	Doripenem	≤0.06-32	4	8	NA
	Ertapenem	0.25->32	8	16	NA
	Meropenem	≤0.06->32	4	8	NA
E. faecium (209)	Cefazolin	2->128	>128	>128	NA
	Cefepime	2->128	>128	>128	NA
	Ceftobiprole	0.25-128	128	128	NA
	Ceftriaxone	0.5->256	>256	>256	NA
	Doripenem	2->32	>32	>32	NA
	Ertapenem	4->32	>32	>32	NA
	Meropenem	2->32	>32	>32	NA

Ceftobiprole MICs interpreted using Health Canada approved breakpoints.
NA = not available

Table 2: Doripenem in vitro activity against aerobic Gram-negative bacteria isolated from patients in Canadian hospitals in 2007-2010

Organism and phenotype (no. of isolates)	Antimicrobial Agent	MIC Range (µg/ml)	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)	% Susceptible
E. coli (4,806)	Amoxicillin-clavulanate	≤0.06->32	4	8	94.3
	Cefazolin	≤0.5->128	2	32	32.8
	Cefepime	≤0.25->32	≤0.25	≤0.25	96.9
	Cefoxitin	≤0.06->128	4	8	91.8
	Ceftobiprole	≤0.06->128	≤0.06	≤0.06	93
	Ceftriaxone	≤0.25->256	≤0.25	≤0.25	91.1
	Doripenem	≤0.06-0.5	≤0.06	≤0.06	100
	Ertapenem	≤0.06-4	≤0.06	≤0.06	99.9
	Meropenem	≤0.06-1	≤0.06	≤0.06	100
	Piperacillin-tazobactam	≤1->512	2	4	97.6
K. pneumoniae (1,432)	Amoxicillin-clavulanate	0.5-32	2	8	96.2
	Cefazolin	≤0.5->128	2	8	36.9
	Cefepime	≤0.25->128	≤0.25	≤0.25	98
	Cefoxitin	0.12->128	4	8	92.7
	Ceftobiprole	≤0.06-2	≤0.06	≤0.06	96.1
	Ceftriaxone	≤0.25->64	≤0.25	≤0.25	95.5
	Doripenem	≤0.06-4	≤0.06	≤0.06	99.8
	Ertapenem	≤0.06-16	≤0.06	≤0.06	99.8
	Meropenem	≤0.06-4	≤0.06	≤0.06	100
	Piperacillin-tazobactam	≤1->512	2	8	96.5
K. oxytoca (347)	Amoxicillin-clavulanate	1->32	2	8	93.1
	Cefazolin	≤0.5->128	8	128	5.9
	Cefepime	≤0.25-16	≤0.25	≤0.25	99.6
	Cefoxitin	1->32	2	4	96.6
	Ceftobiprole	≤0.06-128	≤0.06	2	89.3
	Ceftriaxone	≤0.25-64	≤0.25	≤0.25	91.2
	Doripenem	≤0.06-0.25	≤0.06	≤0.06	100
	Ertapenem	≤0.06-0.25	≤0.06	≤0.06	100
	Meropenem	≤0.06-0.25	≤0.06	≤0.06	100
	Piperacillin-tazobactam	≤1-512	2	128	89.3
E. cloacae (533)	Amoxicillin-clavulanate	2->32	32	>32	19.1
	Cefazolin	1->128	128	>128	0.7
	Cefepime	≤0.25-16	≤0.25	1	99.8
	Cefoxitin	2->32	32	>32	15.8
	Ceftobiprole	≤0.06-64	≤0.06	2	87.5
	Ceftriaxone	≤0.25->256	≤0.25	64	75.5
	Doripenem	≤0.06-8	≤0.06	≤0.12	99.3
	Ertapenem	≤0.06-16	≤0.06	0.5	99.1
	Meropenem	≤0.06-2	≤0.06	≤0.12	100
	Piperacillin-tazobactam	≤1-512	2	32	87.3
E. aerogenes (132)	Amoxicillin-clavulanate	2->32	32	>32	7.1
	Cefazolin	1->128	64	>128	0
	Cefepime	≤0.25-16	≤0.25	1	98.9
	Cefoxitin	2->32	32	>32	7.1
	Ceftobiprole	≤0.06-8	≤0.06	2	98.9
	Ceftriaxone	≤0.25->256	≤0.25	16	78.9
	Doripenem	≤0.06-0.25	≤0.06	≤0.12	100
	Ertapenem	≤0.06-1	≤0.06	0.25	100
	Meropenem	≤0.06-2	≤0.06	≤0.12	100
	Piperacillin-tazobactam	≤1-512	4	32	88.9

Organism and phenotype (no. of isolates)	Antimicrobial Agent	MIC Range (µg/ml)	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)	% Susceptible
C. freundii (110)	Amoxicillin-clavulanate	2->32	16	32	44.1
	Cefazolin	1->128	32	>128	1.2
	Cefepime	≤0.25-4	≤0.25	1	100
	Cefoxitin	2->32	>32	>32	8.5
	Ceftobiprole	≤0.06-8	≤0.06	1	96.5
	Ceftriaxone	≤0.25->256	≤0.25	32	82.4
	Doripenem	≤0.06-0.12	≤0.06	≤0.12	100
	Ertapenem	≤0.06-0.5	≤0.06	0.12	100
	Meropenem	≤0.06-0.25	≤0.06	≤0.12	100
	Piperacillin-tazobactam	≤1-512	2	32	89.4
P. aeruginosa (1,851)	Cefepime	0.25->128	8	16	75.2
	Ceftobiprole	0.25->128	4	16	NA
	Ceftriaxone	≤0.25->256	32	256	22.2
	Doripenem	≤0.06->64	0.5	4	83.9
	Ertapenem	0.06->32	8	>32	NA
	Meropenem	≤0.06->64	0.5	8	88.6
	Piperacillin-tazobactam	≤1->512	4	64	91.9
S. maltophilia (313)	Amoxicillin-clavulanate	2->32	>32	>32	NA
	Cefepime	≤0.25->128	64	128	NA
	Ceftobiprole	0.5->128	128	128	NA
	Ceftriaxone	8->256	256	256	NA
	Doripenem	≤0.06->64	>64	>64	NA
	Ertapenem	0.12->32	>32	>32	NA
	Meropenem	≤0.06->64	>64	>64	NA
	Piperacillin-tazobactam	16->512	256	>512	NA
A. baumannii (91)	Amoxicillin-clavulanate	0.5->32	16	32	NA
	Cefepime	≤0.25->128	4	32	85.7
	Ceftobiprole	0.12-128	1	2	NA
	Ceftriaxone	2->256	16	64	42.9
	Doripenem	≤0.06-32	0.25	1	93.7
	Ertapenem	0.12->32	4	16	NA
	Meropenem	≤0.06-32	0.5	2	95.2
	Piperacillin-tazobactam	≤1->512	2	64	81
H. influenzae (815)	Amoxicillin-clavulanate	≤0.06-8	0.5	2	99.9
	Cefepime	≤0.25-2	≤0.25	≤0.25	100
	Ceftobiprole	≤0.06-2	≤0.06	0.12	NA
	Ceftriaxone	≤0.06->4	≤0.06	≤0.06	99.9
	Doripenem	≤0.06-2	≤0.06	0.5	NA
	Ertapenem	≤0.03->4	≤0.03	0.12	99.9
	Meropenem	≤0.06-2	≤0.06	0.12	99.7
	Piperacillin-tazobactam	≤1-2	≤1	≤1	99.9

Ceftobiprole MICs for Enterobacteriacae interpreted using Health Canada approved breakpoints.
NA = not available

CONCLUSIONS

- Doripenem displayed slightly greater activity than meropenem against Gram-positive cocci.
- Doripenem displayed very similar activity to meropenem against Enterobacteriaceae.
- Doripenem was more active versus *Pseudomonas aeruginosa* and *Acinetobacter baumannii* than meropenem.
- Carbapenem resistance (meropenem, doripenem and ertapenem) in Enterobacteriaceae isolated from patients in Canadian hospitals is rare.

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