E-174

Activity of Doripenem and Other Carbapenems Against 10,035 Canadian Hospital Pathogens: CANWARD 2007 and 2008

D.J. HOBAN*, M. DECORBY, P. BAUDRY, A. WIERZBOWSKI, J.A. KARLOWSKY and G.G. ZHANEL

University of Manitoba and Health Sciences Centre/Diagnostic Services of Manitoba, Winnipeg, Canada

Daryl J. Hoban
Dept of Clinical Microbiology
Health Sciences Centre
MS675B-820 Sherbrook St.
Winnipeg, Manitoba R3A 1R9
Canada
Phone: (204) 787-1191
Fax: (204) 787-4699
Email: dhoban@hsc.mb.ca

ABSTRACT

Background: Carbapenems are used extensively in hospitals to treat a variety of infectious diseases. As part of an annual, ongoing Canadian national surveillance study assessing antimicrobial resistance in patients in Canadian hospitals, we examined the activity of doripenem, meropenem and ertapenem.

Methods: From January 2007 to December 2008, 10-12 sentinel hospital centres across Canada submitted pathogens from patients attending hospital clinics, emergency rooms, medical and surgical wards, and intensive care units. Each centre was asked to submit pathogens (consecutive, one per patient/ infection site) from blood (360), respiratory (200), urine (100), and wound/IV (50) infections. 7881 and 5282 isolates were collected in 2007 and 2008, respectively. Susceptibility testing was performed using CLSI broth microdilution methods.

Results: The in vitro activities ($MIC_{50/90}$ µg/ml) of carbapenems were:

	Doripenem	Meropenem	Ertapenem
E. coli (2833)	≤0.12/≤0.12	≤0.12/≤0.12	≤0.06/≤0.06
P. aeruginosa (1006)	0.5/8	0.5/8	8/>32
K. pneumoniae (771)	≤0.12/≤0.12	≤0.12/≤0.12	≤0.06/≤0.06
E. cloacae (280)	≤0.12/≤0.12	≤0.12/≤0.12	≤0.12/0.5
MSSA (1826)	≤0.12/≤0.12	≤0.12/≤0.12	0.25/0.25
HA-MRSA (477)	8/32	8/>32	16/>32
CA-MRSA (149)	0.5/2	1/4	2/4
S. pneumoniae (1168)	≤0.06/≤0.06	≤0.06/≤0.06	≤0.06/0.12
E. faecalis (254)	4/8	4/8	8/16
E. faecium (107)	>32/>32	>32/>32	>32/>32

MS-methicillin-susceptible, MR-methicillin-resistant, HA-healthcare associated, CA-community associated.

Conclusion: Doripenem displayed similar activity to meropenem. Carbapenem resistance in *Enterobacteriaceae* isolated from patients in Canadian hospitals is rare.

INTRODUCTION

Carbapenems exhibit a broad spectrum of activity within the ß-lactam antimicrobial class. They are bactericidal against many pathogens including gram negative/positive aerobes and anaerobes. They exhibit remarkable stability to most ß-lactamases and have enjoyed excellent clinical success. Microbiologically, imipenem has slightly more in vitro activity against gram positive pathogens and slightly less activity against gram negative pathogens compared to meropenem. Ertapenem was developed as a long half life molecule utilized against pathogens from complicated infections not involving hospital pathogens such as *Enterococcus* spp., *Pseudomonas aeruginosa* and other non-fermenters. Doripenem, a new to market carbapenem, is similar in spectra to imipenem and meropenem but with increased in vitro activity against *P. aeruginosa*. Carbapenems are generally stable to most ß-lactamases including AmpC ß-lactamases and ESBLs. MIC_{90} tend to rise in the presence of these enzymes but MICs generally remain within the susceptible category. Organisms such as methicillin resistant *S. aureus* (MRSA) and *E. faecium* exhibit intrinsic resistance due to poor affinity for $PBP2_a$ and PBP5. However, resistance due to acquired ß-lactamases including class B metallo-ß-lactamases (IMP, VIM, SPM), class A (SME, NMC/IMI, KPC) and class D (OXA) enzymes, generally termed carbapenems, has been increasing. In some organisms (especially *P. aeruginosa*) porin loss and enzyme acquisition can lead to resistance including multi drug efflux pumps expression.

The purpose of this study was to examine the extent of resistance to meropenem, ertapenem and doripenem against a diverse collection of recent (2007/08) clinical isolates collected as part of a Canadian national hospital based surveillance study.

MATERIALS and METHODS

Bacterial Isolates:

12 (2007), 10 (2008) sentinel hospital sites in major population centres in 7 of the 10 provinces in Canada were recruited. These sites were geographically distributed in a population based fashion.

From January 2007 through December 2008, each study site was asked to collect and submit pathogens (consecutive isolates, one per patient) using the following criteria:

- 200 isolates from patients with respiratory tract infections (community or nosocomial)
- 50 isolates from patients with skin/skin structure infections (wound/IV site infections)
- 100 isolates from patients with urinary tract infections (inpatients or outpatients)
- 20 blood stream infection isolates/site/month

All submitted isolates were deemed significant by each site. All organisms were identified at each site using local site criteria and at the reference site, where indicated.

At study site, isolates were subcultured on appropriate solid media and incubated overnight. Isolates were shipped on Amies semi-solid transport media to the coordinating laboratory (Health Sciences Centre, Winnipeg, Canada), where isolates were subcultured on appropriate media, and stocked in skim milk at -80°C.

Susceptibility Studies:

A custom microtitre panel was designed with a variety of antimicrobials. Antimicrobials were obtained as laboratory grade powders from their respective manufacturers. Stock solutions were prepared and dilutions made as described by the Clinical and Laboratory Standards Institute (2009 CLSI). Following two subcultures from frozen stock, the MICs were determined by the CLSI-approved broth microdilution method (M100-S19, 2009). Briefly, 96-well custom designed microtitre plates containing doubling antibiotic dilutions in 100µl/well of cation adjusted Mueller-Hinton broth (eg. for Enterobacteriaceae) with or without lysed horse blood (2.5% V/V) (eg. for S. pneumoniae) was inoculated to achieve a final concentration of approximately $5x10^5$ CFU/ml and incubated in ambient air (35°C) for 20-24 hours prior to reading. Quality control was performed periodically using a variety of ATCC QC organisms including: *S. pneumoniae* 49619, *S. aureus* 29213, *E. faecalis* 29212, *E. coli* 25922 and *P. aeruginosa* 27853. For all antimicrobials tested, MIC interpretive standards were defined according to CLSI breakpoints (M100-S19, 2009).

RESULTS

Table 1. Comparative in vitro activity of doripenem, ertapenem and meropenem

Organism (#)	Doripenem				Ertapenem				Meropenem			
	MIC_{50}	MIC_{90}	Range	% S[1]	MIC_{50}	MIC_{90}	Range	% S	MIC_{50}	MIC_{90}	Range	% S
E. coli – All (2833)	≤0.12	≤0.12	≤0.12 – 0.5	100	≤0.06	≤0.06	≤0.06 – 1	99.7	≤0.06	0.12	≤0.06 – 0.5	100
ESBL + (108)	≤0.12	≤0.12	≤0.12 – 0.5	100	≤0.12	0.25	≤0.12 – 0.5	100	≤0.12	≤0.12	≤0.12 – 0.5	100
ESBL – (2725)	≤0.12	≤0.12	≤0.12 – 0.5	100	0.06	0.06	0.06 – 1	100	≤0.12	≤0.12	≤0.12 – 0.5	100
K. pneumoniae – All (771)	≤0.06	≤0.12	≤0.06 – 0.25	100	≤0.06	≤0.06	≤0.06 – 1	99.8	≤0.06	≤0.12	≤0.06 – 0.25	100
ESBL + (17)	≤0.12	≤0.12	≤0.06 – 0.25	100	≤0.12	0.25	≤0.06 – 0.25	100	≤0.12	≤0.12	≤0.06 – 0.25	100
ESBL – (754)	≤0.12	≤0.12	≤0.12 – 0.25	100	0.06	0.06	0.06 – 1	100	≤0.12	≤0.12	≤0.12 – 0.25	100
P. aeruginosa (1006)	0.5	8	≤0.06 - >64	83.3	8	>32	0.12 - >32	NA	0.5	8	≤0.06 - >64	88.8
E. cloacae (280)	≤0.12	≤0.12	≤0.12 – 2	99.3	≤0.06	0.5	≤0.06 – 8	98.9	≤0.12	≤0.12	≤0.12 – 1	100
S. aureus - All (1825	≤0.06	≤0.12	≤0.06 – 0.5	NA	0.25	0.25	0.12 – 1	100	0.12	0.12	≤0.06 – 1	100
HA-MRSA* (477)	8	32	≤0.06 - >32	NA	16	>32	0.5 - >32	10	8	>32	0.25 - >32	30.8
CA-MRSA* (149)	0.5	2	≤0.06 – 16	NA	2	4	0.25 - >32	66	1	4	0.12 – 16	95.3
S. pneumoniae – All (1168)	≤0.06	0.06	≤0.03 – 2	NA	≤0.06	0.12	≤0.06 – 4	99.9	≤0.06	≤0.06	≤0.06 – 2	96.2
Pen S (928)	≤0.12	≤0.12	≤0.12 – 0.25	NA	0.06	0.06	0.06 – 0.12	100	≤0.12	≤0.12	≤0.12 – 0.5	99.9
Pen I (179)	≤0.06	0.25	≤0.06 – 1	NA	≤0.06	0.25	≤0.06 – 1	100	≤0.06	0.25	≤0.06 – 1	95.5
Pen R (56)	0.5	1	≤0.12 – 2	NA	0.5	1	0.06 – 4	98.2	0.5	1	≤0.12 – 2	37.5
Mac R (174)	≤0.12	0.5	≤0.12 – 2	NA	0.06	0.5	0.06 – 4	99.4	≤0.12	0.5	≤0.12 – 2	83.3
FQ R (Cipro) (52)	≤0.12	0.25	≤0.12 – 1	NA	0.06	0.5	0.06 – 4	98.1	≤0.12	0.25	≤0.12 – 2	92.3
E. faecalis (254)	4	8	≤0.06 - >32	NA	8	16	0.25 - >32	NA	4	8	≤0.06 - >32	NA
E. faecium (107)	>32	>32	2 - >32	NA	>32	>32	4 - >32	NA	>32	>32	2 - >64	NA

* based on oxacillin susceptibility

[1] utilizing FDA breakpoints/OMP product monograph

Table 2. MIC Frequency Distribution for Doripenem, Ertapenem, Meropenem vs. *P. aeruginosa* (n=1006)

	N over Cumulative Percentage									
	0.12	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**Total**
Doripenem	200[a]	197	206	150	85	64	50	34	20[b]	1006
	19.9	39.5	59.9	74.9	83.3	89.7	94.6	98	100	
Ertapenem	8	10	5	27	74	81	108	79	118[b]	510
	1.6	3.5	4.5	9.8	24.3	40.2	61.4	76.9	100	
Meropenem	151[a]	202	204	177	99	60	41	37	35[b]	1006
	15	35.1	55.4	73	82.8	88.8	92.8	96.5	100	

[a] Shown are numbers for the lowest common concentration tested in the chosen study(s); Actual MICs of some isolates may be lower than indicated here.

[b] Shown are numbers for the highest common concentration tested in the chosen study(s); Actual MICs of some isolates may be higher than indicated here.

CONCLUSIONS

1. Doripenem displayed comparable in vitro activity (MIC_{90}) as meropenem against the majority of pathogens studied in Canadian hospitals in 2007 and 2008.
2. Doripenem displayed activity comparable to ertapenem and meropenem for *S. pneumoniae* (all phenotypes).
3. MIC_{90} for doripenem and meropenem were 8 µg/ml with %S comparable (83% vs. 89%) for *P. aeruginosa*.
4. Frequency distribution analysis of doripenem and meropenem vs. *P. aeruginosa* were essentially identical. Susceptibility rates reflect different per cent susceptible breakpoints (2 µg/ml vs. 4 µg/ml).

ACKNOWLEDGEMENTS

The authors would like to thank the following participating centres and laboratory staff: Vancouver Hospital, Vancouver, BC (Dr. D. Roscoe); University of Alberta Hospital, Edmonton, AB (Dr. R. Rennie); Royal University Hospital, Saskatoon, SK (Dr. J. Blondeau); Health Sciences Centre, Winnipeg, MB (Dr. D. Hoban/Dr. G. Zhanel); London Health Sciences Centre, London, ON (Dr. Z. Hussain); St. Joseph's Hospital, Hamilton, ON (Dr. C. Lee); Mount Sinai Hospital, Toronto, ON (Dr. S. Poutanen); Children's Hospital of Eastern Ontario, Ottawa, ON (Dr. F. Chan); Hôpital Maisonneuve-Rosemont, Montréal, QC (Dr. M. Laverdière); Montréal General Hospital, Montréal, QC (Dr. V. Loo); Royal Victoria Hospital, Montréal, QC (Dr. V. Loo); Queen Elizabeth II Health Sciences Centre, Halifax, NS (Dr. R. Davidson). Financial support of Abbott Laboratories Ltd, Affinium Pharmaceuticals, Janssen-Ortho Inc, Merck Frosst Canada, Pfizer Canada, Targanta Therapeutics Corp. and Wyeth Pharmaceuticals is gratefully acknowledged.

Presented at the 49th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy - San Francisco, CA - September 12-15, 2009