E-260

Doripenem Activity Tested Against Gram-Negative Pathogens in the Asia-Pacific (APAC) Region: Report From the SENTRY Antimicrobial Surveillance Program (2006)

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Abstract (Updated)

Background: Doripenem, an investigational parenteral carbapenem, exhibits a broad spectrum of activity and favorable potency. As resistance emergence increases in the Asia-Pacific region, data are needed to assess the activity of new agents.

Methods: Clinically significant Gram-negative isolates (N = 4222) from infected patients in 10 countries (42 laboratories) were submitted to the Asia-Pacific monitor for identification confirmation and susceptibility testing. Broth microdilution panels (TREK Diagnostics) were utilized according to Clinical and Laboratory Standards Institute methods.

Results: Across the Asia-Pacific region, doripenem had excellent activity against Enterobacteriaceae, including strains harboring extended-spectrum β-lactamases (ESBLs) and chromosomally expressed cephalosporinases (CEPs). Occasional strains of Enterobacteriaceae with carbapenemases affecting doripenem were detected in India, Indonesia, Korea, China, and Taiwan. Excluding Singapore (only 6 strains), the percentage of *Pseudomonas aeruginosa* isolates with doripenem MICs above 4 μg/mL varied from only 3.6% in Australia to 50% in Korea. The rates of MICs above 4 μg/mL in *Acinetobacter baumannii* were higher in all countries, but varied greatly between institutions. Doripenem was active against more than 99% of Enterobacteriaceae regardless of CEP or ESBL enzyme production.

Conclusions: Doripenem is a potent β-lactam against Enterobacteriaceae, including strains with documented resistance mechanisms in the Asia-Pacific region. CEPs and other resistances are common in many Asia-Pacific countries and may require new therapeutic options such as doripenem.

Introduction

Doripenem is an investigational parenteral carbapenem that possesses a broad antibacterial spectrum of activity and favorable potency. As resistance among Gram-negative pathogens increases in the Asia-Pacific region, data are needed to assess trends and provide guidance for empiric therapy decisions. Here, we summarize the results of an international surveillance program comparing doripenem and other agents against contemporary isolates of Gram-negative pathogens in the Asia-Pacific region.

Methods

Bacterial Isolates

- A total of 4222 non-duplicate, clinically significant patient isolates were submitted from 42 medical centers in 10 countries in the Asia-Pacific region (Australia, 5 sites; China, 11; Hong Kong, 1; India, 11; Indonesia, 4; Korea, 3; Philippines, 2; Singapore, 1; Taiwan, 2; Thailand, 2) during 2006.
- Isolates originated from patients with documented bloodstream, respiratory tract, and skin and soft tissue infections. The doripenem minimum inhibitory concentration (MIC) distributions of leading species and strains processed are presented in Table 1.

Table 1. Activity of Doripenem Against Gram-Negative Pathogens Collected as Part of the Asia-Pacific SENTRY Surveillance Program (2006)

	MIC (μg/mL)		Number of Isolates Inhibited at Each MIC (μg/mL)							
Organism (no. tested)	50%	90%	≤0.06	0.12	0.25	0.5	1	2	4	8	>8
Escherichia coli (918)											
ESBL-negative (437)	≤0.06	≤0.06	436	1							
ESBL-positive (481)	≤0.06	≤0.06	461	10	2	5			3		
Klebsiella spp. (906)											
ESBL-negative (449)	≤0.06	≤0.06	397	51		1					
ESBL-positive (457)	≤0.06	0.12	356	69	16	4	6	2	3	1	
Enterobacter spp. (360)	≤0.06	0.25	239	82	28	8	2				1
Pseudomonas aeruginosa (721)	0.5	>8	5	104	117	141	105	58	31	79	81
Acinetobacter baumannii (514)	2	>8	2	33	77	53	32	65	28	10	214

- Identification of all isolates was confirmed in a central laboratory (Women's and Children's Hospital, Adelaide, Australia) using reference methodologies.

Susceptibility Tests

- Isolates were tested against a wide range of antimicrobial agents using validated dry-form broth microdilution MIC panels (TREK Diagnostic Systems) according to reference Clinical and Laboratory Standards Institute (CLSI) methods (2006)[1] and interpretive criteria (2007).[2]
- Quality-control strains utilized included *Escherichia coli* ATCC 25922 and 35218, *Pseudomonas aeruginosa* ATCC 27853, *Staphylococcus aureus* ATCC 29213, and *Streptococcus pneumoniae* ATCC 49619. All MIC results were within CLSI-specified ranges.

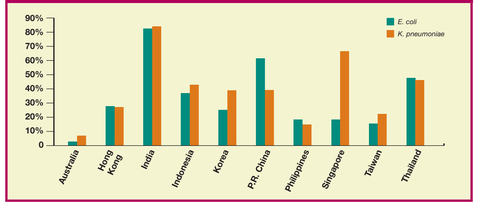
Analysis

- Data were analyzed for MIC_{50} and MIC_{90}. Enterobacteriaceae were analyzed according to whether they contained chromosomal cephalosporinases or potential extended-spectrum β-lactamases (ESBLs).
- Enterobacteriaceae with elevated MIC values (≥2 μg/mL) for ceftazidime and/or ceftriaxone and/or aztreonam were considered as ESBL-producing phenotypes.
- *Acinetobacter* spp. and *Pseudomonas* spp. with imipenem or meropenem MICs ≥8 μg/mL, and Enterobacteriaceae with imipenem or meropenem MICs ≥2 μg/mL were screened for metallo-β-lactamase enzymes and OXA-23, -24, -51, and -58 enzymes.
- Enterobacteriaceae with ertapenem MIC ≥1 μg/mL were screened for KPC-type carbapenemases.

Results

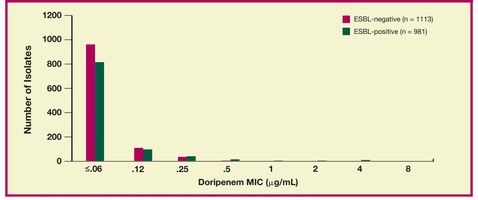
- Doripenem MIC distributions and MIC_{50}/MIC_{90} against common Gram-negative species are shown in Table 1.
- ESBL screen-positive *E. coli* (52%; range: 2.6% [Australia] to 83% [India]) and *K. pneumoniae* (52%; range: 7.1% [Australia] to 84% [India]) were very common in the Asia-Pacific region (Figure 1).

Figure 1. ESBL Phenotypes Among *E. coli* (n = 918) and *K. pneumoniae* (n = 850) Isolates From the Asia-Pacific Region



- The activity of doripenem was unaffected by the presence of presumptive ESBL-producing isolates (Figure 2).

Figure 2. Doripenem MIC Distribution Versus ESBL Phenotype in ESK[a] Group Organisms



[a]ESK = *E. coli*, *Klebsiella* spp., *Proteus mirabilis*, *Salmonella* spp., and *Citrobacter* spp. other than *Citrobacter freundii*.

- 99.7% of all *E. coli* and *Enterobacter* spp. isolates were inhibited by doripenem at concentrations ≤1 μg/mL (MIC_{90}, ≤0.06 to 0.25 μg/mL). Two *E. coli* from India and 1 from Taiwan had doripenem MIC = 4 μg/mL. The comparative activity of doripenem by nation is shown in Table 2.
- Two *K. pneumoniae* isolates from China (1.0%) had doripenem MIC of 4 μg/mL; 1 strain contained KPC-2 and the other bla_{IMP-4}. Two isolates from Korea (4.9%) had doripenem MIC values of 4 and 8 μg/mL; both contained class A/B β-lactamases. Doripenem had activity against these isolates similar to meropenem.

Table 2. Comparative Activity of Doripenem by Nation

	Percent Inhibited at ≤4 μg/mL									
Organism (no. tested)	Australia	Hong Kong	India	Indonesia	Korea	China	Philippines	Singapore	Taiwan	Thailand
ESK[a] (2094)										
ESBL-negative (1113)	100	100	100	100	100	100	100	100	100	100
ESBL-positive (981)	100	100	100	100	96.7	100	100	100	100	100
CEP[b] (589)	100	100	99.2	100	100	100	100	100	100	100
P. aeruginosa (721)	96.4	94.4	72.5	88.9	50.0	79.5	91.2	66.7	68.2	94.2
A. baumannii (514)	87.5	50.0	54.5	98.1	12.8	67.8	100	4.8	36.4	38.3

[a]ESK = *E. coli*, *Klebsiella* spp., *Proteus mirabilis*, *Salmonella* spp., and *Citrobacter* spp. other than *Citrobacter freundii*.
[b]CEP = Enterobacteriaceae with chromosomal Amp-C cephalosporinases.

- Doripenem (76.4%) inhibited a greater percentage of *P. aeruginosa* isolates at ≤4 μg/mL than either meropenem (75.5%) or imipenem (74.1%) (Table 3).
- Against *A. baumannii*, doripenem activity was similar to that of imipenem and meropenem, with 56%-57% inhibited at ≤4 μg/mL (Table 3).

Table 3. Comparative Activity of Doripenem Versus Other Carbapenems

	Percent Inhibited at ≤4 μg/mL		
Organism (no. tested)	Doripenem	Imipenem	Meropenem
ESK[a] group (2094)			
ESBL-negative (1113)	100	99.9	100
ESBL-positive (981)	99.9	99.4	99.2
CEP[b] group (589)	99.8	99.7	99.8
P. aeruginosa (721)	76.4	74.1	75.5
A. baumannii (514)	55.9	57.4	56.2

[a]ESK = *E. coli*, *Klebsiella* spp., *Proteus mirabilis*, *Salmonella* spp., and *Citrobacter* spp. other than *Citrobacter freundii*.
[b]CEP = Enterobacteriaceae with chromosomal Amp-C cephalosporinases.

- Doripenem activity was affected by known carbapenemases, including class A, B, and D (Figures 3-4).

Figure 3. Doripenem MIC Distribution for *Pseudomonas* spp. With or Without Class B β-lactamases

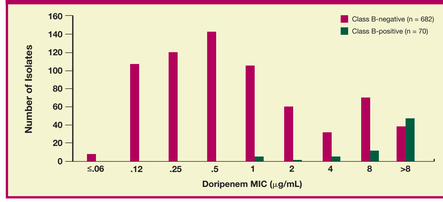
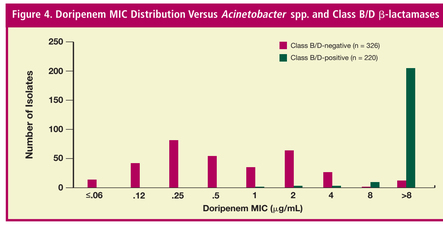


Figure 4. Doripenem MIC Distribution Versus *Acinetobacter* spp. and Class B/D β-lactamases



Conclusions

- The global emergence of resistance, particularly in the Asia-Pacific region, has created a critical need for the accelerated development and introduction of novel antimicrobials.
- Doripenem, an investigational carbapenem, displays potent activity against the most common and problematic Gram-negative hospital pathogens in the Asia-Pacific region, especially the Enterobacteriaceae (including all ESBL- and chromosomal cephalosporinase-producing strains) and non-fermentative bacilli.

References

1. Clinical and Laboratory Standards Institute. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically*; M7-A7. Wayne, PA; CLSI:2006.
2. Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing*; 17th informational supplement, M100-S17. Wayne, PA; CLSI:2007.

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