NA33

Doripenem Activity Against Leading Bacterial Pathogens in the Asia-Pacific Region: Report From the SENTRY Antimicrobial Surveillance Program (2006)

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ABSTRACT

Background: Doripenem, an investigational parenteral carbapenem, exhibits a broad antibacterial spectrum and favourable potency. As resistance emergence increases in the Asia-Pacific region, data are needed to assess trends. We summarize the results of an international surveillance programme comparing doripenem and other agents against contemporary Asia-Pacific pathogens.

Methods: Clinically significant isolates (1389 gram– and 2972 gram+ isolates) from infected patients in 10 countries (37 laboratory centres) were submitted to the Asia-Pacific monitor for identification confirmation and susceptibility testing. Broth microdilution panels (TREK Diagnostics) were utilized according to CLSI recommendations and interpretive criteria. Agents tested included doripenem, imipenem, meropenem, and ertapenem.

Results: Doripenem displays potent activity against oxacillin-susceptible *S. aureus* and *S. pneumoniae* ($MIC_{50/90}$ values, ≤0.06/≤0.06 and ≤0.06/1 mg/L, respectively), similar to other carbapenems. Against Enterobacteriaceae, including ESBL screen-positive strains (41% of *E. coli*; 44% of *K. pneumoniae*), doripenem activity was most similar to meropenem (MIC_{90}, ≤0.06 and 0.12 mg/L, respectively). Doripenem activity vs. *P. aeruginosa* was similar to meropenem, and against *Acinetobacter* spp., was like that of imipenem and meropenem.

Conclusions: Doripenem, an investigational carbapenem with a favourable antimicrobial profile, inhibits the most common and problematic Asia-Pacific hospital pathogens, especially the Enterobacteriaceae and non-fermentative bacilli.

INTRODUCTION

Doripenem is an investigational parenteral carbapenem that possesses a broad antibacterial spectrum of activity and favourable potency. As resistance amongst 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 programme comparing doripenem and other agents against contemporary Asia-Pacific pathogens.

METHODS

Bacterial Isolates

- A total of 4430 non-duplicate, clinically significant patient isolates were submitted from 37 medical centres in ten countries in the Asia-Pacific region (Australia 5 sites; China 10 sites; Hong Kong 1 site; India 10 sites; Indonesia 2 sites; Korea 3 sites; Philippines 2 sites; Singapore 1 site; Taiwan 2 sites; and Thailand 1 site) during 2006.
- Isolates originated from patients with documented bloodstream, respiratory, and skin and soft tissue infections. The MIC distributions of leading species and strains are presented in Table 1.
- 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 CLSI reference methods[1] and interpretive criteria.[2]
- MIC tests were performed in cation-adjusted Mueller-Hinton broth (with the addition of 2%–5% lysed horse blood for testing of *Streptococcus pneumoniae*).
- Quality control strains utilized included *Escherichia coli* ATCC 25922 and 35218, *Pseudomonas aeruginosa* ATCC 27853, *Staphylococcus aureus* ATCC 29213, and *S. pneumoniae* ATCC 49619; all MIC results were within CLSI-specified ranges.

Analysis

- Data were analysed for MIC_{50}, MIC_{90}, and wild-type cut-off values (CO_{WT}).
- Enterobacteriaceae with elevated MIC values (≥2 mg/L) for ceftazidime and/or ceftriaxone and/or aztreonam were considered to have ESBL-producing phenotypes.

RESULTS

- Doripenem was broadly active against oxacillin-susceptible staphylococci (*S. aureus* and coagulase-negative staphylococci, 100% at ≤0.5 mg/L; Table 1).
- Doripenem was also highly active against the tested population of *S. pneumoniae* (MIC_{50}, ≤0.06 mg/L; MIC_{90}, 1 mg/L; Table 1). Increased resistance to penicillin (28.1%) among *S. pneumoniae* resulted in elevations of the MIC_{90}, suggesting that doripenem is similarly affected by changes in penicillin-binding proteins.
- ESBL-screen-positive *E. coli* (41%) and *Klebsiella pneumoniae* (44%) were very common in the Asia-Pacific region. The activity of doripenem was unaffected by the presence of presumptive ESBLs (data not shown).
- All *E. coli* and *Enterobacter* spp. isolates were inhibited by doripenem at concentrations ≤1 mg/L (MIC_{90}, ≤0.06 to 0.12 mg/L). Two *Klebsiella pneumoniae* isolates from Korea (0.3%) had doripenem MIC values at 4 and 8 mg/L; both contained class B/A β-lactamases.
- CO_{WT} values could only be effectively estimated for *P. aeruginosa* and *A. baumannii*, as the lowest concentration of doripenem tested (0.06 mg/L) was too high to be able to demonstrate the MIC distributions of the other species.
- Doripenem inhibited 49% of *Acinetobacter baumannii* isolates at ≤4 mg/L.
- Doripenem inhibited a greater percentage of *Pseudomonas aeruginosa* isolates at ≤4 mg/L than either meropenem or imipenem (80.5%, 78.3%, and 76.4%, respectively) (Table 2).

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

	MIC (mg/L)		Number of Isolates Inhibited at Each MIC (mg/L)									
Organism (number tested)	50%	90%	≤0.06	0.12	0.25	0.5	1	2	4	8	>8	CO_{WT} (mg/L)
Staphylococcus aureus (oxacillin-susceptible, 885)	≤0.06	≤0.06	872	10	1	2						ND
Coagulase-negative staphylococci (oxacillin-susceptible, 52)	0.12	0.25	18	25	4	5						-
Streptococcus pneumoniae												
All (256)	≤0.06	1	178	2	7	22	46	1				
Penicillin-susceptible (159)	≤0.06	≤0.06	159									ND
Penicillin-intermediate (25)	≤0.06	0.25	19	2	2	2						-
Penicillin-resistant (72)	1	1			5	20	46	1				-
Escherichia coli (331)	≤0.06	≤0.06	327	3	1							ND
Klebsiella spp. (331)	≤0.06	0.12	283	39	5	2			1	1		ND
Enterobacter spp. (92)	≤0.06	0.12	62	21	6	2	1					ND
Pseudomonas aeruginosa (267)	0.5	>8	2	39	49	54	40	22	9	22	30	4
Acinetobacter baumannii (163)	8	>8	1	12	27	14	11	11	4	2	81	8

Table 2. Comparative Activity of Doripenem Versus Other Carbapenems

	% Inhibited*			
Organism (number tested)	Doripenem	Imipenem	Meropenem	Ertapenem
Enterobacteriaceae (n = 909)	99.8	99.6	99.6	98.8
Pseudomonas aeruginosa (n = 267)	80.5	76.4	78.3	26.2
Acinetobacter baumannii (n = 163)	49.1	49.7	49.7	24.5
Staphylococcus aureus - oxacillin-susceptible (n = 885)	100.0	100.0	-	100.0
Streptococcus pneumoniae (n = 256)	99.6	71.5	-	91.4

*≤4 mg/L for doripenem, imipenem, and meropenem except for *S. pneumoniae* (doripenem, ≤1 mg/L; imipenem, ≤0.12 mg/L); ≤2 mg/L for ertapenem (≤1 mg/L for *S. pneumoniae*).

CONCLUSIONS

- The emergence of resistance globally, and in the Asia-Pacific region in particular, has created a critical need for accelerated development and introduction of novel antimicrobials.
- Doripenem, an investigational carbapenem with a favourable antimicrobial profile, inhibits the most common and problematic Asia-Pacific hospital pathogens, especially the Enterobacteriaceae (including all ESBL-producing strains) and non-fermentative bacilli.

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