

# *In Vitro* Activity of Biapenem against Gram-Negative Bacteria Isolated from Hospitalized Patients at Siriraj Hospital

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## ABSTRACT

*In vitro* activity of biapenem against 30 clinical isolates each of ESBL-producing *Escherichia coli*, ESBL-producing *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* was determined by disk diffusion and agar dilution method. The susceptibility rates of ESBL-producing *E. coli*, ESBL-producing *K. pneumoniae*, *P. aeruginosa* and *A. baumannii* to biapenem by disk diffusion were 100 percent, 100 percent, 70 percent and 37 percent, respectively. The MIC<sub>50</sub> and MIC<sub>90</sub> of biapenem against ESBL-producing *K. pneumoniae*, ESBL-producing *E. coli*, *P. aeruginosa* and *A. baumannii* were 0.06/0.06, 0.125/0.25, 1/32 and 32/64 mg/L, respectively. (*J Infect Dis Antimicrob Agents* 2010;27:55-9.)

## INTRODUCTION

Biapenem is a parenteral carbapenem anti-bacterial agent.<sup>1,2</sup> Biapenem has a broad spectrum of *in vitro* antibacterial activity against many gram-negative and gram-positive aerobic and anaerobic bacteria, including those producing  $\beta$ -lactamases.

Biapenem is stable to hydrolysis by human renal dihydropeptidase-I (DHP-I) and it does not require the coadministration of a DHP-I inhibitor. Biapenem has been available in Japan since 2002 and it was approved by the Food and Drug Administration, Ministry of Public Health, Thailand in 2009.

The objective of the study is to determine *in vitro* activity of biapenem against common gram-negative bacteria isolated from the patients at Siriraj Hospital.

## MATERIALS AND METHODS

### *Study Organisms*

Clinical isolates of extended-spectrum beta-lactamase enzyme (ESBL)-producing *E. coli* (N=30), *K. pneumoniae* (N=30), *P. aeruginosa* (N=30) and *A. baumannii* (N=30) were included. The studied organisms were isolated from blood, sputum or pus of the hospitalized patients at Siriraj Hospital who

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developed hospital-acquired infections during 2006 and 2009.

### Susceptibility Test

The activity of biapenem against the studied organisms was determined by Kirby-Bauer disk diffusion and agar dilution. The biapenem disk (10 µg, Eiken Chemical Co. Ltd., Japan) and standard powder (Eiken Chemical Co. Ltd., Japan) were provided by Meiji Pharmaceuticals (Thailand). Minimum inhibitory concentration (MIC) of imipenem or meropenem against the tested organisms was also determined. Quality control was performed by testing the susceptibility of *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853. The methodology for susceptibility testing was by direct colony suspension as recommended by the CLSI.<sup>3</sup> Interpretative criteria

for susceptibility of ESBL-producing *E. coli*, ESBL-producing *K. pneumoniae*, *P. aeruginosa* and *A. baumannii* to biapenem are shown in Tables 1 and 2.

### RESULTS

The inhibition zone diameters of the quality control strains were 33 mm. for *E. coli* ATCC 25922 and 31 mm. for *P. aeruginosa* ATCC 27853. The MICs of biapenem against the quality control strains were 0.06 mg/L for *E. coli* ATCC 25922 and 1 mg/L for *P. aeruginosa* ATCC 27853.

The susceptibility of ESBL-producing *E. coli*, ESBL-producing *K. pneumoniae*, *P. aeruginosa* and *A. baumannii* to biapenem determined by inhibition zone diameter are shown in Table 3. The rates of resistance of ESBL-producing *E. coli*, ESBL-producing *K. pneumoniae*, *P. aeruginosa* and *A. baumannii* to

**Table 1. Interpretative criteria for susceptibility (inhibition zone diameter) of ESBL-producing *E. coli*, ESBL-producing *K. pneumoniae*, *P. aeruginosa* and *A. baumannii* to biapenem.**

Antibiotic	Susceptible	Intermediate	Resistant
Biapenem (10 µg per disk)	≥ 20 mm	15-19 mm	≤ 14 mm

**Table 2. Interpretative criteria for susceptibility (MIC) of ESBL-producing *E. coli*, ESBL-producing *K. pneumoniae*, *P. aeruginosa* and *A. baumannii* to biapenem, imipenem and meropenem.**

Antibiotic	Susceptible	Intermediate	Resistant
Biapenem	≤ 4 mg/L	8	≥ 16 mg/L
Imipenem	≤ 4 mg/L	8	≥ 16 mg/L
Meropenem	≤ 4 mg/L	8	≥ 16 mg/L

biapenem were 0 percent, 0 percent, 13 percent and 63 percent, respectively.

The MIC<sub>50</sub> and MIC<sub>90</sub> of biapenem, imipenem and meropenem against the ESBL-producing *E. coli*, ESBL-producing *K. pneumoniae*, *P. aeruginosa* and *A. baumannii* are shown in Table 4. The MIC<sub>90</sub> of biapenem tended to be less than that of imipenem and

meropenem for ESBL-producing *E. coli*, ESBL-producing *K. pneumoniae* and *P. aeruginosa*.

## DISCUSSION

*In vitro* activity of biapenem, imipenem and meropenem against gram-negative and gram-positive pathogens in more than 6,000 clinical isolates worldwide

**Table 3. Susceptibility of ESBL-producing *E. coli*, ESBL-producing *K. pneumoniae*, *P. aeruginosa* and *A. baumannii* to biapenem determined by inhibition zone diameter.**

Organism	Susceptible	Intermediate	Resistant
ESBL-producing <i>E. coli</i>	100%	-	-
ESBL-producing <i>K. pneumoniae</i>	100%	-	-
<i>P. aeruginosa</i>	70%	17%	13%
<i>A. baumannii</i>	37%	-	63%

**Table 4. MIC<sub>50</sub> and MIC<sub>90</sub> of biapenem, imipenem and meropenem against the ESBL-producing *E. coli*, ESBL-producing *K. pneumoniae*, *P. aeruginosa* and *A. baumannii*.**

Organism	Antibiotic	MIC <sub>50</sub> (mg/L)	MIC <sub>90</sub> (mg/L)	MIC Range (mg/L)
ESBL-producing <i>E. coli</i>	Biapenem	0.06	0.06	0.03 - 0.25
	Imipenem	0.13	0.25	0.13 - 0.25
ESBL-producing <i>K. pneumoniae</i>	Biapenem	0.125	0.5	0.06 - 1
	Imipenem	0.25	2	0.06 - 2
<i>P. aeruginosa</i>	Biapenem	1	32	0.5 - > 32
	Meropenem	0.38	>32	0.064 - > 32
<i>A. baumannii</i>	Biapenem	32	64	0.5 - > 32
	Meropenem	0.38	>32	0.064 - > 32

revealed that the activity of biapenem was comparable to imipenem and meropenem.<sup>4</sup> The MIC<sub>50</sub> and MIC<sub>90</sub> values of biapenem and imipenem against more than 1,000 strains of gram-negative and gram-positive pathogens isolated from the patients in Japan were also comparable.<sup>5-7</sup> Our findings demonstrated that biapenem was active against clinical isolates of common multi-drug resistant gram-negative bacteria comparable to imipenem and meropenem. The recommended dosage of intravenous biapenem is 300 mg twice daily which is less than that of imipenem/cilastatin and meropenem. Administration of biapenem is more convenient than imipenem/cilastatin and meropenem since the frequency of administration of biapenem is twice daily whereas that of imipenem/cilastatin and meropenem is 3-4 times daily. Biapenem showed good clinical and bacteriological efficacy similar to that of imipenem/cilastatin for the treatment of adult patients with intra-abdominal infections, lower respiratory infections and complicated urinary tract infections.<sup>8-17</sup> Intravenous biapenem (300 or 500 mg twice daily) was generally well tolerated. In comparative clinical trials, adverse events were reported in 1.9 percent-3.4 percent of patients who received biapenem compared with 1.8 percent- 6.3 percent of recipients of imipenem/cilastatin. Therefore, biapenem should be an effective alternative option of carbapenem for therapy of infections in Thai patients.

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