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ORIGINAL ARTICLE

Activities of doripenem against nosocomial bacteremic drug-resistant Gram-negative bacteria in a medical center in Taiwan

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Background: The majority of nosocomial infections in Taiwan hospitals are caused by drug-resistant Gram-negative bacteria (GNB), including *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and various species of *Enterobacteriaceae*. Carbapenems are important agents for treating infections caused by these GNB. Recently, doripenem was approved for use in Taiwan in August 2009. However, data on its *in vitro* activity against nosocomial GNB isolated from Taiwan remain limited. The study was designed to look into this clinical issue.
Methods: A total of 400 nonduplicated nosocomial blood isolates isolated in 2009, inclusive of *P. aeruginosa* ($n = 100$), *A. baumannii* ($n = 100$), and *Enterobacteriaceae* ($n = 200$), were randomly selected from the bacterial bank preserved at National Taiwan University Hospital. Susceptibilities of these 400 isolates to various antibiotics, including doripenem, imipenem, meropenem, ceftazidime, amikacin, ciprofloxacin, colistin, and tigecycline were determined by using Etest.
Results: Doripenem demonstrated similar *in vitro* activity to imipenem and meropenem against *P. aeruginosa* (87%, vs. 85% and 89%), *A. baumannii* (56%, vs. 60% and 60%), and *Enterobacteriaceae* (100%, vs. 98.5% and 99.5%). The prevalence of carbapenem-resistant (any one of three tested carbapenems) *P. aeruginosa*, *A. baumannii*, and *Enterobacteriaceae* isolates was 15%, 44%, and 0.5%, respectively.
Conclusions: Doripenem was as effective as imipenem and meropenem in our study. However, there was a significant proportion of carbapenem resistance among the tested isolates. Hence, longitudinal surveillance is necessary to monitor the resistance trend.

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Table 1 Minimal inhibitory concentrations (MICs) of and susceptibilities to 8 antimicrobial agents in clinical isolates of *P. aeruginosa* and *A. baumannii*

Antimicrobial agent	MIC (μg/mL) and susceptibility (%S)							
	P. aeruginosa (n = 100)				*A. baumannii*(n = 100)			
	Range	MIC_{50}	MIC_{90}	%S[a]	Range	MIC_{50}	MIC_{90}	%S[b]
Ceftazidime	0.5—>256	1.5	16	87	1—>256	4	>256	60
Doripenem	0.064—>32	0.25	6	87	0.064—>32	0.38	>32	56
Imipenem	0.125—>32	1	24	85	0.125—>32	0.25	>32	60
Meropenem	0.064—>32	0.25	6	89	0.125—>32	0.5	>32	60
Amikacin	1—256	3	8	98	1—>256	6	>256	60
Ciprofloxacin	0.047—>32	0.094	1	90	0.047—>32	0.25	>32	57
Colistin	0.125—4	1	2	95	0.047—0.5	0.25	0.38	100
Tigecycline	1.5—96	12	24		0.094—12	0.5	3	84

[a] The susceptible breakpoints were: ceftazidime, ≤8 μg/mL; doripenem, ≤2 μg/mL; imipenem, ≤4 μg/mL; meropenem, ≤4 μg/mL; amikacin, ≤16 μg/mL; ciprofloxacin, ≤1 μg/mL; colistin, ≤2 μg/mL.
[b] The susceptible breakpoints were: ceftazidime, ≤8 μg/mL; doripenem, ≤1 μg/mL; imipenem, ≤4 μg/mL; meropenem, ≤4 μg/mL; amikacin, ≤16 μg/mL; ciprofloxacin, ≤1 μg/mL; colistin, ≤2 μg/mL; tigecycline, ≤2 μg/mL.

Introduction

The majority of nosocomial infections in Taiwan hospitals are caused by Gram-negative bacteria, including *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and various species of *Enterobacteriaceae*.[1] Among these Gram-negative bacteria causing nosocomial infections, resistance to β-lactam and other antimicrobial agents has increased.[1] Carbapenems have become one of the most important agents for treating infections caused by these multidrug resistance Gram-negative bacteria.[2]

Doripenem was approved use in Taiwan in August 2009. Before that, imipenem/cilastatin and meropenem were the only two antipseudomonal carbapenems available in Taiwan.

Studies in other countries have demonstrated doripenem to have similar *in vitro* activity to meropenem against a wide range of Gram-negative pathogens and to imipenem against Gram-positive pathogens.[3,4]

Doripenem has also been shown to have good activities against extended-spectrum β-lactamase (ESBL) and AmpC producing *Enterobacteriaceae*[5–7] as well as to *P. aeruginosa*[8,9]. It also has limited ability in the selection of resistant strains *in vitro*.[6,10,11] Doripenem has been approved in the United States, European Union, and Taiwan for the treatment of complicated urinary tract and intra-abdominal infections.[12,13] Doripenem has also been approved for a wide range of infections in Japan[14] and for nosocomial pneumonia in the European Union.[13] However, the clinical experience of using doripenem to treat infections caused by multidrug-resistant pathogens and data on its *in vitro* activities against multidrug-resistant pathogens remained limited in Taiwan.[15]

The study was designed to compare the *in vitro* activities of doripenem and other antimicrobial agents including imipenem and meropenem, against drug-resistant Gram-negative pathogens isolated in a medical center in Taiwan.

Materials and methods

Bacterial isolates

A total of 400 nonduplicate nosocomial blood isolates isolated in 2009, including *P. aeruginosa* (n = 100), *A.*

Table 2 Minimal inhibitory concentrations (MICs) of and susceptibilities to 8 antimicrobial agents in clinical isolates of *Enterobacteriaceae*

Antimicrobial agent	MIC (μg/mL) and susceptibility (%S)											
	Enterobacteriaceae (n = 200)				*Escherichia coli* (n = 81)				*Klebsiella pneumoniae* (n = 57)			
	Range	MIC_{50}	MIC_{90}	%S[a]	Range	MIC_{50}	MIC_{90}	%S[a]	Range	MIC_{50}	MIC_{90}	%S[a]
Ceftazidime	<0.016—>256	0.19	32	80	0.064—>256	0.19	16	76.5	0.064—>256	0.19	0.75	91.2
Doripenem	0.004—0.75	0.032	0.094	100	0.012—0.25	0.023	0.047	100	0.023—0.38	0.032	0.047	100
Imipenem	0.032—4	0.38	0.19	98.5	0.094—1	0.19	0.25	100	0.094—4	0.19	0.25	98.2
Meropenem	0.004—1.5	0.032	0.094	99.5	0.012—0.19	0.023	0.094	100	0.016—1.5	0.023	0.047	98.2
Amikacin	0.032—64	2	3	98.5	1—64	2	4	97.5	1—48	2	2	98.2
Ciprofloxacin	0.004—>32	0.032	16	86	0.006—>32	0.19	>32	72.8	0.008—>32	0.032	0.5	93
Colistin	0.125—>256	0.38	12	89	0.125—0.38	0.125	0.38	100	0.125—1	0.5	0.75	100
Tigecycline	0.094—32	0.5	1.5	97.5	0.094—1.5	0.25	0.5	100	0.125—6	0.75	1.5	94.7

[a] The susceptible breakpoints were: ceftazidime, ≤4 μg/mL; doripenem, ≤1 μg/mL; imipenem, ≤1 μg/mL; meropenem, ≤1 μg/mL; amikacin, ≤16 μg/mL; ciprofloxacin, ≤1 μg/mL; colistin, ≤2 μg/mL; tigecycline, ≤2 μg/mL.

baumannii ($n = 100$) and *Enterobacteriaceae* ($n = 200$), were randomly selected from the bacterial bank preserved at National Taiwan University Hospital. Nosocomial isolates were defined as those isolated after 48 hours after admission. The 200 *Enterobacteriaceae* isolates consisted of 81 *Escherichia coli*, 57 *Klebsiella pneumoniae*, 34 *Enterobacter cloacae*, 12 *Serratia marcescens*, seven *Proteus mirabilis*, four *Citrobacter freundii*, three *Morganella morgannii* and two *Citrobacter koseri*. These isolates were reidentified using recommended traditional method prior to susceptibility testing.[16–18]

Antimicrobial susceptibility test

In vitro susceptibilities to various antimicrobial agents of all enrolled bacterial isolates were determined by minimum inhibitory concentrations (MICs) using Etest (AB bioMérieux, Marcy-l'Etoile, France). The tested antibiotics included doripenem, imipenem, meropenem, ciprofloxacin, ceftazidime, amikacin, colistin, and tigecycline. The methodology used for susceptibility testing was direct colony suspension, according to the manufacturer's instructions. *P. aeruginosa* ATCC 27853 and *Escherichia coli* ATCC 25922 were used for quality control in each run of test.

The susceptibility test results of ceftazidime, imipenem, meropenem, amikacin, ciprofloxacin, and colistin were interpreted using the criteria provided by the Clinical and Laboratory standards Institute (CLSI), 2010.[19,20] For tigecycline, we applied the criteria suggested by the US Food and Drug Administration (US-FDA) for *Enterobacteriaceae* (susceptibility $\leq$2 μg/mL) to *A. baumannii*.

The susceptibility of doripenem for *Enterobacteriaceae* was also interpreted using the CLSI criteria.[20] However, CLSI dose not provide interpretive criteria on doripenem for *P. aeruginosa* and *A. baumannii*, hence, the US-FDA criteria were used (susceptibility $\leq$2 μg/mL for *P. aeruginosa* and $\leq$1 μg/mL for *A. baumannii*). In this study, carbapenem resistance was defined as resistance to either doripenem, imipenem, or meropenem.

Results

The MIC distributions of and susceptibilities to the eight tested antimicrobial agents against the 400 isolates are shown in Table 1 (*P. aeruginosa* and *A. baumannii*) and Table 2 (*Enterobacteriaceae*). For the 100 isolates of *P. aeruginosa*, the proportion of carbapenem resistance was 15%. Among the carbapenem-resistant *P. aeruginosa*, the susceptibility rates of ceftazidime, amikacin, ciprofloxacin, and colistin were 53.3%, 80%, 60%, and 93.3%, respectively.

For the 100 isolates of *A. baumannii*, the proportion of carbapenem resistance was 44%. Among the carbapenem-resistant *A. baumannii*, the susceptibility rates of ceftazidime, amikacin, ciprofloxacin, tigecycline, and colistin were 18.2%, 18.2%, 20.5%, 70.5%, and 100%, respectively.

Among the *Enterobacteriaceae* nonsusceptible to ceftazidime, the susceptibility rates of doripenem, imipenem, meropenem, tigecycline, and colistin were 100%, 97.5%, 100%, 92.5%, and 95%, respectively (Table 2).

The cumulative MIC distributions of three tested carbapenems for *P. aeruginosa*, *A. baumannii* and *Enterobacteriaceae* are plotted in Figs. 1. Fig. 1A and C showed a similar trend of the MIC distributions of doripenem and meropenem against *P. aeruginosa* and *Enterobacteriaceae*, while the MIC distributions curve of imipenem showed a rightward shift indicating a higher MIC distribution. Fig. 1B shows the nearly overlapping MIC distributions curves of doripenem, meropenem and imipenem against *A. baumannii* (a similar MIC distribution).

Comparisons of the susceptibility rates and non-susceptibility rates of *P. aeruginosa*, *A. baumannii*, and

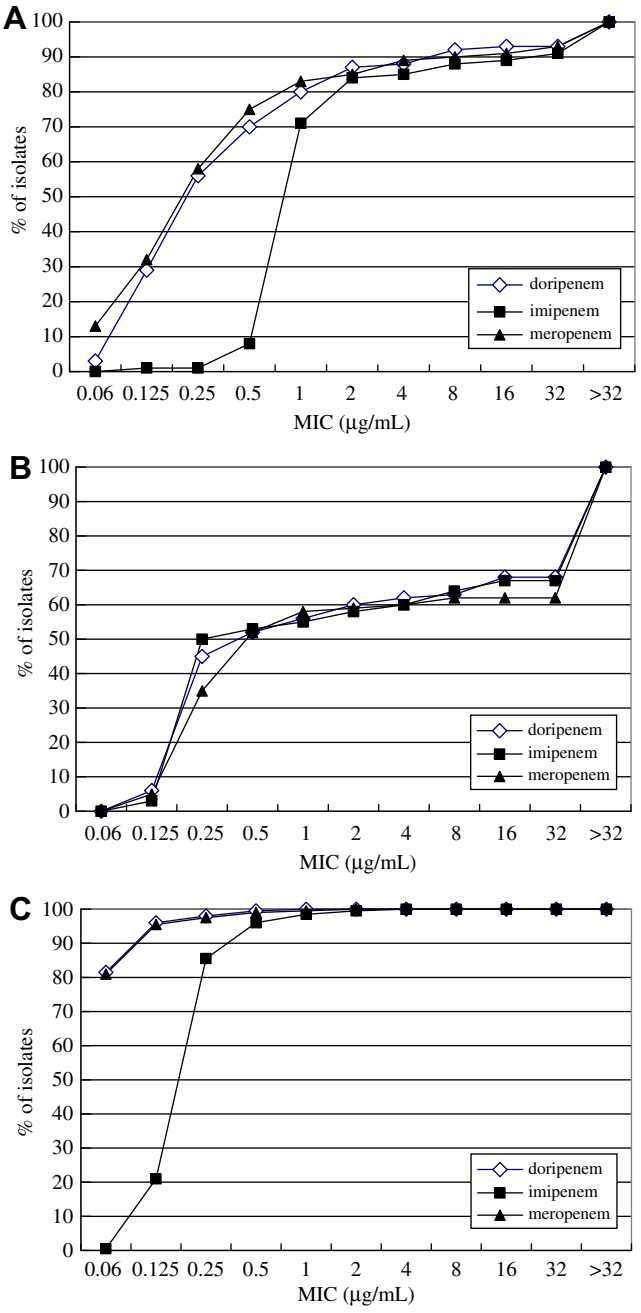

Figure 1. Cumulative MIC distributions of doripenem, imipenem, and meropenem among (A) *Pseudomonas aeruginosa*, (B) *Acinetobacter baumannii*, and (C) *Enterobacteriaceae* isolates.

Table 3 Comparison of doripenem and imipenem susceptibilities

Number of isolates	Susceptible to doripenem[a]	Not susceptible to doripenem[a]	Kappa
Pseudomonas aeruginosa			
Susceptible to imipenem[b]	83	1	
Not susceptible to imipenem[b]	4	12	0.799
Acinetobacter baumannii			
Susceptible to imipenem[b]	56	4	
Not susceptible to imipenem[b]	0	40	0.918
Enterobacteriaceae			
Susceptible to imipenem[b]	197	0	
Not susceptible to imipenem[b]	3	0	Could not be calculated

[a] Based on the breakpoints approved by the US Food and Drug Administration (FDA) in April 2009.
[b] Based on CLSI M100-S20 interpretive criteria.

Enterobacteriaceae between doripenem and imipenem are shown in Table 3. The susceptibility rates and non-susceptibility rates of *P. aeruginosa*, *A. baumannii*, and *Enterobacteriaceae* between doripenem and imipenem were similar. Comparisons of the susceptibility rates and nonsusceptibility rates of *P. aeruginosa*, *A. baumannii*, and *Enterobacteriaceae* between doripenem and meropenem are shown in Table 4. The kappa values of these comparisons were 0.905, 0.918, and >0.999, respectively. The susceptibility rates and non-susceptibility rates of *P. aeruginosa*, *A. baumannii*, and *Enterobacteriaceae* between doripenem and meropenem were also similar.

Discussion

When an antimicrobial agent is launched and planned to be used for treating infections in a region, it is important to know first its *in vitro* activity against clinical relevant pathogens in that region. Before our investigation, there has only been one study in Taiwan, which reported the susceptibility and *in vitro* activity of doripenem against clinically important bacteria.[15] Since the bacterial isolates used in that study were collected in 2005,[15] there might have been significant changes in drug resistance during this time period. Therefore, we conducted the present study using more contemporary clinical isolates.

The current study demonstrated that doripenem has similar *in vitro* activity to imipenem and/or meropenem against *P. aeruginosa*, *A. baumannii*, and various species of *Enterobacteriaceae*. However, susceptibility to doripenem in *P. aeruginosa* was slightly higher than imipenem (87% vs. 85%). In contrast, susceptibility rate of doripenem for *A. baumannii* was slightly lower compared to imipenem and meropenem (56% vs. 60% and 60%; Table 3 and Table 4). This result was similar to prior studies conducted in the United States and worldwide.[21,22] Doripenem also had a slightly higher susceptibility rate for *Enterobacteriaceae* (100% vs. 98.5% & 99.5%) compared to imipenem and meropenem (Table 3 and Table 4).

For the susceptibility of *Enterobacteriaceae* to ceftazidime, we applied the new 2010 CLSI criteria. Therefore, we did not test for the presence of ESBL producer.[19] Among the *Enterobacteriaceae* isolates not susceptible to ceftazidime, the susceptibilities to doripenem, imipenem, meropenem, tigecycline and colistin were still high but the susceptibility rate of ciprofloxacin was only 65%.

This study revealed similar rates of susceptibility to doripenem in *P. aeruginosa*, *A. baumannii*, and *Enterobacteriaceae* compared to previous studies conducted in different countries (87% vs. 77.2—100%, 56% vs. 41.8—75.8%,

Table 4 Comparison of doripenem and meropenem susceptibilities

Number of isolates	Susceptible to doripenem[a]	Not susceptible to doripenem[a]	Kappa
Pseudomonas aeruginosa			
Susceptible to meropenem[b]	87	2	
Not susceptible to meropenem[b]	0	11	0.905
Acinetobacter baumannii			
Susceptible to meropenem[b]	56	4	
Not susceptible to meropenem[b]	0	40	0.918
Enterobacteriaceae			
Susceptible to meropenem[b]	200	0	
Not susceptible to meropenem[b]	0	0	>0.999

[a] Based on the breakpoints approved by the US Food and Drug Administration (FDA) in April 2009.
[b] Based on CLSI M100-S20 interpretive criteria.

and 100% vs. 98.5—99.5%, respectively).[8,21—25] Similar trends were also seen in other tested antibiotics.[21—29]

Compared to the study conducted by Jean et al, the only study investigated the susceptibilities to doripenem in Taiwan before our study,[15] we found that the MIC_{90}s of doripenem and meropenem in *P. aeruginosa* and *A. baumannii* were both increased (6 μg/mL and 6 μg/mL vs. 1 μg/mL and 4 μg/mL, >32 μg/mL and >32 μg/mL vs. 16 μg/mL and 16 μg/mL, respectively). We could not compare the differences in susceptibility rates, because Jean et al did not report these rates in their study. The increase in MIC_{90} values might be due to different source of enrolled bacteria (single center vs. multicenter); however, it might be also due to a real increase of drug resistance during this 4-year interval. Increased prevalence of carbapenem resistance among clinical isolates of *A. baumannii* has been noted recently worldwide.[30] It is necessary to conduct a longitudinal study for continuous monitoring of carbapenem resistance.

The MIC_{90} values of carbapenems in *Enterobacteriaceae* in the study did not increase in comparison to that of Jean et al (0.047 μg/mL vs. 0.06—0.12 μg/mL). This might imply that carbapenem resistance among *Enterobacteriaceae* remains low and stable in Taiwan, unlike some reports indicating rapid increase of carbapenem resistance in *Enterobacteriaceae* from Europe and USA.[31]

In conclusion, our study revealed that doripenem exerted similar *in vitro* activity against the tested bacteria compared to imipenem and meropenem. With comparison to the prior study conducted in Taiwan in 2005, the MIC_{90} values of doripenem, imipenem, and meropenem have increased in *P. aeruginosa* and *A. baumannii*. Longitudinal surveillance to monitor carbapenem resistance trend is needed.

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