

# *In vitro* Antibacterial Activity of Doripenem against Gram-Negative Blood Isolates in a Korean Tertiary Care Center

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**Background:** Doripenem is the most recently introduced antimicrobial agent of the carbapenem class. It is a valuable therapeutic option in the context of increasing antimicrobial resistance to imipenem and meropenem among gram-negative bacilli (GNB) clinical isolates. However, clinicians are usually reluctant to prescribe doripenem, because susceptibility to doripenem is not automatically reported by most clinical laboratories and the *in vitro* activity of doripenem against clinically significant GNB isolates remains uncertain.

**Materials and Methods:** We investigated the *in vitro* antibacterial activity of doripenem in GNB blood isolates in a tertiary care center. Over a period of 10 months, 212 adult bacteremia cases were treated at the study hospital. Doripenem susceptibility testing was performed for the 212 blood isolates by the disk diffusion method, and clinical data were collected.

**Results:** Among the blood isolates, the rate of doripenem resistance (7.5%) was lower than that of imipenem (12.9%) or other anti-GNB antimicrobial agents, except amikacin (2.1%). Almost all imipenem-susceptible GNB blood isolates (181/182, 99.5%) were susceptible to doripenem. Whereas doripenem resistance was rarely observed in Enterobacteriaceae (2/181, 1.1%), it was frequently observed in patients with non-fermentative GNB (12/27, 44.4%), hospital-acquired infections (7/27, 25.9%), and pneumonia (11/49, 22.4%).

**Conclusion:** Doripenem exhibited more potent *in vitro* activity against GNB blood isolates than other anti-GNB antimicrobial agents in a tertiary care center where it was infrequently prescribed compared with other carbapenems. However, its clinical utility may be limited due to the increasing number of carbapenem-resistant non-fermentative GNB infections.

**Key Words:** Doripenem; Gram-negative bacteria; Bacteremia

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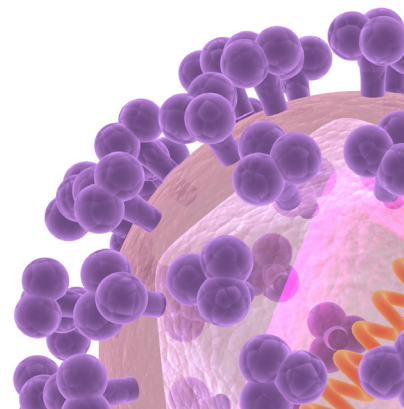
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## Introduction

Carbapenems (imipenem and meropenem) have been effective in the treatment of serious infections caused by antibiotic-resistant bacteria, especially multidrug-resistant gram-negative bacilli (MDR-GNB), during the last two or three decades [1, 2]. However, the number of serious MDR-GNB infections with decreased antimicrobial susceptibility to carbapenems has recently increased [3, 4]. In this context, doripenem, the latest introduced agent of the carbapenem class, may be a useful alternative treatment option as it shows potent *in vitro* antimicrobial activity against MDR-GNB and clinical effectiveness comparable with other carbapenems [5-9]. However, clinicians are usually reluctant to prescribe doripenem, because data regarding doripenem susceptibility are rarely available from widely used automated susceptibility testing panels [10] and the *in vitro* activity of doripenem against clinically significant isolates such as blood isolates has not been reported separately in the context of recent increases in carbapenem resistance, except for a few studies [11, 12]. One included only blood isolates from bacteremic urinary tract infections, and the other did not include distinct clinical information on bacteremia cases. Therefore, we investigated the doripenem susceptibility of GNB blood isolates from adult patients and correlated it with their clinical data, and compared the *in vitro* antimicrobial activity of doripenem to those of imipenem and other anti-GNB antimicrobial agents in a tertiary care center where doripenem was infrequently prescribed and carbapenem resistance was increasing.

## Materials and Methods

This study was performed at Chung-Ang University Hospital, an 850-bed tertiary care-affiliated hospital in Seoul, Republic of Korea. Between March and December 2012, we identified adult ( $\geq 20$  years of age) patients whose blood cultures yielded GNB using the computerized database of the study hospital. We reviewed the electronic medical charts of the study patients and collected data on patient demographics, acquisition of infection, underlying diseases/conditions, initial severity of infection, antimicrobial therapy, and mortality.

Bacteremia was classified as community-acquired, health-care-associated, or hospital-acquired, as described elsewhere [13]. Systemic inflammatory response syndrome (SIRS) criteria were defined as described elsewhere [14]. A site of infection was identified if it was clinically or microbiologically doc-

umented. If multiple sites of infection were found in one case, each site was separately recorded. The amount of carbapenem utilization during 2012 at the study hospital was quantified using the total number of defined daily dose (DDD) of the prescribed carbapenems. Carbapenem DDDs were as follows: meropenem (2.0 g), imipenem (2.0 g), and doripenem (1.5 g).

Identification and susceptibility testing of clinical isolates were performed using a Vitek II system (bioMérieux, Hazelwood, MO, USA). During the study period, meropenem susceptibility was not reported for 177 cases (83.5% of 212) due to the process of changing antimicrobial susceptibility panels in the study hospital. Thus, we excluded the reported meropenem susceptibilities of the remaining 35 isolates from the study analysis. Doripenem susceptibility testing was performed separately using the disk diffusion method in accordance with the recommendations of the Clinical and Laboratory Standards Institute (CLSI), because doripenem was not included in the susceptibility panels of the system. Susceptibility was determined based on the diameters of inhibition zones as follows: for Enterobacteriaceae,  $\geq 23$  mm (susceptible), 20-22 mm (intermediate resistant),  $\leq 19$  mm (resistant); for *Pseudomonas aeruginosa*,  $\geq 19$  mm (susceptible), 16-18 mm (intermediate resistant),  $\leq 15$  mm (resistant); for *Acinetobacter* spp.,  $\geq 18$  mm (susceptible), 15-17 mm (intermediate resistant),  $\leq 14$  mm (resistant) [15]. Isolates with the result of either "intermediate resistant" or "resistant" were regarded as "resistant". This study was approved by the Institutional Review Board of the Chung-Ang University Hospital [IRB number, C2012019(714)].

## Results

In the study hospital, the doripenem DDD was 7.3% that of other carbapenems (499 of 6,871 DDDs; 5,418 DDDs for meropenem and 1,453 DDDs for imipenem) in 2012. A total of 212 episodes of GNB bacteremia occurred during the study period. Of these, 8 were polymicrobial cases of GNB and other bacteria, especially gram-positive cocci. Clinical characteristics of the cases are presented in Table 1. More than half of the cases were health-care-associated or hospital-acquired infections (119, 56.1%). Diabetes mellitus was the most common underlying disease (60, 28.3%), followed by solid tumor (55, 25.9%), neurologic disorders (49, 23.1%), and heart failure (24, 11.3%). *Escherichia coli* and *Klebsiella pneumoniae* were most commonly detected (151, 71.2%). Other Enterobacteriaceae and non-fermentative GNB were each found in 30 cases

**Table 1.** Clinical characteristics of gram-negative bacilli (GNB) bacteremia cases in a tertiary care center and rates of antimicrobial resistance of the GNB blood isolates

Characteristics	No. (%) of bacteremia cases (n = 212)
Male sex	96 (45.3)
Mean age in years (SD)	65.9 (15.2)
Type of acquisition of infection	
Community-acquired	92/211 (43.6)
Healthcare-associated	92/211 (43.6)
Hospital-acquired	27/211 (12.8)
Underlying disease or condition	
Diabetes mellitus	60 (28.3)
Solid tumor	55 (25.9)
Neurologic disorder	49 (23.1)
Heart failure	24 (11.3)
Hematologic malignancy	16 (7.5)
Hemodialysis	16 (7.5)
Chronic obstructive pulmonary disease	12 (5.7)
Liver cirrhosis	9 (4.2)
Immunosuppressant use within a month	49 (23.1)
Pathogen	
<i>Escherichia coli</i>	112 (52.8)
<i>Klebsiella pneumoniae</i>	39 (18.4)
<i>Enterobacter</i> spp.	15 (7.1)
<i>Citrobacter freundii</i>	5 (2.4)
<i>Serratia marcescens</i>	4 (1.9)
<i>Morganella morganii</i>	3 (1.4)
<i>Proteus mirabilis</i>	3 (1.4)
<i>Pseudomonas aeruginosa</i>	10 (4.7)
<i>Acinetobacter</i> spp.	17 (8.0)
<i>Stenotrophomonas maltophilia</i>	3 (1.4)
<i>Aeromonas hydrophila</i>	1 (0.5)
Resistance to antimicrobial agent	
Ciprofloxacin	67/211 (31.8)
Ceftriaxone	62/209 (29.7)
Aztreonam	57/209 (27.3)
Amikacin	4/194 (2.1)
Gentamicin	50/209 (23.9)
Ceftazidime	47/210 (22.4)
Cefepime	37/209 (17.7)
Piperacillin-tazobactam	27/184 (14.7)
Imipenem	26/209 (12.4)
Doripenem	16 (7.5)
Colistin	3/31 (9.7)

**Table 1.** Continued

Characteristics	No. (%) of bacteremia cases (n = 212)
Initial severity of bacteremia	
No sepsis	52/211 (24.6)
Sepsis	99/211 (46.9)
Severe sepsis	12/211 (5.7)
Septic shock	48/211 (22.7)
Site of infection	
Urinary tract	96 (45.3)
Lungs	49 (23.1)
Central venous catheter	36 (17.0)
Abdomen	19 (9.0)
Skin and soft tissue	14 (6.6)
Bone and joint	4 (1.9)
Central nervous system	4 (1.9)
Appropriate antimicrobial therapy within 2 days of bacteremia	171 (80.7)
Length of hospital admission, mean days (SD)	31.8 (50.2)
In-hospital mortality	40/210 (19.0)
28-day mortality	35/210 (16.7)

SD, standard deviation.

**Table 2.** Doripenem and imipenem susceptibilities of 208 GNB blood isolates (after the exclusion of *Aeromonas hydrophila* and *Stenotrophomonas maltophilia*)

Number of isolates	Susceptible to doripenem	Resistant to doripenem
All GNB		
Susceptible to imipenem	181	1
Resistant to imipenem	13	13
<i>Enterobacteriaceae</i>		
Susceptible to imipenem	168	0
Resistant to imipenem	11	2
Non-fermentative GNB		
Susceptible to imipenem	13	1
Resistant to imipenem	2	11

GNB, gram-negative bacilli.

(14.2%). The rate of doripenem resistance (7.5%) was lower than that of imipenem (12.9%) and those of the other anti-GNB antimicrobial agents except amikacin (2.1%). More than a quarter of cases (60, 28.3%) initially presented with severe sepsis or septic shock. The urinary tract was the most common site of infection (96, 45.3%), followed by the lungs

**Table 3.** Antimicrobial resistances of anti-gram negative bacilli (GNB) antimicrobial agents according to type of pathogen, site of infection, and type of acquisition among GNB blood isolates in a tertiary care center

Characteristics	No. (%) of antimicrobial resistant organisms											
	AMP	AMK	ATM	CIP	CST	FEP	GEN	CRO	CAZ	TZP	IPM	DPM
Type of pathogen												
<i>Escherichia coli</i>	74/112 (66.1)	0/112	16/112 (14.3)	39/112 (34.8)	0/3	14/112 (12.5)	26/112 (23.2)	16/112 (14.3)	16/112 (14.3)	5/96 (5.2)	2/112 (1.8)	0/112
<i>Klebsiella pneumoniae</i>	39/39 (100)	0/39	8/39 (20.5)	10/39 (25.6)	0/1	8/39 (20.5)	5/39 (12.8)	8/39 (20.5)	8/39 (20.5)	2/31 (6.5)	2/39 (5.1)	2/39 (5.1)
<i>Enterobacter</i> spp.	15/15 (100)	1/15 (6.7)	5/15 (33.3)	1/15 (6.7)	0/3	1/15 (6.7)	2/15 (13.3)	5/15 (33.3)	5/15 (33.3)	2/15 (13.3)	4/15 (26.7)	0/15
<i>Citrobacter freundii</i>	5/5 (100)	0/5	4/5 (80.0)	1/5 (20.0)	ND	0/5	0/5	4/5 (80.0)	4/5 (80.0)	4/5 (80.0)	0/5	0/5
<i>Serratia marcescens</i>	4/4 (100)	2/4 (50.0)	2/4 (50.0)	2/4 (50.0)	2/2 (100)	0/4	2/4 (50.0)	2/4 (50.0)	0/4	0/4	0/4	0/4
<i>Morganella morgannii</i>	3/3 (100)	1/3 (33.3)	1/3 (33.3)	1/3 (33.3)	ND	1/3 (33.3)	0/3	1/3 (33.3)	1/3 (33.3)	1/3 (33.3)	3/3 (100)	0/3
<i>Proteus mirabilis</i>	1/3 (33.3)	0/3	1/3 (33.3)	1/3 (33.3)	ND	1/3 (33.3)	1/3 (33.3)	1/3 (33.3)	1/3 (33.3)	0/3	2/3 (66.7)	0/3
<i>Pseudomonas aeruginosa</i>	10/10 (100)	0/10	3/10 (30.0)	3/10 (30.0)	0/9	2/10 (20.0)	6/9 (66.7)	10/10 (100.0)	2/10 (20.0)	3/10 (30.0)	5/10 (50.0)	4/10 (40.0)
<i>Acinetobacter</i> spp.	12/16 (75.0)	0/2	16/16 (100)	9/17 (52.9)	12/12 (100)	10/17 (58.8)	7/17 (41.2)	15/17 (88.2)	10/17 (58.8)	9/15 (60.0)	8/17 (47.1)	8/17 (47.1)
Site of infection												
Lung	43/48 (89.6)	2/36 (5.6)	30/48 (62.5)	23/48 (47.9)	0/15	18/48 (37.5)	21/48 (43.8)	32/48 (66.7)	25/48 (52.1)	16/48 (33.3)	16/49 (32.7)	11/49 (22.4)
Urinary tract	68/94 (72.3)	3/92 (3.3)	28/96 (29.2)	28/95 (29.5)	1/8 (12.5)	18/95 (18.9)	25/95 (26.3)	28/95 (29.5)	23/95 (24.2)	11/83 (13.3)	10/96 (10.4)	4/96 (4.2)
Abdomen	15/19 (78.9)	0/17	4/18 (22.2)	10/19 (52.6)	0/3	4/19 (21.1)	5/19 (26.3)	5/19 (26.3)	4/19 (21.1)	3/18 (16.7)	4/19 (21.1)	2/19 (10.5)
Central catheter	30/34 (88.2)	2/28 (7.1)	17/33 (51.5)	15/36 (41.7)	0/10	11/34 (41.2)	14/34 (41.2)	21/34 (61.8)	13/35 (37.1)	7/28 (25.0)	8/34 (23.5)	5/36 (13.9)
Type of acquisition												
Healthcare-associated	73/90 (81.1)	2/82 (2.4)	29/89 (32.6)	34/92 (37.0)	3/16 (18.8)	18/90 (20.0)	22/89 (24.7)	34/90 (37.8)	24/91 (26.4)	13/76 (17.1)	15/90 (16.7)	7/92 (7.6)
Hospital-acquired	22/25 (88.0)	2/22 (9.1)	20/27 (74.1)	16/26 (61.5)	0/8	14/26 (53.8)	12/27 (44.4)	19/26 (73.1)	17/26 (65.4)	10/25 (40.0)	10/27 (37.0)	7/27 (25.9)

AMP, ampicillin; AMK, amikacin; ATM, aztreonam; CIP, ciprofloxacin; CST, colistin; FEP, cefepime; GEN, gentamicin; CRO, ceftriaxone; CAZ, ceftazidime; TZP, piperacillin-tazobactam; IPM, imipenem; DPM, doripenem; ND, not determined.

(49, 23.1%), central venous catheter (36, 17.0%), abdomen (19, 9.0%), and skin/soft tissue (14, 6.6%).

Doripenem and imipenem susceptibilities are compared in Table 2. Almost all imipenem-susceptible isolates were susceptible to doripenem (181/182, 99.5%). One half of the imipenem-resistant isolates (13/26, 50.0%) were also susceptible to doripenem. Doripenem resistance was observed only rarely in the Enterobacteriaceae (2/181, 1.1%). However, for non-fermentative GNB, doripenem resistance was observed in the

majority of imipenem-resistant isolates (84.6%, 11/13) and even in a case of imipenem-susceptible *A. baumannii* bacteremia.

Table 3 presents the rates of antimicrobial resistances of GNB bacteremia isolates according to type of pathogen, site of infection, and type of acquisition. The rate of doripenem resistance was lower than those of the other anti-GNB antimicrobial agents, including imipenem. However, the rate of doripenem resistance was high in cases of *Pseudomonas aeruginosa*

bacteremia (40.0%) and *Acintobacter* spp. bacteremia (47.1%). It was also high in cases of pneumonia and hospital-acquired infection (22.4% and 25.9%, respectively). Among hospital-acquired pneumonia cases, the rate of doripenem resistance was 33.3% (4 of 12).

## Discussion

Imipenem-susceptible GNB blood isolates were also susceptible to doripenem in almost all cases. Doripenem was more active *in vitro* against GNB blood isolates than other anti-GNB antimicrobial agents, including imipenem. However, in non-fermentative GNB blood isolates and in clinical infections frequently associated with these organisms, especially hospital-acquired pneumonia, the *in vitro* activity of doripenem was limited like that of imipenem.

Imipenem-susceptible GNB blood isolates were also susceptible to doripenem in almost all cases. Although doripenem susceptibility is not routinely reported due to the absence of doripenem in automated susceptibility testing panels, our data suggest that if a GNB blood isolate is susceptible to imipenem, doripenem may be utilized effectively against it. The majority of previous studies also support this suggestion, finding that the *in vitro* activity of doripenem is similar to those of imipenem or meropenem, or sometimes superior to that of imipenem [5-9]. A recent study specifically noted that meropenem and imipenem are reliable surrogate markers of doripenem susceptibility according to the surrogate predictive value based on the 2012 CLSI and FDA breakpoints [10]. However, the majority of previous studies included clinical isolates collected before 2010 [5-10]. At that time, doripenem had just been introduced and was not yet widely utilized in clinical practice. This study is not different from previous studies in some ways - doripenem was prescribed only at a rate of 7.4% compared to other carbapenems in this study. Thus, in a clinical setting where doripenem is more frequently prescribed than other carbapenems, doripenem susceptibility may not be predicted based on the susceptibilities of other carbapenems.

Our data showed that doripenem had potent *in vitro* activity against GNB blood isolates compared with other antimicrobial agents, including imipenem. *In vitro* activity of doripenem is reported to be comparable to those of other carbapenems [5-9]. In addition, regarding clinical outcomes of complicated urinary tract infection, complicated intra-abdominal infection, nosocomial pneumonia, and bacteremia cases, doripen-

em shows similar effectiveness compared with other carbapenems [16-18]. These data suggest that doripenem is a valuable antimicrobial treatment option against serious GNB infections. Additionally, considering that the majority of imipenem-resistant Enterobacteriaceae (11/13, 84.6%) were susceptible to doripenem in this study, we suggest that if antimicrobial treatment options are limited against imipenem-resistant Enterobacteriaceae blood isolates, antimicrobial susceptibility tests for doripenem would be helpful to detect additional therapeutic options.

We frequently observed antimicrobial resistance to doripenem among non-fermentative GNB blood isolates in this study. In a previous study that investigated the *in vitro* activity of doripenem in antibiotic-resistant clinical isolates collected from 2001-2002, doripenem was more potent than imipenem or meropenem even against non-fermentative GNB [19]. However, more recent studies of blood GNB isolates reported that doripenem and other carbapenems had similar *in vitro* activity against non-fermentative GNB, similar to the results of our study [11, 12]. Thus, doripenem should not be considered a treatment option against imipenem- or meropenem-resistant non-fermentative GNB blood isolates, or against hospital-acquired infections or pneumonia in which these GNB isolates are suggested as likely pathogens.

This study has a few important limitations. First, clinical data were retrospectively collected. It might affect the accuracy of the classification of hospital-acquired, healthcare-associated, and community-acquired infection. Second, meropenem susceptibilities could be evaluated only in 35 isolates. Thus, these were not included in the study analysis.

In conclusion, doripenem had more potent *in vitro* activity against GNB blood isolates than other anti-GNB antimicrobial agents, including imipenem, in a clinical setting where doripenem was infrequently utilized. However, its usefulness in clinical practice may be limited by the increasing number of carbapenem-resistant non-fermentative GNB.

## Conflicts of Interest

This study was sponsored by IL DONG Pharmaceutical Co., Ltd. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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