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Original Article

Comparative efficacy of doripenem versus meropenem for hospital-acquired and ventilator-associated pneumonia

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Abstract *Background:* Doripenem shows good *in vitro* activity against common nosocomial pathogens, such as extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*. However, the use of doripenem for hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) remains controversial. The aim of this study was to compare the efficacy and safety between doripenem and meropenem for patients with HAP or VAP.
Methods: Adult patients diagnosed with HAP and VAP at National Taiwan University Hospital, who received doripenem or meropenem for more than 48 h between January 2015 and November 2017, were retrospectively reviewed. All-cause mortality on the 30th day was used as the primary outcome measurements.
Results: Fifty-seven patients with doripenem and 252 patients with meropenem were analyzed. Compared to the meropenem group, the doripenem group was younger and had a higher Sequential Organ Failure Assessment (SOFA) score. Multivariable Cox regression analysis revealed that presence of solid organ malignancies (adjusted hazard ratio [AHR], 1.82; 95% CI, 1.04–3.19, p = 0.003) and SOFA score (AHR, 1.10; 95% CI, 1.03–1.17, p = 0.003) were independent factors associated with mortality. There was no survival difference of 30-day mortality between patients receiving doripenem and meropenem for HAP or VAP (log-rank p = 0.113). However, a poorer outcome was observed among patients with hematological disease in the doripenem group (log-rank p = 0.012).

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Conclusion: Our results demonstrate that doripenem has similar efficacy as meropenem in HAP or VAP patients. With an aim to enhance antibiotic diversity, doripenem could be an alternative choice for patients with HAP or VAP, except for those with hematological malignancies.

Introduction

Hospital-acquired pneumonia (HAP) is defined as a respiratory infection that develops within 48 h after admission, and is the most common nosocomial infection leading to death.[1] Of those patients who were equipped with mechanical ventilation, ventilator-associated pneumonia (VAP) described a subset condition of HAP arising after more than 48 h of intubation. Patients developing HAP or VAP are prone to have a higher rate of morbidity, mortality, and prolonged hospitalization days, most notably in those with a greater instance of severe underlying comorbidities.[2–8] The mortality rates of HAP and VAP at intensive care units (ICU) may occur up to 50%.[6–8] A longitudinal prospective study conducted at the ICU scale, which analyzed 4479 patients from the a French multicenter Outcomerea database, estimated that the population-attributable fraction of ICU mortality to VAP equals 4.4% and 5.9% on day 30 and day 90, respectively, after ICU admission. In other words, if VAP is prevented, 4.4% of the ICU deaths observed within 30 days after ICU admission could be avoided.[4] Bundle care program was administered in order to decrease VAP rate and consequent mortality. However, even though good adherence to bundle care program indeed decrease mortality rate, the mortality rate caused by VAP remains high. Therefore, the antibiotics strategy should be optimized.[9–12]

HAP and VAP are manifested with infections caused by pathogens with increased antimicrobial resistance, including extended spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae, carbapenem-resistance non-fermentative Gram-negative bacilli (NFGNB), methicillin-resistant *Staphylococcus aureus* (MRSA) and even vancomycin-resistant *Enterococcus* (VRE).[13–15] As a result, the bacteriology of HAP and VAP is essential for evaluation, in order to make a more precise antibiotic choice. According to the report from International Nosocomial Infection Control Consortium (INICC), which analyzed data from 36 countries between 2004 and 2009, *Klebsiella pneumoniae* and *Escherichia coli* isolated from patients with VAP showed a resistance of more than 70% to third or fourth generation cephalosporins, and even 4%—7% to carbapenems. For *Pseudomonas aeruginosa*, 37.5%—47% were resistant to fluoroquinolones, anti-Pseudomonal cephalosporins, and piperacillin-tazobactam.[16] Furthermore, the percentage of multidrug-resistant *P. aeruginosa* is on the rise, while more than half of the members of *A. baumannii* complex leading to VAP are carbapenem-resistant.[16,17]

With an increasing trend of drug-resistant pathogens observed in HAP and VAP patients, carbapenems were suggested by the Infectious Diseases Society of America (IDSA) to be an empirical treatment option under specific circumstances.[18,19] Imipenem/cilastatin, meropenem, and doripenem, with the benefit of broad-spectrum and safety, are three anti-Pseudomonal carbapenems that are commonly prescribed for infections at hospitals. Nevertheless, carbapenem-resistant pathogens could cause outbreak at hospitals and long-term care facilities, and the prescription of carbapenems is the most important factor to the acquisition of CR-pathogens. Hence, prudent and diverse use of carbapenems are crucial issue, which might decrease the antimicrobial selection pressure at wards or ICUs and the consequent nosocomial outbreak.[20,21]

Currently, the use of doripenem to treat HAP and VAP is still controversial. Therefore, we aimed to compare the efficacy and safety of doripenem and meropenem for patients with HAP or VAP.

Methods

Study design and study population

Adult patients who were aged 20 years or older received a diagnosis of pneumonia at National Taiwan University Hospital (NTUH) between January 2015 and November 2017 and had ever been prescribed with doripenem or meropenem were included.

An online antimicrobial-stewardship program was implemented in NTUH, where all antipseudomonal carbapenems (imipenem, meropenem and doripenem) prescription required approval from infectious diseases (ID) physicians. All inpatient settings were allocated and preassigned to ID physicians practicing in the hospital. Each ID physician was informed by a reminding message when the antimicrobial agents were prescribed to patients admitted to his or her preassigned wards or ICUs. Primary care physicians are authorized to prescribe antipseudomonal carbapenems for a 2-day course, and a course longer than 3-day required ID physicans' approval.[22]

Primary doses of meropenem and doripenem were 1 g every eight hours and 500 mg every eight hours before renal dose adjustment, respectively. Causative pathogens with carbapenem high level resistance with minimal inhibitory concentration of doripenem/meropenem 8 mg/L were excluded. Monte Carlo simulations to evaluate optimal dosing of doripenem in critically ill HAP patients with obesity, augmented renal clearance, and decreased bacterial susceptibility were performed after clinical pharmacist consultation.[23] In addition, the dosage of doripenem

and meropenem were adjusted for renal dysfunction according to The Sanford Guide to Antimicrobial Therapy 2015.[24] The detailed dosage adjustment as creatinine clearance [CCr] 30—50 mL/min, 250 mg Q8H; CCr 10—30 mL/min, 250 mg Q12H; CCr <10 mL/min and under hemodialysis, 250 mg QD for doripenem. CCr 25—50 mL/min, 1 g Q12H; CCr 10—25 mL/min, 500 mg Q12H; CCr <10 mL/min and under hemodialysis, 500 mg QD for meropenem, respectively.[24]

Only patients fit the diagnosis of HAP or VAP were enrolled. The clinical definition of HAP and VAP was basically followed by 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATC). In brief, patients must have new or progressive parenchymal lung infiltrates over chest X ray or computed tomography. In addition to radiographic infiltrates, patients diagnosed with HAP or VAP must have at least two following clinical manifestations or laboratory results suggest that the infiltrates are infectious in origin. The symptoms and signs include temperature alteration (<36°C or 38.3°C), a white blood cell count <5000 cells/mm^3 or >10,000 cells/mm^3, or purulent-appearing sputum or endotracheal aspirate.[18] Moreover, in our study, at least one of the following microbiologic criteria was required in order to strengthen our enrollment, including a positive result of blood culture not from another source, a positive result of pleural fluid culture, a positive culture from sputum with good quality on smear (25 white blood cells/field, <10 epithelial cells/field), positive results of quantitative culture of specimens from bronchoalveolar lavage (BAL) (significance threshold, 10^4 CFU/mL), a protected brush (significance threshold, 10^3 CFU/mL) or a positive culture of tracheal secretions obtained by tracheal aspiration (significance threshold, 10^6 CFU/mL), >5% intracellular bacteria seen on a Gram stain of BAL fluid, or any histologic evidence of pneumonia. Patients with etiologies other than pneumonia which lead to fit the criteria of HAP or VAP were excluded, including patients with atelectasis after operation or tumor-related obstructive pneumonitis. Those who were treated with doripenem or meropenem for less than 48 h were also excluded.

Medical records were retrospectively reviewed to obtain information, including age, gender, hemogram, renal and liver profile, C-reactive protein (CRP), microbiological evidence including blood culture and sputum culture, ICU admission, and ventilator use. We recorded Sequential Organ Failure Assessment (SOFA) Score at the time of doripenem or meropenem prescription while also reviewing the use of antibiotics, including those the patient received before carbapenems.

Ethics declaration

The study has been approved by the Institutional Review Board (Ethics Committee) of National Taiwan University Hospital (IRB number, 201711022 RINB).

Outcomes assessment

Patients were followed-up for all-cause mortality from the diagnosis of HAP or VAP. Each patient was observed until death or 60 days after the diagnosis of pneumonia. Primary outcome measures were all-cause mortality on the 30th day. Subgroup analysis included the 30-day all-cause mortality among patients with the diagnosis of HAP or VAP. Other analyses included those with solid-organ malignancies and hematological malignancies at the time of pneumonia occurrence. Adverse events of seizures and other life-threatening episodes were also recorded.

Statistical analysis

Categorical variables, such as gender, underlying diseases, types of pneumonia, co-infection with bacteremia, antibiotics prescribed before carbapenems, were compared between treatment groups using Pearson's chi-squared test. Continuous variables, such as SOFA score and age at the time of diagnosis were analyzed using Mann—Whitney U test. We used Cox proportional hazards models to estimate the unadjusted and adjusted hazard ratios (aHRs) for mortality between doripenem and meropenem, using doripenem as reference group. Models were adjusted for age at diagnosis, gender, underlying diseases, and co-infection with bacteremia. All analyses were performed using Stata/SE software, Version 11.0 (https://www.stata.com).

Results

Overall, 309 patients were included, with 57 (18.4%) patients belonging to the doripenem group and 252 (81.6%) to the meropenem group. The demographic characteristics of patients are shown in Table 1. There were no differences in gender, underlying diseases of solid organ or hematologic malignancies, solid organ or bone barrow transplants, chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), congestive heart failure (CHF), diabetes mellitus (DM), rheumatology diseases and human immunodeficiency virus (HIV), distributions of HAP or VAP, and duration of carbapenem prescription between the two groups. The doripenem group showed a propensity of being younger (66 and 75 years, respectively, $p = 0.002$), with liver cirrhosis ($p = 0.004$), receiving hemodialysis ($p < 0.001$), and steroid use ($p = 0.001$). Patients of doripenem group had higher SOFA score at the time of carbapenem prescription compared to those receiving the meropenem group ($p = 0.028$).

The distribution of causative pathogens is shown in Table 2. Eighteen (31.6%) patients of the doripenem group and 63 (25.0%) of the meropenem group were affected with bacteremia at the time of HAP or VAP ($p = 0.308$). In the meropenem group, *P. aeruginosa* (8.3%), *K. pneumoniae* (4.8%), and *E. coli* (4.4%) were the most common pathogens detected in blood cultures, while *Enterococcus species*. (7.0%) and *A. baumannii complex* (5.3%) (including *Acinetobacter baumannii, Acinetobacter nosocomialis and Acinetobacter pitti*) were most commonly observed (Table 2).

Bacteria yielded from sputum culture were recorded. In our cohort, 34 (59.6%) patients of doripenem group and 129 (50.8%) of meropenem group reported *P. aeruginosa*. *K. pneumoniae* and *A. baumannii complex* were also commonly seen, with a rate of 21.1% and 8.8%, and 12.2%

Table 1 Baseline characteristics of the included patients.

	Total (N = 309)	Doripenem (N = 57)	Meropenem (N = 252)	p
HAP, n (%)	254 (82.2)	49 (86.0)	205 (81.3)	0.411
VAP, n (%)	55 (17.8)	8 (14.0)	47 (18.7)	0.411
Median age (IQR), years	74 (61–82)	66 (52–77)	75 (63–82)	0.002
Men, n (%)	214 (69.3)	42 (73.7)	172 (68.2)	0.422
Underlying disease, n (%)				
Solid-organ malignancy	115 (37.2)	25 (43.9)	90 (35.4)	0.234
Solid-organ transplant	8 (2.6)	2 (3.5)	6 (2.4)	0.642
Hematological malignancy	43 (13.9)	11 (19.3)	32 (12.6)	0.185
Stem cell transplant	6 (1.9)	3 (5.3)	3 (1.2)	0.077
COPD	27 (8.7)	4 (7.0)	23 (9.1)	0.797
CAD	62 (20.1)	11 (19.3)	51 (20.2)	0.873
CHF	59 (19.1)	12 (21.1)	47 (18.5)	0.657
CVA	75 (24.3)	8 (14.0)	67 (26.6)	0.046
Liver cirrhosis	15 (4.9)	7 (12.3)	8 (3.2)	0.004
ESRD or Dialysis	45 (14.6)	17 (29.8)	28 (11.0)	<0.001
Type 2 diabetes mellitus	88 (28.5)	18 (31.6)	70 (27.6)	0.543
Rheumatology disease	19 (6.1)	5 (8.8)	14 (5.5)	0.353
Glucocorticoid use	43 (13.9)	16 (28.1)	27 (10.6)	0.001
HIV infection	3 (1.0)	1 (1.8)	2 (0.8)	0.456
History of tuberculosis	20 (6.5)	5 (8.8)	15 (5.9)	0.425
SOFA score, IQR	6 (3–8)	7 (4–10)	5 (3–8)	0.028
Co-infection with bacteremia	81 (26.2)	18 (31.6)	63 (25.0)	0.308
Median duration of drug use (IQR), days	11 (7–15)	10 (5–17)	11 (7–15)	0.423

Abbreviations: HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia; IQR, interquartile range; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; CHF, congestive heart failure; CVA, cerebral vascular accident; ESRD, end-stage renal disease, HIV, human immunodeficiency virus; SOFA score, Sequential Organ Failure Assessment Score.

and 13.4% between doripenem and meropenem group (Table 3).

Antibiotics use prior to doripenem and meropenem was recorded. Eight (14.0%) patients from doripenem group and 96 (37.8%) from meropenem group were treated with piperacillin/tazobactam prior to doripenem or meropenem prescription ($p < 0.001$). There was no difference in anti-Pseudomonas cephalosporin use between the doripenem (13, 31.6%) and meropenem groups (106, 41.7%) ($p = 0.185$). There were seven (12.2%) patients whose

Table 2 Distribution of baseline qualifying pathogens from blood culture.

	Total (N = 81)	Doripenem (N = 18)	Meropenem (N = 63)
Enterobacteriaceae			
Escherichia coli	17 (21.0)	6 (33.3)	11 (17.5)
Klebsiella pneumoniae	14 (17.3)	2 (11.1)	12 (19.0)
Proteus mirabilis	1 (1.2)	0	1 (1.6)
Enterobacter aerogenes	6 (7.4)	2 (11.1)	4 (6.3)
Citrobacter koseri	3 (3.7)	1 (5.6)	2 (3.2)
Aeromonas hydrophila	1 (1.2)	0	1 (1.6)
NFGNB			
Pseudomonas aeruginosa	22 (27.2)	1 (5.6)	21 (33.3)
ACB complex	8 (9.9)	3 (16.7)	5 (7.9)
Stenotrophomonas maltophilia	1 (1.2)	0	1 (1.6)
Burkholderia cepacia	3 (3.7)	0	3 (4.8)
Achromobacter xylosoxidans	1 (1.2)	0	1 (1.6)
Elizabethkingia meningoseptica	1 (1.2)	1 (5.6)	0
Others			
MRSA	5 (6.2)	2 (11.1)	3 (4.8)
Enteroccocus spp.	9 (11.1)	4 (22.2)	5 (7.9)

Abbreviations: NFGNB, Non-fermentative gram-negative bacilli; ACB, Acinetobacter calcoaceticus-baumannii; MRSA, methicillin-resistant *Staphylococcus aureus*.

Table 3 Distribution of baseline qualifying pathogens from sputum culture.

	Total (N = 255)	Doripenem (N = 48)	Meropenem (N = 207)
Enterobacteriaceae			
Escherichia coli	10 (3.9)	4 (8.3)	6 (2.9)
Klebsiella pneumoniae	43 (16.9)	12 (25)	31 (15.0)
Proteus mirabilis	10 (3.9)	1 (2.1)	9 (4.3)
Enterobacter aerogenes	10 (3.9)	1 (2.1)	9 (4.3)
Citrobacter koseri	3 (1.2)	1 (2.1)	2 (1.0)
Serratia marcescens	8 (3.1)	2 (4.2)	6 (2.9)
NFGNB			
Pseudomonas aeruginosa	163 (63.9)	34 (70.8)	129 (62.3)
ACB complex	39 (15.3)	5 (10.4)	34 (16.4)
Stenotrophomonas maltophilia	28 (11.0)	10 (20.8)	18 (8.7)
Burkholderia cepacia	11 (4.3)	4 (8.3)	7 (3.4)
Achromobacter xylosoxidans	4 (1.6)	1 (2.1)	3 (1.4)
Elizabethkingia meningoseptica	4 (1.6)	2 (4.2)	2 (1.0)
Others			
MRSA	22 (8.6)	5 (10.4)	17 (8.2)

Abbreviations: NFGNB, Non-fermentative gram-negative bacilli; ACB, Acinetobacter calcoaceticus-baumannii; MRSA, methicillin-resistant *Staphylococcus aureus*.

antibiotic treatment regimen was changed from imipenem/cilastatin to doripenem, while only 10 (3.9%) patients were treated with imipenem prior to meropenem ($p < 0.001$).

During the 30-day observation, 59 (19.1%) deaths occurred, 13 (22.8%) and 46 (18.1%) in the doripenem and meropenem groups, respectively. There was no statistical difference in all-cause mortality between the two groups (log-rank test, $p = 0.284$) (Fig. 1). In the multivariable Cox regression analysis, among all included patients, independent factors associated with mortality were presence of solid organ malignancies (adjusted hazard ratio [AHR], 1.82; 95% CI, 1.04—3.19, $p = 0.003$), SOFA score (AHR, 1.10; 95% CI, 1.03—1.17, $p = 0.003$), after adjusting for age, presence of solid-organ malignancies or hematological malignancies, co-infection with bacteremia, disease severity of SOFA score, and the use of doripenem or meroepenem (Table 4).

Subgroup analysis of 30-day mortality among HAP and VAP patients was performed (Fig. 2). There was no survival difference in 30-day mortality among patients with HAP (log-rank test, $p = 0.113$). Moreover, there was no survival difference in 30-day mortality among those with VAP, either (log-rank test, $p = 0.224$). Patients of preexisting solid-organ malignancies and hematological malignancies were selected for subgroup analysis. Poorer outcome of 30-day mortality was seen among patients with hematological disease in doripenem group than in meropenem group (log-rank test, $p = 0.012$) (Fig. 3).

Only one patient of meropenem group reported a seizure after meropenem infusion, while no patient of doripenem group had a seizure associated with the use of doripenem. None of the patients in our analysis reported life-threatening adverse events of anaphylaxis, allergic angioedema, Stevens-Johnson syndrome, or toxic epidermal necrolysis.

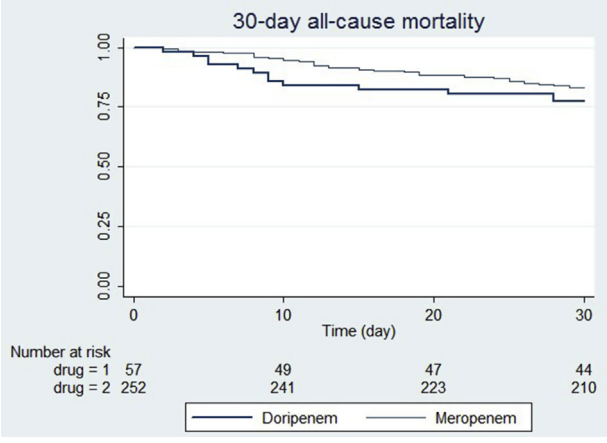

Figure 1. Kaplan—Meier survival curve for 30-day all-cause mortality (log-rank test, $p = 0.284$).

Discussion

Doripenem exhibits a broad spectrum of activity against Gram-positive and Gram-negative bacteria, including ESBL and Amp-C β-lactamase producing Enterobacteriaceae and anaerobes. One study examined 34 carbapenem-resistant *P. aeruginosa* isolates and found that doripenem displayed the lowest rates of resistance when compared to the carbapenems.[25] Doripenem therefore, not only provided antibiotics diversity when treating healthcare-associated infections, but also displayed an alternative choice for MDRO infection. However, the clinical utility of doripenem in the treatment of HAP and VAP is still limited. In this retrospective study of 309 patients with the diagnosis of HAP or VAP at a university hospital, we observed that the overall mortality was not affected by the prescription of doripenem or meropenem. Subgroup analysis showed that mortality was higher only for the patients in the doripenem group who had hematological malignancies.

Survival did not differ among HAP and VAP patients treated by doripenem or meropenem. No difference in

Table 4 Multivariate Cox regression of the 30-day survival among all patients.

	Univariate analysis			Multivariate analysis		
	HR	p	95% CI	HR	p	95% CI
Age, per 1-year increase	0.997	0.683	0.980–1.010	1.001	0.843	0.983–1.020
Solid organ malignancy	1.44	0.167	0.86–2.43	1.82	0.003	1.04–3.19
Hematological malignancy	1.63	0.145	0.84–3.15	2.11	0.057	0.98–4.57
Co-infection with bacteremia	1.63	0.080	0.94–2.80	1.17	0.601	0.64–2.14
SOFA, per 1 score increase	1.09	0.005	1.03–1.16	1.10	0.003	1.03–1.17
Meropenem (Reference as doripenem)	0.71	0.287	0.38–1.33	0.88	0.691	0.46–1.66

HR, Hazard Ratio; 95% CI, 95% confidence interval.

survival was observed among patients with confirmed infections caused by *P. aeruginosa*. Three randomized trials were identified that compared doripenem to other antibiotic regimens in a subgroup of patients with *P. aeruginosa*.[26–28] The comparisons were to either imipenem/cilastatin[26,27] or piperacillin-tazobactam.[28] No significant differences between doripenem and the other regimens in terms of mortality or treatment failure were found. Nevertheless, a randomized trial of 7-day doripenem versus 10-day imipenem/cilastatin for VAP was terminated early due to a higher 28-day all-cause mortality rate and a lower clinical cure rate in doripenem group, which resulted in the Food and Drug Administration (FDA) modifying the label of doripenem.[27,29] However, such change based on these trial results has been controversial. The poorer outcome in doripenem group might be due to a shorter course of treatment rather than the medication administered. Moreover, there is no direct comparison between doripenem and meropenem for patients with HAP or VAP until now.

Nevertheless, doripenem showed a tentative trend of inferiority to meropenem, even though not reaching statistical significance. In the subgroup analysis of patients with hematological malignancies, the prescription of doripenem was associated with a higher mortality rate. In our cohort, patients of the doripenem group had a high SOFA score at the time of carbapenem initiation, which might have contributed to the higher mortality trend. Notably, the doripenem dose prescribed in our hospital was standard at 500 mg three time per day. In an animal model evaluated by Bretonnière et al., the standard dose of doripenem had lower efficacy compared to other carbapenems for *P. aeruginosa* bacteremia, while high dose of doripenem (1 g three times per day) correspondingly showed similar efficacy as others.[30] A clinical trial conducted in Japan demonstrated that high dose of doripenem is effective and relatively safe.[31] Pharmacokinetic parameters can be altered in hematological patients. In a study with Monte-Carlo simulations in patients with febrile neutropenia, a higher dose of 1 g doripenem is suggested to optimally treat

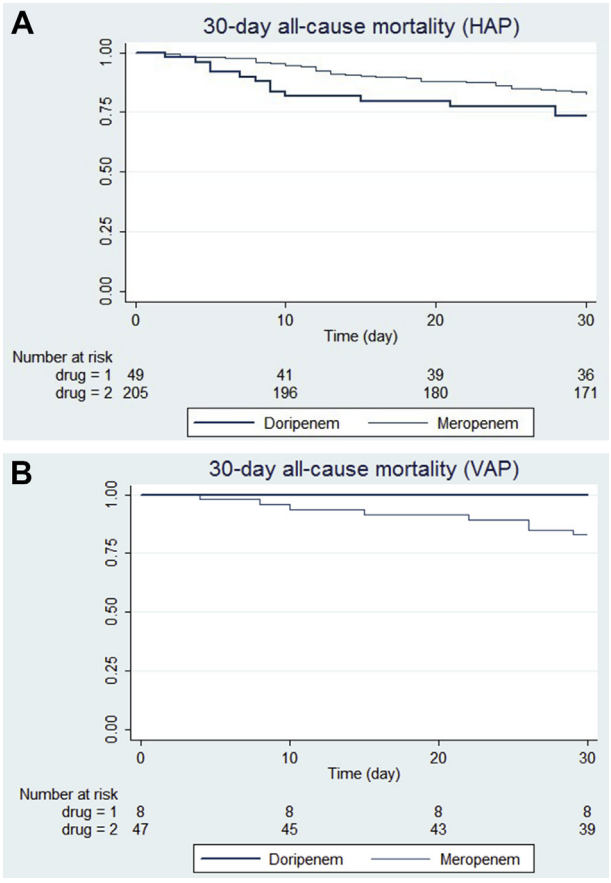

Figure 2. Kaplan–Meier survival curve for 30-day all-cause mortality among patients with HAP, log-rank test, p = 0.113 (A) and VAP, log-rank test, p = 0.224 (B).

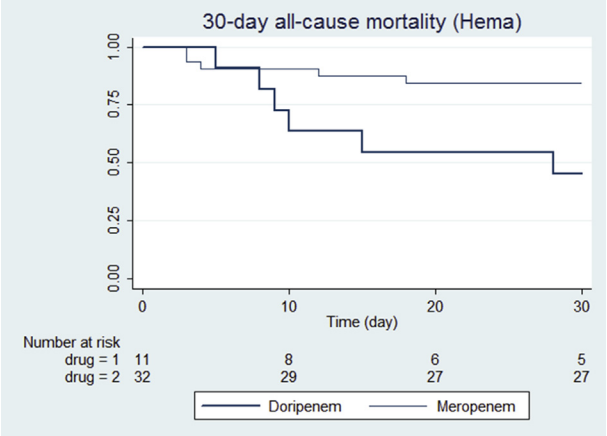

Figure 3. Kaplan–Meier survival curve for 30-day all-cause mortality among patients with underlying disease of hematological malignancies (log-rank test, p = 0.012).

selected gram-negative bacteria associated with infections in patients with febrile neutropenia.[32] However, the high dose strategy of doripenem still lacks of clinical experience and there is no direct comparison between high dose doripenem and other carbapenems in clinical circumstances.

In our study, only one patient of meropenem group developed seizures after the infusion of antibiotics. Other fatal allergic events were not observed among the included patients. According to previous research, carbapenems are generally well-tolerated. All carbapenems have a risk of seizures, which is believed to be associated with their structural similarity with γ-aminobutyric acid (GABA) and antagonism at the receptor site.[33] Compared to imipenem/cilastatin (1—2%), meropenem and doripenem (0.1—0.3%) showed a lower incidence rate of seizure.[29,34] Previous clinical studies also showed convincing safety for doripenem and relatively low risk of seizure.[26—28] Additionally, an independent meta-analysis by Cannon et al. demonstrated that neither meropenem nor doripenem were associated with elevated risk of seizures.[35] Due to a limited number of seizure events, the incidence rates of seizures between doripenem and meropenem could not be compared in our study. However, we believe that doripenem or meropenem is safe to be administered to patients with HAP or VAP.

Our study had several limitations. Firstly, it was a retrospective study with a relatively small number of patients enrolled, which resulted in a recording bias and a relatively low statistical power to precisely evaluate the difference between the studied carbapenems. Second, we have focused only on the outcome of mortality rather than other clinical outcomes and microbiological eradication. Third, drug susceptibility tests of isolated pathogen were not analyzed owing to limited data. Pathogens with different MICs might interfere with our results. In addition, the requirement of microbiologic evidence in our inclusion criteria might lead to over- or under-diagnosis of pneumonia. Besides, it's difficult to differentiate colonization or true infection since most of the patients fit the diagnosis of HAP or VAP by microbiologic evidence from sputum culture or tracheal aspiration. Consequently, the difference of the effectiveness between doripenem and meropenem might be underestimated.

In conclusion, we show doripenem has similar efficacy as meropenem on patients with HAP or VAP. With an aim to enhance antibiotics diversity, doripenem could be an alternative choice for hospitalized patients with HAP or VAP, except for patients with hematological malignancies.

Conflicts of interest

The authors have no conflict of interest to declare.

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