Prospective randomized comparison study of piperacillin/tazobactam and meropenem for health care-associated pneumonia in Japan

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Abstract

Health care-associated pneumonia (HCAP) may have a more severe course than community-acquired pneumonia (CAP); hence, it is more likely to be caused by drug-resistant bacterial pathogens and anaerobes involved in aspiration pneumonia. We compared the efficacy and safety of initial empiric therapy with piperacillin/tazobactam (PIPC/TAZ: 13.5 g/day) with that of meropenem (MEPM: 1.5 g/day) as single broad-spectrum regimens with gram-negative and anaerobic coverage in patients with HCAP in Japan. The clinical cure rate was 75.9% (22/29 cases) in the PIPC/TAZ group and 64.3% (18/28 cases) in the MEPM group. The clinical efficacy rate was 87.9% (29/33 cases) in the PIPC/TAZ group and 74.2% (23/31 cases) in the MEPM group. The bacteriological eradication rate was 94.4% (17/18) in the PIPC/TAZ group and 87.5% (14/16) in the MEPM group. Adverse drug reactions were seen in 22.4% (11/49 cases) of patients in the PIPC/TAZ group and 17.4% (8/46 cases) of patients in the MEPM group. Although not statistically different, the PIPC/TAZ group had a slightly higher efficacy rate than the MEPM group. Both treatment regimens are tolerable and might be appropriate to use as initial empiric therapy for HCAP in Japan. To investigate the differences in efficacy profiles of those two regimens, a further confirmatory study with a larger cohort as determined by a power analysis is recommended.

Keywords: health care-associated pneumonia, nursing and health care-associated pneumonia, piperacillin/tazobactam, meropenem, antimicrobials

Introduction

Pneumonia is the third leading cause of death in Japan, and mortality is especially high among elderly patients [1]. The Japanese Respiratory Society guidelines were established in August 2011 for the management of patients with nursing and health care-associated pneumonia (NHCAP) [2]. NHCAP differs from the health care-associated pneumonia (HCAP) that was described by the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA); its definition was modified in order to fit the Japanese health care system [3]. This study was started in 2009, and the definition of NHCAP had not been established at that time. Hence, patients with HCAP were recruited in this study. In Japan, general hospitals have extended-care wards, and patients in these wards tend to stay in hospitals longer as compared to those in western countries. Therefore, in this study, patients who resided in extended-care wards were included as HCAP cases.

HCAP may have a more severe course than community-acquired pneumonia (CAP) and is more likely to be caused by drug-resistant bacterial pathogens and anaerobes involved in aspiration pneumonia [4-8]. Inappropriate therapy is a major risk factor for mortality and leads to extended hospital stay [9]. ATS/IDSA guidelines for nosocomial pneumonia recommend that all such patients receive empiric therapy with a

multidrug regimen directed against drug-resistant organisms [3]. Nevertheless, Kett et al. [10] reported that compliance with ATS/IDSA guidelines for dual gram-negative coverage in patients, who are at risk from multidrug-resistant pathogens, was associated with increased mortality. This can be explained by antibiotic-specific toxic effects such as acute deterioration of renal function or neurotoxic effects. Brito et al. [11] developed an algorithm for empiric therapy of HCAP that suggests that not all such patients require a broad-spectrum multidrug regimen to achieve appropriate and effective therapy. Patients at risk for multidrug-resistant pathogens included those with severe illness or those with other risk factors including hospitalization in the past 90 days, antibiotic therapy in the past 6 months, poor functional status, and immune suppression.

For HCAP treatment, piperacillin/tazobactam hydrate (PIPC/TAZ) and carbapenems such as meropenem hydrate (MEPM) are recommended. However, limited data is available for comparing the effects of these two antibiotics against HCAP. In this study, the efficacy and safety of initial empiric therapy with PIPC/TAZ was compared to that with MEPM in patients with HCAP in Japan.

Patients and Methods

Patients

We enrolled patients with HCAP from Nagasaki University Hospital and 14 affiliated facilities in Nagasaki Prefecture from October 1, 2009, to May 31, 2010. The study was conducted with prior approval from the ethics committee of each of the participating medical facilities and was registered on a clinical trial registry (UMIN ID No.: UMIN000002269). The study protocol was explained thoroughly to the patients or their legal representatives before the start of treatment, and written informed consent was obtained from each patient.

Patients with HCAP and a pneumonia severity index score [12] in risk class III or IV were required to fulfill all four of the following criteria: (1) appearance of new infiltrates on chest radiography or computed tomography; (2) either (a) resided in a nursing home, long-term care facility or extended-care ward (for more than 48 h), (b) been hospitalized for ≥2 days in the last 90 days, (c) receiving outpatient intravenous therapy, or (d) receiving home wound care; (3) positive findings of at least one sign of inflammation such as white blood cell (WBC) count >10,000/mm^3 or <4,500/mm^3, increased C-reactive protein level, or fever ≥37°C; and (4) positive findings of at least one of the clinical symptoms or signs, such as cough, purulent sputum, moist rales, dyspnea, and tachypnea.

The following participants were excluded: (1) patients with bronchial

obstruction or history of obstructive pneumonia; (2) those unable to receive treatment every 8 h; (3) those with severe hepatic dysfunction or renal dysfunction (creatinine clearance ≤30 mL/min); (4) those for whom evaluation of clinical efficacy was difficult (including patients with cancer or other underlying diseases); (5) those infected with methicillin-resistant *Staphylococcus aureus* (MRSA), including suspected cases; (6) those receiving corticosteroids (prednisolone >10 mg/day); (7) those with a history of hypersensitivity to carbapenems, penicillins, or other beta-lactam antibiotics with or without beta-lactamase inhibitors; (8) those who were pregnant or lactating; (9) those with pneumonia severity index score in risk class V; and (10) those who were judged as otherwise ineligible by the attending physicians.

For the safety analysis, all randomized patients who received at least one dose of the study medication were included. Among full analysis set (FAS) which included all subjects who received at least one dose of the study medication during this study and had a valid baseline and at least one post-baseline follow-up assessment of the primary outcome measure, all patients who completely met the inclusion and exclusion criteria with no protocol violations (per-protocol set; PPS) were included for efficacy analysis.

Study design, dosage, and administration method

This study was a multi-centered, randomized, exploratory study. The patients

were randomly allocated to receive either PIPC/TAZ (4.5 g) every 8 h or MEPM (0.5 g) every 8 h. Randomization by the minimization method was performed at a centralized web site by attending physicians after obtaining written informed consent from each patient. Minimization factors included age and gender. The treatment period was 3-14 days in principle, but could be extended up to a maximum of 21 days. Concomitant use of other antimicrobial agents was not allowed.

Evaluation

The primary endpoint of this study was clinical cure rate at the test-of-cure visit. Clinical cure was evaluated as (i) cure which indicated continued improvement or complete resolution of the symptoms and no requirement for additional antimicrobial agents 7 days after the end of treatment (EOT); (ii) failure which indicated the treatment was ineffective; or (iii) indeterminate which indicated evaluation of the clinical cure was enabled for any reason. The clinical cure rate was calculated within the evaluable patients; those who were evaluated as indeterminate were excluded.

The secondary endpoint of this study was clinical efficacy rate at EOT, which was determined by the evaluation committee based on the changes in the clinical symptoms, laboratory findings, and infiltrates on chest radiographs, by referring to the criteria of the Japan Society of Chemotherapy [13]. Clinical efficacy was evaluated as (i) effective based on improvement or complete resolution of symptoms, improvement in body temperature to 37°C, chest radiograph score of ≤70% of the previous value, WBC count <9,000/mm^3, and C-reactive protein count ≤30% of the previous value; (ii) ineffective based on no satisfaction of the efficacy standards; or (iii) indeterminate due

to the inability to evaluate the clinical cure for any reason. The clinical efficacy rate was calculated within the evaluable patients; those who were evaluated as indeterminate were excluded.

The tertiary endpoints include bacteriological eradiation, survival, and safety parameters. Bacteriological eradiation was determined by the evaluation committee based on the criteria of the Japan Society of Chemotherapy [13] and evaluated as (i) eradication which indicated absence of pathogen, (ii) reduction which indicated quantitative reduction of the original pathogen, (iii) persistence which indicated presence of the pathogen even after the complete course of antimicrobial agent therapy, (iv) microbial substitution which included appearance of new pathogens, or (v) indeterminate which indicated inability to evaluate bacteriological eradiation for any reason. Survival was evaluated 30 days after EOT. For evaluation of safety parameters, all adverse events, including abnormal laboratory findings noted after the initiation of antibacterial agents, were recorded. An adverse event was considered to be an adverse drug reaction if a causal relationship with the antibacterial agent could not be ruled out; type of adverse event, and severity were recorded and evaluated for such events.

Statistical analysis

The data were analyzed using SAS version 9.2 (SAS Institute Inc., Cary, NC). *P*-values less than 0.05 were considered statistically significant. The characteristics and underlying conditions of the patients between treatment groups were compared using the Fisher's exact test for categorical variables and Wilcoxon rank sum test for continuous variables. Fisher's exact test was performed to compare clinical cure rate

and clinical efficacy rate in addition to the incidence of adverse drug reactions between treatment groups.

Results

Patients

A total of 95 patients were recruited from 15 facilities during the study period. A total of 49 and 46 patients were randomized to the PIPC/TAZ and MEPM treatment groups, respectively. Six and 22 patients were excluded from the FAS and PPS, respectively. The trial profile is presented in Fig 1. The characteristics and underlying conditions of the patients (PPS) are summarized in Table 1. The TAZ/PIPC and MEPM groups were well matched, and no significant differences were observed between the groups in the PPS.

Clinical efficacy

For clinical cure rate, five patients in each of the PIPC/TAZ group and MEPM group were evaluated as indeterminate. Among those who were not evaluated as indeterminate, the clinical cure rate was 75.9% (22/29 cases) in the PIPC/TAZ group and 64.3% (18/28 cases) in the MEPM group; the rate did not differ significantly between the two groups. For clinical efficacy rate, one patient in the PIPC/TAZ group

and two patients in the MEPM group were evaluated as indeterminate. Among those who were not evaluated as indeterminate, the clinical efficacy rate was 87.9% (29/33 cases) and 74.2% (23/31 cases) in the PIPC/TAZ group and MEPM group, respectively; the rate did not differ significantly between the two groups (Table 2).

Bacteriological efficacy

The most frequently isolated pathogen was *Streptococcus pneumoniae* (PIPC/TAZ: 5 cases, MEPM: 4 cases), followed by *Pseudomonas aeruginosa* (4 cases for each group), *Haemophilus influenzae* (PIPC/TAZ: 4 cases, MEPM: 2 cases), *Klebsiella pneumoniae* (PIPC/TAZ: 5 cases, MEPM: 1 case), methicillin-sensitive *S. aureus* (PIPC/TAZ: 3 cases, MEPM: 2 cases), and *Moraxella catarrhalis* (PIPC/TAZ: 2 cases, MEPM: 1 case). Polymicrobial infection was observed in 22.2% of patients (8/36 cases). The eradication rates were 94.4% (17/18) and 87.5% (14/16) in the PIPC/TAZ and MEPM groups, respectively (Table 3).

Survival

Thirty days after EOT, overall survival rate of PPS population was 93.7% (excluding 4 cases unknown, 59/63 cases were still alive). Survival rate was 96.9% in the PIPC/TAZ group (excluding 2 cases unknown, 31/32 cases were still alive) and 90.3% in the MEPM group (excluding 2 cases unknown, 28/31 cases were still alive).

Overall survival rate of the twelve cases who failed to the treatment was 83.3% (10/12 cases); one case died one day after EPT and another one was confirmed his death thirty days after EOT.

Adverse drug reactions

In the PIPC/TAZ group, adverse drug reactions, such as diarrhea and hepatic dysfunction, were seen in 22.4% of patients (11/49 cases). In the MEPM group, adverse drug reactions were seen in 17.4% of patients (8/46 cases), and included hepatic dysfunction. No significant differences were found between the two groups. All adverse drug reactions were mild or moderate in severity (Table 4).

Discussion

We designed a trial to compare two broad-spectrum single-agent regimens with gram-negative and anaerobic coverage; we compared the efficacy and safety of PIPC/TAZ with those of MEPM in patients with HCAP in Japan. The dosages of the drugs under study were 13.5 g/day (PIPC/TAZ) and 1.5 g/day (MEPM). MEPM was not approved for use at dosages of more than 1.5 g/day during the study period in Japan. Although not statistically different, the PIPC/TAZ group had a slightly higher efficacy rate than the MEPM group. Similarly, a previous study demonstrated a clinical efficacy

rate of 83% (62/75) for PIPC/TAZ that was used for the treatment of HAP patients [14]. Another study of PIPC/TAZ plus tobramycin versus ceftazidime plus tobramycin for HAP showed that PIPC/TAZ had a clinical efficacy rate of 74.4% at 10-14 days after discontinuation of the study drugs [15]. In a study by Joshi that compared PIPC/TAZ and imipenem/cilastatin, both in combination with tobramycin for HAP, PIPC/TAZ had a clinical cure rate of 68.4% at 7-21 days after treatment [16]. The lower efficacy of MEPM may have been related to the low dose (1.5 g/day), but not to any background factors of the patients. As no renal dysfunction was reported in MEPM-treated patients (either in the PPS analysis or in the 5 MEPM-treated patients who were excluded from the PPS due to low creatinine clearance rate), increasing the dosage to 3 g/day may be a potential option in HCAP. Although PIPC/TAZ at a dosage of 13.5 g/day showed a reasonable efficacy rate, it may be increased up to 18 g/day if needed. We observed diarrhea and hepatic dysfunction in the PIPC/TAZ group and hepatic dysfunction in the MEPM group; hence, caution is required when using higher dosages of these drugs.

Dysphagia caused by cerebrovascular diseases and disturbance of consciousness are well recognized in HCAP patients, and these are known to influence clinical outcomes [17, 18]. Risk factors of dysphagia such as neurological diseases, gastroesophageal diseases, presence of a feeding tubing, and dementia were present in

65.7% (44/67 cases) of patients in the PPS population. Additionally, because dysphagia may not be completely cured, aspiration pneumonia in such patients can frequently recur. Risk factors for dysphagia were observed in 87.5% (7/8 cases) of patients who achieved clinical efficacy but not cure in our study. Along with antimicrobial treatment, evaluation of dysphagia and early initiation of rehabilitation in HCAP patients are important factors to consider.

Microbiological analyses revealed that the most frequent pathogen was *S. pneumoniae*, followed by *P. aeruginosa*: both are major pathogens involved in CAP and HAP, respectively. Causative agents of HCAP varied, and included pathogens such as aerobic gram-positive cocci, including *S. pneumonia* and *S. aureus*, gram-negative bacilli, including *P. aeruginosa* and *K. pneumonia*, and anaerobes. It is important to consider local patterns of microbiology, as each hospital or facility has unique bacteriology, and regimens of antimicrobial agents must be modified according to such local data [19]. *P. aeruginosa* and *K. pneumoniae* were frequently detected in our study. Therefore, PIPC/TAZ and MEPM were considered appropriate choices as empirical treatment, although there was no statistical difference in the bacteriological efficacy rate.

For safety profiles of the two regimens, adverse drug reactions were seen in

22.4% of the PIPC/TAZ group and 17.4% of the MEPM group; there was no statistically significant difference in the incidence rate between the two groups. In comparison, the incidence rate of adverse drug reactions of PIPC/TAZ (4.5 g 3-4 times daily) and MEPM (1 g 3 times daily) in clinical studies conducted in Japan were was 61.1% (297/486 cases) [20] and 46.7% (50/107 cases), respectively [21]. Thus, the incidence of adverse drug reactions of both PIPC/TAZ and MEPM were less in this study than in previously conducted clinical studies. Moreover, all adverse drug reactions seen in this study were mild or moderate in severity. Taken together, both treatment regimens are tolerable and might be appropriate to use as initial empiric therapy for HCAP in Japan. A further confirmatory study with a larger cohort as determined by a power analysis is recommended.

In conclusion, although not statistically different, the PIPC/TAZ group had a slightly higher efficacy rate than the MEPM group. Both treatment regimens are considered to be safe as initial empiric therapy for HCAP in Japanese patients. To investigate the differences in efficacy profiles of these two regimens, a further confirmatory study with a larger number of patients is necessary.

FIGURE LEGEND

Fig. 1. The analysis sets investigated in this study

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CONFLICT OF INTEREST

Shigeru Kohno has received honoraria, lecture fees, and research grants for activities other than this trial from Taisho-Toyama Pharma Co., Ltd. and Dainippon Sumitomo Pharma Co., Ltd. No other co-authors declare any conflicts of interest.

Appendix: Participating institutions and chief investigator of this study

Japanese Red Cross Nagasaki Genbaku Isahaya Hospital (Kiyoyasu Fukushima), Japanese Red Cross Nagasaki Genbaku Hospital (Koji Hashiguchi), Isahaya Health-Insurance General Hospital (Yuichi Inoue), Sasebo City General Hospital (Yuichi Fukuda), Senju Hospital (Hikaru Tanaka), Sasebo Chuo Hospital (Tsutomu Kobayashi), Hokusho Central Hospital (Yasuhito Higashiyama), National Hospital Organization Nagasaki Medical Center (Eisuke Sasaki), Nagasaki Municipal Hospital (Naofumi Suyama), Nagasaki Municipal Medical Center (Yoji Futsuki), Saiseikai Nagasaki Hospital (Keiko Iida), Izumikawa Hospital (Yoshihisa Kohno), Nagasaki Goto Chuoh Hospital (Hideki Ikeda), all in Nagasaki, and National Hospital Organization Ureshino Medical Center (Toyomitsu Sawai), Saga, Japan.

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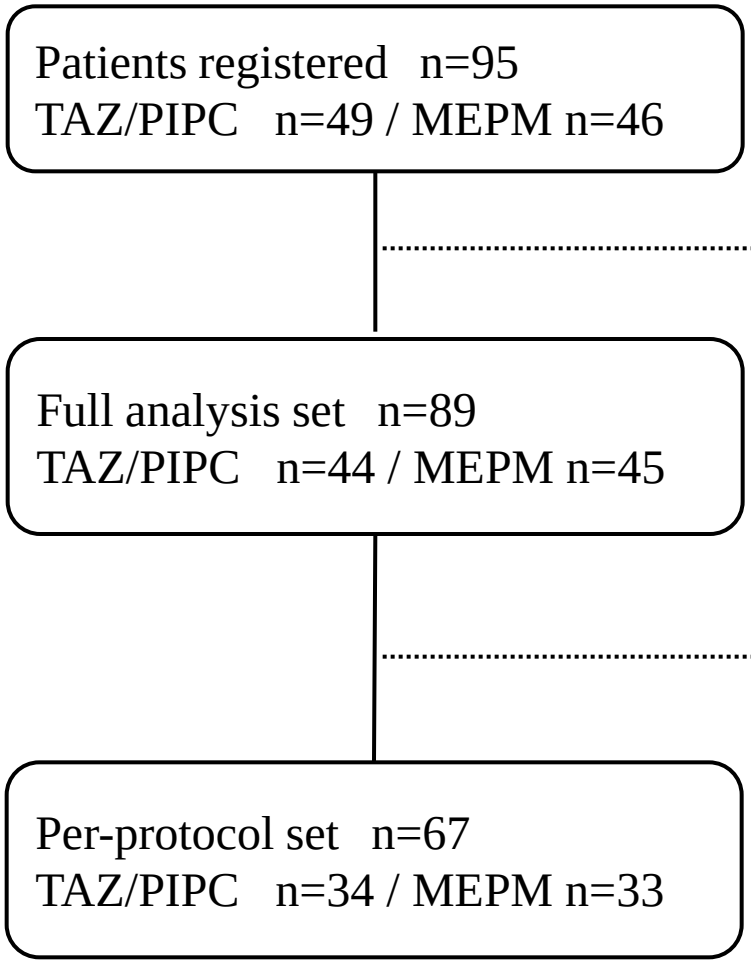

6 patients excluded

TAZ/PIPC n=5（empyema, aspergillosis, drug-induced pneumonia, non-tuberculosis mycobacterial infection, others）
MEPM n=1（pulmonary tuberculosis）

22 patients excluded

	TAZ/PIPC	MEPM
PSI classV	3	3
Prednisolone > 10mg/day		1
Inappropriate usage of study drug		1
Ccr<30 ml/min	5	5
Obstructive pneumonia	1	
Antibiotic premedication	1	2

Fig 1.

Table1. Characteristics of the patients

		overall	TAZ/PIPC	MEPM	P-value
Number of patients		67	34	33	
sex	Male/female	36/31	18/16	18/15	1.000[1)]
Age (years)	-59 60 - 69 70 - 74 75 - 79 80 – 89 90 -	6 10 5 8 26 12	3 6 2 5 13 5	3 4 3 3 13 7	0.5117[2)]
mean age		78.3	77.6	79.1	
Weight (kg)	-30 30 - 40 40 - 50 50 -	3 20 27 17	1 7 19 7	2 13 8 10	0.4502[2)]
mean weight		44.4	45.4	43.4	
PSI class	III IV	11 56	6 28	5 28	1.000[1)]
mean PSI score		105	104	107	
Underlying disease, complication	+ -	66 1	33 1	33 0	1.000[1)]
Treatment duration (days)	4 - 7 8 - 14 15 - 21	20 40 7	9 22 3	11 18 4	0.7665[2)]
Mean treatment duration (days)		9.5	9.6	9.4	

1) Fisher’s extract test 2) Wilcoxon rank sum-test

Table 2. The clinical cure and efficacy rate of TAZ/PIPC and MEPM

	TAZ/PIPC (n=34)	MEPM (n=33)	P-value※
Clinical cure rate	75.9% (22/29)	64.3% (18/28)	0.395
Clinical efficacy rate	87.9% (29/33)	74.2% (23/31)	0.2076

※ Fisher's extract test

For clinical cure rate, five patients in each of the PIPC/TAZ group and MEPM group who were evaluated as indeterminate were excluded. For clinical efficacy rate, one patients in the PIPC/TAZ group and two patients in the MEPM group who were evaluated as indeterminate were excluded.

Table 3. Bacteriological efficacy

Causative organism	TAZ/PIPC						MEPM						P-value※
	n	Eradication	Persisted	Substitutio	Indeterminat	Eradication(%)	n	Eradication	Persisted	Substitutio	Indeterminate	Eradication(%)	
S. pneumoniae	3	3	0	0	0	3 / 3	3	3	0	0	0	3 / 3	
K. pneumoniae	3	3	0	0	0	3 / 3	1	1	0	0	0	1 / 1	
H. influenzae	3	3	0	0	0	3 / 3	1	1	0	0	0	1 / 1	
P. aeruginosa							3	1	1	1	0	2 / 3	
MSSA	1	1	0	0	0	1 / 1	2	1	0	1	0	2 / 2	
M. catarrhalis	2	2	0	0	0	2 / 2							
Others	1	1	0	0	0	1 / 1	5	1	0	3	1	4 / 4	
S. pneumoniae + H. influenzae	1	1	0	0	0	1 / 1							
MSSA + *K. pneumoniae*	1	1	0	0	0	1 / 1							
MSSA + *P. aeruginosa*	1	1	0	0	0	1 / 1							
P. aeruginosa + E. coli	1	0	1	0	0	0 / 1							
P. aeruginosa + E. cloacae	1	0	0	0	1								
P. aeruginosa + H. influenzae							1	0	1	0	0	0 / 1	
S. Pneumoniae + M.catarrhalis							1	1	0	0	0	1 / 1	
PSSP + *K. pneumoniae + E. coli + P. aeruginosa*	1	0	0	1	0	1 / 1							
total	19	16	1	1	1	17 / 18 (94.4)	17	9	2	5	1	14 / 16 (87.5)	0.5909

Eradication (%) = (Eradication + Substitution) / (Total - Indeterminate) x 100, ※ Fisher's extract-test

Table 4. adverse drug reactions

TAZ/PIPC			MEPM			P-value※
22.4% (11/49)			17.4% (8/46)			0.613
type	severity	n	type	severity	n	
diarrhea	mild	2	hepatic dysfunctio	mild	7	
diarrhea	moderate	1	diarrhea	mild	1	
Loose stool	mild	1				
hepatic dysfunction	mild	2				
hepatic dysfunction	moderate	1				
cardiomyopathy	moderate	1				
leukopenia	mild	1				
hematuria	moderate	1				
hyperkalemia	mild	1				

※Fisher's exact test