ORIGINAL PAPER

Comparison of twice a day and three times a day meropenem administration in elderly patients in a Japanese community hospital

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ABSTRACT

Meropenem (MEPM) is a broad-spectrum antibiotic prescribed to patients with moderate or severe pneumonia. It is well recognized that appropriate medicine reduces the burden on not only young patients but elderly ones as well. We enrolled 56 patients aged 75 and over who were diagnosed with moderate or severe pneumonia (body temperature: $\geqq 37.5$ °C; white blood cell (WBC) count: $\geqq 10,000/\mu L$; C-reactive protein (CRP): $\geqq 4$ mg/dL) on the basis of Clinical Evaluation Methods for New Antimicrobial Agents to Treat Respiratory Infections defined by the Japanese Society of Chemotherapy, at the National Hospital Organization Kanazawa Medical Center from January 1, 2007 to May 31, 2010.

Forty-two patients were given MEPM twice a day and 14 were given the same drug three times a day in a Japanese community hospital. After four days, the three times a day group showed significant decreases in body temperature, WBC count, and CRP level, which are commonly used indices for evaluating therapeutic effects. Similarly, the twice a day group showed decreases of those indices, and both treatments had no serious adverse effects. Simulation analysis based on the pharmacokinetics-pharmacodynamics (PK/PD) theory revealed that both treatments effectively inhibited the activities of *Pneumococcus*, *Haemophilus influenzae*, *Providencia stuartii*, and *Staphylococcus aureus*, which are the major bacteria in the patients. In this retrospective study, simulation analysis based on the PK/PD theory revealed that even the twice a day MEPM administration has sufficient effectiveness against pneumonia. It also may pave the way for the use of personalized medicine in the patients.

Keywords: meropenem, elderly patient, pneumonia

INTRODUCTION

Pneumonia is the third most frequent cause of death in Japan, with mortality exceeding 120,000 in 2012, according to a report by The Japanese Ministry of Health, Labour and Welfare. For patients with moderate or severe pneumonia, meropenem (MEPM), a carbapenem antibiotic, is widely used.[1,2] MEPM is a broad-spectrum antibiotic that has been used for more than 20 years against Gram-positive, Gram-negative, and anaerobic bacteria, but not multi-drug-resistant bacteria, such as MRSA.[1,3] MEPM is classified as a "time-dependent" drug on the basis of its action. The antimicrobial effects of MEPM are dependent on the time above the minimum inhibitory concentration (%T>MIC) and not the peak of concentration.[4] MEPM of 0.5 g (up to 3 g/day) has been prescribed for febrile neutropenia as well as serious infections.[1,5] Regarding hospital-acquired pneumonia in adults, the committee for the JAID/JSC guidelines recommends a dosage regimen of 1.0 g MEPM 2–3 times a day[6]. However, there is no recommended MEPM dosage regimen for elderly pneumonia patients. In general hospitals in Japan, the typical dosage regimen is 0.5 g MEPM 2–3 times a day.[7,8,9] National Hospital Organization Kanazawa Medical Center has 25 departments and 554 beds, and is one of the large general hospitals in Japan. Approximately 70–80% of patients in the Department of Respiratory Diagnosis are elderly. Although MEPM is prescribed for those patients, it is unclear whether the dose is appropriate or not. Thus, it is necessary to clarify which treatment regimen is effective against pneumonia. In order to provide the most appropriate treatment for pneumonia patients, pharmacodynamics knowledge and experience based data are needed. In this study, we retrospectively surveyed electronic medical records to compare the differences between two and three times a day MEPM administration. We focused on elderly (≧75 years old) moderate or severe pneumonia patients in our community hospital. We measured body temperature, white blood cell (WBC) count, and C-reactive protein (CRP) level after a four day MEPM administration. We also examined AST and serum creatinine levels to determine the adverse effects.

METHODS

1. Subjects

Fifty six patients aged 75 and over were selected from 237 patients diagnosed with pneumonia, including acute bronchitis and acute bronchiolitis, at the Department of Respiratory Diagnosis of National Hospital Organization Kanazawa Medical Center, for the period January 1, 2007 to May 31, 2010 (prior to the change from proprietary drug to generic drug). In accordance with previous reports, patients aged ≧75 years, who were diagnosed on the basis of background characteristics, underlying disease, physical findings, fever, laboratory test values (WBC count and CRP level), and chest X-rays, were enrolled as the subjects of this study (237 patients) and those undergoing dialysis that could affect laboratory test results, those receiving anticancer drugs or immunosuppressive drugs, and those with MRSA infection were excluded.[10]

Fifty-six patients also met the criteria for moderate or severe pneumonia (body temperature: ≧37.5 °C; WBC count: ≧10,000/μL; CRP: ≧4 mg/dL) according to the Clinical Evaluation Methods for New Antimicrobial Agents to Treat Respiratory Infections defined by the Japanese Society of Chemotherapy.[10] We performed bacterial culture of sputum and venous blood samples during the pharmacotherapy. The pharmacotherapy was considered effective when three or more of the following criteria were satisfied after administration of the drug: ① body temperature: decreased to <37 °C; ② chest X-ray score: decreased to <70% of previous value; ③ WBC count: decreased to <9,000/μL; ④ CRP level: decreased to <30% of previous value.[10]

Analytical set (Survey period: January 1, 2007 to March 31, 2010)
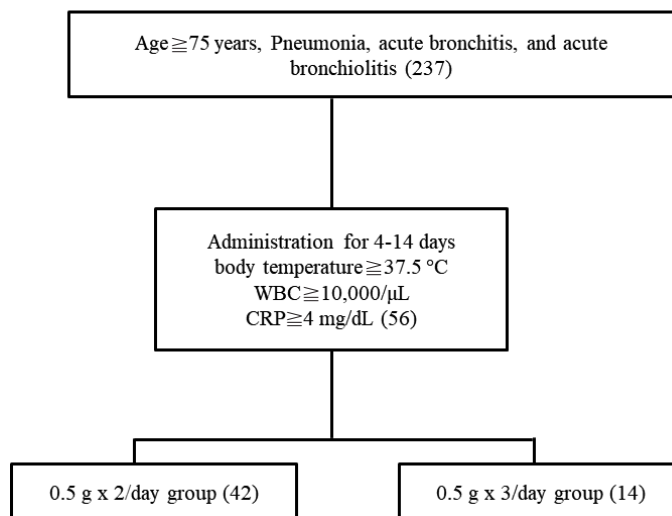
Fig. 1 Patient population in this study. Numbers of patients are shown in parenthesis. The subjects were 237 patients aged ≧75 years who were diagnosed on the basis of background characteristics, underlying disease, physical findings, fever, laboratory test values (WBC count and CRP), and chest X-rays. Those undergoing dialysis that could affect laboratory test results, those receiving anti-cancer drugs or immunosuppressive drugs, and those with MRSA infection were excluded.

The patients were administered 0.5 g of MEPM via intravenous drip infusion (Sumitomo-Dainippon Pharma Co., Ltd., Osaka) and divided into two treatment groups: 42 patients were in the twice a day MEPM administration (0.5 g × 2/day) group and 14 patients, the three times a day MEPM administration (0.5 g × 3/day) group (Figure 1). Patient background is shown in Table 1.

2. Evaluation of pharmacotherapy

We measured body temperature, WBC count, and CRP level at the time of admission and after the four day pharmacotherapy. In order to examine hepatic and renal functions, AST and serum creatinine levels were measured by following the same schedule as above.

3. Monte-Carlo simulation analysis based on PK/PD theory

We also performed simulation analysis of MEPM concentration in the patients by using Monte-Carlo simulation (Omegamon™ ver. 3, Pharmacist Support Ltd., Hiroshima, Japan; kindly provided by Dr. Norifumi Morikawa, Hiroshima University, Japan).[11] We input the patients' physical and biochemical data (age, sex, body weight, serum creatinine level, and dose of MEPM) into this simulation. Because the expected values of the percentage of time above the minimum inhibitory concentration (%T>MIC) are reliable to have bactericidal action,[11,12] we calculated MIC_{50} for each bacterium. The bactericidal action of MEPM can be expected if %T>MIC is 40% or higher.[11,12]

4. Statistical analysis

All results are presented as means ± standard deviation (SD). Mean age (years), duration of administration (days), body temperature, WBC count, and CRP, AST (GOT), and serum creatinine

levels were analyzed using the unpaired t-test. The paired t-test was used for within-group comparisons of body temperature between before and four days after MEPM administration and of WBC count and CRP level between before and 4 days after administration. The χ^2 test was done for gender in the patients' background, the presence or absence of concomitant antibiotic injection, and abnormal values in the safety evaluation. P<0.05 was regarded as significant.

This study was approved by the National Hospital Organization Kanazawa Medical Center Ethics Committee according to the Ethical Guidelines for Clinical Research, and performed retrospectively (#2017-No.44). Data were analyzed after unlinkable anonymization in order to protect the personal information of the patients.

RESULTS

1. Patient background

No differences were found in patient background at the time admission, including sex, mean age, number of patients with community-acquired pneumonia, number of patients with nursing and healthcare-associated pneumonia, number of patients with hospital-acquired pneumonia, severity of pneumonia infection, duration of MEPM administration, concomitant antibiotic injection (with/without), body temperature, WBC count, CRP level, AST level, and serum creatinine level, between the 42 patients in the 0.5 g × 2/day group and the 14 patients in the 0.5 g × 3/day group (Table 1).

2. Bacterial culture

The results of bacterial culture of sputum and venous blood samples before MEPM administration are summarized in Table 2. In sputum, commonly detected bacteria included *Streptococcus pneumoniae, Staphylococcus aureus*, and *Escherichia coli*. In addition, *Haemophilus influenzae* and *Klebsiella pneumoniae* were detected in the 0.5 g × 2/day group, and *Staphylococcus epidermidis* was detected in the 0.5 g × 3/day group. *Providencia stuartii* was detected in venous blood from the 0.5 g × 2/day group, and *S. aureus*, from the 0.5 g × 3/day group. At the end of MEPM administration, neither *P. stuartii* in venous blood from the 0.5 g × 2/day group nor *S. aureus* from the 0.5 g × 3/day group was detected.

3. Effects of MEPM treatment

(1) Body temperature: Body temperature significantly decreased from 38.2 ± 0.5 °C to 37.2 ± 0.4 °C in the 0.5 g × 2/day group, and from 38.2 ± 0.4 °C to 37.3 ± 0.6 °C in the 0.5 g × 3/day group (P<0.01). No significant differences were observed in the change of body temperature between the 0.5 g × 2/day group and the 0.5 g × 3/day group, regardless of whether antipyretic was concomitantly administered or not (Figure 2).

(2) WBC count: WBC count significantly decreased from 15,600 ± 6,400/μL to 10,800 ± 5,500/μL in the 0.5 g × 2/day group (P<0.01) and from 14,700 ± 5,600/μL to 10,400 ± 5,100/μL in the 0.5 g × 3/day group (P<0.05). No significant differences were observed in the change of WBC count between the 0.5 g × 2/day group and the 0.5 g × 3/day group, regardless of whether antipyretic was concomitantly administered or not (Figure 2).

(3) CRP: CRP levels significantly decreased from 15.5 ± 7.2 mg/dL to 10.5 ± 6.9 mg/dL in the 0.5 g × 2/day group (P<0.01) and from 17.8 ± 7.9 mg/dL to 11.0 ± 5.5 mg/dL in the 0.5 g × 3/day group (P<0.05). No significant differences were observed in the change of CRP level between the 0.5 g × 2/day group and the 0.5 g × 3/day group, regardless of whether antipyretic was concomitantly administered or not (Figure 2).

Table 1 Patient background. Data are shown as means ± SD.

	0.5 g × 2/day group	0.5 g × 3/day group	Statistical significance by t-test or χ^2-test
Number of patients	42	14	–
Sex (male/female)	17 /25	6/8	n.s.
Mean age (years)	83.9±5.0/ 85.9±5.1	82.2±4.0/ 82.3±5.1	n.s.
Community-acquired pneumonia	22	10	n.s.
Nursing and healthcare-associated pneumonia	17	3	n.s.
Hospital-acquired pneumonia	3	1	n.s
Severity of pneumonia infection			
Mild	0	0	n.s
Moderate	39	12	n.s
Severe	3	2	n.s
Duration of administration (days)	9.7±4.1	10.9±2.4	n.s
Concomitant antibiotic injection (with/without)	5	2	n.s
Body temperature (°C)	38.2±0.5	38.2±0.4	n.s
WBC count (/μL)	15,600±6,400	14,700±5,600	n.s
CRP (mg/dL)	15.5±7.2	17.8±7.9	n.s
AST (U/L)	31.3±27.2	34.3±32.7	n.s
Serum creatinine (mg/dL)	0.9±0.5	0.9±0.5	n.s

Mean age (years), duration of administration (days), body temperature, WBC count, CRP level, AST (GOT) level, and creatinine level were analyzed using the unpaired t-test. The χ^2 test was conducted for gender in the patient background, the presence or absence of concomitant antibiotic injection, and abnormal values in the safety evaluation. n.s.: no significance.

Table 2 Isolates on bacterial cultures before MEPM administration.

Sample	0.5 g × 2/day group	Number of patients	Sample	0.5 g × 3/day group	Number of patients
Sputum	*Streptococcus pneumoniae*	2	Sputum	*Streptococcus pneumoniae (PRSP)*	1
	Staphylococcus aureus	2		*Staphylococcus aureus*	2
	Haemophilus influenzae	2		*Staphylococcus epidermidis*	1
	Klebsiella pneumoniae	2		*Escherichia coli (ESBL)*	1
	Escherichia coli	2			
Venous blood	*Providencia stuartii*	1	Venous blood	*Staphylococcus aureus*	1
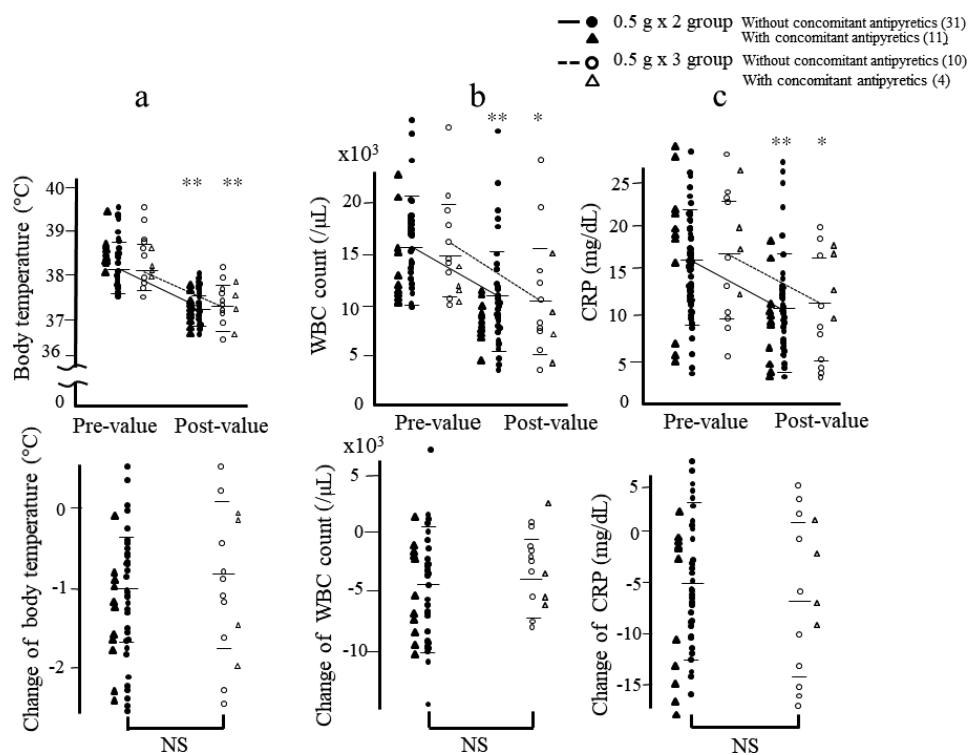
Fig. 2 Moderate or severe pneumonia induced body temperature (a), WBC count (b), and CRP level (c) before and after MEPM administration in the 0.5 g × 2/day group and the 0.5 g × 3/day group. Data are shown as means ± SD. *P<0.05, **P<0.01 vs corresponding pre-value (paired t-test). NS: not significant. △: With concomitant antipyretics: Average (▬), : Standard error (—)

(4) AST and serum creatinine: No significant differences were detected between the two groups. In addition, we could not find any severe adverse effects in the two groups (Table 3).

(5) Clinical assessment: The pharmacotherapy was effective in five of 42 cases in the 0.5 g × 2/day group (11.9%) and two of 14 cases in the 0.5 g × 3/day group (14.3%). When an antipyretic was concomitantly administered, effectiveness against pneumonia was noted in the 0.5 g × 2/day group (one case) but not in the 0.5 g × 3/day group. No significant difference was noted between the two groups.

4. Monte-Carlo simulation

In this study, *S. pneumoniae*, *K. pneumoniae*, *H. influenzae*, *S. epidermidis*, *S. aureus*, and *P. stuartii* were detected in the 56 patients. Therefore, assuming that MIC of MEPM is 1.0 μg/mL[3], we determined %T>MIC of MEPM when it was administered twice a day or three times a day using Monte-Carlo simulation analysis. As a result, we obtained %T>MIC values of 78.7 ± 16.7% (18.8 ± 4.0 hours) when MEPM was administered twice a day and 95.9 ± 7.0% (23.0 ± 1.7 hours) when it was administered three times a day, suggesting that the values exceeded the target treatment goal of 40%T>MIC. Significant difference was noted between the two groups. (Figure 3).

Table 3 Criteria for evaluating abnormal laboratory test values (top panel) and incidence of abnormal laboratory values after MEPM administration (bottom panel)

Item	Evaluation criterion	
AST (GOT)	When an increase from below the normal upper limit (33 U/L) to ≧250% of the normal upper limit (82.5 U/L) is observed post-administration	or
	When the pre-administration value exceeds 33 U/L (normal upper limit) and the post-administration value is ≧2-fold of the pre-administration value	
Serum creatinine	When an increase from below the normal upper limit (0.8 mg/dL) to ≧150% of the normal upper limit (2.0 mg/dL) is observed post-administration	or
	When the pre-administration value exceeds 0.8 mg/dL (normal upper limit) and the post-administration value is ≧2-fold of the pre-administration value	

Incidence of abnormal laboratory values after MEPM administration

		Number of patients	Number of abnormal laboratory test values	Incidence of abnormal laboratory test values	t-test
AST (GOT)	0.5 g × 2/day group	35	3	8.5%	n.s.
	0.5 g × 3/day group	13	1	7.7%	
Serum creatinine	0.5 g × 2/day group	35	0	0 %	n.s.
	0.5 g × 2/day group	14	0	0 %	

● 0.5 g x 2/day group (42)
○ 0.5 g x 3/day group (14)
P<0.05
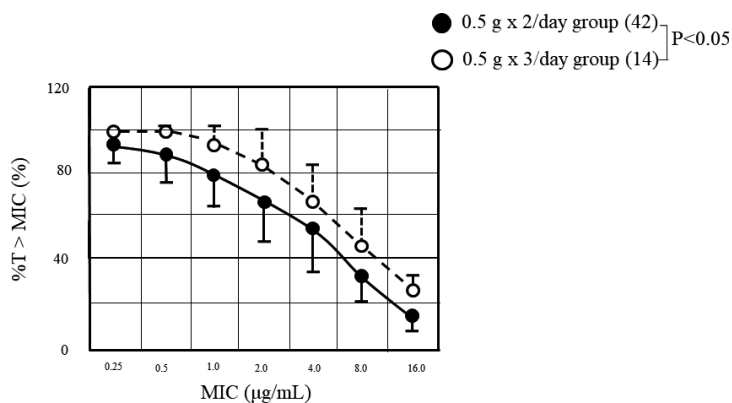
Fig. 3 Monte-Carlo simulation analysis of MEPM in elderly patients. Data are shown as means ± SD. *P<0.05 vs corresponding pre-value (paired t-test). We obtained %T>MIC values of 78.7 ± 16.7% (18.8± 4.0 hours) when MEPM was administered twice a day and 95.9 ± 7.0% (23.0 ± 1.7 hours) when it was administered three times a day, suggesting that the values exceeded the target treatment goal of 40%T>MIC.

5. Two cases in which bacteria were detected from venous blood prior to MEPM administration

A 79 year old woman (body temperature, 38.0 °C; systolic blood pressure, 94 mmHg; SpO$_2$, 97% (while inhaling oxygen); BUN, 26.9 mg/dL) from whom *P. stuartii* (MIC ≦0.5 μg/mL) was detected received MEPM (0.5 g) twice a day for 12 days. Improvements in body temperature from 38.0 °C to 37.3 °C, WBC count from 11,600/μL to 8,100/μL, CRP level from 19.9 mg/dL to 7.8 mg/dL, SpO$_2$ of 97% (room air), and systolic blood pressure of 120 mmHg were observed, with no detection of bacteria.

An 80 year old woman (body temperature, 39.1 °C; systolic blood pressure, 97 mmHg; SpO$_2$, 98% (while inhaling oxygen); BUN, 16.1 mg/dL (somnolence tendency)) from whom *S. aureus* (MIC ≦1.0 μg/mL) was detected received MEPM (0.5 g) three times a day for 14 days. Improvements in body temperature from 39.1 °C to 36.8 °C, WBC count from 11,500/μL to 4,100/μL, CRP level from 24.1 mg/dL to 21.3 mg/dL, SpO$_2$ of 95% (room air), and systolic blood pressure from 97 mmHg to 140 mmHg were observed, with no detection of bacteria.

DISCUSSION

Pneumonia is the third leading cause of death in Japan following cancer and heart disease, and compared to other diseases, these three major diseases have been on the rise for almost 20 years. The main cause of pneumonia is inflammation due to bacterial infection, and the only solution to this is the use of antimicrobials in drug therapy. Among antimicrobials, MEPM has a broad spectrum ranging from Gram-positive bacteria to Gram-negative bacteria and even anaerobic bacteria. For this reason, it has been used widely for many types of bacteria that cause serious refractory infections in patients having underlying diseases or those with a weakened immune system, including immunocompromised hosts.[1,2,5]

It has been reported that in general, MEPM used in the treatment of pneumonia exhibits a stronger antimicrobial effect when a larger number of doses are given.[4,5,13] On the other hand, it has been reported that no difference was observed when 1.0 g of MEPM was administered three times a day, as compared to when 0.5 g of MEPM was administered three or four times a day.[14] However, patient age, disease, and severity diagnosis were unclear in those reports, and thus, in order to evaluate the effects of MEPM administration, in this study, we targeted elderly patients presenting with moderate or severe pneumonia according to the "Clinical evaluation methods for new antimicrobial agents to treat respiratory infections."[10]

Some patients had other diseases as well, but as the main disease was pneumonia, treatment was mainly with MEPM. On day 4 from the initiation of MEPM administration, the levels of inflammation markers (body temperature, CRP, WBC count), which had been increased due to bacterial infection, tended to recover toward normal values in both groups. In addition, blood culture and chest X-rays performed four days after completion of MEPM administration yielded negative results in both the 0.5 g × 2/day group (one patient) and the 0.5 g × 3/day group (one patient). These results suggest that the bactericidal action of MEPM was induced in both groups.

Antimicrobials can be classified into "time-dependent" and "concentration-dependent" drugs according to their action. In the case of time-dependent antimicrobials, "the duration during which a concentration higher than MIC is maintained" is important, and there is no dependence on Cmax (maximum concentration in blood). In other words, the antimicrobial action of these drugs, when allowed to act for a long time at a blood concentration higher than MIC, could be maximized or even likely suppress resistant bacteria formation. As MEPM is a time-dependent antimicrobial, it is necessary that its blood concentration be higher than its MIC while taking into account the time required for metabolic excretion (time above MIC).[13] Unfortunately, in the

present study, we did not regularly measure MEPM concentrations in patients' blood. Therefore, we conducted a simulation analysis of predicted blood MEPM concentration in the two groups based on the test values obtained for each patient before MEPM administration. The MIC for the four most frequently detected bacteria presumed to be pneumonia-causing pathogens (*S. pneumoniae, K. pneumoniae, H. influenzae*, and *P. stuartii*) was 1.0 μg/mL.[3] Drusano reported that in the case of MEPM, sufficient bactericidal effect can be achieved if %T>MIC = 40(%), that is, longer than 9.6 hours.[12] Therefore, in this study as well, it is likely that the same action was observed when MEPM was administered twice a day, as compared to three times a day administration, because the concentration that induced the bactericidal action was sufficiently maintained. Theoretically, the greater the frequency of administration, the longer the time a drug remains in blood at a high concentration. In our simulation as well, %T>MIC showed a significant difference between the two groups. On the other hand, in both groups, ① a sufficiently high concentration of the drug was maintained to exert its antibacterial effect, and ② comparable effectiveness against pneumonia was noted. The difference observed in our simulation was not reflected in the clinical effect.

Next, based on AST and serum creatinine levels as indicators, we assessed the adverse effects on hepatic and renal function according to the "Criteria for safety evaluation of antimicrobial agents."[15] Two patients in the twice a day administration group showed abnormal AST levels, but these patients had hepatitis in addition to pneumonia, and their values were abnormal even before the initiation of MEMP administration. On the other hand, the two groups had similar AST and serum creatinine levels. In general, hepatic and renal function declines with age. Given that MEPM is a renal excretory drug, in order to conduct a prospective study in the future, it will be necessary to perform therapeutic drug monitoring (TDM) and then administer MEPM in a more careful manner, especially in patients with decreased renal function, while assessing particularly their renal function. From the above, the twice a day administration of 0.5 g MEPM is likely to be sufficiently effective and comparable to the three times a day administration, in elderly patients with moderate or severe pneumonia. Although a significant difference was found between %T>MIC of the two groups, because there was no significant difference in their effectiveness against pneumonia, this result had little meaning. Of course, when administering antimicrobials, it is important to select the appropriate agents while keeping in mind their ability to suppress the increase of resistant bacteria as well as the effective use of medical resources. Some of the patients in this study had been administered drugs other than MEPM. Given that there are cases in which patients have multiple diseases, fewer prescription drugs and less frequent prescription to the extent possible could shorten the time spent for administering medication. As a result, it can be expected that reducing medication and therapy that induce both physical and mental burden on patients as well as increasing the time spent on rehabilitation could eventually lead to enhanced social reintegration. In similar evaluative studies in the future, we plan to perform separate studies using CAP,[7] NHCAP,[8] and HAP.[9] We hope to propose more efficient methods for treatment and administration by investigating in detail the relationship between the effects of MEPM administration and renal function in the elderly.

ACKNOWLEDGEMENTS

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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