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Clinical effect of 3g/day administration of meropenem on severe pneumonia

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ABSTRACT We examined the clinical effect of Meropenem (MEPM) on severe pneumonia. We administered 3g of Meropenem daily to 20 patients with severe pneumonia: 8 community-acquired pneumonia patients, 9 nursing and healthcare-associated pneumonia patients, and 3 hospital-acquired pneumonia patients. It was effective in 15 of the 20 patients (75%): 8 of 8 community-acquired pneumonia patients (100%), 6 of 9 nursing and healthcare-associated pneumonia patients (66.6%), and 1 of 3 hospital-acquired pneumonia patients (33.3%). Bacteriologically, 9 of a total of 10 strains (90%) were eradicated: 4 of 4 *Streptococcus pneumoniae* strains, 2 of 2 methicillin-sensitive *Staphlococcus aureus* strains, 1 of 2 *Enterococcus faecalis* strains, 1 of 1 *Klebsiella pneumoniae* strain, and 1 of 1 *Escherichia coli* strain. Hepatic dysfunction was observed as a side effect in 8 patients (40%). Based on the above, administration of MEPM daily 3 g is extremely effective for community-acquired pneumonia, while it appears ineffective in many cases of nursing and healthcare-associated pneumonia or hospital-acquired pneumonia, and results in hepatic dysfunction at a high frequency.

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Key words：**Meropenem, 3g/day administration, Severe pneumonia**

INTRODUCTION

Recently, the Japanese Ministry of Health recognized an increase in the daily dosage of MEPM from 1g to 3g for severe refractory infections, allowing coverage by the national health insurance system. To date, however, no investigations of the clinical effect of this treatment have been published. Therefore, we examined the clinical efficacy of a daily dose of 3g MEPM on severe pneumonia.

SUBJECTS AND METHODS

Subjects

Subjects were 20 patients with severe pneumonia (8 community-acquired pneumonia, 9 nursing and healthcare-associated pneumonia, and 3 hospital-acquired pneumonia) treated with a single 1g dose of MEPM, three times daily at Kawasaki Hospital, Kawasaki Medical School from June 2011 to June 2012.

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Methods

Underlying diseases, causative organisms, clinical efficacy, bacteriological efficacy, and side effects of these subjects were retrospectively examined.

Causative organisms were identified when 10^6/ml or greater was detected in the culture of purulent sputum. Effectiveness was determined in accordance with the criteria of the Japanese chemotherapy society[1]. This study was performed with the approval of the Kawasaki Medical School ethical committee.

RESULTS

Cases (Table 1)

Subjects were 15 males and 5 females aged 50 to 88 years (72.6 ± 11.1 years) comprising 8 community-acquired pneumonia[2] patients and 9 nursing and healthcare-associated pneumonia[3] patients classified as severe according to the A-DROP system and 3 hospital-acquired pneumonia[4] patients classified as severe according to the I-ROAD system.

Underlying diseases (Table 2)

Underlying diseases included chronic obstructive pulmonary disease in 6, cerebrovascular disorder in 3, Parkinson's disease in 3, bronchial asthma in 2, and lung cancer, bronchiectasis, pneumoconiosis, old pulmonary tuberculosis, cerebral paralysis, and schizophrenia in 1 patient each.

Causative organisms (Table 3)

Causative organisms were identified in 10 of 20 patients: 4 strains of *Streptococcus pneumonia*, 2 strains of methicillin-sensitive *Staphlococcus aureus*, 2 strains of *Enterococcus faecalis*, and each 1 strain of *Klebsiella pneumoniae* and *Escherichia coli*.

Clinical efficacy (Table 4)

Treatment with 3g/day MEPM was effective in 15 of a total of 20 patients (75%): 8 of 8 community-acquired pneumonia patients (100%), 6 of 9 nursing and healthcare associated pneumonia patients (66.6%), and 1 of 3 hospital- acquired patients(33.3%).

Bacteriological efficacy (Table 5)

Nine of a total of 10 strains (90%) were eradicated : 4 of 4 strains of *S.pneumoniae*, 2 of 2

Table 1. Subjects

No. of patients	20	(M15, F 5)
Age (years)	50 ～ 88	(72.6 ± 11.1)
Community – acquired pneumonia (severe)	8	
Nursing and Healthcare – associated pneumonia (severe)	9	
Hospital – acquired pneumonia (severe)	3	

Table 2. Underlying diseases

Chronic obstructive pulmonary diseases	6
Cerebrovascular diseases	3
Parkinsonism	3
Bronchial asthma	2
Lung cancer	1
Bronchiectasis	1
Pneumoconiosis	1
Old pulmonary tuberculosis	1
Cerebral palsy	1
Shizophrenia	1
None	1

Table 3. Causative organisms

Streptococcus pneumoniae	4
methicillin – sensitive *Staphylococcus aureus*	2
Enterococcus faecalis	2
Klebsiella pneumoniae	1
Escherichia coli	1

(10/20 patients)

Table 4. Clinical efficacy

		Good	Poor	Efficacy rate(%)
Community – acquired pneumonia	8	8	0	100.0
Nursing and Healthcare - associated pneumonia	9	6	3	66.6
Hospital – acquired pneumonia	3	1	2	33.3
Total	20	15	5	75.0

Table 5. Bacteriological efficacy

Causative organisms	No. of strains	Eradicated	Persisted	Efficacy rate(%)
S. pneumoniae	4	4		100
MSSA	2	2		100
E. faecalis	2	1	1	50
K. pneumoniae	1	1		100
E. coli	1	1		100
Total	10	9	1	90

Table 6. Side effects

Clinical adverse reaction	diarrhea	3	(3/20=6.0%)
Abnormal laboratory findings			
AST ↑ . ALT ↑		3	
LDH ↑		2	
AST ↑ . AIP ↑		1	
ALT ↑		1	
BUN ↑		1	
AIP ↑		1	
			(9/20=45%)

strains of MSSA, 1 of 2 strains of *E.faecalis*, 1 of 1 strain of *K. pneumoniae*, and 1 of 1 strain of *E. coli*.

Side effects (Table 6)

Clinical adverse reaction included diarrhea in 3 (6.0%). Abnormal laboratory findings included increased AST.ALT in 3, increased LDH in 2, increased AST.ALP, ALT, BUN, and ALP in 1 patient each (9 patients: 45%). All were mild, and there were no patients who discontinued treatment or underwent treatment for side effects.

DISCUSSION

Administration of carbapenems is recommended for ICU patients with pneumonia in the JRS guidelines for the management of community-acquired pneumonia in adults[2], for pneumonia which requires hospitalization in the JRS guideline for nursing and healthcare-associated pneumonia[3], and for all hospital-acquired pneumonia in the JRS guidelines for the management of hospital-acquired pneumonia in adults[4]. It has been pointed out, however, that satisfactory clinical effect with carbapenems is elusive due to dosages that are smaller compared with those prescribed overseas[5, 6].

In overseas countries, daily administration of 3g imipenem/cilastatin (IPM/CS) or MEPM is recommended in severe infections, and its effectiveness has been reported in many cases.

Comparison of 3g IPM/CS daily and 3g MEPM daily in hospitalized patients with severe bacterial infections reported by Colardyn *et al*.[7] showed an effective rate of 77% in the IPM/CS group and 76% in the MEPM group. In ICU patients with severe bacterial infections, Hartenauer *et al*.[8] reported an effective rate of 85% in the IPM/CS group and 88% in the MEPM group. In ICU patients with serious bacterial infections, Verwaest *et al*.[9] reported an effective rate of 69% in the IPM/CS group and 68% in the MEPM group. These results suggest that the clinical effect of 3g IPM/CS daily and 3g MEPM daily in severe infections is nearly equivalent.

Comparison of 3g MEPM daily and a combination of 6g ceftazidime (CAZ) daily plus 15mg/kg amikacin (AMK) daily in patients with serious bacterial infections reported by Mouton *et al*.[10]

showed an effective rate of 88% in MEPM group and 78% in a CAZ plus AMK group. In patients with ventilator-associated pneumonia, Lerma *et al*.[11] reported an effective rate of 88% in the MEPM group and 78% in the CAZ plus AMK group. Furthermore, comparison of 3g MEPM daily and a combination of 6g CAZ daily plus 3mg/kg tobramycin (TOB) daily in patients with hospital-acquired lower respiratory tract infections[12] showed an effective rate of 89% in the MEPM group and 72% in the CAZ plus TOB group. These results suggest that clinical effect of 3g MEPM daily in severe infections is more efficacious than that of a combination of CAZ plus aminoglycosides.

While administration of 3g MEPM daily in severe refractory pneumonia has been allowed in Japan since 2011, no reports have been published to date describing the clinical effect of 3g MEPM daily in severe pneumonia.

Our results showed that 3g MEPM daily was effective in 15 of a total of 20 patients (75%): 8 of 8 community-acquired pneumonia patients (100%), 6 of 9 nursing and healthcare-associated pneumonia patients (66.6%), and 1 of 3 hospital-acquired pneumonia patients (33.3%). Prognosis of severe pneumonia was excellent in community-acquired pneumonia, extremely poor in hospital-acquired pneumonia, and intermediate in nursing and healthcare-associated pneumonia, which may reflect the state of the host. Even if high dose of MEMP is administered to a patient, if the state of the host is poor, the effect may be poor.

Hayashida *et al*.[13] also reported a patient with bacterial meningitis who died in spite of administration of 3g MEMP daily.

Bacteriological efficacy included eradication of 9 of a total of 10 strains(90%): 4 of 4 *S. pneumoniae* strains, 2 of 2 methicillin-sensitive *S. aureus* strains, 1 of 2 *E.faecalis* strains, 1 of 1 *K. pneumonia* strain, and 1 of 1 *E.coli* strain, which reflects the excellent antibacterial effect of MEPM[14].

Side effects included diarrhea in 3 (6.0%) and abnormal laboratory findings, mainly on hepatic dysfunction, in 9 (45%). Due to the high dose, the incidence of side effects is high, so that and it is necessary to pay particular attention to hepatic dysfunction.

It is concluded that administration of 3g MEPM daily was useful in community-acquired pneumonia, but ineffective in many cases of nursing and healthcare-associated pneumonia and hospital-acquired pneumonia, and hepatic dysfunction may occur at a high frequency. Hereafter, it is necessary to examine whether 6g MEPM daily would be appropriate in nursing and healthcare-associated pneumonia and hospital-acquired pneumonia and whether switching to a therapeutic dose of 1g daily would be effective in preventing the onset of hepatic dysfunction when clinical symptoms are improved.

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