Optimal Usage of Meropenem Based on Recommended Regimen Derived from Monte Carlo Simulation

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Long-term treatment with antibacterial agents is thought to be a cause of increased susceptibility to resistance. To prevent resistance in bacteria, a method of determining adequate regimens is needed and the Monte Carlo simulation (MCS) has proved useful for this purpose. In order to evaluate the inhibitory effect of the meropenem (MEPM) usage amount according to the recommended regimen based on the results of the MCS, we conducted a retrospective study using data from a database of inpatients at Iizuka hospital in 2006. We estimated the usefulness of the recommended regimen by comparing MEPM daily doses and the integrated frequency rate (IFR) of the percentage time it was above the MIC (%T > MIC) with those of the actual regimens. The results of doing this indicated that switching the actual regimens to MCS results-based regimens would have decreased the daily dose of MEPM by 43.9%. We also found that for the same dosing interval and daily dose, a regimen with a shorter infusion time achieved a higher IFR for %T > MIC values of 30% and 50%. This finding serves as a caution that just selecting a prolonged infusion time is not certain to raise the IFR of %T > MIC. Thus, the selection of appropriate dosages in consideration of the MIC of the pathogen and achieving high IFR levels will provide accurate and effective administration of MEPM

Key words Monte Carlo simulation, meropenem, daily dose, time above the MIC, decrease consumption

Introduction

Meropenem (MEPM) belongs to the carbapenem group of antibacterial agents with a broad spectrum and high antimicrobial activity¹⁾. Therefore MEPM is used as a first-line antibiotic against hospital-acquired pneumonia²⁾ and many other infectious diseases defined in a number of guidelines^{3,4)}. Carbapenems constitute one of the most active groups of beta-lactams against *P. aeruginosa* and, are frequently employed as an empirical treatment of serious infections that may be caused by *P. aeruginosa*¹⁾. However, drug-resistant microorganisms have become a major problem all over the world and there are carbapenem resistant *P. aeruginosa* strains. Furthermore, nosocomial infections caused by multiple-drug-resistant strains of *P. aeruginosa* (MDRP) have become a severe problem throughout Japan^{5,6)}. Meropenem has high antimicrobial activity against *P. aeruginosa*. Nevertheless, *P. aeruginosa* rapidly developed resistance to many antibacterial agents, via diverse and complex mechanisms⁶⁻¹¹⁾. Long-term treatment with antibacterial agents is regarded as one of the causes of the increased susceptibility to resistance¹²⁾. Thus, a number of trials to inhibit

antibiotic use and to develop other methods of preventing resistance are being conducted¹³⁻¹⁹⁾. The theories of pharmacokinetics and pharmacodynamics have been brought together to design an optimized evidence-based regimen. The relationship between the antimicrobial effect and the concentration of antibiotics has previously been established²⁰⁾. In animal studies using carbapenems such as MEPM, bacteriostatic and bactericidal responses were observed when drug concentrations remained above their minimum inhibitory concentration (MIC) for approximately 20% to 30%, and 40% to 50%, respectively, of the dosing interval^{18,21,22)}. This ratio of the time when drug concentrations exceeds MIC all over the dosing interval is called the percentage of the time above the MIC (%T > MIC). For the last few years, the Monte Carlo simulation (MCS) has been used as an acceptable method of evaluating the probability of experimental dosage regimens in attaining pre-specified pharmacodynamic target attainments against specific pathogens²³⁻³¹⁾. The output of these simulations represents the likelihood of a drug regimen achieving a defined exposure against these microorganisms, such as the %T > MIC required for a bacteriostatic or bactericidal effect³¹⁾. Concretely, this simulation uses the pharmacokinetic data of antibiotics, the frequency rate of the

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MIC of a specific bacterial species, experimental dosage regimens and a calculating equation of the %T > MIC. Then the results are obtained as the integrated frequency rate (IFR) at the %T > MIC of each value.

Earlier, we showed that a therapeutic drug monitoring (TDM) system reduced the amount and duration of prescribed anti-methicillin-resistant *Staphylococcus aureus* (MRSA) agents and considered that a similarly operated TDM system for anti-MRSA agents is necessary to ascertain the adequate regimens for carbapenems¹⁹⁾. Then we considered that the MCS is a useful method for this purpose, to decrease the dosage of carbapenems.

Thus, to evaluate the inhibition effect on the dosage of carbapenems of using recommended regimens according to the results of MCS, we conducted a retrospective study using a database of inpatients.

Patients and methods

This study was conducted as follows :

1. A survey of actual regimens was used to estimate the IFR of %T > MIC
2. A comparison of the IFR of %T > MIC was made among several regimens to find regimens that show higher IFR than actual regimens
3. A comparison of daily doses was made to estimate the inhibiting effect of recommended regimen use according to the results of the MCS

Parameters used in the MCS

Pharmacokinetics and Renal function groups

Pharmacokinetic data of MEPM were obtained from literature of Japanese health volunteers and patients with various degrees of renal impairment. Degrees of renal function were categorized into four groups (Table 1 A)^{32, 33)}.

Target microorganism

Bearing in mind the object of preventing drug resistance, the antibiotics dose regimen needs to be established focusing on bacteria with the highest MIC for administered antibiotics in causative pathogens against infectious diseases. Thus, *P. aeruginosa* was selected.

MIC values

MIC values of MEPM against *P. aeruginosa* and their frequencies were derived from our database of 852 samples taken from clinical patients at Iizuka hospital between January 2005 and December 2006.

MIC values were measured by VITEK[®] 2 (manufactured by bioMérieux INDUSTRY) and assigned by category to one of the following : <0.25, 0.5, 1, 2, 4, 8, and >16 µg/mL. We categorized MIC values into eight ranges to calculate by Monte Carlo simulation : 0.06 to 0.25, 0.25 to 0.50, 0.5 to 1, 1 to 2, 2 to 4, 4 to 8, 8 to 16, and 16 to 256 µg/mL. A minimum value was defined according to surveillance data available in Japan. Twice the value of the de-

tected maximum MIC range according to the same surveillance data (>128) was defined as a maximum value (Table 1 B)¹⁾.

Calculation of the IFR of %T > MIC

The IFR of %T > MIC in each renal function group was calculated using a 10,000-subject MCS on Crystal Ball 7 professional (Decisioneering Inc.).

According to the literature²⁸⁾, a one-compartment equation that combined an intravenous infusion during the distribution phase of the concentration-time curve and an intravenous bolus during the elimination phase was used :

$$\%T > MIC = (t_{inf} - (\ln((Ro / CL) / (Ro / CL - MIC)) * (t_{1/2} / 0.693))) + ((\ln(Ro / CL) - \ln(MIC)) * (t_{1/2} / 0.693))) * (100 / DI)$$

(Equation 1)

t_{inf} : infusion time, Ro : infusion rate in mg/h, CL : clearance, MIC : minimum inhibitory concentration, $t_{1/2}$: half-life, DI : dose interval

In simulation, distributions of CL and $t_{1/2}$ were assumed the log normality distribution. The MIC values were defined as distribute with constant probability in continuous ranges and applied the custom distribution on Crystal Ball 7 professional. Those continuous ranges were applied eight ranges above. Those probabilities were obtained from actual detective rates.

1. The survey of actual regimens used in Iizuka hospital in 2006

From actual regimens obtained from 714 adult patients prescribed MEPM at Iizuka hospital in 2006, regimens of 299 adult patients in whom we were able to estimate the CL_{CR} were selected to conduct the comparison study. The CL_{CR} of patients were calculated using the Cockcroft-Gault equation. Degrees of renal function were categorized into the same four groups as above. According to several reports^{18, 21, 22)}, the bacteriostatic and the bactericidal exposure %T > MICs were defined as 30 and 50, respectively. The IFRs at the %T > MIC values of 30 and 50 of patients were extrapolated the results of the MCS. Then, the average IFR and the number of patients who achieved the target attainment rate of over 80% and over 90% were calculated at the %T > MIC values of 30 and 50. In addition, the totals of daily doses were calculated in each renal function group.

2. Finding regimens that show higher IFR than actual regimens

Regimens

Regimens were selected by combining the following :

Dosage : 250, 500 and 1000 mg

Dose interval : 48, 24, 12, 8, 6 and 3 h

Infusion time : 0.5, 1 and 3 h

The daily dose was accommodated within 250 to 2000 mg according to the instructions printed on the package insert in Japan³⁴⁾. Therefore, for the renal function group creatinine clearance (CL_{CR}) < 70 mL/min, we adopted limited

Table 1. Summary of Parameters Used in the Monte Carlo Simulation

A. Pharmacokinetics parameters and variability for meropenem

Dose (mg)	Renal function (mL / min)	Pharmacokinetic parameter, mean (S.D.)	
		$t_{1/2}$ (h)	CL (L / h)
250	$CL_{CR} \geq 70$	0.98 (0.20) ^a	16.27 (4.50) ^a
500	$CL_{CR} \geq 70$	1.03 (0.13) ^a	14.88 (1.54) ^a
500	$50 \leq CL_{CR} < 70$	1.54 (0.70) ^b	14.60 (3.90) ^b
500	$30 \leq CL_{CR} < 50$	3.36 (1.02) ^b	7.70 (3.00) ^b
500	$CL_{CR} < 30$	5.00 (1.05) ^b	3.00 (1.00) ^b
1000	$CL_{CR} \geq 70$	1.02 (0.12) ^a	17.46 (2.17) ^a

CL_{CR} : creatinine clearance, $t_{1/2}$: half-life, CL : clearance

a. $t_{1/2}$ and CL data of group of 70 mL/min < CL_{CR} adapted from Mitsuyoshi Nakashima et al

b. $t_{1/2}$ and CL data of group of $CL_{CR} < 70$ mL/min adapted from Minoru Chimata et al³³⁾

B. Frequency distributions of the MIC values of meropenem against *P.aeruginosa*

Range of MICs (μ g / mL)		n	Frequency (%)
Minimum	Maximum		
0.06	0.25	432	50.7
0.25	0.50	3	0.4
0.50	1.00	62	7.3
1.00	2.00	100	11.7
2.00	4.00	28	3.3
4.00	8.00	89	10.4
8.00	16.00	73	8.6
16.00	256.00	65	7.6

MIC values of MEPM against *P.aeruginosa* and their frequencies were derived from our database of 852 samples taken from clinical patients at Iizuka hospital between January 2005 and December 2006.

MIC values were measured by VITEK[®]2 (manufactured by bioMerieux INDUSTRY).

We categorized MIC values into eight ranges to calculate by Monte Carlo simulation.

Range of MICs was defined according to surveillance data in Japan.¹⁾

MICs : minimum inhibitory concentrations

regimen : 500 mg for the dose, because we did not obtain the pharmacokinetic parameters for other amounts (Table 1 A).

Comparison of the IFR of the % T > MIC among dose regimens on daily doses at each renal function group

The class frequencies at each point at 5 intervals between 0 and 100 of %T > MICs were calculated from results of the MCS. They were then divided into the group achieving the

bacteriostatic exposure %T > MIC and other groups in each dose regimen. In addition, they were divided into groups achieving the bactericidal exposure of the %T > MICs and others on each dose regimen. Using the above divided class frequencies, in each renal function group the Chi square test was used to compare the achievement rate at the %T > MIC values of 30 and 50 among dose regimens of several daily doses in each renal function group.

Comparison of the IFR of %T > MIC among daily dose in several renal impairment groups

Regimens achieving the highest attainment rate at both the bacteriostatic and the bactericidal of the %T > MICs in each daily dose were selected. Then, the Chi square test was used to compare these achievement rates among daily doses on each renal function group by the above method.

$P < 0.01$ was deemed significant for all tests.

3. Estimating the inhibiting effect of recommended regimen use according to the results of the MCS

Definition of the alternate regimens and improved regimens

In regimens simulated by the MCS in each renal function group, those achieving the closest IFRs to the average IFR of the actual regimens using the smallest daily dose were defined as alternate regimens.

Next, from the results of the survey of actual regimens used, the daily dose of each renal function group was obtained and averages of daily doses were calculated. Then, in simulated regimens in each renal function group, those achieving the highest IFR by using less than the average daily doses of actual regimens were defined as improved regimens.

Comparison of daily doses and comparison of the IFR at the %T > MIC values of 30 and 50

First, in each renal function group, the totals of daily doses of actual regimens used were compared to the totals of daily doses of hypothetical use in alternate regimens. Next, in each renal function group, the average IFR at the %T > MIC values of 30 and 50 of actual regimens used were compared to the IFRs of hypothetical use in improved regimens. Then the two-tailed Mann-Whitney U-test was used to compare. $P < 0.01$ was deemed significant.

Results

MIC values of MEPM against *P.aeruginosa* and their rates of frequencies (Table 1 B) showed that 50.7% of samples were categorized in $\text{MIC} < 0.25 \mu\text{g/mL}$ and 7.6% of samples were categorized in $\text{MIC} > 16 \mu\text{g/mL}$.

A summary of actual dose regimens of the 299 adult patients in whom we were able to calculate the %T > MIC is shown in Table 2. The IFR average was 85.2% at the %T > MIC value of 30 and 74.9% at the %T > MIC value of 50. However, the percentage of patients whose IFR was over 80% was 68.2% at the %T > MIC value of 30 and 44.1% at the %T > MIC value of 50. In addition, the number of patients whose IFR was over 90% was less than 50% at the %T > MIC values of 30 and 50. Patients who had lower CL_{CR} had a higher IFR and a higher target attainment rate at the %T > MIC values of 30 and 50.

Table 3 is the list of regimens that show higher IFR of %T > MIC than actual regimens and shows the results of comparing the IFR of %T > MIC among dose regimens in each daily dose in each renal function group. With the same daily

dose, the regimen of a shorter dose interval achieved a higher IFR at both targets of %T > MIC values of 30 and 50. In addition, with the same dose interval and daily dose, the regimen of shorter infusion time achieved a higher IFR at the %T > MIC values of 30 and 50. Most dose regimens with the same daily dose showed a significant difference. The pair in which significant difference was not recognized was defined as coordinate. The regimens of a higher daily dose achieved a higher IFR at the %T > MIC values of 30 and 50. However, some assortments showed no significant difference.

Table 4 shows the results of comparing the daily dose of the actual regimens and the alternate regimens. Alternated regimens enabled the daily dose to be decreased by 43.9%. The improved regimens were defined as regimens achieving the highest IFR by using less than the average daily dose of the actual regimens. The results of comparing the IFR of %T > MIC between the actual regimens and the improved regimens is shown in Table 4. At %T > MIC = 30, for all renal function groups, improved regimens increased the IFR significantly. Furthermore, at %T > MIC = 50, in total of patients, improved regimens increased the IFR significantly. In the renal function groups, in only one group: $\text{CL}_{\text{CR}} > 70 \text{ mL/min}$, did the IFR show a significant increase. However, for the other renal function groups, the IFR increased.

Discussion

The purpose of this study was to simulate the optimal usage of MEPM by recommended regimen defined by the MCS. The results of this study indicate that using recommended regimens based on results of MCS contribute to a decrease in the consumption of MEPM.

Our study had two major findings. First, the results show that following the Japanese recommended dose from the instructions, the blind choice of the prolonged infusion causes the IFR of %T > MIC rise to be uncertain. With the same dose interval and the same daily dose, the regimen of shorter infusion time achieved a higher IFR at the %T > MIC values of 30 and 50. This finding is in disharmony with divers reports^{18, 28, 35, 36, 37)}. In general, the regimen of rapid infusion speed such as bolus injection achieves a higher maximum drug concentration than the regimen of slow infusion speed such as continuous infusion. This is because even during infusion, the drug concentration is decreasing according to its half-life. In addition, the regimen of slower infusion speed has a longer maximum drug concentration time³⁵⁾. Therefore, if the MIC of the target pathogen is high, there is a possibility that the regimen of slow infusion speed cannot raise the drug concentration above the MIC of the target pathogen. To keep the time above the MIC, the high dose or the short interval is required³⁶⁾. Concerning MEPM, the half-life is 0.98 to 1.03 hours in the renal function groups: $\text{CL}_{\text{CR}} > 70 \text{ mL/min}$ and one of the shortest half-lives in beta-lactams⁴⁾. Therefore, its blood concentration is relative to the infusion speed. Mikamo reported in his study that MEPM

Table 2 . Summary of actual dose regimens of 299 adult patients prescribed meropenem :
patients in whom we were able to calculate the % T > MIC

Renal function (mL/min)	Dose regimens			n	Frequency(%)	IFR(%)at each target of the%T > MIC		
	Dose (mg)	Dose interval (h)	Infusion time (h)			%T > MIC = 30	%T > MIC = 50	
CL _{CR} < 30	500	8	1	6	2.0	95.7	95.2	
			0.5	1	0.3	98.6	97.9	
		12	1	37	12.4	95.3	94.5	
			0.5	4	1.3	98.0	96.6	
		24	1	38	12.7	94.0	92.9	
			0.5	4	1.3	95.9	94.3	
		48	0.5	1	0.3	93.5	86.1	
			IFR average*					95.0 ± 1.0
		Number of patients (rate)						
		total					91	
IFR > 90%						91(100.0%)		
IFR > 80%						91(100.0%)		
30 < CL _{CR} < 50	500	8	2	1	0.3	91.4	88.9	
			1	10	3.3	93.4	92.8	
			0.5	1	0.3	94.5	93.7	
		12	1	19	6.4	93.0	90.8	
			0.5	4	1.3	93.8	92.6	
		24	1	4	1.3	88.7	77.6	
			IFR average*					92.7 ± 1.4
		Number of patients (rate)						
		total					39	
		IFR > 90%						35(89.7%)
IFR > 80%						39(100.0%)		
50 < CL _{CR} < 70	500	8	2	1	0.3	77.6	67.7	
			1	9	3.0	85.0	75.0	
			0.5	2	0.7	90.5	83.1	
		12	1	16	5.4	77.8	62.6	
			0.5	4	1.3	85.4	70.6	
		24	1	1	0.3	54.9	25.5	
			IFR average*					80.7 ± 6.2
		Number of patients (rate)						
		total					33	
		IFR > 90%						2(6.1%)
IFR > 80%						15(45.5%)		
CL _{CR} > 70	500	8	1	25	8.4	80.7	68.8	
			12	2	1	0.3	65.8	47.1
		24	1	33	11.0	71.7	53.1	
			0.5	4	1.3	79.1	61.0	
			1	3	1.0	42.7	0.3	
		1000	8	1	20	6.7	87.8	73.6
				0.5	4	1.3	92.1	82.2
			12	2	1	0.3	71.0	52.3
				1	31	10.4	77.0	59.1
	24		0.5	10	3.3	85.7	67.2	
			1	2	0.7	50.8	0.9	
			0.5	2	0.7	57.6	3.8	
			IFR average*					77.6 ± 9.0
		Number of patients (rate)						
		total					136	
IFR > 90%						4(2.9%)		
IFR > 80%						59(43.4%)		
IFR average*					85.2 ± 10.3	74.9 ± 19.4		
Number of patients (rate)								
total					299			
IFR > 90%						132(44.1%)		
IFR > 80%						204(68.2%)		
						132(44.1%)		

The creatinine clearance of patients were calculated using the Cockcroft-Gault equation.

The integrated frequency rate (IFR) of the % T > MIC values of 30 and 50 of patients were extrapolated the results of the Monte Carlo simulation on same renal function group and same regimens as actual.

CL_{CR} : creatinine clearance

* : average ± SD

Table 3 . The list of regimens that show higher IFR of %T > MIC than actual regimens

Renal function (mL/min)	Dose regimens				Target of the %T > MIC							
					%T > MIC = 30				%T > MIC = 50			
	Daily dose(mg)	Dose(mg)	Dose interval(h)	Infusion time(h)	IFR(%)	Ranking 1 ^{a)}	Ranking 2 ^{b)}	Mark ^{c)}	IFR(%)	Ranking 1 ^{a)}	Ranking 2 ^{b)}	Mark ^{c)}
CL _{CR} < 30	500	500	24	0.5	95.9	1	4	A & I	94.3	1	4	A & I
		1000	500	12	0.5	98.0	1	3	96.6	1	3	
	500	500	12	1	95.3	2			94.5	2		
		1500	500	8	0.5	98.6	1	2	97.9	1	2	
	500	500	8	1	95.7	2			95.2	2		
		2000	500	6	0.5	99.0	1	1	98.4	1	1	
	500	500	6	1	96.0	2			95.5	2		
30 < CL _{CR} < 50	1000	500	12	0.5	93.8	1	1	I	92.6	1	2	I
		500	12	1	93.0	2		A	90.8	2		A
	1500	500	8	0.5	94.5	1	1		93.7	1	1	
		500	8	1	93.4	2			92.8	2		
	2000	500	6	0.5	94.9	1	1		94.2	1	1	
		500	6	1	93.6	2			93.2	2		
50 < CL _{CR} < 70	1000	500	12	0.5	85.4	1	3	A & I	70.6	1	3	A & I
		1500	500	8	0.5	90.5	1	2	83.1	1	2	
	500	500	8	1	85.0	2			75.0	2		
		2000	500	6	0.5	92.0	1	1	88.2	1	1	
	500	500	6	1	88.7	2			81.3	2		
CL _{CR} > 70	750	250	8	0.5	78.2	1	4	A	65.4	1	4	A
		1000	250	6	0.5	83.8	1	3	73.5	1	3	
	250	250	6	1	76.4	3			67.6	2		
		500	12	0.5	79.1	2			61.0	3		
		1500	250	4	0.5	89.0	1	2	81.8	1	2	I
		250	4	1	81.2	2			74.8	2		
	250	250	4	3	69.7	3			62.4	4		
		500	8	0.5	89.4	1	2	I	76.1	2		
		500	8	1	80.7	2			68.8	3		
		2000	250	3	0.5	91.0	2		86.7	1		
	250	250	3	1	83.9	4			78.5	3		
		250	3	3	71.5	6			67.1	5		
		500	6	0.5	92.3	1	1		84.3	2	1	
		500	6	1	86.1	3			75.0	4		
	500	500	6	3	72.1	6			64.9	6		
		1000	12	0.5	85.7	3			67.2	5		

The integrated frequency rate (IFR) was calculated by Monte Carlo simulation.

The target microorganism : *P. aeruginosa*

The Chi square test was used to compare the integrated frequency rate of %T > MIC. P < 0.01 was deemed significant.

a) : The order was acquired according to the results of comparing the IFR of %T > MIC among dose regimens in each daily dose.

b) : The order was acquired according to the results of comparing the IFR of %T > MIC among daily doses in each renal function group.

a), b) : The pair in which significant difference was not recognized was defined as coordinate.

c) : The mark A and I mean alternative regimens and improved regimens, respectively.

CL_{CR} : creatinine clearance

concentrations immediately following drip infusion were 29.7µg/mL on 0.5 h-infusion and 8.6µg/mL on 4 h-infusion³⁶⁾. These results are congruent with the theory above. However, the %T > MIC on 4 h-infusion was higher than on 1 h-infusion. In his study, The MIC of MEPM against *P. aeruginosa* used to calculate %T > MIC was a value of an actual detected pathogen : 4µg/mL. Thus, the calculation method of his study was not the MCS method. The MCS method can calculate the %T > MIC involving the

distribution of MIC. Besides, the MIC value using this study showed that 41.6% of samples were MIC > 1µg/mL and 26.6% of samples were MIC > 4µg/mL. We consider that these samples of high MIC influenced results of the MCS and make a difference in the results of comparisons of infusion times. In the other studies^{18, 35)}, the MIC of MEPM against *P. aeruginosa* used to calculate %T > MIC were less than our study. On the other hand, in the prestigious study by Kuti et al²⁸⁾, the distribution of MICs used to calculate

Table 4 . Summary of the effect of alternative regimens and improved regimens

Actual regimens					Alternative regimen				Improved regimen			
Renal function (mL/min)	n	The average IFR(%)		Totals of daily doses (mg) ^(a)	IFR(%)		Totals of daily doses (mg) ^(b)	Reduction rate(%) ^(c)	IFR(%)		p Value ^(d)	
		%T> MIC = 30	%T> MIC = 50		%T> MIC = 30	%T> MIC = 50			%T> MIC = 30	%T> MIC = 50	%T> MIC = 30	%T> MIC = 50
CL _{CR} < 30	91	95.0 ± 1.0	93.9 ± 1.4	72750	96.0	94.3	45500	37.5	96.0	94.3	p < 0.01	NS
30 < CL _{CR} < 50	39	92.7 ± 1.4	90.2 ± 4.4	43000	93.0	90.8	39000	9.3	93.8	92.6	p < 0.01	NS
50 < CL _{CR} < 70	33	80.7 ± 6.2	67.2 ± 9.8	38500	85.4	70.6	33000	14.3	85.4	70.6	p < 0.01	NS
CL _{CR} > 70	136	77.6 ± 9.0	59.8 ± 15.8	237000	78.2	65.4	102000	57.0	89.4	81.8	p < 0.01	p < 0.01
total	299	85.2 ± 10.3	74.9 ± 19.4	391250	88.1	80.3	219500	43.9	91.1	84.8	p < 0.01	p < 0.01

The creatinine clearance of patients were calculated using the Cockcroft-Gault equation.

The integrated frequency rate (IFR) of %T > MIC values of 30 and 50 of patients were extrapolated the results of the Monte Carlo simulation on same renal function group and same regimens as actual.

^(c)The reduction rate was calculated by ((b) - (a))/(a).

^(d)The two-tailed Mann-Whitney U-test was used to compare the integrated frequency rate between actual regimens and recommended regimens. P < 0.01 was deemed significant.

CL_{CR} : creatinine clearance. NS : no significant

was similar to ours. However, their regimens selected for comparison were 1000 mg per 8 h and 2000 mg per 8 h and these doses were higher than ours, within a range 250 mg to 1000 mg as the daily dose. With the same infusion time, the higher dose achieves a higher maximum drug concentration and reaches the maximum drug concentration faster³⁸⁾. Therefore, the length of time above the MIC on the high dose regimens is not influenced so much by an increase in the drug concentration during infusion time. Li et al developed an MEPM population pharmacokinetic model using patient data and used it to compare the %T > MIC among regimens with variant infusion times³⁷⁾. They researched the IFR of %T > MIC at several MIC values. The results lead us to conclude that prolonged infusion improves the attainment rate of the %T > MIC. However, in their study, regimens used for comparison were 1000 mg per 8 h and were higher doses than our regimens considering the combination of dose and frequency of administration. Therefore, these results suggest that the dose of our selected regimens in the current study is not enough to keep concentration above the MIC against a decrease during 3 h-infusion. However, these regimens were selected according to the instructions printed on the package insert in Japan. Thus, the results of this study show that using these instructions, the view that longer infusion time increases the IFR of %T > MIC is unsupported. That value is influenced by the distribution of MICs. In the situation of low daily dose or low dosage and high rate of resistance, the possibility that the longer infusion time may decrease the IFR of %T > MIC should be considered. In the other hand, the results show that shorter dose interval and higher daily dose improve the IFR of %T > MIC. Results are congruent with several reports³⁵⁾.

Secondly, the recommended regimen from the results of the MCS makes it possible to decrease the consumption of MEPM while keeping the IFR of %T > MIC. Because the improved regimens of this study increase the IFR significantly, the MCS method is suited for defined regimens to increase the effectiveness of antibiotics. In addition, it is ex-

pected that the recommended regimen based on MCS enables shortening of the duration of administration.

The limitation of our study is that change in the clinical effect was not compared between the actual regimen use and the recommended regimen use. However, the relationship between %T > MIC and the clinical effect is under intense study^{18, 28, 35, 37, 38)} and the effectiveness of the increase %T > MIC has reached a consensus^{23 - 31)}. More studies concerning the total dose during administration term are needed to confirm the inhibitory effect of consumption of antibiotics using the MCS method. In this study, the rate of patients whose CL_{CR} < 70 was over 50%. Thus, an accumulation-related problem may be concerned. However, the CL value of the patient was included in the calculating formula of %T > MIC in this study. Moreover, it is reported that the bioaccumulation potential of meropenem is low³²⁾.

In conclusion, this study demonstrates that the recommended regimen used by the MCS makes it possible to decrease the consumption of MEPM. The results of this study warn that the blind choice of the prolonged infusion causes the rise in the IFR of %T > MIC to be uncertain. By selection of the appropriate dosage depending on the MIC of the pathogen, the rise in the IFR can be accurately gauged and administered.

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