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Consideration of dosage regimen for meropenem in mixed infusions containing L-cysteine and/or SBS

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The purpose of this study was to simulate the concentration–time profile, C_{max} and area under the curve (AUC) of serum meropenem (MEPM) when administered in mixed infusions containing L-cysteine and/or SBS, and to determine the percentage of time that free drug concentrations remain above the minimum inhibitory concentration (MIC) of an unspecified pathogen (%TAM), with a target attainment (TA) of 40%TAM. The mixed infusions were administered over a period of 0.5 or 2 hr. after being kept for 0, 1 or 2 hr. at 4ºC or 25ºC after mixing. Dosage regimens tested were 500 mg quaque 24hr. (q24hr.), 1000 mg q12hr. or q8hr.. When MEPM was mixed with AMINOFLUID® Injection (AM-F) or AMIGRAND® Injection (AM-G), both of which contain L-cysteine and SBS, to obtain a MIC of <0.5 mg/L, 40%TAM was achieved under nearly all conditions. With MIC 2 mg/L, TA% >80% was achieved under nearly all conditions when the mixture was stored for 0 or 1 hr. and infused over 0.5 hr.. However, TA% declined markedly when the mixed infusion was administered over 2 hr., even if administered immediately after mixing. In infusions of MEPM mixed with AM-F or AM-G, MEPM levels were all lower than when MEPM was administered in normal saline. When MEPM was mixed with Fructlact Injection (Fru), which contains SBS but not L-cysteine, no differences in TA% were found in comparison with MEPM in normal saline. When MEPM was mixed with Fru TA% >80% could be achieved by extending the duration of the infusion. However, when mixed with AM-F or AM-G, MEPM must be administered over a 0.5-hr. period immediately after mixing to achieve TA% >80%.

Key Words: : meropenem, %TAM, PK-PD parameters, MIC, stability

Introduction

Meropenem (MEPM) is a carbapenem antibacterial agent with broad-spectrum activity against Gram-negative, Gram-positive and anaerobic bacteria[1]. Carbapenems are particularly important for the treatment of severe infections caused by multi-resistant Gram-negative bacteria[2]. The main pharmacokinetic–pharmacodynamic (PK-PD) parameter that correlates best with the therapeutic efficacy of carbapenems is the percentage of Time that free drug concentrations remain Above the Minimum inhibitory concentration (MIC) of the pathogen (%TAM), and extended infusion is the preferred route of administration to maximize this parameter[3–5].

It has been reported that the stability of carbapenems declines markedly when they are administered in mixed infusions which include L-cysteine and/or sodium bisulfite (SBS)[6–8]. Recently, Takasu *et al.* reported on the stability of MEPM when administered together with commercially available mixed infusions[6]. In their article, the concentration of MEPM declined according to first-order kinetics but the rate of decline varied considerably when the antibiotic was administered with different mixed infusions.

MEPM is generally administered as an infusion in normal saline. Although MEPM is rarely mixed with parenteral nutrition fluids, MEPM may be

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mixed in the infusion management of highly invasive patient, such as sepsis. There have been no reports on the serum concentration of MEPM when administered after mixing with such infusions, so it was decided to investigate the rate of decline of MEPM concentrations in these situations.

In the present study, we aimed to predict the serum MEPM concentration–time profile, C_{max}, area under the curve (AUC) and obtained target attainment (TA) of 40%TAM based on different MICs (0.5, 1, 2 and 4 mg/L) of infectious organisms using a Monte Carlo simulation. The effects of storage conditions (temperature and time after mixing) were also investigated. MEPM was administered as either a 0.5-hr. or 2-hr. infusion after storage of mixtures with Fructlact Injection (Fru), AMINOFLUID® Injection (AM-F) or AMIGRAND® Injection (AM-G) for periods of 0, 1 or 2 hr. and at 4℃ or 25℃. Fru contains SBS, while AM-F and AM-G contain both L-cysteine and SBS.

Methods

1. Mixed injections and infusion conditions

Using information from the package insert and actual clinical practice, we selected 0.5 and 2 hr. as infusion times and 0, 1 and 2 hr. after mixing as storage times. Mixtures of MEPM with Fru (500mL), AM-F (500mL) or AM-G (500mL) were examined, as shown in Table 1. The storage temperature was fixed at either 4℃ or 25℃. MEPM injection preparations contained either 500 mg or 1000 mg MEPM.

Table 1 Mixed injections and infusion conditions

					Storage	
MEPM dose	Infusion time (hr.)	Mixed with	L-Cysteine (g/L)	SBS (g/L)	Temp (˚C)	Time (hr.)
500 mg	0.5 or 2	Fructlact Injection	-	0.2	4 or 25	0, 1 or 2
		AMINOFLUID® Injection	0.3	0.2		
		AMIGRAND® Injection	0.3	0.02		
1000 mg	0.5 or 2	Fructlact Injection	-	0.2	4 or 25	0, 1 or 2
		AMINOFLUID® Injection	0.3	0.2		
		AMIGRAND® Injection	0.3	0.02		

SBS: sodium bisulfite
Temperature: Temp

2. Stability prediction of MEPM in mixed infusions

In the article of Takasu et al., MEPM was shown to decrease according to first-order degradation kinetics in mixtures with AM-F, AM-G and Fru[6]. In the present study, therefore, first-order degradation kinetics (ka in the following equation) were used to simulate the decline of MEPM levels during infusion.

$$dX_1/dt=-ka \cdot X_1 \qquad \text{Equation 1}$$

where X_1 is the amount of MEPM in the compound compartment (mg) and ka is its degradation rate constant (h^{-1}). At 25 ° C, ka values of AM-F, AM-G and Fru were 0.695, 0.828 and 0.0060, respectively, while at 4℃, ka values were 0.329, 0.453 and 0.0008, respectively[6].

3. Pharmacokinetic analysis

As PK parameters, clearance and distribution volume for MEPM were estimated from population parameters of Japanese adult patients, as reported previously[9].

$CL=0.0905\times CCR+2.03$; $Q=4.02$

$V_1=0.199\times WT$; $V_2=4.55$

where CL = total body clearance (L/hr), CCR = creatinine clearance (mL/min), Q = inter-compartmental (central–peripheral) clearance, V_1 and V_2 = the distribution volumes of the central and peripheral compartments (L), respectively, and WT = bodyweight (kg)

The input rate of MEPM followed the reduction in concentration (equation 1) was incorporated into *in vivo* simulation using population pharmacokinetic parameter of Japanese considering model based on dosage frequency, quaque 8hr.(q8hr.), q12hr. or q24hr..

The dosage and frequency of dosing required to

maintain serum MEPM concentrations, in view of the degradation rate described in equation 1, was incorporated into a Monte Carlo simulation model using pharmacokinetic parameters from the Japanese population. A thousand simulated serum concentration curves were produced for each dosage regimen (500 mg q24hr., 1000 mg q12hr. and 1000 mg q8hr.), assuming a normal distribution. The range of possible values was restricted to the 95% confidence interval in order to discard marginal variable values in the random process. The simulation was performed using Microsoft Excel 2007.

The drug dosages and dosage frequencies of MEPM were based on the following Sanford Guide regimens: CCR<10, 500 mg q24hr.; 10≤CCR≤50, 1000 mg q12hr.; CCR>50, 1000 mg q8hr.[10].

The serum concentration–time profiles of MEPM were described using the corresponding system of differential equations.

$$\frac{dX2}{dt} = R - \left(\frac{CL}{V_1} + \frac{Q}{V_1}\right) X_2 + \frac{Q}{V_2} X_3 \qquad \text{equation 2}$$

$$\frac{dX3}{dt} = -\frac{Q}{V_2} X_3 + \frac{Q}{V_1} X_2 \qquad \text{equation 3}$$

For model outputs, serum concentration = X_2/V_1.

The differential equations give the rate of change of the amount of MEPM (mg) in the serum compartment (equation 2) and the peripheral compartment (equation 3), where *R* is the piece-wise input function for MEPM intravenous administration, CL represents clearances (L/hr), and V_1 and V_2 are the volume terms for the plasma compartments.

We used Microsoft Excel 2007 to solve the system of ordinary differential equations using Laplace transformation. As the criterion of efficacy, %TAM was calculated according to the following equation[5]:

%TAM = ln [Dose/(Vd × MIC)) × ($T_{1/2}$/ln2) × (100/DI)

Where $T_{1/2}$ = half-life (hr), DI = dosing interval (hr), Vd = volume of distribution.

As reported previously, a TAM of over 40% is essential for bactericidal action of MEPM[5]. The target %TAM was therefore fixed at >40% in this study, and the probability of target attainment for each antibiotic regimen was then calculated as the fraction of 1000 subjects achieving >40% TAM across a range of MICs, chosen on the basis of MEPM susceptibilities determined in a surveillance study. Typical MICs (0.5, 1, 2 and 4 mg/L) were used in the simulations[11].

A protein-binding fraction derived from the package inserts of MEPM (2.4%), was applied to correct for the plasma protein-binding fraction in the simulation.

Results

We simulated the serum MEPM concentration–time profile, C_{max}, AUC and obtained target attainment of 40%TAM by Monte Carlo simulation after different dosage regimens of MEPM were mixed with infusions (AM-G, AM-F or Fru) containing L-cysteine and/or SBS, stored for 0, 1 or 2 hr. at 4℃ or 25℃, and infused over a 0.5-hr. or 2-hr. period. Our aim was to propose the optimum dosage regimen for mixtures of MEPM with infusions containing L-cysteine and/or SBS at different MICs (0.5, 1, 2 and 4 mg/L, depending on the organism causing the infectious disease). MEPM reconstituted in normal saline was used as control, and MEPM plasm concentration-time profile in vivo were simulated with or without considering the drug degradation rate.

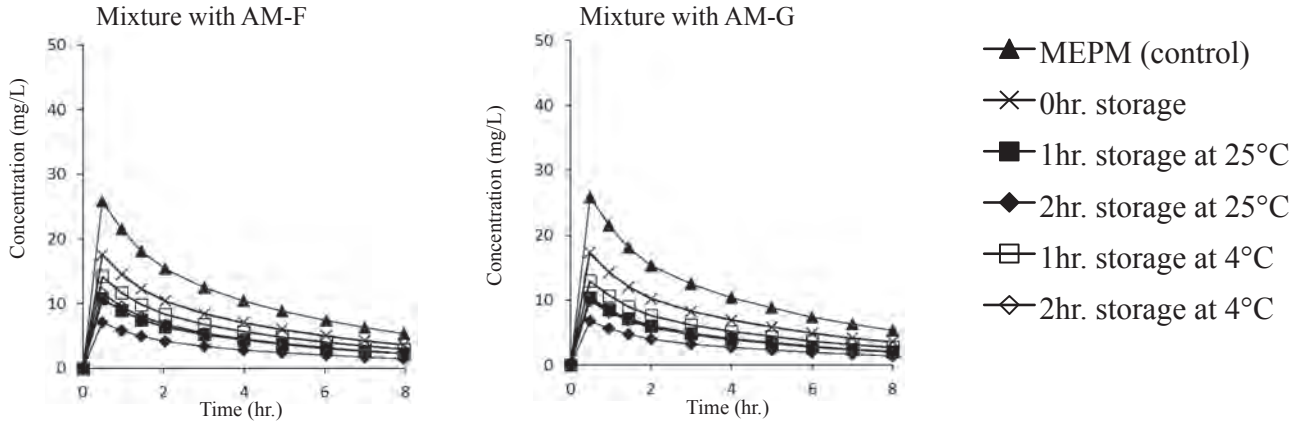
1. MEPM 0.5-hr. infusion after mixture with AM-F or AM-G

Figure 1 (a, b and c) shows simulated serum MEPM concentration–time profiles, with dosages and duration of infusion determined by three CCR grades (CCR<10, 10≤CCR≤50, CCR>50) on the basis of the Sanford Guide when MEPM is mixed with AM-F or AM-G and injected over 0.5 hr. under various conditions.

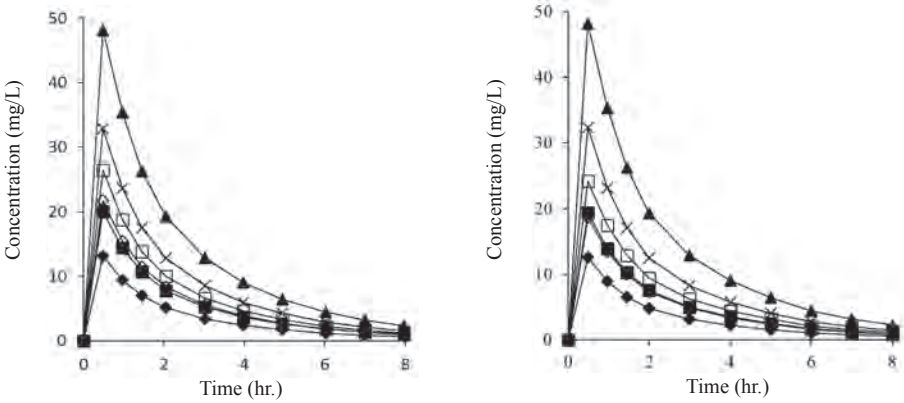
The figure shows that the serum concentration of MEPM is dramatically decreased compared with control when MEPM is administered in a mixed infusion with AM-F or AM-G and injected over 0.5 hr..

The simulated C_{max}, AUC and the percentage reaching 40%TAM as a function of MIC is summarized in Table 2. With a 0.5-hr. infusion, both C_{max} and AUC decreased compared with control when MEPM was administered as a mixed infusion. For example, with CCR<10, 500 mg q24hr., both C_{max} and AUC decreased (C_{max}, 18.4

a) CCR<10, MEPM 500 mg q24hr.



b) 10≤CCR≤50, MEPM 1000 mg q12hr.



c) 50<CCR, MEPM 1000 mg q8hr.

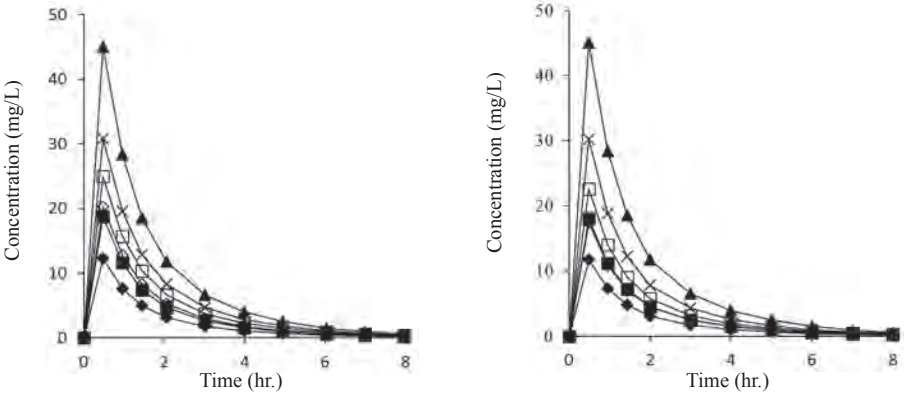


Fig. 1 Simulated serum MEPM concentration-time profile when infused over 0.5 hr. after mixture with AM-F or AM-G

Median of simulated serum MEPM concentrations for three typical MEPM dosage regimens (a) CCR<10, 500 mg q24hr. (b) 10≤CCR≤50, 1000 mg q12hr. and (c) CCR>50, 1000 mg q8hr., incorporating degradation as well as pharmacokinetic variability in 1000 simulations. It was assumed that MEPM, mixed with AM-F or AM-G, was administered by a 0.5-hr. infusion. KEY: Control (filled triangles), 0 hr. storage after mixing (X-marks), 1 hr. storage at 4°C (open squares) or 25°C (filled squares) after mixing, and 2 hr. storage at 4°C (open diamonds) or 25°C (filled diamonds) after mixing.

Table 2 TA% for MEPM when mixed with AM-F or AM-G and infused over 0.5 hr. after storage for 0, 1 or 2 hr. at 4 or 25˚C

			Storage				TA (%)			
Figure part	Dosage regimen	Mixture	Temp (°C)	Time (hr.)	Cmax (mg/L)	AUC (mg･h/L)	MIC=0.5	MIC=1	MIC=2	MIC=4
Figure 1(a)	CCR<10 500 mg q24hr.	MEPM (control)	-	-	25.7	120.7	100	100	99.8	41.9
		MEPM+AM-F	-	0	18.4	85.8	100	100	96.4	0.4
			4	1	14.2	65.9	100	100	73.7	0
			4	2	11.6	54.0	100	99.5	18.3	0
			25	1	11.9	55.6	100	99.7	27.0	0
			25	2	8.2	38.2	100	89.5	0	0
		MEPM+AM-G	-	0	17.3	80.4	100	100	93.7	0
			4	1	13.0	60.2	100	100	73.7	0
			4	2	9.9	46.1	100	99.5	18.3	0
			25	1	10.4	48.3	100	98.6	4.4	0
			25	2	6.7	31.5	99.8	47.0	0	0
Figure 1(b)	10≤CCR≤50 1000 mg q12hr.	MEPM (control)	-	-	47.8	110.1	100	100	100	97.9
		MEPM+AM-F	-	0	34.4	78.3	100	100	100	77.2
			4	1	26.5	60.3	100	100	99.4	22.5
			4	2	21.7	49.5	100	100	97.0	0.7
			25	1	22.3	50.8	100	100	97.0	0.7
			25	2	15.4	34.9	100	99.9	52.0	0
		MEPM+AM-G	-	0	32.2	73.5	100	100	100	61.5
			4	1	24.1	55.0	100	100	99.4	22.5
			4	2	18.6	42.3	100	100	97.0	0.7
			25	1	19.5	44.2	100	100	91.1	0
			25	2	12.6	28.8	100	98.6	4.4	0
Figure 1(c)	CCR ! 50 1000 mg q8hr.	MEPM (control)	-	-	45.2	70.3	100	100	100	97.5
		MEPM+AM-F	-	0	32.2	50.6	100	100	99.9	56.9
			4	1	24.6	39.0	100	100	98.6	6.2
			4	2	20.4	32.0	100	100	87.6	0
			25	1	20.9	32.8	100	100	92.5	0
			25	2	14.2	22.5	100	99.2	41.9	0
		MEPM+AM-G	-	0	30.2	47.5	100	100	99.8	41.9
			4	1	22.6	35.6	100	100	98.6	6.2
			4	2	17.4	24.5	100	100	87.6	0
			25	1	18.2	28.5	100	100	80.2	0
			25	2	11.9	18.6	100	98.6	6.2	0

TA: target attainment
CCR: creatinine clearance rate (mL/min)
Temperature: Temp

mg/L; AUC 85.8 mg･h/L), compared with control (C_{max}, 25.7 mg/L, AUC 120.7 mg･h/L) when MEPM was administered as a mixed infusion with AM-F immediately after mixing, as shown in Table 2 (upper part) and Figure 1a. The decrease of C_{max} and AUC when MEPM was administered as a mixed infusion with AM-F were very similar. When kept at 4℃ or 25℃ after mixing, the C_{max} and AUC of MEPM administered as a mixed infusion decreased more rapidly when the storage time was extended from 1 to 2 hr..

The TA% based on different MICs (0.5, 1, 2 and 4 mg/L) is also shown in Table 2 and the evolution of TA% is described in Figure 2 (a, b and c).

With an MIC of 0.5 mg/L, TA% in all regimens was maintained at nearly 100% as shown in Table 2. With an MIC of 2 mg/L, all regimens with a 0.5-hr. infusion maintained TA% >80% when mixed infusion were stored for 0 hr. after mixing. TA% decreased when storage time was extended from 1 to 2 hr. after mixing with AM-F both at 25 ° C (500 mg q24hr.: 27.0% to 0%, 1000 mg q12hr.: 97.0% to 52.0%, 1000 mg q8hr.: 92.5% to 41.9%) and at 4° C (500 mg q24hr.: 73.7% to 18.3%, 1000 mg q12hr.: 99.4% to 97.0%, 1000 mg q8hr.: 98.6% to 87.6%).

2. MEPM 2-hr. infusion after mixing with AM-F or AM-G

Figure 3 (a, b and c) shows simulated serum MEPM concentration–time profiles, with dosages and duration of infusion determined by three CCR grades (CCR<10, 10≤CCR≤50, CCR>50) on the basis of the Sanford Guide, when MEPM is mixed with AM-F or AM-G and injected over 2 hr. under various storage conditions.

Simulated C_{max}, AUC and TA% calculated as a function of MIC are summarized in Table 3 and the evolution of the TA% is represented in Figure 4 (a, b and c). With a 2-hr. infusion, the AUC and C_{max} decreased dramatically compared with control under all storage conditions and for all dosage regimens when MEPM was administered as a mixed infusion with both AM-F and AM-G (Table 3).

With an MIC of 0.5 mg/L, nearly all regimens maintained TA%>80% (Table 3). With an MIC of 2 mg/L and a 2-hr. infusion, TA% could not be maintained>80% when MEPM was administered immediately after mixing, under all storage conditions. The TA% dropped to 0–14.6% when mixed infusions were stored for 1 or 2 hr. at 4℃ or 25℃ after mixing.

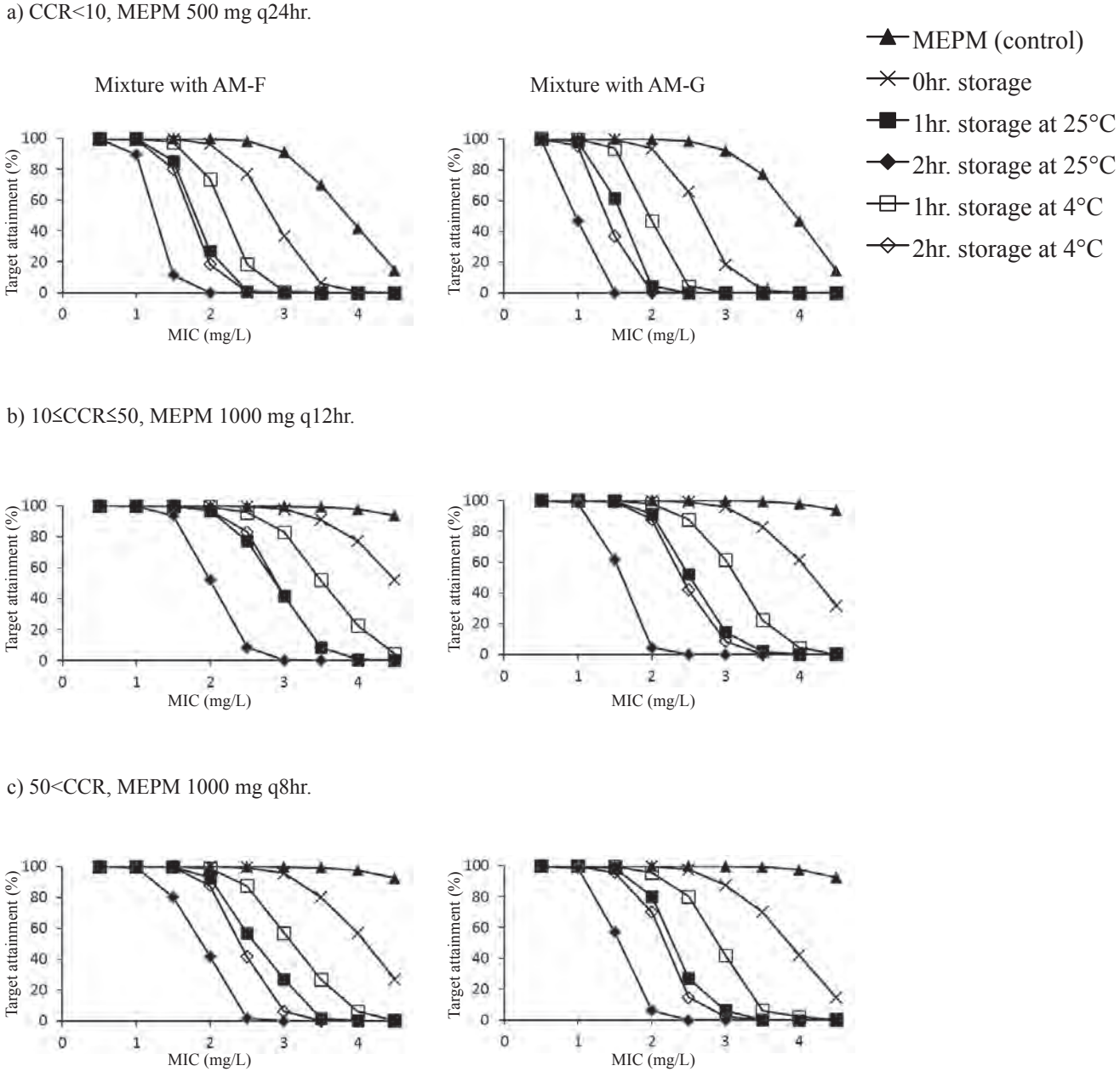
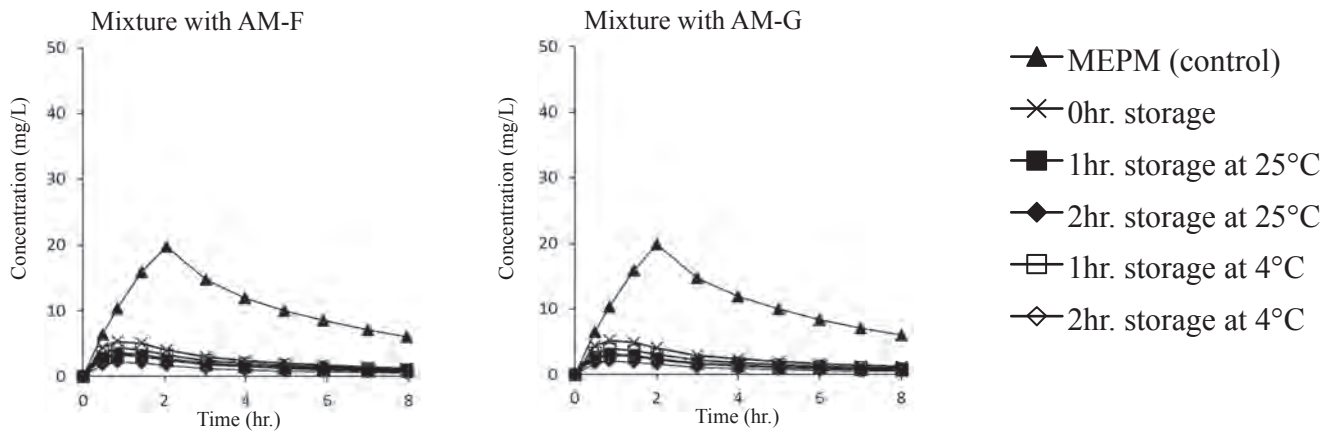


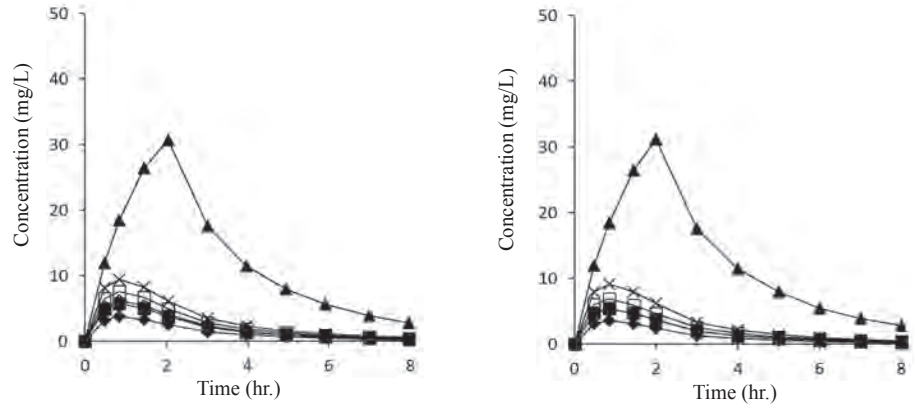
Fig. 2 Calculated attainment rate of 40%TAM as a function of MIC after mixture with AM-F or AM-G

The attainment rate of 40%TAM as a function of MIC was calculated for three typical MEPM dosage regimens (a) CCR<10, 500 mg q24hr., (b) 10 ≤CCR≤50, 1000 mg q12hr. and (c) CCR>50, 1000 mg q8hr.. MEPM mixed with AM-F or AM-G was administered as a 0.5-hr. infusion. KEY: Control (filled triangles), 0 hr. storage after mixture (X-marks), 1 hr. storage after mixture at 4°C (open squares) or 25°C (filled squares), and 2 hr. storage after mixture at 4°C (open diamonds) or 25°C (filled diamonds).

a) CCR<10, MEPM 500 mg q24hr.



b) 10≤CCR≤50, MEPM 1000 mg q12hr.



c) 50<CCR, MEPM 1000 mg q8hr.

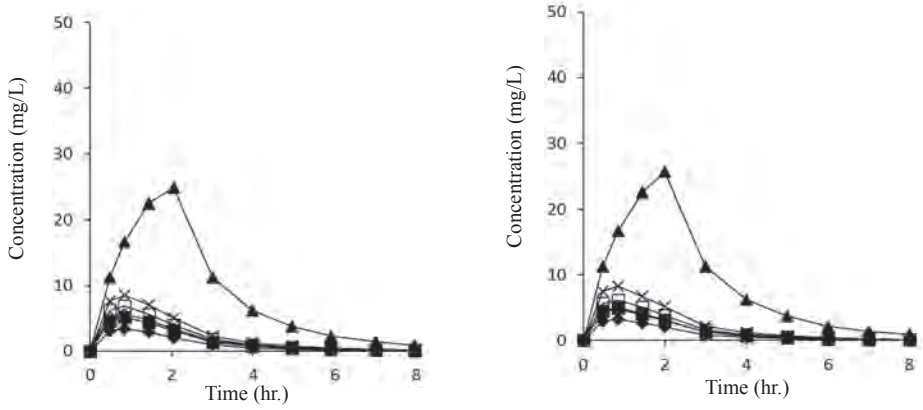
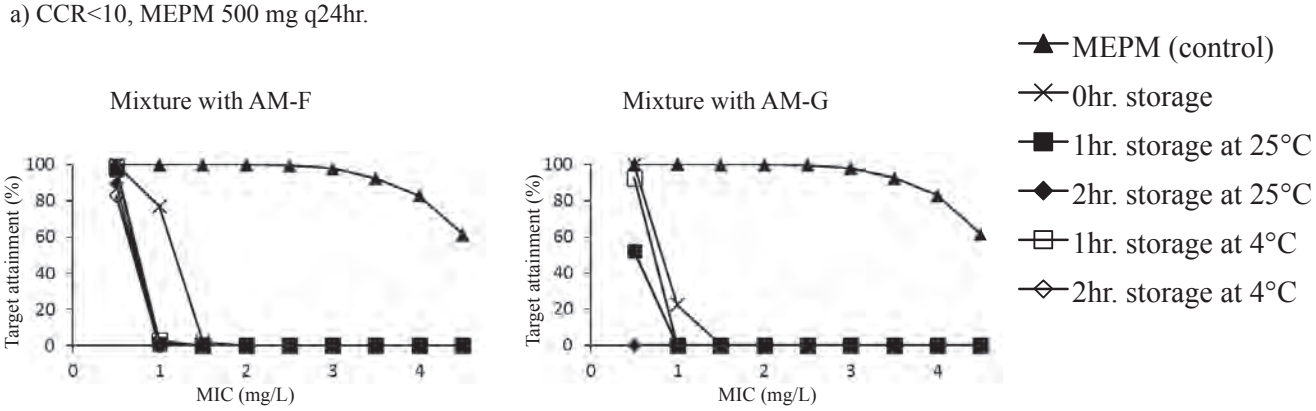


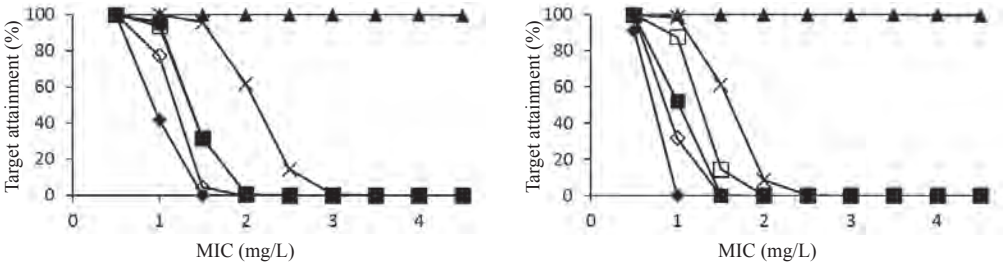
Fig. 3 Simulated serum MEPM concentration–time profile after administration as a 2-hr. infusion regimen when mixed with AM-F or AM-G

Medians of simulated serum MEPM concentrations for three typical MEPM dosage regimens (a) CCR<10, 500 mg q24hr., (b) 10≤CCR≤50, 1000 mg q12hr. and (c) CCR>50, 1000 mg q8hr., incorporating degradation as well as pharmacokinetic variability in an average of 1000 simulations. MEPM mixed with AM-F or AM-G was administered as a 2-hr. infusion. KEY: Control (filled triangles), 0 hr. storage after mixture (X-marks), 1 hr. storage after mixture at 4˚C (open squares) or 25˚C (filled squares), and 2 hr. storage after mixture at 4˚C (open diamonds) or 25˚C (filled diamonds).

a) CCR<10, MEPM 500 mg q24hr.



b) 10≤CCR≤50, MEPM 1000 mg q12hr.



c) 50<CCR, MEPM 1000 mg q8hr.

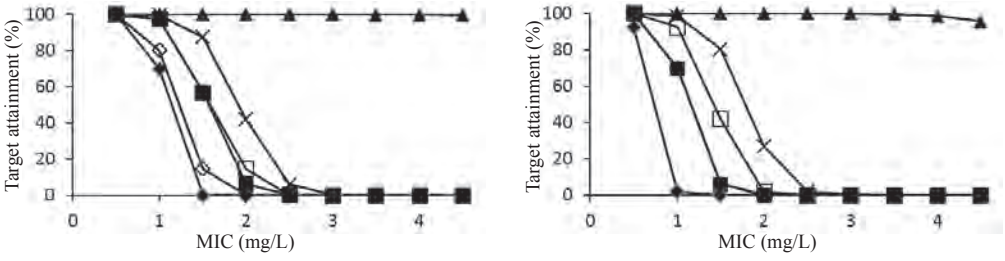


Fig. 4 Calculated rate of attainment of 40%TAM as a function of MIC after mixture with AM-F or AM-G

The rate of attainment of 40%TAM as a function of MIC was calculated for three typical MEPM dosage regimens (a) CCR<10, 500 mg q24hr., (b) 10<CCR<50, 1000 mg q12hr. and (c) CCR>50, 1000 mg q8hr., assuming administration of MEPM mixed with AM-F or AM-G by 2-hr. infusion. KEY: Control (filled triangles), 0 hr. storage after mixture (X-marks), 1 hr. storage after mixture at 4˚C (open squares) or 25˚C (filled squares), and 2 hr. storage after mixture at 4˚C (open diamonds) or 25˚C (filled diamonds).

Table 3 TA% for MEPM when mixed with AM-F or AM-G and infused over 2 hr. after storage for 0, 1 or 2 hr. at 4 or 25˚C

			Storage				TA (%)			
Figure part	Dosage regimen	Mixture	Temp (°C)	Time (hr.)	Cmax (mg/L)	AUC (mg･h/L)	MIC=0.5	MIC=1	MIC=2	MIC=4
Figure 3(a)	CCR<10 500 mg q24hr.	MEPM (control)	-	-	19.9	120.7	100	100	100	83.0
		MEPM+AM-F	-	0	6.0	34.1	100	77.2	0	0
			4	1	4.4	23.1	98.8	3.0	0	0
			4	2	3.6	18.9	83.0	0	0	0
			25	1	3.9	22.1	97.5	1.2	0	0
			25	2	2.7	15.2	41.9	0	0	0
		MEPM+AM-G	-	0	5.3	27.1	99.7	22.4	0	0
			4	1	3.9	20.3	98.8	3.0	0	0
			4	2	3.0	15.6	83.0	0	0	0
			25	1	3.1	16.3	52.0	0	0	0
			25	2	2.1	10.6	0.1	0	0	0
Figure 3(b)	10≤CCR≤50 1000 mg q12hr.	MEPM (control)	-	-	31.1	110.1	100	100	100	99.9
		MEPM+AM-F	-	0	10.4	34.7	100	98.6	61.5	0
			4	1	7.6	23.9	100	93.7	0.7	0
			4	2	6.3	19.6	100	77.2	0	0
			25	1	6.8	22.5	100	95.6	0.7	0
			25	2	4.6	15.4	99.6	41.9	0	0
		MEPM+AM-G	-	0	9.2	28.3	100	98.6	8.5	0
			4	1	7.0	21.2	100	93.7	0.7	0
			4	2	5.3	16.3	100	77.2	0	0
			25	1	5.5	17.0	99.9	52	0	0
			25	2	3.6	11.1	91.1	0.1	0	0
Figure 3(c)	CCR！50 1000 mg q8hr.	MEPM (control)	-	-	25.6	70.3	100	100	100	99.9
		MEPM+AM-F	-	0	8.5	20.9	100	99.6	41.9	0
			4	1	6.9	16.9	100	97.5	14.6	0
			4	2	5.6	6.9	100	80.2	0.4	0
			25	1	5.2	12.8	100	97.5	0.1	0
			25	2	3.4	8.4	99.9	70.0	0	0
		MEPM+AM-G	-	0	8.2	20.0	100	98.6	27.0	0
			4	1	6.2	15.0	100	97.5	14.6	0
			4	2	4.8	11.5	100	80.2	0.4	0
			25	1	8.2	12.0	99.9	70.0	0	0
			25	2	3.3	7.8	92.5	6.2	0	0

TA ; target attainment

CCR:creatinine clearance rate (mL/min)

Temperature: Temp

3. MEPM mixed with Fru

Serum MEPM concentration–time profiles were simulated, with dosages and duration of infusion determined by three CCR grades (CCR<10, 10≤CCR ≤50, CCR>50) on the basis of the Sanford Guide, after mixing MEPM with Fru and subjecting the mixture to various storage conditions. The simulated serum MEPM concentration–time profile after mixture with Fru was almost the same as that of the control MEPM solution. The calculated TA% as a function of MIC is summarized in Table 4. No differences in TA% in comparison with control were found when the infusion was stored for 0, 1 or 2 hr. after mixing.

Discussion

According to the drug package insert, MEPM is usually administered as an infusion in normal saline. However, in clinical practice, MEPM is occasionally administered in mixed with infusions containing L-cysteine and/or SBS. By adopting this method of mixture-administration, it is possible that serum MEPM concentrations may fall below the MIC for the pathogen concerned. Therefore, it was considered important to evaluate whether or not such mixture-administration would increase the risk of a significant decline in serum concentrations of MEPM.

In the present study, we performed simulations which included not only population pharmacokinetics for MEPM and but also degradation rates after mixing with an infusion containing L-cysteine and/or SBS. Commonly used dosage regimens and storage conditions were tested and efficacy was evaluated as %TAM, considering a range of MICs from 0.5 to 4 mg/L. A simulation study was conducted to evaluate the decrease of %TA for different dosage regimes when the infusions are stored for 0, 1 or 2 hr. and at 4℃ or 25℃ after mixing with Fru, AM-F or AM-G.

When MEPM was mixed with Fru, which contains only SBS, the simulations indicate that >80% TAM

Table 4 TA% obtained with different infusion regimens of MEPM when mixed with Fru and stored for 0, 1 or 2 hr. at 4°C or 25°C

Dosage regimen	Mixture	Storage		TA (%)			
		Temp (°C)	Time (hr.)	MIC=0.5	MIC=1	MIC=2	MIC=4
CCR<10 500 mg q24hr. 0.5-hr. infusion	MEPM (control)	-	-	100	100	99.8	47.0
	MEPM+Fru	-	0	100	100	99.8	47.0
		4 or 25	1	100	100	99.7	47.0
		4 or 25	2	100	100	99.7	47.0
CCR<10 500 mg q24hr. 2-hr. infusion	MEPM (control)	-	-	100	100	100	77.2
	MEPM+Fru	-	0	100	100	100	77.2
		4 or 25	1	100	100	100	77.2
		4 or 25	2	100	100	100	77.2
10≤CCR≤50 1000 mg q12hr. 0.5-hr. infusion	MEPM (control)	-	-	100	100	100	97.9
	MEPM+Fru	-	0	100	100	100	97.9
		4 or 25	1	100	100	100	97.9
		4 or 25	2	100	100	100	97.9
10≤CCR≤50 1000 mg q12hr. 2-hr. infusion	MEPM (control)	-	-	100	100	100	99.6
	MEPM+Fru	-	0	100	100	100	99.6
		4 or 25	1	100	100	100	99.6
		4 or 25	2	100	100	100	99.6
CCR ! 50 1000 mg q8hr. 0.5-hr. infusion	MEPM (control)	-	-	100	100	99.2	97.5
	MEPM+Fru	-	0	100	100	99.2	97.5
		4 or 25	1	100	100	99.2	97.5
		4 or 25	2	100	100	99.2	97.5
CCR>50 1000 mg q8hr. 2-hr. infusion	MEPM (control)	-	-	100	100	100	100
	MEPM+Fru	-	0	100	100	100	100
		4 or 25	1	100	100	100	100
		4 or 25	2	100	100	100	100

TA: target attainment

CCR: creatinine clearance rate (mL/min)

Temperature: Temp

is likely to be attained in all dosage regimes, similar to the performance of MEPM in normal saline, regardless of extending the storage time from 1 to 2 hr.. In previous studies, MEPM concentrations in normal saline have been reported to reduce by 1.66% after 2 hr. after storage at room temperature[12, 13]. The degradation rate constant of MEPM mixed with Fru was also very small, and similar to that obtained with normal saline solution.

This result suggests that the concentration of SBS contained in Fru (0.2 g/L according to the package insert), has extremely small influence on %TA in storage time or infusion time under study condition. To maintain serum drug concentrations above the MIC for intermediate or resistant microorganisms (MIC >2 mg/L) such as *Acinetobacter* spp. and *Pseudomonas aeruginosa*[11], it may just be necessary to extend the infusion time to 2 hr.[2]. Fru could always be administered separately if MEPM needed to be administered as a 2-hr. infusion.

The present study also showed that, in mixed infusion with AM-F or AM-G, %TA decreases when either the length of the infusion is increased (from 0.5 to 2 hr.) or the storage time after mixing (from 1 to 2 hr.). When considering bacteria with MIC 0.5 mg/L, nearly all regimens, except 500 mg q24hr. (2-hr. infusion), maintained 40%TAM. This result suggests that, under all storage conditions tested, infusion of MEPM in normal saline or in combination with AM-F or AM-G would be equally effective against *Escherichia coli* (MIC<0.06–0.25), an organism that causes a significant proportion of all Gram-negative infections in the urinary tract[14]. For an MIC of 2 mg/L, the simulations indicate that

nearly all MEPM 0.5-hr. infusion regimens with no storage after mixture maintained 40%TAM. For intermediate or resistant microorganisms (MIC >2 mg/L) like *Acinetobacter* spp. and *Pseudomonas aeruginosa*[11], however, the results suggest that 40%TAM cannot be maintained due to degradation caused by contact with the amino acid solutions. Treatments for infections caused by the abovementioned organisms are limited, however, and carbapenems may be the only option. Our results suggest that, in this situation, MEPM should be administered as a 0.5-hr. infusion immediately after mixing with AM-F or AM-G, so as to minimize the decrease in concentration of MEPM.

In many clinical situations, MEPM is also administered through a Y-site, together with amino acid injection preparations containing L-cysteine and SBS. In this case, MEPM is generally administered via a 0.5-hr. infusion, keeping the contact time with amino acids short. It was previously thought that the extent of degradation of MEPM when administered via a Y-site would be lower than if it were to be mixed directly with the amino acid preparations[15]. However, when dealing with intermediate or resistant microorganisms, MEPM administration must be extended, which can increase the potential contact time, thereby leading to an increased risk of MEPM degradation. Yoshioka *et al*. reported that the effectiveness of doripenem in the resolution of fever was decreased (75.1%) by a Y-site administration with an amino acid infusion line[16]. The effectiveness of a 0.5 hr. MEPM infusion may therefore be decreased even in Y-site administration. This will need to be confirmed in future studies.

This interaction between carbapenems and amino acid infusions, will need to be considered in order to maximize the effectiveness of the antibiotics.

In conclusion, using a Monte Carlo simulation, our study showed that co-administration of MEPM and an amino acid solution does not allow the same exposure to be achieved as an infusion of MEPM in normal saline. For microorganisms susceptible to MEPM (MIC ≥2 mg/L), co-administration with Fru, which contains SBS, can be made safe and effective by extending the length of the infusion to maintain TA% >80%. MEPM have to be administered as an infusion in normal saline, but not in parenteral nutrition fluids containing SBS or L-cysteine such as AM-F or AM-G. But in the infusion management of highly invasive patient, such as sepsis, parenteral nutrition fluids is administrated mixed with MEPM. Infusions of MEPM mixed with AM-F or AM-G, which contain L-cysteine and SBS, must be administered as a 0.5-hr. infusion immediately after mixing to maintain TA% >80%.

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