J Infect Chemother 25 (2019) 437–443

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: http://www.elsevier.com/locate/jic

Original Article

Clinical pharmacokinetic and pharmacodynamic analysis of daptomycin and the necessity of high-dose regimen in Japanese adult patients☆

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ARTICLE INFO

Article history:
Received 5 November 2018
Received in revised form
13 January 2019
Accepted 22 January 2019
Available online 16 February 2019

Keywords:
Daptomycin
Pharmacokinetic
Pharmacodynamic
Japanese
Dose optimization

ABSTRACT

The objective of this study was to explore the optimal dosage regimen of daptomycin and to determine the necessity and validity of a high-dose regimen from the perspectives of PK/PD parameters using Monte Carlo Simulation (MCS) and therapeutic drug monitoring (TDM) in a Japanese clinical setting. The volume of distribution (0.13 ± 0.012 L/kg) in this study was greater than that in healthy volunteers reported in Japan. The range of half-lives was between 8.9 and 34.9 h, which were gradually prolonged as creatinine clearance decreased. In MCS, the cumulative fractions of response (CFR) of the peak/MIC ≧ 60 and the AUC/MIC ≧ 666 at the 6 mg/kg q 24 h were 72.0% and 78.8% but at the 10 mg/kg q 24 h, the CFRs improved to both 99%. In TDM with 6 mg/kg q 24 h regimen, the patients who reached the peak and AUC target were 40% (2 out of 5 patients), respectively. The intraindividual variability in daptomycin PK may indicate the necessity of TDM and high-dose regimen, such as over 8 mg/kg, may be needed to ensure the effectiveness especially on Japanese patients with normal renal function.

1. Introduction

Gram-positive pathogens, especially *Staphylococcus* species, are a common cause of life-threatening infections [1]. Daptomycin, a cyclic lipopeptide antibiotic with bactericidal activity against gram-positive resistant strains, is one of the therapeutic options. It has a concentration-dependent activity and is approved for use at 4–6 mg/kg q 24 h as a standard regimen in many countries. Although some guidelines and experts recommend high-dose regimen of daptomycin at 8–12 mg/kg q 24 h, excessive dosing may result in an increased risk of adverse reactions, such as musculoskeletal toxicity [2–4].

Daptomycin is excreted mainly by the kidney; therefore, it is important to adjust the dosage of daptomycin based on renal clearance. Daptomycin pharmacokinetics (PK) has been reported in many countries; however, for Japanese adult patients, the PK parameters, the clinical efficacy and safety of daptomycin have rarely been corroborated with serum concentrations, which poses a clinical question as to whether a high-dosage regimen is optimal.

Adequate antibiotic dosing that ensures therapeutic concentrations is also pivotal to reduce the risk of therapeutic failure. There are two major approaches of pharmacokinetics/pharmacodynamics (PK/PD) for dose optimization of antibiotics, application of Monte Carlo Simulation (MCS) and therapeutic drug monitoring (TDM). Accordingly, the objective of this study was to explore the optimal dosage regimen of daptomycin and to determine the necessity and validity of a high-dose regimen from the perspective of PK/PD parameters using MCS and TDM in a Japanese clinical setting.

2. Patients and methods

2.1. Monte Carlo Simulation

The concentration-time curve for single infusion daptomycin, which was based on the one-compartment model for the variable

☆ ICMJEstatement: All authors meet the ICMJE authorship criteria.

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https://doi.org/10.1016/j.jiac.2019.01.011
1341-321X/

dosage regimens (4 mg/kg q 24 h, 6 mg/kg q 24 h, and 10 mg/kg q 24 h), was obtained from 5000-subject MCS over a range of doubling MICs between 0.25 and 4.0 μg/mL using the Crystal Ball ® (Oracle, CA, USA). The infusion time of daptomycin was 30 min. The MIC distributions that was applied to the PK/PD analysis was derived from the clinical strains of MRSA (n = 1114) isolated between January 2013 and December 2017 in Saga University Medical Center. The Japanese PK parameters were obtained from published studies (Phase I study) [5]. Pharmacodynamic variables targeted the ratio of peak serum concentration to the MIC (peak/MIC) and the ratio of area under the serum concentration-time curve for 24 h (AUC) to the MIC (AUC/MIC) of at least 60, and 666, respectively. These parameters allowed for the estimation of the probability of target attainment (PTA) as well as the cumulative fraction of response (CFR). Both PTA and CFR being at least 90% for a regimen were defined as optimal antimicrobial strategy against that bacterial population [6].

2.2. Patients

Patients who had an indication to receive daptomycin intravenously for methicillin-resistant *Staphylococcus aureus* (MRSA) infections were included in this study. The exclusion criteria included patients aged <20 years, a history of allergy to daptomycin, pregnancy, and lactation. As a result, 16 patients (8 males and 8 females; mean age ± standard error of mean (SEM), 70.0 ± 3.4 years; actual body weight, 47.6 ± 5.0 kg) were enrolled in this study. This study was a prospective clinical trial carried out from August 2014 to July 2018. The study protocol was approved by the institutional review board of Saga University Medical Center (No. 2014-05-07), which conforms to the ethical guidelines of the Medical and Health Research Involving Human Subjects of the Ministry of Health, Labor, and Welfare of Japan. A written informed consent was obtained from each patient or the first-degree relative if the patient was unable to provide informed consent for any reasons. Demographic and laboratory data were collected. Creatinine clearance (CrCl) was estimated using the commonly used Cockcroft-Gault equation [7]. The MIC of daptomycin for MRSA strains was measured by the broth microdilution method.

2.3. Determination of daptomycin concentrations

The initial dosage of daptomycin was chosen empirically, based on an infectious disease (ID) physician's chosen dosage. Infusion times for daptomycin were 30 min. Samples (5 mL) of venous blood were collected. Blood samples were then centrifuged at 5000×*g* for 10 min in a and plasma was stored at −30 °C until analysis. Daptomycin serum concentrations were determined by a validated high-performance liquid chromatography (HPLC) assay with ultraviolet detection, as previously described, with a slight modification [8]. The lowest limit of quantification for this assay was 0.78 μg/mL. The analytical column was TSK gel Octyl −80Ts, 5 μ, 250 × 4.6 mm (TOSOH, Tokyo, Japan), with a UV wavelength of 214 nm, and the mobile phase was 40 mM ammonium phosphate buffer (pH 4.5): acetonitrile = 60 v/v: 40 v/v. All solvents were of HPLC-grade.

2.4. Therapeutic drug monitoring

We obtained the pharmacokinetic parameters based on three individual concentrations measured 1) prior to the administration (trough level), 2) 30 min after the infusion ended (peak level) and 3) at any given time past 30 min after the end of administration (during the elimination phase). The data of serum concentrations were fitted to a one-compartment model. Using the Sawchuk-Zaske method [9], the pharmacokinetic parameters were determined

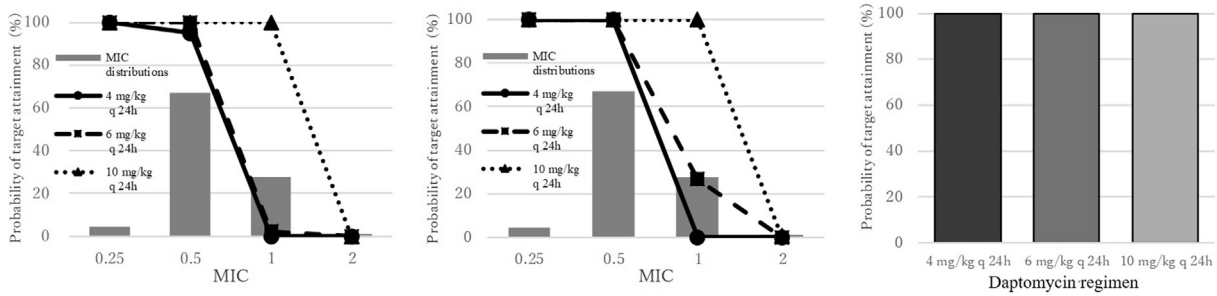

Fig. 1. Probability of target attainment (PTA) using various regimens for a target of the peak level 60 μg/mL (the left), AUC 666 μg· h/mL (the center) with daptomycin susceptibility (MIC distributions) and trough ≦ 24.3 μg/mL (the right).

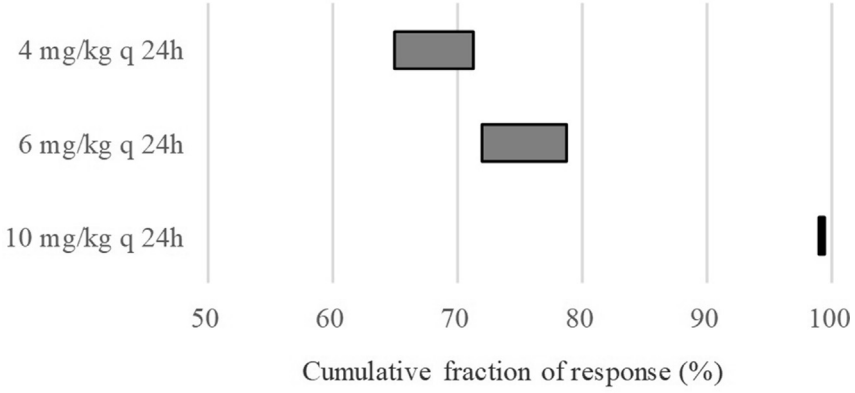

Fig. 2. Cumulative fraction of response (CFR) for each regimen. The box represents the range of CFR attained between the peak/MIC ≧60 and the AUC/MIC ≧ 666. Abbreviations: AUC/MIC the ratio of area under the serum concentration-time curve to the MIC, peak/MIC the ratio of peak serum concentration to the MIC.

Table 1
Patient characteristics and case summaries.

No. Age/ gender	Height (cm)	Weight (kg)	CrCl (mL/min)	Infection/ Pathogen· MIC (μg/mL)	Daptomycin regimen and duration	Prior and concurrent anti-MRSA agents	Serum concentrations (μg/mL)		Clinical response	Microbiological response	Adverse reactions
							Trough level	Peak level			
#1 70/F	140.0	29.0	ESRD on HD	SSTI, bacteremia/ MRSA· 1.0	250 mg (9 mg/kg) after thrice-weekly HD on days 1–16		2.3 (day 6)	34.2 (day 6)	Effective	Eradication	None
#2 65/F	160.0	40.5	ESRD on HD	Endocarditis/ MRSA· 1.0	350 mg (9 mg/kg) every 48 h on days 1–45	Gentamicin-IV on days 2–7 Linezolid-PO on days 8–17, Minocycline-PO on days 18–45	26.9 (day 9, prior to HD)*	76.5 (day 9)	Unevaluable	Eradication	None
#3 70/F	146.0	31.7	ESRD on HD	Arteriovenous graft infection, Bacteremia/ MRSA· 0.5	350 mg (11 mg/kg) after thrice-weekly HD on days 2–17	Teicoplanin-IV on days 1–2, rifampicin-PO on days 6–17	20.5 (day 9)	88.6 (day 9)	Effective	Eradication	None
#4 56/M	169.9	96.5	ESRD on HD	Mediastinitis, bacteremia/ MRSA· 0.5	700 mg (7 mg/kg) after thrice-weekly HD on days 1–14, and a 50% increase for the 72-h interdialytic period		9.0 (day 9)	73.4 (day 9)	Effective	Eradication	None
#5 81/F	150.0	55.3	ESRD on HD	CRBSI/ MRSA· 0.5	350 mg (6 mg/kg) after thrice-weekly HD on days 1–31, and a 50% increase for the 72-h interdialytic period	Cotrimoxazole-PO on days 10–11 and 18–22, linezolid-PO on days 12-18, minocycline-PO on days 22–31	10.8 (day 19)	80.7 (day 19)	Failure	Persistence	None
#6 81/M	166.0	67.7	22.4	Prosthetic joint infection, bacteremia/ MRSA· 0.5	540 mg (8 mg/kg) every 24 h on days 8–19	Vancomycin-IV on days 1–7, rifampicin-PO on days 2–15	49.4 (day 11)	108.3 (day 11)	Unevaluable	Eradication	CPK 2435 U/L
#7 88/M	154.7	47.0	28.5	Pyelonephritis, bacteremia/ MRSA· 0.5	350 mg (7 mg/kg) every 48 h on days 2–14	Vancomycin-IV on day 1	2.5 (day 5)	37.8 (day 5)	Effective	Eradication	None
#8 76/M	155.5	52.0	32.6	Mediastinitis, bacteremia/ MRSA· 0.5	550 mg (11 mg/kg) every 24 h on days 2–36	Vancomycin-IV on day 1, rifampicin-PO on days 3–16	27.7 (day 5)	87.2 (day 5)	Failure	Eradication	None
#9 70/F	141.5	40.9	46.3	Mediastinitis, bacteremia/ MRSA· 0.5	350 (9 mg/kg) every 24 h on days 3–30	Vancomycin-IV on days 1–3, linezolid-PO on days 3–16	25.8 (day 18)	102.0 (day 18)	Unevaluable	Eradication	None
#10 73/M	165.0	38.2	48.0	Endocarditis/ MRSA· 1.0	350 mg (9 mg/kg) every 24 h on days 2–40	Vancomycin-IV on day 1 Linezolid-IV on days 16–26 Cotrimoxazole-PO on days 27–40	11.7 (day 7)	60.0 (day 7)	Failure	Persistence	None
#11 57/M	160.0	60.0	56.7	LVAD-related infection, bacteremia/ MRSA· 0.5	350 mg (6 mg/kg) every 24 h on days 1–3 700 mg (12 mg/kg) every 24 h on days 4–75	Linezolid-PO on days 1–16	43.0 (day 18)	130.0 (day 18)	Effective	Eradication	None
#12 58/F	147.0	38.2	64.9	Osteomyelitis, bacteremia/ MRSA· 1.0	350 mg (9 mg/kg) every 24 h on days 1–14		12.6 (day 11)	59.9 (day 11)	Effective	Eradication	None
#13 38/F	148.0	31.5	88.2	Osteomyelitis, bacteremia/ MRSA· 0.5	350 mg (11 mg/kg) every 24 h on days 2–17	Vancomycin-IV on day 1	8.2 (day 10)	64.3 (day 10)	Effective	Eradication	None
#14 76/M	169.9	80.8	89.8	Prosthetic joint infection, bacteremia/ MRSA· 0.5	700 mg (9 mg/kg) every 24 h on days 2–11	Vancomycin-IV on days 1–2	17.5 (day 11)	63.5 (day11)	Failure	Persistence	None

(*continued on next page*)

Table 1 (*continued*)

No. Age/ gender	Height (cm)	Weight (kg)	CrCl (mL/min)	Infection/ Pathogen· MIC (μg/mL)	Daptomycin regimen and duration	Prior and concurrent anti-MRSA agents	Serum concentrations (μg/mL)		Clinical response	Microbiological response	Adverse reactions
							Trough level	Peak level			
#15 64/M	167.5	48.2	98.0	SSTI, bacteremia/ MRSA· 1.0	350 mg (7 mg/kg) every 24 h on days 1–14		0.13 (day 8)**	44.5 (day 8)	Unevaluable	Eradication	None
#16 44/F	158.2	81.1	213.8	Stent-graft infection, bacteremia/ MRSA· 0.5	700 mg (9 mg/kg) every 24 h on days 1–28	Linezolid-PO on days 3–9, rifampicin-PO on days 10–28	17.7 (day 20)	90.9 (day 20)	Effective	Eradication	None

Abbrevations: CrCl creatinine clearance estimated by Cockcroft-Gault equation, CPK creatine phosphokinase, CRBSI Catheter-related bloodstream infections, ESRD end-stage renel disease, HD hemodialysis, LVAD left ventricular assist device, SSTI skin and soft tissue infections.
*Unavailable timing to collect blood sample, **Lower limit of detection.

using systemic clearance (CL) in L/h/kg, volume of distribution (Vd) in L/kg, elimination rate constant (k_{el}) in/h, and elimination half-life ($t_{1/2}$) in h. In each patient, the concentration-time curve was simulated using patient-specific pharmacokinetic values at various single doses (6 mg/kg, 8 mg/kg, 10 mg/kg, and 12 mg/kg) and dosing intervals (24 h and 48 h).

2.5. Response to therapy

The clinical response was categorized by ID physicians as either effective, failure, or unevaluable. The category "effective" was comprehensibly defined as improvement of signs and symptoms. The bacteriological response was categorized by bacterial cultures as either eradication, persistence, or undetermined. An eradication was confirmed by at least one set of negative follow-up culture. Adverse reactions observed during daptomycin administration were recorded, including abnormalities in laboratory tests. Creatine phosphokinase (CPK) levels were measured both before and after daptomycin started.

3. Results

3.1. Monte Carlo Simulation

The PTA values reached 100% with MIC ≦ 1 μg/mL for 10 mg/kg q 24 h at both peak/MIC target and AUC/MIC target (Fig. 1). Fig. 2 indicates the range of the CFR attained between the peak/MIC and the AUC/MIC target. At 4 mg/kg q 24 h and 6 mg/kg q 24 h, the CFR values were less than 80%. At 10 mg/kg q 24 h, the CFR values improved to 99%. The PTA of trough levels ≦ 24.3 μg/mL was 100% at all regimens (Fig. 1).

3.2. Patients and response to therapy

Patient characteristics are shown in Table 1. Five patients had end-stage renal disease (ESRD) and were on hemodialysis (HD); two patients had severe renal dysfunction (CrCl < 30 mL/min); and three patients had moderate renal dysfunction (30 ≦ CrCl < 50 mL/min). The infectious diseases requiring daptomycin treatment were mediastinitis (n = 3), skin and soft-tissue infection (n = 2), endocarditis (n = 2), prosthetic joint infection (n = 2), osteomyelitis (n = 2), arteriovenous graft infection (n = 1), catheter-related bloodstream infection (n = 1), pyelonephritis (n = 1), left ventricular assist device-related infection (n = 1), and stent-graft infection (n = 1), and all patients had bacteremia. Clinical efficacy was noted in 67% (8/12) of patients and microbiological eradication in 81% (13/16) of patients. Ten patients received other anti-MRSA agents during daptomycin therapy.

3.3. PK analysis

In total, 42 daptomycin serum concentrations from 14 patients were obtained for PK analysis. Two patients could not proceed with the PK analysis (patient #2 and #15; Table 1). The PK parameters are summarized in Table 2. Median Vd ± SEM, CL, k_{el}, and $t_{1/2}$ were 0.13 ± 0.012 L/kg, 0.0062 ± 0.00092 L/h/kg, 0.058 ± 0.0058/h and 12.1 ± 2.34 h, respectively. The $t_{1/2}$ was gradually prolonged as CrCl decreased, and there was a statistically significant difference between CrCl <30 mL/min and CrCl ≧ 30 mL/min (Fig. 3).

3.4. PK-PD-based dose optimization

Table 3 indicates the peak levels and AUCs simulated from individual PK profiles based on a one-compartment model in a variable regimen. Table 4 indicates trough levels.

4. Discussion

4.1. Therapeutic range of daptomycin

Daptomycin exhibits concentration-dependent activity, and the surrogate markers for clinical improvement are both peak/MIC and AUC/MIC. As a specific value of the peak/MIC for a bacteriostatic effect, a peak/MIC ≧ 60 was reported [10]. Falcone et al. reported

Table 2
Estimated pharmacokinetic parameters.

No.	Vd (L/kg)	CL (L/h/kg)	k_{el} (/h)	$t_{1/2}$ (h)
#1	0.25	0.0080	0.032	21.4
#2	NA	NA	NA	NA
#3	0.16	0.0044	0.028	24.6
#4	0.10	0.0030	0.031	22.5
#5	0.13	0.0028	0.022	32.2
#6	0.13	0.0026	0.020	34.9
#7	0.19	0.0114	0.060	11.5
#8	0.12	0.0056	0.048	14.4
#9	0.08	0.0047	0.058	11.9
#10	0.14	0.0112	0.078	8.9
#11	0.09	0.0049	0.057	12.2
#12	0.14	0.0101	0.070	9.9
#13	0.16	0.0126	0.077	9.0
#14	0.13	0.0093	0.072	9.7
#15	NA	NA	NA	NA
#16	0.09	0.0068	0.076	9.2

Abbrevations: AUC area under the concentration time curve for 24 h, CL total clearance, k_{el} elimination rate constant, NA not applicable, $t_{1/2}$ elimination half-life, Vd volume of distribution.

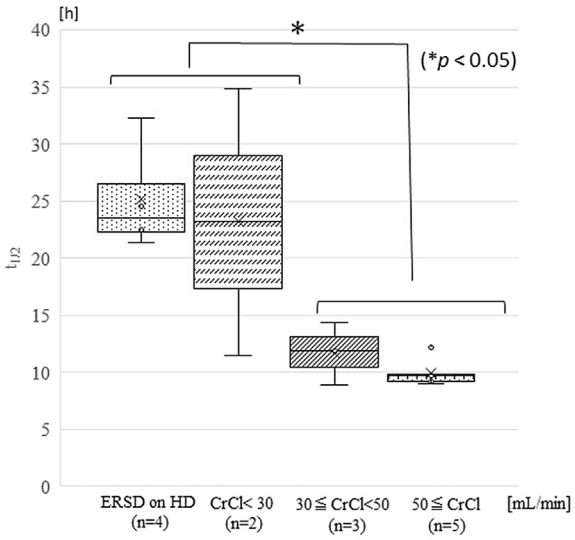

Fig. 3. Relationship of daptomycin half-life to renal clearance illustrated as box-and-whisker plot (n = 14). Abbrevations: CrCl creatinine clearance estimated by Cockcroft-Gault equation, $t_{1/2}$ elimination half-life.

that an AUC/MIC value ≧ 666 should be achieved [11]. Because >90% of MRSA isolates had MICs ≤1 μg/mL in this study, the target peak and AUC were predicted to be 60 μg/mL and 666 μg· h/mL, respectively, in empirical therapy. In this study, there was no relationship between the peak/MIC and clinical efficacy because of limited cases, so we could not verify the adequacy of therapeutic range for the effectiveness. Since most studies on PK-PD indices of daptomycin have not measured free concentrations, we also used total concentration (free and unbound fraction).

One of the common adverse reactions of daptomycin treatment is elevated CPK, which occurred in 2.8–6.7% of patients; rhabdomyolysis is quite rare [12,13]. Bhavnani et al. demonstrated that the trough level <24.3 μg/mL was associated with an increased probability of CPK elevation [4]. In this study, one patient whose trough level was 49.4 μg/mL with CrCl 22.4 mL/min experienced a CPK increase (patient #6, with a CPK 2435 U/L). This patient had received high dose DAP of 8 mg/kg, but high dose regimen caused no musculoskeletal toxicity in any other patient. And furthermore, bacterial sepsis has also been associated with the rhabdomyolysis. Although we can't always necessarily say that high dose DAP should not be considered with severe renal impairment, this case demonstrated the importance of closely monitoring CPK level and TDM to maintain trough level <24.3 μg/mL, especially in patients with severe renal impairment. No other adverse reactions attributable to daptomycin were noted (Table 1).

4.2. Therapeutic drug monitoring

Daptomycin PK using Bayesian estimation or population analysis have been reported [14,15]. In this study, we estimated individual PK parameters of daptomycin which has been no reported in Japanese clinical setting. We selected a one-compartment PK model which is a better fit than a two-compartment model [16]. The volume of distribution in this study was greater than that in healthy volunteers reported in Japan [5]. The inflammation induced by infection could cause fluids to leak from the systemic circulation to extravascular space, resulting in an increased Vd [11,17]. There was a significant prolongation in daptomycin $t_{1/2}$ in patients with CrCl <30 mL/min (Fig. 3). This characteristic indicated the need for daptomycin TDM, especially in the patients with severe renal failure.

In addition, these PK parameters have marked variability. Likewise, recent studies reported that intraindividual variability in daptomycin PK is not predictable [11,18]. These variabilities also lead to requirement for daptomycin TDM with the aim of standardization of serum concentration. In this study, we could collect blood samples any day because of using Sawchuk-Zaske method. But in general, TDM samples should be drawn from the third day on DAP therapy in the aspect of steady-state. It is advisable to measure peak level as effectiveness indicator and trough level as safety indicator. Calculating AUC is impractical in the same way as vancomycin.

4.3. Dose optimization

Of patients with ESRD on HD and CrCl <30 mL/min, the percentage of patients achieving a peak ≧ 60 μg/mL was merely 50% with the 6 mg/kg q 48 h regimen. While at the same time, a single dose of >6 mg/kg may maintain the peak target even in ESRD patients.>50% achieved a trough level higher than 24.3 μg/mL in the

Table 3
The simulated the peak levels and the AUCs in various regimens.

		Peak level (μg/mL)								AUC (μg· h/mL)			
		6 mg/kg	8 mg/kg	10 mg/kg	12 mg/kg	6 mg/kg	8 mg/kg	10 mg/kg	12 mg/kg	6 mg/kg	8 mg/kg	10 mg/kg	12 mg/kg
		q 48 h				q 24 h				q 24 h			
#1	ESRD on HD	29.9	39.3	49.9	59.8	43.7	58.2	72.8	87.4	753.1	1004.1	1255.2	1506.2
#2		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
#3		49.9	66.6	83.2	102.7	75.3	100.4	125.5	150.8	1351.1	1801.4	2251.8	2702.2
#4		78.1	104.2	130.2	156.2	115.5	154.0	192.5	231.0	2021.8	2695.7	3369.7	4043.6
#5		69.0	92.0	114.9	137.9	110.1	146.8	183.6	220.3	2110.1	2813.5	3516.9	4220.3
#6	CrCl <30 mL/min	72.9	97.2	121.5	145.8	118.1	157.5	196.9	236.2	2300.1	3066.8	3833.5	4600.2
#7		31.7	42.3	52.8	63.4	39.1	52.2	65.2	78.3	527.4	703.2	879.0	1054.7
#8	30 ≦ CrCl <50 mL/min	54.2	72.2	90.3	108.3	71.2	94.9	118.6	142.4	1062.5	1416.6	1770.8	2124.9
#9		75.0	100.1	125.1	150.1	93.6	124.8	156.0	187.2	1282.8	1710.4	2138.0	2565.6
#10		39.4	52.7	65.7	78.8	45.5	60.8	75.9	91.0	534.4	714.1	891.5	1068.9
#11	CrCl ≧50 mL/min	70.4	93.9	117.4	140.9	88.4	117.9	147.3	176.8	1224.7	1632.9	2041.1	2449.3
#12		40.3	53.9	67.2	80.6	47.8	63.8	79.7	95.5	594.5	794.3	991.6	1188.9
#13		34.9	46.5	58.1	69.7	40.3	53.8	67.2	80.6	475.6	634.2	792.7	951.2
#14		44.6	59.4	74.3	89.2	52.6	70.0	87.6	105.2	647.7	862.7	1079.1	1295.4
#15		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
#16		63.7	84.9	106.1	127.3	74.1	98.7	123.4	148.0	886.1	1180.9	1475.7	1770.4

Paint in black means within the range of the peak ≧ 60 μg/mL and the AUC ≧ 666 μg h/mL.
Abbreviations: AUC the area under the concentration-time curve, CrCl creatinine clearance estimated by Cockcroft-Gault equation, ESRD end-stage renal disease, HD hemodialysis, NA not applicable.

Table 4
The simulated the trough levels in various regimens.

		6 mg/kg	8 mg/kg	10 mg/kg	12 mg/kg	6 mg/kg	8 mg/kg	10 mg/kg	12 mg/kg
		q 48 h				q 24 h			
#1	ESRD on HD	6.5	8.7	10.9	13.1	20.8	27.7	34.6	41.5
#2		NA	NA	NA	NA	NA	NA	NA	NA
#3		13.4	17.8	22.3	26.7	39.6	52.9	66.1	79.3
#4		18.6	24.8	30.9	37.1	57.4	76.5	95.6	114.8
#5		25.2	33.7	42.1	50.5	67.5	90.1	112.6	135.1
#6	CrCl < 30	28.8	38.4	48.0	57.6	75.2	100.2	125.3	150.3
#7		1.9	2.5	3.1	3.8	9.9	13.2	16.5	19.8
#8	30 ≦ CrCl < 50	5.7	7.6	9.5	11.4	23.8	31.7	39.6	47.5
#9		4.9	6.6	8.2	9.9	24.9	33.2	41.5	49.8
#10		1.0	1.4	1.7	2.1	7.7	10.3	12.9	15.5
#11	CrCl ≧ 50	4.9	6.6	8.2	9.8	24.2	32.3	40.3	48.4
#12		1.5	2.0	2.5	3.0	9.7	12.9	16.1	19.3
#13		0.9	1.3	1.6	1.9	6.9	9.3	11.6	13.9
#14		1.6	2.1	2.6	3.1	10.3	13.7	17.2	20.6
#15		NA	NA	NA	NA	NA	NA	NA	NA
#16		1.9	2.5	3.1	3.7	13.3	17.7	22.2	26.6

Paints in black means trough < 24.3 μg/mL; Abbreviations: CrCl creatinine clearance estimated by Cockcroft-Gault equation, ESRD end-stage renel disease, HD hemodialysis, NA not applicable.

high-dose regimen. So, the dosing interval in these patients should be 48 h while maintaining high-dose regimen. As an alternative, Patel et al. reported that when the inter-dialytic period is 72 h, clinicians should consider increasing the post-HD daptomycin dose by 50% to optimally provide comparable AUC/MIC [19].

In patients with 30 ≦ CrCl <50, their dosing interval was q 24 h as described in the Japanese package insert. But the relatively low percentage of patients (33%) who achieved trough level < 24.3 μg/mL with a high-dose regimen and dosing interval of 24 h was noteworthy.

Our results showed that the PTA about peak level and AUC based on MCS increases as the total daily dose increases, and at the MIC 1.0 μg/mL (MIC_{90}), only the PTA values of the high-dose regimen (10 mg/kg q 24 h) were sufficient at both peak/MIC and AUC/MIC targets. In patients with CrCl ≧ 50, the standard regimen (6 mg/kg q 24 h) tended to be insufficient with respect to both peak and AUC (40%). Inadequate exposure may result in clinical failures or emergence of resistant organisms; therefore, the high-dose regimen should be considered in this population [20].

Judging from the PTA, the trough levels of all regimens were not a cause for safety concern. Since the percentage of patients achieving trough level <24.3 μg/mL at 8 mg/kg q 24, 10 mg/kg q 24 h, and 12 mg/kg q 24 h was 80%, 80%, and 60%, respectively, in patients with CrCl ≧ 50. We could expect the high-dose regimen to be safe in this population. The TDM results as well the MCS considerations reveal that the high-dose regimen is reasonable with respect to both efficacy and safety in patients with normal renal function.

4.4. Limitations

This study has some limitations. First, the enrolled patients had heterogeneous medical conditions. Since the isolation frequency of MRSA is on a declining trend in Japan, it is difficult to enroll patients on a large scale in a single hospital. Second, it is not clear whether the time points of blood sampling were at the steady-state. However, judging from the individual $t_{1/2}$, the times of blood sampling were likely appropriate.

5. Conclusion

In summary, we observed insufficient exposure a with standard-dose regimen and the variable PK profiles in Japan. Our study suggests that a high-dose regimen is necessary to ensure the potential effectiveness especially on Japanese patients with normal renal function. In addition, our study may suggest the necessity of daptomycin TDM for standardization of serum concentration.

Authorship

All authors meet the ICMJE authorship criteria. Study conception and design: TU and YA. Data acquisition: YH, YO, TO, HY and HM. Analysis and interpretation of data: TU. Drafting the article: TU and YA. Final approval of the submitted version: All authors.

Conflicts of interest and source of funding

YA has received research funding from Shionogi & Co., Ltd., and MSD K.K., and a speaker's honoraria from MSD K.K., Pfizer Japan, Inc., and Taisho Toyama Pharmaceutical Co., Ltd. All the others have no conflict of interests.

Acknowledgments

The authors thank the staff of the antimicrobial stewardship team at Saga University Medical Center who participated in this study.

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