Therapeutics and Clinical Risk Management

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Safety of high-dose daptomycin in patients with severe renal impairment

This article was published in the following Dove Press journal:
Therapeutics and Clinical Risk Management

Chih-Hsun Tai[1]
Chi-Hao Shao[2]
Chen-You Chen[2]
Shu-Wen Lin[1–3]
Chien-Chih Wu[1,2]

[1]Department of Pharmacy, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan; [2]School of Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan; [3]Graduate Institute of Clinical Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan

Background: Treatment options are limited for infections due to multidrug-resistant Gram-positive pathogens. Daptomycin is a lipopeptide antibiotic with concentration-dependent killing characteristic and dose-dependent post-antibiotic effect. To achieve optimized pharmacodynamic effect, some experts advocated using a high dose of daptomycin (≥9 mg/kg) for severe infections. However, the safety of high-dose therapy in patients with renal impairment remains unknown. This study was aimed to evaluate the safety of daptomycin in patients with severe renal impairment.

Methods: This was a retrospective study performed by reviewing electronic medical records. Patients with severe renal impairment who were treated with daptomycin in a tertiary teaching hospital between January 1, 2013, and June 30, 2016, were included for evaluation. The incidence rates of creatine kinase (CK) elevation between high-dose (≥9 mg/kg) and standard-dose (<9 mg/kg) groups were compared.

Results: Overall, 164 patients met the inclusion criteria, and 114 (69.5%) of them were on renal replacement therapy. Vancomycin-resistant enterococci were the most common pathogens (61.3%) of the patients with documented pathogens. The treatment success rate was 51.6% in the 91 patients with bacteremia. The average dose of daptomycin was 8.0±2.3 mg/kg, and 37 (22.6%) patients received ≥9 mg/kg. CK levels were followed in 108 (65.9%) patients. Significantly higher incidence of CK elevation was found in the high-dose group compared with that in the standard-dose group (10.8% vs 1.6%, $P<0.05$). Moreover, patients with elevated CK received a higher dose of daptomycin than those without (9.3±1.2 vs 7.9±2.3 mg/kg, $P<0.05$). There was no significant difference in the rate of CK elevation between patients treated with different dosing frequency or with the concurrent use of statins, fibrate, or colchicine.

Conclusions: In patients with severe renal impairment, high-dose (≥9 mg/kg) daptomycin therapy may result in a significantly higher incidence of CK elevation. More frequent CK monitoring is warranted to avoid potential harm in this population.

Keywords: daptomycin, safety, renal impairment, rhabdomyolysis

Introduction

Infections caused by multidrug-resistant Gram-positive pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA) or vancomycin-resistant enterococci (VRE), usually result in significant morbidity and mortality. According to the Taiwan surveillance data, the proportion of VRE among all enterococcal isolates causing nosocomial infections in intensive care units (ICUs) in medical centers increased from 12.4% in 2007 to 42.9% in 2016, and the proportion of MRSA among all staphylococcus isolates decreased from 83.7% in 2007 to 68.5% in 2016.[1] However, therapeutic options for these resistant pathogens are limited, particularly for strains with high minimum inhibitory concentration.

Correspondence: Chien-Chih Wu
Department of Pharmacy, National Taiwan University Hospital, College of Medicine, National Taiwan University, 7 Chung Shan S. Rd., Taipei 110, Taiwan
Tel +886 22 312 3456 ext 63702
Fax +886 22 331 0930
Email 101440@ntuh.gov.tw

submit your manuscript | www.dovepress.com
Dovepress
http://dx.doi.org/10.2147/TCRM.S159587

Daptomycin is a lipopeptide antibiotic approved for the treatment of Gram-positive pathogens-associated complicated skin infections and bacteremia. The recommended dose is 4–6 mg/kg once daily by manufacturer information. The optimal dose for certain difficult-to-treat infections has not been defined. Because of its characteristic of concentration-dependent killing and dose-dependent post-antibiotic effect, recent guidelines advocated increasing daptomycin dose to 8–10 mg/kg once daily to optimize therapy for infective endocarditis.[2,3] Indeed, a multicenter prospective cohort study conducted at our hospital system revealed that high-dose daptomycin (≥9 mg/kg/day) was associated with better survival rates in the treatment of VRE bacteremia.[4] In the present study, we adapted the same criteria and defined daptomycin use of ≥9 mg/kg/day as the high dose, and that <9 mg/kg/day was defined as the standard dose.

The major safety concern with daptomycin is the elevation of creatine kinase (CK) level, which may progress to rhabdomyolysis. Although the incidence of CK elevation was quite low, few studies examined the safety of daptomycin in patients with renal impairment, and most of the study populations were treated with the standard dose of <9 mg/kg.[5–8] Accumulation of daptomycin was documented in patients with renal impairment due to decreasing renal clearance,[9] and the previous study showed that higher daptomycin trough concentration (>24.3 mg/L) was associated with a higher probability of CK elevation. Therefore, the primary aim of this study was to investigate the safety of daptomycin use in this fragile population.

Methods

Study design and setting

This was a retrospective single-center study conducted at National Taiwan University Hospital (NTUH), a 2600-bed tertiary medical center located in Taipei City, Taiwan. The Research Ethics Committee of NTUH approved the study protocol (201503064RINB). The requirement for informed consent was waived because of the retrospective nature of the study and using data from which the patients' identification information had been removed.

Patient inclusion and data collection

We retrospectively reviewed the electronic medical records for data collection. All adult patients treated with daptomycin at NTUH from January 1, 2013, to June 30, 2016, were included if they had renal impairment. Patients were excluded if the medical records were incomplete or the treatment duration of daptomycin was <3 days. A standardized case report form was used to collect data including demographic characteristics (age, gender, body weight, body height, body mass index [BMI]), creatinine clearance (CL_{Cr}), type of renal replacement therapy, concurrent use of medication (statins, fibrates, and colchicine), and use of antimicrobial agents, isolated pathogens, indications for daptomycin, dosage, dosing frequency, treatment duration and response, frequency of CK monitoring, and CK level.

Definition

Renal impairment was defined as CL_{Cr} <30 mL/min or receiving renal replacement therapy. The Cockcroft–Gault equation was used to calculate CL_{Cr}.[10] Patients with a BMI ≥30 were considered obese according to WHO definition. High-dose daptomycin therapy was defined as doses of daptomycin ≥9 mg/kg, and doses <9 mg/kg were defined as the standard dose. Daptomycin treatment success was defined by resolving clinical signs and symptoms, no additional antibiotic therapy, and eradication of the causative pathogen documented at the end of daptomycin therapy. Elevated CK level was defined as CK level >1,000 U/L during daptomycin therapy. Evaluation of daptomycin-related CK elevation was based on the judgment of two clinical pharmacists who retrospectively reviewed the medical records. Surgery, trauma, and seizure attack during daptomycin therapy were considered the possible causes for CK elevation, and subjects were excluded for safety analysis if these conditions were attributed to the main causes for CK elevation according to the clinical pharmacists' judgment. Patients with no record of CK level during the treatment course were considered as no CK elevation. The primary outcome was to compare the percentages of patients with elevated CK between the groups receiving high doses vs standard doses of daptomycin.

Statistical analysis

Data were described as means ± SDs or numbers with percentages. The Mann–Whitney *U*-test was used for continuous data; either chi-square or Fisher's exact test was used for categorical data. A *P*-value ≤0.05 was considered statistically significant. Multivariate logistic regression was performed to identify the factors associated with CK elevation. Explanatory variables were included in the multivariate analysis if they showed significance in univariate analysis ($P<0.2$). The statistical analysis was performed by Microsoft Office Excel 2003 (Microsoft, Redmond, WA, USA) and SPSS 18 (SPSS Inc, Chicago, IL, USA).

Results

Patient characteristics

From January 1, 2013, through June 30, 2016, 365 patients treated with daptomycin were screened, and 164 patients met the inclusion criteria. The demographic characteristics of the patients included are listed in Table 1. Patients had a mean age of 68.1±16.5 years, and 62.2% were >65 years old. Eighty-seven patients (53.0%) were male, and 10 patients (6%) were obese. One hundred and seven patients (65.2%) were admitted in ICU. There were 114 patients (69.5%) who received concurrent renal replacement therapy during the treatment course. Before the use of daptomycin, 105 (64%) patients received other antibiotic treatments. More patients in high-dose group had been treated with other antibiotic before daptomycin than those in the standard-dose group (81.1% vs 59.1%, respectively; P=0.014). Significant differences in body weight existed between high- and standard-dose groups (P<0.001); there was only one obese patient in the high-dose group, whereas nine patients were obese in the standard-dose group.

Antimicrobial therapy and microbiological results

The most documented type of infection treated with daptomycin was bloodstream infection (55.5%), followed by urinary tract infection (12.8%) and intra-abdominal infection (11.0%).

Table 1 Demographic characteristics of patients with renal impairment who received daptomycin therapy

Demographic characteristics	All patients, N=164	High dose, N=37 (≥9 mg/kg)	Standard dose, N=127 (<9 mg/kg)	*P*-value
Male	87 (53.0)	20 (54.1)	67 (52.8)	0.889
Age (years), range	68.1±16.5 (19.8–93.9)	68.3±15.5	68.0±16.8	0.937
Elderly ≥65 years old	102 (62.2)	24 (64.9)	78 (61.4)	0.704
ICU admission	107 (65.2)	23 (62.2)	84 (66.1)	0.655
Mean body weight (kg)	58.5±11.9 (36.3–103.1)	53.2±10.2	60.0±12.0	<0.001
Obesity (BMI >30)[a]	10 (6.1)	1 (2.7)	9 (7.4)	0.459
Types of renal failure				
CL_{Cr} <30 mL/min	27 (16.5)	6 (16.2)	21 (16.5)	0.963
Dialysis (iHD/SLED/PD)	101 (61.6)	25 (67.6)	76 (59.8)	0.395
CRRT	13 (7.9)	0 (0.0)	13 (10.2)	0.042
AKI	23 (14.0)	6 (16.2)	17 (13.4)	0.663
Mean dose (mg/kg)	8.0±2.3	10.8±2.5	7.1±1.4	<0.001
Duration (days), median (IQR)	12.5 (11)	13 (11)	12 (11)	0.343
Type of infections				
Bloodstream infection	91 (55.5)	27 (73.0)	64 (50.4)	0.015
Skin and soft tissue infection	17 (10.4)	0 (0.0)	17 (13.4)	0.014
Urinary tract infection	21 (12.8)	2 (5.4)	19 (15.0)	0.166
Infective endocarditis	4 (2.4)	1 (2.7)	3 (2.4)	1.000
Septic arthritis	5 (3.0)	1 (2.7)	4 (3.1)	1.000
Intra-abdominal infection	17 (10.4)	5 (13.5)	12 (9.4)	0.540
Empirical use	9 (5.5)	2 (5.4)	7 (5.5)	1.000
Dose frequency				
QD	13 (7.9)	6 (16.2)	7 (5.5)	0.076
QOD	129 (78.7)	29 (78.4)	100 (78.7)	0.962
TIW	22 (13.4)	2 (5.4)	20 (15.7)	0.168
Creatine kinase follow-up	108 (65.9)	25 (67.6)	83 (65.4)	0.803
Number of CK follow-ups per week[b]	0.8±1.2	0.7±0.8	0.8±1.3	0.946
Prior antibiotic use	105 (64.0)	30 (81.1)	75 (59.1)	0.014
Seizure or surgery during therapy	28 (17.1)	6 (16.2)	22 (17.3)	0.875
Concurrent drug[c]	15 (9.1)	3 (8.1)	12 (9.4)	1.000
Concurrent antibiotic therapy	132 (80.5)	32 (86.5)	100 (78.7)	0.295
β-Lactams	128 (78.0)	31 (83.8)	97 (76.3)	0.338
Gentamicin	3 (1.8)	1 (2.7)	2 (1.6)	0.538
Rifampin	12 (7.3)	6 (16.2)	6 (4.7)	0.029
Co-trimoxazole	12 (7.3)	6 (16.2)	6 (4.7)	0.029

Notes: Data are presented as number (%) or mean±SD (range) unless stated otherwise. [a]BMI was available in 158 patients; [b]Calculated by the number of CK measurement/duration (days) ×7; [c]Statins, fibrate, or colchicine.

Abbreviations: AKI, acute kidney injury; BMI, body mass index; CK, creatine kinase; CL_{Cr}, creatinine clearance; CRRT, continuous renal replacement therapy; ICU, intensive care unit; iHD, intermittent hemodialysis; IQR, interquartile range; PD, peritoneal dialysis; QD, every 24 h; QOD, every 48 h; SLED, sustained low-efficiency dialysis; TIW, thrice per week.

Table 2 Characteristics of the patients who had creatine kinase elevation

Patient	Age (years)/ sex	Renal failure	Indication (microbe)	Dose (mg/kg)	Dosing frequency	Treatment duration (days)	CK level (U/L)		Muscle symptoms	Action	Recovery
							Baseline	Peak			
1	74.9/F	CKD	Bacteremia (MRSA)	10.7	QOD	21	15	2,895	Nil	Stop	Yes
2	55/M	SLED	Bacteremia (VRE)	7.6	QOD	8	53	2,801	NA	Stop	Yes
3	36.7/M	iHD	Bacteremia (MRSA)	9.8	QOD	31	–	1,449	NA	Closely monitor	Yes
4	78.4/F	iHD	Empirical therapy (–)	9.3	QOD	11	10	1,939	Muscle soreness	Stop	Yes
5	38.9/F	AKI	Skin and soft tissue infection (–)	8.3	QOD	13	23	4,697	Muscle soreness	Stop	Yes
6	76.6/F	AKI	Septic arthritis (–)	10.2	QD	7	23	1,299	Myalgia	Stop	Yes

Abbreviations: AKI, acute kidney injury; CK, creatine kinase; CKD, chronic kidney disease; iHD, intermittent hemodialysis; MRSA, methicillin-resistant *Staphylococcus aureus*; NA, not available, because of intubation and poor consciousness; QD, every 24 h; QOD, every 48 h; SLED, sustained low-efficiency dialysis; VRE, vancomycin-resistant enterococci.

VRE was the most frequently isolated pathogen (61.3%) among the 142 patients with documented pathogens. The mean daptomycin dose was 8.0±2.3 mg/kg, and 37 (22.6%) patients received the high dose (≥9 mg/kg) of daptomycin therapy. The dosing frequency of every 48 h was prescribed in 129 patients (78.7%). The median treatment duration was 12.5 (11) days. One hundred and thirty-two patients had concurrent antibiotic therapy including β-lactams (78%), rifampin (7.3%), co-trimoxazole (7.3%), and gentamicin (1.8%). In our study, obese patients received a significantly lower dose of daptomycin than nonobese patients (6.8±1.7 vs 8.1±2.3 mg/kg, P=0.027).

Treatment safety and response

CK levels were measured in 108 (65.9%) patients. Six patients had significant CK elevation during daptomycin therapy, and three of them had muscle symptoms, as detailed in Table 2. Recovery from CK elevation was observed in all patients after the discontinuation of daptomycin treatment. We also found a significantly higher incidence rate of CK elevation in the high-dose group compared with that in the standard-dose group (10.8% vs 1.6%, P=0.025; Table 3). Patients with CK elevation received a significantly higher average dose of daptomycin than those who did not have elevated CK (9.3±1.2 vs 7.9±2.3 mg/kg, P=0.034). For multivariate analysis, ICU admission, acute kidney injury, septic arthritis, and high dose of daptomycin use were put in the final model, and the result confirmed that high-dose daptomycin was the only significant factor associated with CK elevation (odds ratio 7.46; 95% CI, 1.22–45.69; P=0.03.)

There was no significant difference in the incidence rate of CK elevation between patients with different dosing frequency or the concurrent use of statins, fibrates, or colchicine. The overall treatment success rate was 51.6% in the 91 patients with bloodstream infection. Among patients with monomicrobial bloodstream infections, the treatment success rates were 60.9% for MRSA and 40.6% for VRE, respectively.

Discussion

This study explored the important safety issue of using high doses of daptomycin in patients with renal impairment. Almost 70% of our patients were under renal replacement therapy during daptomycin treatment course. In patients with renal impairment, especially those treated with hemodialysis, the administration of various antimicrobial agents remains a challenging job. The recommended dosing regimen of daptomycin for the patients with CL_{Cr} <30 mL/min or under renal replacement therapy is 4–6 mg/kg every 48 h based on approved indications.[11] However, there may be a discrepancy between the approved dosing regimen and the hemodialysis schedule. Daptomycin can be removed by hemodialysis, and dosing regimen to give the doses three times a week coinciding with each dialysis session was proposed.[12] Twenty-two patients in our study were treated

Table 3 Possible factors contributing to creatine kinase elevation

Variables	Elevation of creatine kinase level, N (%)		*P*-value
	No, 158 (96.3)	Yes, 6 (3.7)	
Dosage (mg/kg)			0.024
≥9	33 (89.2)	4 (10.8)	
<9	125 (98.4)	2 (1.6)	
Dosing frequency			0.484
QD	12 (92.3)	1 (7.7)	
QOD	124 (96.1)	5 (3.9)	
TIW	22 (100)	0 (0.0)	
Concurrent drugs[a]			0.443
Yes	14 (93.3)	1 (6.7)	
No	144 (96.6)	5 (3.4)	

Note: [a]Statin, fibrate, or colchicine.
Abbreviations: QD, every 24 h; QOD, every 48 h; TIW, thrice per week.

with daptomycin according to this thrice-weekly dosing. A previous research has shown that the pharmacokinetics of daptomycin was linear with doses up to 12 mg/kg in healthy volunteers.[13] Compared with healthy subjects, exposure to daptomycin was increased two- to threefold in patients with severe renal impairment and those on hemodialysis.[14] Daptomycin accumulated in patients with renal impairment may result in higher trough levels and therefore increase the probability of CK elevation.[15] As recommended by the prescribing information, CK level should be monitored at least once per week during daptomycin treatment. In adult patients with renal impairment, both renal function and CK should be monitored more frequently than once a week.[9] A pooled analysis of CORE (Cubicin® Outcomes Registry and Experience) and EUCORE (European Cubicin Outcomes Registry and Experience) revealed that blood CK levels were measured only in 43.5% of patients during daptomycin therapy.[16] Monitoring of CK level was performed in 65.9% of patients in our study. In previous studies, the incidence rate of CK elevation due to daptomycin was considered low (1.9%–2.0%, CK level >5× the normal upper limit),[5,6,16] and there was no significant difference of CK elevation rate between different dosage groups.[16] This low incidence rate might be explained by the low percentage of patients with renal impairement[5,16] or a relatively lower dose of daptomycin.[6]

Although the rate of CK monitoring in our study was greater than that in previous studies, 34.1% of our patients did not have CK level for assessment, and we assumed these patients did not have CK elevation. Comparisons between patients with or without CK measurement are listed in Table 4. Significantly different factors between two groups were types of renal failure, treatment duration, seizure or surgery during therapy, and concurrent antibiotic therapy with gentamicin. It is reasonable to monitor CK if treatment duration is longer and patients had seizure or surgery, which are the well-known etiologies for CK elevation. Patients receiving dialysis may lead to more drug accumulation, which could increase the risk of CK elevation. Therefore, it would be reasonable to assume that patients without CK measurement during treatment had normal CK because of shorter treatment duration, less dialysis, seizure, and surgery in this group. The issue of antibiotic doses is a critical one in the era of antibiotic resistance. Updated guidelines for infectious diseases advocate optimizing antibiotic pharmacokinetics and pharmacodynamics for better outcome.[17,18] A trend toward the use of higher doses over time was observed.[16] We defined daptomycin dose ≥9 mg/kg as the high-dose therapy based on the finding of a previous study conducted at our hospital system.[4] We found that patients with CK elevation received higher doses of daptomycin than those with no documented CK elevation and a significantly higher rate of CK elevation in the high-dose group than that in the standard-dose group. In addition, the difference remained significant when the patients without records of CK levels were excluded (16.0% vs 2.4%, P=0.025). Although the number of events was small, we observed a trend of decreasing rate of CK elevation as the dosing frequency decreased: 7.7% (1/13) for once daily, 3.9% (5/129) for once every 48 h, and 0.0% for thrice weekly. The result was not statistically significant (P=0.52), but it was consistent with the finding of a previous study reporting more frequent dosing led to increased muscle toxicity.[11] Use of high-dose daptomycin in patients with renal impairment is still a concern, and the dosing frequency should be included for clinical consideration.[7]

Table 4 Demographic characteristics of patients with and without CK measurement

Demographic characteristics	CK unavailable, N=56	CK available, N=108	*P*-value
Male	30 (53.6)	57 (52.8)	0.923
Age (years), range	66.3±16.2	69.0±16.6	0.305
Elderly ≥65 years old	31 (55.4)	71 (65.7)	0.193
ICU admission	36 (64.3)	71 (65.7)	0.853
Mean body weight (kg)	58.6±12.2	58.5±11.9	0.983
Obesity (BMI >30)[a]	4 (7.1)	6 (5.6)	0.736
Types of renal failure			
CL_{Cr} <30 mL/min	15 (26.8)	12 (11.1)	0.010
Dialysis (iHD/SLED/PD)	26 (46.4)	75 (69.4)	0.004
CRRT	6 (10.7)	7 (6.5)	0.370
AKI	9 (16.1)	14 (13.0)	0.587
Mean dose (mg/kg)	8.0±2.9	7.9±1.9	0.611
Duration (days), median (IQR)	7 (6)	15 (13.75)	0.001
Dose frequency			
QD	7 (12.5)	6 (5.6)	0.135
QOD	43 (76.8)	86 (79.6)	0.673
TIW	6 (10.7)	16 (14.8)	0.465
High dose (≥9 mg/kg)	12 (21.4)	25 (23.1)	0.803
Prior antibiotic use	35 (62.5)	70 (64.8)	0.770
Seizure or surgery during therapy	5 (8.9)	23 (21.3)	0.046
Concurrent drug[b]	8 (14.3)	7 (6.5)	0.100
Concurrent antibiotic therapy	44 (78.6)	88 (81.5)	0.656
β-Lactams	42 (75.0)	86 (79.6)	0.497
Gentamicin	3 (5.4)	0 (0.0)	0.038
Rifampin	5 (8.9)	7 (6.5)	0.546
Co-trimoxazole	2 (3.6)	10 (9.3)	0.224

Notes: Data are presented as number (%) or mean±SD (range) unless stated otherwise. [a]BMI was available in 158 patients; [b]Statins, fibrate, or colchicine.

Abbreviations: AKI, acute kidney injury; BMI, body mass index; CK, creatine kinase; CL_{Cr}, creatinine clearance; CRRT, continuous renal replacement therapy; ICU, intensive care unit; iHD, intermittent hemodialysis; IQR, interquartile range; PD, peritoneal dialysis; QD, every 24 h; QOD, every 48 h; SLED, sustained low efficiency dialysis; TIW, thrice per week.

Obese patients in our study received relatively lower doses of daptomycin per kg of body weight. Renal clearance of daptomycin is reduced in obese patients, and they have been identified as a high-risk population for CK elevation.[19] The prescribing information recommends to use total body weight for daptomycin dosing, and no dosage adjustment is warranted in obese subjects. While most available studies used the recommended dose of 4–6 mg/kg in obese patients,[20] the safety of high-dose daptomycin in this patient group had not been examined. In the present study, 70% of the obese patients received 500 mg of daptomycin, which was the dose supplied in each single-dose vial, resulting in the relatively lower doses than that in the other patients in this study. The efficacy and safety of daptomycin in obese patients with renal impairment need to be carefully evaluated to establish an appropriate dosing regimen for this population.

Lower treatment success rates of daptomycin in treating bloodstream infections were found in our study as compared with a large-scale study by Seaton et al reporting success rates of 78.1% for MRSA and 68.8% for VRE.[16] This is partly because, in our hospital, daptomycin is reserved for rescue therapy after first-line treatment failed. Also, more than half of our patients (65.2%) were admitted to the ICU and had multiple organ failures. Therefore, the higher disease severity has likely contributed to the lower treatment success rates in our study.

Limitations

The most important limitation of the present study is the retrospective nature of the study design, which prevented a delineation of the causality of CK elevation. Also, the serum concentrations of daptomycin were unavailable for risk evaluation. In addition, we cannot address the risk of CK elevation in the patients without renal impairment, who were treated with high doses of daptomycin. Although the rate of CK monitoring in our study was greater than previous studies, 34.1% of our patients did not have CK level for assessment. This may lead to an underestimation of the real incidence of CK elevation.

Conclusion

Our study revealed that compared with standard doses, high-dose daptomycin therapy was associated with a significantly higher rate of CK elevation in patients with severe renal impairment. When increasing the doses of daptomycin to optimize its pharmacokinetic and pharmacodynamic effects, more frequent CK monitoring is highly recommended in this fragile population.

Acknowledgment

The authors acknowledge statistical assistance provided by the Department of Medical Research in National Taiwan University Hospital.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Statistics of Taiwan Nosocomial Infection Surveillance Report. Centers for Disease Control, Ministry of Health and Welfare: Taiwan; 2016. Available from: https://www.syndriver.com/portal/#/sharing/d1b39e56648849f898802e0c01259a17. Accessed March 8, 2018.
2. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. *Circulation*. 2015;32(15):1435–1486.
3. Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC guidelines for the management of infective endocarditis: the task force for the management of infective endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J*. 2015;36(44):3075–3128.
4. Chuang YC, Lin HY, Chen PY, Lin CY, Wang JT, Chang SC. Daptomycin versus linezolid for the treatment of vancomycin-resistant enterococcal bacteraemia: implications of daptomycin dose. *Clin Microbiol Infect*. 2016;10:890.e1–890.e7.
5. Durante-Mangoni E, Andini R, Parrella A, et al. Safety of treatment with high-dose daptomycin in 102 patients with infective endocarditis. *Int J Antimicrob Agents*. 2016;48(1):61–68.
6. Lai CC, Sheng WH, Wang JT, et al. Safety and efficacy of daptomycin for the treatment of hospitalized adult patients in Taiwan with severe staphylococcal infections. *J Microbiol Immunol Infect*. 2012;45(1):52–57.
7. Kullar R, McClellan I, Geriak M, Sakoulas G. Efficacy and safety of daptomycin in patients with renal impairment: a multicenter retrospective analysis. *Pharmacotherapy*. 2014;34(6):582–589.
8. Moise PA, Amodio-Groton M, Rashid M, et al. Multicenter evaluation of the clinical outcomes of daptomycin with and without concomitant beta-lactams in patients with *Staphylococcus aureus* bacteremia and mild to moderate renal impairment. *Antimicrob Agents Chemother*. 2013;57(3):1192–1200.
9. Cubicin® (daptomycin for injection): US [prescribing information]. Lexington, MA: Cubist Pharmaceuticals Inc; 2007.
10. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16(1):31–41.
11. Mueller BA, Crompton JA, Donovan BJ, Yankalev S, Lamp KC. Safety of daptomycin in patients receiving hemodialysis. *Pharmacotherapy*. 2011;31(7):665–672.
12. Haselden M, Leach M, Bohm N. Daptomycin dosing strategies in patients receiving thrice-weekly intermittent hemodialysis. *Ann Pharmacother*. 2013;47(10):1342–1347.
13. Gould IM, Miro JM, Rybak MJ. Daptomycin: the role of high-dose and combination therapy for Gram-positive infections. *Int J Antimicrob Agents*. 2013;42(3):202–210.
14. Hair PI, Keam SJ. Daptomycin: a review of its use in the management of complicated skin and soft-tissue infections and *Staphylococcus aureus* bacteraemia. *Drugs*. 2007;67(10):1483–1512.

15. Bhavnani SM, Rubino CM, Ambrose PG, Drusano GL. Daptomycin exposure and the probability of elevations in the creatine phosphokinase level: data from a randomized trial of patients with bacteremia and endocarditis. *Clin Infect Dis*. 2010;50(12):1568–1574.
16. Seaton RA, Gonzalez-Ruiz A, Cleveland KO, Couch KA, Pathan R, Hamed K. Real-world daptomycin use across wide geographical regions: results from a pooled analysis of CORE and EU-CORE. *Ann Clin Microbiol Antimicrob*. 2016;15:18.
17. Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Med*. 2017;43(3):304–377.
18. Erb CT, Patel B, Orr JE, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia. *Ann Am Thorac Soc*. 2016;3(12):2258–2260.
19. Bookstaver PB, Bland CM, Qureshi ZP, et al; SERGE-45 Investigators. Safety and effectiveness of daptomycin across a hospitalized obese population: results of a multicenter investigation in the southeastern United States. *Pharmacotherapy*. 2013;33(12):1322–1330.
20. Polso AK, Lassiter JL, Nagel JL. Impact of hospital guideline for weight-based antimicrobial dosing in morbidly obese adults and comprehensive literature review. *J Clin Pharm Ther*. 2014;39(6):584–608.