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Musculoskeletal Safety Outcomes of Patients Receiving Daptomycin with HMG-CoA Reductase Inhibitors

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Daptomycin, a cyclic lipopeptide antibiotic, and 3-hydroxy-3-methylglutaryl–coenzyme A (HMG-CoA) reductase inhibitors (statins) are commonly administered in the inpatient setting and are associated with creatine phosphokinase (CPK) elevations, myalgias, and muscle weakness. Safety data for coadministration of daptomycin with statins are limited. To determine the safety of coadministration of daptomycin with statin therapy, a multicenter, retrospective, observational study was performed at 13 institutions in the Southeastern United States. Forty-nine adult patients receiving statins concurrently with daptomycin were compared with 171 patients receiving daptomycin without statin therapy. Detailed information, including treatment indication and duration, infecting pathogen, baseline and subsequent CPK levels, and presence of myalgias or muscle complaints, was collected. Myalgias were noted in 3/49 (6.1%) patients receiving combination therapy compared with 5/171 (2.9%) of patients receiving daptomycin alone ($P = 0.38$). CPK elevations of >1,000 U/liter occurred in 5/49 (10.2%) patients receiving combination therapy compared to 9/171 (5.3%) patients receiving daptomycin alone ($P = 0.32$). Two of five patients experiencing CPK elevations of >1,000 U/liter in the combination group had symptoms of myopathy. Three patients (6.1%) discontinued therapy due to CPK elevations with concurrent myalgias in the combination group versus 6 patients (3.5%) in the daptomycin-alone group ($P = 0.42$). CPK levels and myalgias reversed upon discontinuation of daptomycin therapy. Overall musculoskeletal toxicity was numerically higher in the combination group but this result was not statistically significant. Further prospective study is warranted in a larger population.

Daptomycin is a cyclic lipopeptide antibiotic that has become an important agent in the treatment of Gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) species. It is FDA approved for use in Gram-positive skin and skin structure infections (SSSI) and *S. aureus* bacteremia, including right-sided infective endocarditis at doses of 4 mg/kg of body weight and 6 mg/kg once daily, respectively (1). Myalgias, serum creatine phosphokinase (CPK) elevations, and muscle weakness were noted in preapproval clinical trials at doses of 4 mg/kg twice daily (2). Decreasing the dosing interval to once daily (the FDA-approved dosing interval) significantly reduced the incidence of drug-induced musculoskeletal toxicity. In postmarketing studies, higher doses of daptomycin (>6 mg/kg) have been associated with modest increases in toxicity risk (3, 4). CPK monitoring is recommended once every 7 days during daptomycin therapy (1).

Concomitant use of daptomycin and 3-hydroxy-3-methylglutaryl–coenzyme A (HMG-CoA) reductase inhibitors (statins) is not uncommon, but it carries concerns for potential synergistic musculoskeletal toxicities. Risk factors for statin-induced muscle toxicity include older age, high statin dosage, female gender, and renal disease (5). Concomitant use of cytochrome P450 inhibitors such as amiodarone and other myotoxic drugs such as fibric acid derivatives increases the risk of statin-induced rhabdomyolysis (6). Daptomycin product labeling recommends that consideration be given to discontinuing statin therapy while administering daptomycin due to potential for additive toxicity, primarily myopathic toxicities. Limited data exist regarding safety of coadministration of daptomycin with statin therapy (4, 7, 8, 9). The objective of our study was to report on the safety of concomitant statin and daptomycin therapy among hospitalized patients.

(These data were presented in part at the 48th Annual Meeting of the Infectious Diseases Society of America [IDSA], Vancouver, BC, Canada, October 2010.)

MATERIALS AND METHODS

This study was a retrospective, multicenter study of adult patients hospitalized from 2005 to 2010 who received daptomycin with or without statin therapy. The first dose of daptomycin was used to determine inclusion into the study, with dosing based on actual body weight. The Institutional Review Board at each participating site approved the study prior to data collection. Patients ≥18 years of age hospitalized from January 2005 to May 2010 who received daptomycin for a minimum of 7 days with concurrent statin therapy for at least 24 h as part of routine care during hospitalization were included in the combination group. Patients receiving daptomycin for at least 7 days without statin therapy comprised the other group. CPK monitoring was left at the discretion of the treating clinician. CPKs were considered baseline from 1 month prior to the day of initiation of daptomycin therapy. Utilizing medical records and data documented on standardized case report forms collected during the complete course of therapy, we obtained detailed information on patient demographics, treatment indication, estimated creatinine clearance (CrCl), sta-

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tin therapy, serum CPK concentrations, presence of myalgias or muscle complaints, and reason for daptomycin discontinuation (if applicable). Estimated renal clearance was calculated with the Cockcroft-Gault formula using actual body weight as recommended by the manufacturer (1).

Primary safety outcomes were compared between the two groups (the combination daptomycin and statin group and the daptomycin-alone group) as follows: (i) incidence of serum CPK levels of >1,000 U/liter at any point during therapy; (ii) documented myalgias or related muscle pains during therapy; and (iii) number of patients requiring discontinuation of therapy or dose modification due to increased serum CPK levels with or without signs/symptoms of myopathy.

Data were abstracted into a central spreadsheet database for analysis. Logistic regression models predicted the probability of significant adverse event occurrence, defined as CPK levels of >1,000 U/liter or myalgias. Categorical variables were compared with the chi-squared or Fisher's exact test, as appropriate. Two independent-sample *t* tests were used to compare continuous variables. For model-building purposes, variables in the logistic regression model were based on evidence from our exploratory analysis, literature, and our research questions. All variables used were categorical for rational interpretation of beta-coefficients and odds ratios (ORs). Continuous variables were converted into appropriate categories. Differences were considered statistically significant at *P* values of ≤0.05. Categorical predictors included age (<65 years versus ≥65 years), gender (male versus female), race (African American [AA] versus not AA), body mass index (BMI) (<30 kg/m^2 versus ≥30 kg/m^2), statin use (yes versus no), per kilogram daptomycin dosage (high dose or >6 mg/kg versus low dose or ≤6 mg/kg), and renal function (CrCl <40 ml/min versus ≥40 ml/min). To study the effect of statin use we conducted a separate analysis for patients treated with and those treated without statins. Additionally, data were analyzed using automated hierarchically optimal classification tree analysis, an exact (assumption-free) nonlinear statistical model which explicitly maximizes classification accuracy for the data sample (10). All analyses were performed using Microsoft Excel 2007 and SAS (SAS Institute Inc., Cary, NC, USA) at the 5% level of significance.

RESULTS

The study sample included 220 patients, of whom a total of 49 patients received concomitant daptomycin and statin therapy. Demographic characteristics of patients who received statins versus those who did not are shown in Table 1. Patients with statin use were older and received higher absolute doses of daptomycin, although the mg/kg doses were similar in the two groups. The primary diagnoses among the groups included bacteremia/endocarditis ($n = 106$), SSSI ($n = 33$), and bone/joint infections, including osteomyelitis ($n = 32$). Thirteen patients with bone/joint infections, including osteomyelitis, and 7 patients with SSSI had concurrent bacteremia. Primary pathogens included *S. aureus* (53%), *Enterococcus* species (18%), and coagulase-negative staphylococci (9%). Ninety-two of 117 *S. aureus* isolates were MRSA (79%). The mean duration of daptomycin therapy was 21 days (range, 7 to 74 days).

Patients with and without statin use had similar patterns of musculoskeletal side effects (Table 2). Serum CPK elevations of >1,000 U/liter occurred in 5 (10.2%) patients receiving statins versus 9 (5.3%) not receiving statins ($P = 0.32$). Table 3 reports characteristics of patients with statin therapy who experienced an adverse effect. All patients were 50 years of age or older, although the mean age of the population was 63 years. The median time to a CPK elevation of >1,000 U/liter occurred at 11.5 days of daptomycin therapy. Three of the five patients receiving concurrent statins also reported symptoms of myopathy. One patient who experienced toxicity had a CrCl of <40 ml/min and was receiving approximately 9 mg/kg of daptomycin daily. All patients in the combination group who experienced a CPK of >1,000 U/liter or myalgias were on either atorvastatin or simvastatin. One patient experienced rhabdomyolysis, which resolved upon discontinuation of therapy.

Our unadjusted logistic regression analysis showed that compared to patients using daptomycin alone, those using both daptomycin and statin were associated with 2.05 times the risk of experiencing musculoskeletal side effects (OR, 2.05); however, this finding was not statistically significant (95% confidence interval [CI], 0.65 to 6.41). Results were similar after controlling for potential confounders (Table 4). Statin use was not significantly associated with potential musculoskeletal side effects (OR, 1.35; 95% CI, 0.35 to 5.18) in the adjusted logistic regression analysis. African-American race was significantly associated with an increased risk for musculoskeletal side effects (OR, 3.95; 95% CI, 1.12 to 13.91). We further performed a subanalysis using multivariable logistic regression to examine the dose-response effect and to determine whether patients receiving high doses of statin (≥40 mg) were more likely to experience CPK elevations or myalgias than patients with low doses of stain (<40 mg). We did not find a statistically significant association (OR, 4.60; 95% CI, 0.47 to 44.60). Similar results were obtained for lower daptomycin dosages (~4 mg/kg) (OR, 2.84; 95% CI, 0.84 to 9.60).

DISCUSSION

This multicenter, retrospective, comparator study of patients receiving daptomycin alone versus daptomycin with statin therapy demonstrated similar rates of musculoskeletal toxicity with low discontinuation rates in the two groups. In interpreting our findings, several factors should be considered.

Daptomycin product labeling advises caution on the combination of daptomycin and statin therapy, but coprescribing is not a contraindication. Although controversial, continuation of statin therapy has been associated with decreased mortality in patients with bacteremia, possibly due to its anti-inflammatory effects (11).

Safety data with daptomycin and statin coadministration are limited. A retrospective review of 94 patients included in the Cubicin Outcomes Registry and Experience (CORE) database who received doses of ≥8 mg/kg of daptomycin demonstrated similar adverse event rates, with 3.2% of patients experiencing increases in CPK levels, but only 14 patients were on concomitant statin therapy (4). A recent multicenter study examined safety and efficacy of high-dose daptomycin in patients with invasive Gram-positive infections (3). Of 250 patients studied, 24 (9.6%) received a median dose of 9.7 mg/kg of daptomycin with concomitant statin therapy. Three of 24 patients (12.5%) experienced CPK values of >200 U/liter on high-dose daptomycin therapy. While on statin therapy, no patient discontinued daptomycin therapy due to myopathy or myalgias. A recent two-center study found the combination to be safe compared to daptomycin therapy alone (9). However, the dose for morbidly obese patients was based on ideal body weight (IBW) according to the average weight of their population, which was approximately 30 kg below that of our population (75 kg versus 106 kg). None of these studies reported the safety of daptomycin based on an absolute dose. A recent single-center study revealed a 2-fold increased risk of CPK elevation, which was similar to our multicenter data but was not statistically significant (7). The mean daptomycin dosage and BMI were 5.3

TABLE 1 Demographics and clinical characteristics

Characteristics	Daptomycin and statin ($n = 49$)	Daptomycin only ($n = 171$)	P
Age (mean ± SD) (yr)	63.02 ± 13.14	56.50 ± 16.70	0.0125
Gender (no. [%])			0.6906
Female	19 (38.78)	61 (35.67)	
Male	30 (61.22)	110 (64.33)	
Race (no. [%])			0.3859
Caucasian	37 (75.51)	113 (66.08)	
African American	11 (22.44)	49 (28.65)	
Not identified	1 (2.04)	9 (5.26)	
Body mass index (no. [%])			0.1305
18.5–24.9 kg/m^2	5 (10.20)	45 (26.32)	
25.0–29.9 kg/m^2	9 (18.37)	35 (20.47)	
30–34.99 kg/m^2	10 (20.41)	29 (16.96)	
35–39.99 kg/m^2	12 (24.49)	26 (15.20)	
≥40 kg/m^2	13 (26.53)	36 (21.05)	
Creatinine clearance (mean ± SD) (ml/min)	70.47 ± 47.21	86.52 ± 57.81	0.0918
Weight (mean ± SD) (kg)	105.80 ± 25.82	99.01 ± 33.96	0.1947
Daptomycin absolute dose (mean ± SD) (mg)	706.20 ± 198.20	641.50 ± 189.40	0.0381
Daptomycin dose (mean ± SD) (mg/kg)	6.78 ± 1.33	6.75 ± 1.54	0.9118
Statin type and dose (no. [%])			
Atorvastatin	14 (28.57)		
10 mg	3		
20 mg	4		
40 mg	4		
80 mg	3		
Simvastatin	22 (44.90)		
10 mg	1		
20 mg	10		
40 mg	9		
80 mg	2		
Pravastatin	7 (14.29)		
10 mg	2		
20 mg	1		
40 mg	2		
80 mg	2		
Rosuvastatin	3 (6.12)		
5 mg	1		
10 mg	1		
20 mg	1		
Lovastatin	2 (4.08)		
20 mg	2		
Unknown	1 (2.04)		

mg/kg and 30 kg/m^2, respectively, which were less than our study population.

Coadministration of daptomycin with statin therapy in our study was associated with rates of CPK elevation of >1,000 U/liter (10%), which were similar to those of previously reported studies of high-dose daptomycin (3, 4, 12). Three of six patients in our study who experienced myalgias or CPK levels of >1,000 U/liter had baseline CPK levels of >200 U/liter. The daptomycin product labeling does not specify a baseline CPK that should be obtained; however, clinical interpretation without this baseline value may be limited, especially in deconditioned patients or those receiving concomitant myotoxic agents. Concomitant statin therapy was well tolerated, with a low overall discontinuation rate of 6% in our study, similar to the rates reported in the limited published data available.

High-dose daptomycin therapy has been traditionally based on a milligram-per-kilogram basis, defined as >6 mg/kg or even 8 to 10 mg/kg of actual body weight (13). Nearly half (24/49) of our study population received 6 mg/kg or less, while nearly 70% were considered obese (BMI, >30 kg/m^2). The pharmacokinetic and pharmacodynamic profiles of daptomycin demonstrate linearity up to 12 mg/kg in a normal-weight patient; however, there is divergence in obese patients. Exposure to daptomycin (maximum concentration and area under the curve) following a 4-mg/kg dose is increased by approximately 25 to 30%, respectively, in moderately and morbidly obese healthy patients compared to matched,

TABLE 2 Summary of safety endpoints

Side effect(s)	Daptomycin and statin ($n = 49$) (no. [%])	Daptomycin only ($n = 171$) (no. [%])	*P*
CPK > 1,000 U/liter			0.3152
Yes	5 (10.20)	9 (5.26)	
No	44 (89.80)	162 (94.74)	
Presence of myalgias/muscle pains			0.3809
Yes	3 (6.12)	5 (2.92)	
No	46 (93.88)	166 (97.08)	
Patients requiring discontinuation of therapy due to musculoskeletal toxicity			0.4205
Yes	3 (6.12)	6 (3.51)	
No	46 (93.88)	165 (96.49)	

TABLE 4 Logistic regression of predictors of significant adverse events

Variable	OR	95% CI
Statin user	1.35	0.35–5.18
Age ≥ 65 yr	1.48	0.44–5.01
Male	1.17	0.34–4.05
African American	3.95	1.12–13.91
BMI ≥ 30 kg/m^2	3.80	0.89–16.28
High dose (>6 mg/kg) of daptomycin	3.53	0.98–12.71
Creatinine clearance < 40 ml/min	0.85	0.25–2.90

nonobese controls (14). A subsequent study revealed an approximate 60% increase in maximum concentration and area under the curve following a 4-mg/kg dose in morbidly obese healthy patients compared to normal-weight patients (15). A recent study showed an increased rate of CPK elevation in obese patients, but discontinuation rates remained low (16). Use of actual body weight in all patients is currently recommended for daptomycin. This implies some assumption that the safety profile of the drug in obese patients with invasive disease is also maintained.

One of five patients experiencing CPK elevations or myalgias in our study had a creatinine clearance of <40 ml/min. In our analysis, one patient (patient 4 from Table 3) with CPK levels of >1,000 U/liter on combination therapy would have received every-other-day dosing if the CrCl rate was based on their IBW but received daily dosing. The use of actual body weight with the Cockcroft-Gault formula has been demonstrated to overestimate glomerular filtration rate (GFR) in obese patients receiving daptomycin (15). Overestimation of GFR may lead to more frequent dosing of daptomycin than appropriate, increasing drug exposure and subsequent risk of toxicity. The package insert currently recommends using actual body weight in calculations of creatinine clearance for daptomycin dosing (1). Further studies are needed to delineate the best formulas to calculate renal function estimation in obese patients requiring daptomycin therapy.

Most patients (45%) in our study received simvastatin as their concomitant statin. Four of five patients with musculoskeletal toxicity in the daptomycin-plus-statin group received 40 mg or more of atorvastatin or simvastatin. Published data have implicated primarily higher doses of simvastatin (40 mg or 80 mg). Limited case reports demonstrating rhabdomyolysis with coad-

TABLE 3 Clinical characteristics of subjects with CPK elevation of >1,000 U/liter or myalgias

Subject no.	Age (yr)	Gender[a]	Race[b]	Body mass index	Daptomycin indication	Day of occurrence	CrCl[c] (ml/min)	Daptomycin dose, mg (mg/kg)	Peak CPK[d] after baseline (U/liter)	Myalgias	Statin and dose (mg)	Daptomycin discontinued
1	53	M	AA	35	Osteomyelitis	7	131	650 (5.7)	768	Yes	Simvastatin 80	Yes
2	58	M	C	32	Osteomyelitis	9	36	750 (8.9)	4,885	Yes	Simvastatin 40	Yes[e]
3	74	M	C	36	Skin/skin structure infection with bacteremia	4	136	1,000 (8.4)	1,582	No	Atorvastatin 80	No
4	60	F	C	51	Osteomyelitis	14	94	750 (5.8)	15,354	Yes	Atorvastatin 40	Yes
5	71	M	C	43	Abdominal abscess	14	115	575 (4.0)	1,936	No	Atorvastatin 20	No
6	70	M	AA	42	Joint infection/ osteomyelitis	13	57	800 (5.9)	1,623	No	None	Yes
7	51	F	C	39	Joint infection/ osteomyelitis	20	56	800 (7.8)	2,718	No	None	Yes
8	66	F	C	40	Osteomyelitis with bacteremia	19	123	750 (6.6)	2,457	No	None	Yes
9	80	M	C	22	Bacteremia	5	32	553 (7.5)	31	Yes	None	No
10	23	F	AA	19	Bacteremia	17	65	350 (6.8)	1,864	Yes	None	Yes
11	61	F	AA	39	Bacteremia	2	15	735 (7.9)	27	Yes	None	No
12	46	M	AA	30	Bacteremia	4	14	840 (8.1)	132	Yes	None	No
13	87	M	AA	28	Bacteremia	14	13	580 (6.1)	37	Yes	None	No
14	38	F	AA	39	Bacteremia	11	150	650 (5.8)	4,037	No	None	Yes

[a] M, male; F, female.
[b] AA, African American; C, Caucasian.
[c] CrCl, creatinine clearance.
[d] CPK, creatine phosphokinase.
[e] Patient developed rhabdomyolysis which resolved upon discontinuation of daptomycin therapy.

ministration of daptomycin and statins have involved primarily simvastatin (17, 18). Higher doses of simvastatin (specifically the 80-mg dose) have been associated with increased rates of musculoskeletal adverse events and rhabdomyolysis compared to lower doses (19, 20). Recently, the FDA changed the product labeling for simvastatin to reflect these higher risks of myopathy. One of our patients who discontinued therapy was receiving 80 mg simvastatin daily. Documented literature reports of patients requiring discontinuation of daptomycin with concurrent statin therapy due to severe myalgias or rhabdomyolysis have mostly involved simvastatin (18, 21).

Some limitations of our study should be acknowledged. First, the study was nonblinded and retrospective in nature, and thus it was difficult to establish a causal relationship. Second, the study endpoints are generally rare events, so the study may be potentially subject to type II error, which requires a larger sample size. Third, the logistic regression model may be subject to overparameterization due to rare events, which may lead to larger confidence intervals. Based on the data, we did not find daptomycin combination therapy with statins to be statistically associated with the reported adverse events. Baseline and subsequent CPK values were available for most but not all patients. Receipt of drugs known to pose additional risk for myopathies and rhabdomyolysis when added to statin therapy (e.g., fibrates and inhibitors of cytochrome P450 3A4 [CYP3A4]) was not assessed.

In summary, higher rates of CPK elevation of >1,000 U/liter or myalgias were seen in patients receiving daptomycin with concomitant statin therapy, but this value was not statistically significant compared to rates observed in patients receiving no statin therapy. Concomitant administration of both agents was well tolerated, with a low discontinuation rate. Statin therapy should not impede practitioners from prescribing daptomycin concurrently when clinically indicated to hospitalized patients who develop serious infections. Future study in larger populations is warranted.

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