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Daptomycin Pharmacokinetics in Adult Oncology Patients with Neutropenic Fever▽

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Daptomycin is the first antibacterial agent of the cyclic lipopeptides with in vitro bactericidal activity against gram-positive organisms, including vancomycin-resistant enterococci, methicillin-resistant staphylococci, and glycopeptide-resistant *Staphylococcus aureus*. The pharmacokinetics of daptomycin were determined in 29 adult oncology patients with neutropenic fever. Serial blood samples were drawn at 0, 0.5, 1, 2, 4, 8, 12, and 24 h after the initial intravenous infusion of 6 mg/kg of body weight daptomycin. Daptomycin total and free plasma concentrations were determined by high-pressure liquid chromatography. Concentration-time data were analyzed by noncompartmental methods. The results (presented as means ± standard deviations and ranges, unless indicated otherwise) were as follows: the maximum concentration of drug in plasma (C_{max}) was 49.04 ± 12.42 μg/ml (range, 21.54 to 75.20 μg/ml), the 24-h plasma concentration was 6.48 ± 5.31 μg/ml (range, 1.48 to 29.26 μg/ml), the area under the concentration-time curve (AUC) from time zero to infinity was 521.37 ± 523.53 μg · h/ml (range, 164.64 to 3155.11 μg · h/ml), the volume of distribution at steady state was 0.18 ± 0.05 liters/kg (range, 0.13 to 0.36 liters/kg), the clearance was 15.04 ± 6.09 ml/h/kg (range, 1.90 to 34.76 ml/h/kg), the half-life was 11.34 ± 14.15 h (range, 5.17 to 83.92 h), the mean residence time was 15.67 ± 20.66 h (range, 7.00 to 121.73 h), and the median time to C_{max} was 0.6 h (range, 0.5 to 2.5 h). The fraction unbound in the plasma was 0.06 ± 0.02. All patients achieved C_{max}/MIC and AUC from time zero to 24 h ($AUC_{0–24}$)/MIC ratios for a bacteriostatic effect against *Streptococcus pneumoniae*. Twenty-seven patients (93%) achieved a C_{max}/MIC ratio for a bacteriostatic effect against *S. aureus*, and 28 patients (97%) achieved an $AUC_{0–24}$/MIC ratio for a bacteriostatic effect against *S. aureus*. Free plasma daptomycin concentrations were above the MIC for 50 to 100% of the dosing interval in 100% of patients for *S. pneumoniae* and 90% of patients for *S. aureus*. The median time to defervescence was 3 days from the start of daptomycin therapy. In summary, a 6-mg/kg intravenous infusion of daptomycin every 24 h was effective and well tolerated in neutropenic cancer patients.

Daptomycin is the first antibacterial agent of a new class of antibiotics, the cyclic lipopeptides, derived from the natural fermentation of *Streptomyces roseosporus*. Daptomycin's bactericidal activity results from its binding to the cell membrane of gram-positive bacteria, which causes the rapid depolarization of the membrane potential. Rapid bacterial cell death due to the loss of membrane potential leads to the inhibition of protein, DNA, and RNA synthesis (2). Daptomycin exhibits in vitro bactericidal activity against gram-positive organisms, including vancomycin-resistant enterococci, methicillin-resistant staphylococci, and glycopeptide-resistant *Staphylococcus aureus* (1, 5, 26). In vitro pharmacodynamic studies indicate that daptomycin exhibits concentration-dependent killing and that efficacy is best correlated with the maximum plasma concentration (C_{max})-to-MIC ratio and the area under the plasma concentration-time curve (AUC)-to-MIC ratio (29).

Neutropenic fever in cancer patients carries an overall mortality rate of 4 to 30% (30). Mortality correlates with the duration and the severity of neutropenia and the time that has elapsed until the first dose of antibiotics is administered following the initial spike in body temperature (16). Mortality associated with untreated infection in neutropenic patients is rapid, and studies of empirical antibiotic therapy have led to the recognition that the early diagnosis and treatment of infection are mandatory for optimal patient care (23). Of great concern has been the increasing frequency of antibiotic-resistant gram-positive organisms (25). These pathogens include coagulase-negative staphylococci, methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, and penicillin (ceftriaxone)-resistant *Streptococcus pneumoniae*. Treatment with vancomycin, a slowly bactericidal glycopeptide antibiotic, which is the agent most commonly used to treat infections caused by gram-positive organisms in patients with febrile neutropenia, is associated with a delayed response and the development of resistant organisms (18). Daptomycin is an attractive agent for improving outcomes in this vulnerable patient group because of its broad spectrum of activity and bactericidal action.

Because cancer patients often have low levels of serum proteins and significant shifts of fluid between body compartments, the optimal daptomycin dosing strategy is uncertain. Previously, pharmacokinetic (PK) and pharmacodynamic studies of daptomycin have not been conducted with cancer patients. Characterization of the PKs of daptomycin in this group

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of acutely ill patients would facilitate future dosing recommendations. The purpose of this study was to evaluate the PKs of daptomycin in adult oncology patients with neutropenic fever.

MATERIALS AND METHODS

Study protocol. The study protocol was approved by the Institutional Review Board and the Cancer Institute Committee at the Oregon Health & Science University. All patients provided signed informed consent prior to inclusion in the study.

Inclusion criteria. Patients who fulfilled the following criteria were eligible to participate in this study. (i) They had to be males or females 18 years of age or older. (ii) They had to be oncology patients with an absolute neutrophil count of less than 500 cells/mm^3 and one or more of the following: mucositis, concomitant skin or soft tissue infection, indwelling catheter and/or suspected catheter infection, recent quinolone prophylaxis, positive blood cultures for gram-positive cocci before final identification or a documented infection with another gram-positive pathogen, colonization with β-lactam-resistant gram-positive organisms (commonly, colonization of the nares or the skin), hypotension, tachycardia, narrowed pulse pressures, tachypnea, or other signs of cardiovascular compromise. (iii) They had to have a temperature of >38.3°C (101°F) once or ≥38°C (100.4°F) twice within 12 h. (iv) They had to have an expected duration of neutropenia for at least 3 days. (v) They had to have a life expectancy of at least 2 weeks. (vi) They had to have a performance status with an Eastern Cooperative Oncology Group score of ≤2.

Exclusion criteria. Patients were not eligible for participation in the study if any of the following criteria were met: (i) they had a known allergic reaction to daptomycin or product excipients; (ii) they had suspected meningitis or osteomyelitis; (iii) they were known to be infected with a daptomycin-resistant organism or a gram-negative organism and did not yet meet the criteria for the addition of antimicrobial therapy for the treatment of an infection caused by a gram-positive organism; (iv) they had been treated with daptomycin or other antibiotic agents covering gram-positive organisms in the preceding 7 days; (v) they were pregnant, were positive for serum human chorionic gonadotropin, or were lactating; (vi) they had a creatinine clearance (CL_{CR}) level of <50 ml/min; (vii) they were on hemodialysis or continuous ambulatory peritoneal dialysis; (viii) they had rhabdomyolysis or a history of rhabdomyolysis; (ix) they were positive for human immunodeficiency virus; (x) they had psychiatric disorders with an inability to comply with study protocols; (xi) they had documented or suspected pneumonia caused by a gram-positive organism; (xii) they had a life expectancy of <2 weeks; (xii) they had suspected or proven endocarditis; (xiii) the had signs and symptoms of myopathy with an elevation of the creatine phosphokinase (CPK) level of >1,000 U/liter (approximately five times the upper limit of normal); or (xiv) they had reported signs or symptoms of myopathy and elevations of the CPK level of >10 times the upper limit of normal.

Dosing and sample collection. The daptomycin (Cubicin; Cubist Pharmaceuticals, Inc.) dose of 6 mg/kg based on the total body weight was administered as a 30-min intravenous infusion every 24 h. Blood samples for measurement of plasma daptomycin concentrations were collected before administration of the dose (predosing); at the end of infusion (time zero); and at the following times after the beginning of the infusion: 0.5, 1, 2, 4, 8, 12, and 24 h. Serum samples for protein binding studies were collected at 0.5, 2, and 8 h after the end of the infusion.

Analytical procedures. Daptomycin total and free plasma concentrations were determined by a validated high-pressure liquid chromatography method in the laboratory at the Center for Anti-infective Research and Development at Hartford Hospital (Hartford, CT). A similar methodology for the assay has been reported in a previously published article (9). The standard curve was linear (R = 0.996) from 1 to 100 μg/ml. The intrarun (n = 10) coefficients of variation (CVs) for the low-concentration (0.1 μg/ml) and the high-concentration (80 μg/ml) quality controls were 6.4% and 2.6%, respectively. The interrun (n = 7) CVs for the low-concentration (0.1 μg/ml) and the high-concentration (80 μg/ml) quality controls were 2.9% and 2.8%, respectively. The lower limit of detection was 1 μg/ml.

Samples collected for the purpose of determining protein binding were processed by ultrafiltration with Amicon Centrifree micropartition devices (Millipore, Bedford, MA) with 30,000-molecular-weight-cutoff filters, according to the instructions in the manufacturer's package insert. The standard curve constructed in a saline aqueous matrix was linear (R = 0.996) from 0.25 to 100 μg/ml. The intrarun (n = 10) CVs for the low-concentration (1 μg/ml) and the high-concentration (75 μg/ml) quality controls were 4.1% and 0.75%, respectively. The interrun (n = 6) CVs for the low-concentration (1 μg/ml) and the high-concentration (75 μg/ml) quality controls were 4.9% and 1.1%, respectively.

TABLE 1. Patient demographic data, laboratory data, and renal function test results

Characteristic[a]	Mean ± SD	Range
Age (yr)	50 ± 16	19–71
Total body wt (kg)	89.4 ± 19.9	56.2–137
Ideal body wt (kg)	70.5 ± 11.9	50–98
Height (cm)	177 ± 11	158–205
Body surface area (m^2)	2.08 ± 0.26	1.60–2.56
BMI (kg/m^2)	28.7 ± 6.3	18.8–45.9
Maximum temp (°C)	38.4 ± 1.1	36.7–40.8
Blood urea nitrogen concn (mg/dl)	9 ± 4	2–21
Mean serum creatinine concn (mg/dl)	0.80 ± 0.19	0.5–1.2
CL_{CR} (ml/min)[b]	139.31 ± 46.76	76.53–273.29
eGFR (ml/min/1.73 m^2) by six-variable MDRD[c]	104.07 ± 31.65	55.04–173.18
eGFR (ml/min/1.73 m^2) by four-variable MDRD[c]	107.30 ± 31.57	64.79–177.19

[a] The study included 10 females and 19 males.
[b] Determined by the Cockcroft and Gault equation by the use of total body weight (6).
[c] Determined by the MDRD equation (20).

PK analysis. Plasma daptomycin concentration-time data were analyzed by noncompartmental and compartmental methods with the WinNonLin software program. The C_{max} and the time to C_{max} (T_{max}) of daptomycin were the observed values. The AUC from time zero until the last concentration-time point, which was at 24 h (AUC_{0-24}) was calculated by use of the linear trapezoidal rule. The terminal area was the quotient of the last concentration divided by the terminal elimination rate constant (λ_z). This constant was determined from regression analysis of the concentration-time points in the terminal elimination phase. The AUC from time zero to infinity ($AUC_{0-\infty}$) was the sum of the AUC_{0-24} plus the terminal area. The terminal elimination half-life ($t_{1/2}$) was calculated as $0.693/\lambda_z$, clearance (CL) was calculated as dose/$AUC_{0-\infty}$, and the volume of distribution (V) was calculated as CL/λ_z. The percentage of daptomycin bound was calculated as the total (bound and free) plasma daptomycin concentration minus the free daptomycin concentration divided by the total concentration multiplied by 100. The fraction unbound in the plasma (f_u) was calculated as the free daptomycin concentration divided by the total plasma daptomycin concentration.

Pharmacodynamic analysis. C_{max}/MIC ratios, and AUC_{0-24}/MIC ratios were calculated for MICs ranging from 0.12 to 0.5 μg/ml and were compared to the values in the literature (27). Although the killing of bacteria by daptomycin is considered to be concentration dependent, the time above the MIC ($T > MIC$) and the percentage of the time above the MIC ($\%T > MIC$) were determined due to the use of an antibiotic with a long dosing interval (τ) in an immunocompromised patient population and were calculated as follows: $T > MIC = [\ln(C_{max,free}/MIC)/\lambda_z]$ and $\%T > MIC = (T > MIC/\tau)/100$, where $C_{max,free}$ is the maximum free concentration of daptomycin measured 0.5 h after administration of the dose and τ is equal to 24 h.

Statistical analysis. The data were normally distributed and are reported as means ± standard deviations (SD) for all parameters except T_{max}, which was not normally distributed and which is reported as the median and range. Comparisons between two groups (e.g., two groups separated by gender) were made by using Student's t test. Multiple-group comparisons (e.g., groups separated by obesity categories and ethnicity) were compared by using analysis of variance with Tukey's posttest. Categorical data were analyzed by the chi-square test. Correlations were tested as Pearson's product correlation coefficient. Statistical significance was defined as a P value of <0.05. SPSS for Windows (version 15.0; SPSS Inc., Chicago, IL) was used for the statistical analyses.

RESULTS

Subject demographics. Patient demographic data, laboratory data, and renal function test results are summarized in Table 1. Fifty-three patients were screened; 30 patients met the inclusion criteria, and 29 patients completed the study. In

TABLE 2. Single-dose daptomycin PK parameters[a]

Patient population	Wt (kg)	Dose (mg/kg)	C_{max} (μg/ml)	C_{24} (μg/ml)	$AUC_{0-\infty}$ (μg · h/ml)	$t_{1/2}$ (h)	CL
Healthy, male volunteers ($n = 6$)	78.5 ± 9.0	4	77.5 ± 8.3		529.7 ± 13	7.74 ± 0.63	9.84 ± 0.26 ml/min
Young, healthy volunteers ages 18–30 yr ($n = 11$)	64.9 ± 9.76	4	42.32 (15.35)	<LLQ	300.64 (11.53)[b]	6.79 (7.78)	15.09 (16.35) ml/h/kg
Old, healthy volunteers ages ≥75 yr ($n = 12$)	77.0 ± 8.16	4	43.98 (16.67)	6.38 (29.43)	473.66 (23.21)[b]	11.85 (18.98)	9.86 (25.09) ml/h/kg
Moderately obese adult volunteers ($n = 6$)	85.7 ± 9.0	4	57.75 (12.59)	3.44 (52.34)	420.53 (15.99)[c]	7.34 (12.67)	16.24 (5.17)[c] ml/h/kg
Nonobese adult volunteers ($n = 6$)	64.3 ± 7.0	4	46.28 (14.51)	<LLQ	322.37 (10.29)[c]	6.83 (9.67)	14.72 (6.63)[c] ml/h/kg
Morbidly obese adult volunteers ($n = 6$)	125.8 ± 17.0	4	67.00 (10.37)[c]	5.88 (49.36)	547.78 (24.61)[c]	8.12 (21.08)	7.82 (19.78)[c] ml/h/kg
Nonobese adult volunteers (matched controls) ($n = 6$)		4	53.22 (11.31)[c]	3.39 (90.43)	418.76 (24.91)[c]	8.04 (29.05)	10.19 (32.53)[c] ml/h/kg
Morbidly obese adult volunteers ($n = 7$)	114.3 ± 15.8	4	67.3 ± 12.3[c]	6.55 ± 2.31[c]	581 ± 104[c]	8.68 ± 1.67	0.0071 ± 0.0013[c] liter/h/kg
Nonobese adult volunteers (matched controls) ($n = 7$)	58.8 ± 6.2	4	42.3 ± 11.9[c]	3.39 ± 0.79[c]	346 ± 63[c]	7.72 ± 0.76	0.012 ± 0.0020[c] liter/h/kg
Adult volunteers w/hepatic impairment ($n = 10$)	92.66	6	113.72 (14.68)		867.43 (22.75)	8.97 (19.28)	7.10 (19.54) ml/h/kg
Adult volunteers (matched controls) ($n = 9$)	84.18	6	118.33 (12.81)		928.02 (12.91)	9.44 (8.77)	6.55 (12.85) ml/h/kg
Healthy, adult men ($n = 6$)	15% of IBW	6	82 ± 20.4		598 ± 110	8.06	10.26 ± 1.68 ml/h/kg

[a] Data are presented as means ± SDs or mean (percent CV). A_e, amount excreted unchanged; CL_R, renal clearance; LLQ, lower limit of quantitation (which was 3.3 μg/ml); IBW, ideal body weight. The other abbreviations are defined in the text.
[b] $P \leq 0.0001$
[c] $P < 0.05$.
[d] The data represent V in the elimination phase.

terms of ethnicity, 24 patients were white, 1 patient was Hispanic, and 1 patient was a Pacific Islander. The ethnicities of three patients were unknown. Patients were classified as being of normal weight, overweight, obese, and morbidly obese according to their body mass indices (BMIs) and the obesity categories put forth in the Obesity Education Initiative by the National Heart, Lung, and Blood Institute (http://www.nhlbisupport.com/bmi/bmicalc.htm). Ten patients were of normal weight (BMI = 18.5 to 24.9 kg/m^2), eight patients were overweight (BMI = 25 to 29.9 kg/m^2), nine patients were obese (BMI = 30 kg/m^2 or greater), and two patients were morbidly obese (BMI > 40 kg/m^2). The Modification of Diet in Renal Disease (MDRD) equation was used to classify the estimated glomerular filtration rate (eGFR) into various stages (20). Thirteen patients had excellent renal function, with six patients having eGFRs of 100 to 120 ml/min/1.73 m^2 and seven patients having eGFRs of >120 ml/min/1.73 m^2. According to the classification put forth by the National Kidney Foundation (21), 3 patients in our study had eGFRs of ≥90 ml/min/1.73 m^2 (stage 1 chronic kidney disease [CKD]), 12 patients had eGFRs of 60 to 89 ml/min/1.73 m^2 (stage 2 CKD), and 1 patient had an eGFR of 55 to 59 ml/min/1.73 m^2 (stage 3 CKD).

PKs. Tables 2 and 3 summarize the results of previously published studies reporting the values of the PK parameters for daptomycin after the administration of single and multiple doses, respectively. Twenty-nine adult cancer patients completed the PK studies. All data were analyzed by noncompartmental analysis. The results of our study are found in Table 4. No differences in the values of the PK parameters were observed between male and female patients. The data for 23 of the 29 patients fit a two-compartment model with first-order elimination, in agreement with the results of two single-dose studies conducted with healthy volunteers (12, 31). In these 23 patients, the distribution-phase $t_{1/2}$ was 1.2 ± 1.5 h, and the V in the central compartment (V_1) was 8,866 ± 3,897 ml, which was higher than the V_1 of 3,420 ± 1,070 ml reported by Wise et al. (31). T_{max} occurred within an hour in all patients except for one patient, who had a prolonged T_{max} of 2.5 h. The daptomycin C_{max} ranged from 21.54 to 75.20 μg/ml, which is below the average plasma concentrations reported in healthy adult volunteers following the administration of single and multiple doses of 6 mg/kg daptomycin (Tables 1 and 2) (3, 10, 12, 13). The 24-h plasma concentration (C_{24}) was below the detectable limit of 1 μg/ml in 3 patients, ≤5 μg/ml in 16 patients, >5 and ≤10 μg/ml in 8 patients, and >10 and ≤15 μg/ml in 1 patient. In one obese patient, C_{24} was markedly elevated (29.26 μg/ml), resulting in a large $AUC_{0-\infty}$ of 3,155.11 μg · h/ml (extrapolated area of 83%), a CL of 1.90 ml/h/kg, and a prolonged $t_{1/2}$ of 83.92 h. This patient was deemed an outlier according to the T procedure outlier test. The $AUC_{0-\infty}$ for the remaining 28 patients ranged from 164.64 to 697.69 μg · h/ml.

The mean CL reported in the literature range from 6.6 to 9.9 ml/h/kg (3, 12, 13). In our study, CL was ≥10 and <15 ml/h/kg in 14 patients, ≥15 and <20 ml/h/kg in 5 patients, ≥20 and <25 ml/h/kg in 5 patients, and ≥30 ml/h/kg in 1 patient. The mean V was 16,496 ± 5,811 ml, which is higher than the average value of 6,350 ± 533.4 ml reported by Wise et al. (31). The average V at steady state (V_{SS}) in our patients (0.18 ± 0.05 liter/kg) was also slightly higher than the values previously reported for patients who received the same 6-mg/kg dose (range, 0.08 to 0.106 liter/kg). Higher values of CL and V

TABLE 2—*Continued*

V_{SS}	V_1 (ml)	V_z	MRT (h)	A_e (% of dose)	CL_R (ml/h/kg)	Reference
6,057 ± 679 ml	3,420 ± 1,070	6,350 ± 533.4 ml	10.94 ± 0.93	59.7 ± 10.2		Wise et al. (31)
0.14 (12.86) liter/kg		0.15 (12.81) liter/kg	9.05 (6.00)	42.29 (16.42)	7.20 (25.53)	Dvorchik et al. (12)
0.15 (28.83) liter/kg		0.17 (28.93) liter/kg	15.91 (17.25)	34.31 (45.85)	4.27 (29.97)	Dvorchik et al. (12)
0.15 (11.27) liter/kg				51.82 (12.44)	9.35 (13.71)	Dvorchik and Damphousse (14)
0.13 (5.78) liter/kg				52.33 (15.63)	8.37 (12.71)	Dvorchik and Damphousse (14)
0.18 (14.55)[c] liter/kg				42.74 (13.68)	8.06 (31.26)	Dvorchik and Damphousse (14)
0.11 (16.48)[c] liter/kg				48.64 (17.29)	5.88 (18.71)	Dvorchik and Damphousse (14)
0.09 ± 0.01[c] liter/kg						Pai et al. (22)
0.13 ± 0.02[c] liter/kg						Pai et al. (22)
0.08 (15.12) liter/kg			12.04 (20.02)	49.27 (39.19)	3.65 (49.28)	Dvorchik et al. (12)
0.08 (13.22) liter/kg			12.44 (9.55)	39.81 (21.59)	2.72 (17.70)	Dvorchik et al. (12)
0.12 ± 0.020 liter/kg[d]					3.84 ± 1.08	Woodworth et al. (32)

accounted for the lower C_{max} and $AUC_{0-\infty}$ observed in our patients. $t_{1/2}$ and the mean residence time (MRT) ranged from 5.2 to 12.5 h and 7.0 to 17.7 h, respectively, if we exclude the data for the patient with the markedly elevated C_{24}. These values did not differ markedly from the values reported for daptomycin in the literature (3, 12, 13). $t_{1/2}$ did not change because of an increase in both V and CL in our patients. As predicted, linear regression analysis showed a decrease in $t_{1/2}$ as CL increased, an increase in $t_{1/2}$ as V increased, and an increase in V with an increase in f_u.

The daptomycin CL declined with increasing BMI (data not shown). The daptomycin CL were 18.93 ± 7.24 ml/h/kg in normal-weight subjects, 14.65 ± 3.08 ml/h/kg in overweight subjects, 11.86 ± 5.16 ml/h/kg in obese subjects, and 11.41 ± 4.29 ml/h/kg in morbidly obese subjects. The estimated CL_{CR} and eGFR declined in a similar manner. Post-hoc analysis revealed a significant difference in CL between normal-weight subjects and obese subjects ($P = 0.015$). No other significant differences in PK parameters according to BMI stratification were observed.

Daptomycin exhibited a high degree of protein binding, with 94.2% ± 1.8% binding at 0.5 h, 93.7% ± 2.1% binding at 2.0 h, and 93.2% ± 2.1% binding at 8.0 h after administration of the dose. Accordingly, the values of f_u were 0.06 ± 0.02 at 0.5 and

TABLE 3. Multiple-dose daptomycin PK parameters in healthy volunteers[a]

Day	Dose (mg/kg)	C_{max} (μg/ml)	$AUC_{0-\infty}$ (μg · h/ml)	$t_{1/2}$ (h)	CL (ml/h/kg)	$CL_{R,u}$ (ml/h/kg)	V_D (liter/kg)	f_u	Reference
1	4	54.6 ± 5.4	425 ± 58	7.4 ± 0.9	9.6 ± 1.3	84.6 ± 33.6	0.101 ± 0.013	0.08 ± 0.02	Dvorchik et al. (13)
	6	86.4 ± 7.1	705 ± 67	7.8 ± 1.0	8.6 ± 0.8	59.5 ± 16.7	0.096 ± 0.009	0.07 ± 0.01	Dvorchik et al. (13)
	8	116.3 ± 10.1	1,127 ± 161	9.6 ± 1.1	7.2 ± 1.1	50.0 ± 5.2	0.099 ± 0.014	0.09 ± 0.01	Dvorchik et al. (13)
7	4	57.8 ± 3.0	494 ± 75	8.1 ± 1.0	8.3 ± 1.3	62.9 ± 18.5	0.096 ± 0.009	0.08 ± 0.01	Dvorchik et al. (13)
	6	98.6 ± 12.0	747 ± 91	8.9 ± 1.3	8.1 ± 1.0	59.8 ± 13.8	0.104 ± 0.013	0.08 ± 0.02	Dvorchik et al. (13)
	8	133.0 ± 13.5	1,130 ± 117	9.0 ± 1.2	7.1 ± 0.8	40.9 ± 6.28	0.092 ± 0.012	0.09 ± 0.01	Dvorchik et al. (13)
14	8	129.5 ± 14.5	1,090 ± 114	8.9 ± 0.8	7.4 ± 0.8	44.7 ± 9.8	0.095 ± 0.013	0.09 ± 0.01	Dvorchik et al. (13)
1	6	95.7 (31.8)	729.8 (32.2)	7.5 (10.9)	9.9 (12.5)		0.1059 (13.3)		Benvenuto et al. (3)
	8	106.2 (20.0)	773.3 (20.3)	7.3 (18.4)	10.1 (24.0)		0.1029 (11.8)		Benvenuto et al. (3)
	10	129.7 (11.3)	1,013.5 (16.2)	8.4 (12.0)	9.9 (20.7)		0.1172 (11.5)		Benvenuto et al. (3)
	12	164.8 (7.4)	1,269.2 (22.2)	7.8 (12.1)	10.0 (23.7)		0.1111 (13.7)		
4	6	93.9 (6.4)	631.8 (12.3)	7.9 (12.8)	9.1 (16.9)		0.1014 (7.1)		Benvenuto et al. (3)
	8	123.3 (13.0)	858.2 (24.9)	8.3 (26.1)	9.0 (33.0)		0.1013 (12.8)		Benvenuto et al. (3)
	10	141.1 (17.0)	1,038.8 (17.2)	7.9 (8.0)	8.8 (25.3)		0.0983 (17.2)		Benvenuto et al. (3)
	12	183.7 (13.6)	1,277.4 (19.8)	7.7 (13.0)	9.0 (30.5)		0.0976 (18.3)		Benvenuto et al. (3)
14	10	139.3 (13.9)	1,082.1 (15.3)	7.9 (6.1)	7.5 (18.6)		0.0858 (16.7)		Benvenuto et al. (3)
	12	181.7 (13.2)	1,290.5 (22.0)	7.9 (13.8)	9.0 (32.3)		0.0992 (18.7)		Benvenuto et al. (3)
1–3	6	95.7 ± 11.3	645 ± 91[b]	7.6 ± 0.6	9.47 ± 1.36				DeRyke et al. (10)

[a] Data are presented as means ± SDs or mean (percent CV). CL_{Ru}, renal clearance of unbound daptomycin; V_D, terminal exponential apparent V. The other abbreviations are defined in the text.

[b] The data represent the AUC from time zero to τ.

TABLE 4. Daptomycin PKs in adult oncology patients with neutropenic fever[a]

Parameter	C_{max} (μg/ml)	T_{max} (h)	C_{24} (μg/ml)	$AUC_{0-\infty}$ (μg · h/ml)	V_{SS} (liter/kg)	CL (ml/h/kg)	$t_{1/2}$ (h)	MRT (h)
Mean ± SD	48.92 ± 12.63	0.6[b]	5.67 ± 3.05	427.31 ± 134.73	0.18 ± 0.05	15.51 ± 5.65	8.75 ± 2.38	11.89 ± 3.36
Range	21.54–75.5	0.5–2.5	1.48–15.08	164.64–697.69	0.13–0.36	8.38–34.76	5.17–12.45	7.00–17.74

[a] Data are means ± standard deviations and ranges for 28 patients (data for 1 outlier were excluded), unless indicated otherwise.
[b] Median.

2.0 h and 0.07 ± 0.02 at 8.0 h after administration of the dose, which are in agreement with the values reported by Dvorchik et al. (12, 13).

Various measures of body weight have been used in the Cockcroft-Gault equation (6) to estimate CL_{CR}. Poor correlations between the daptomycin CL and CL_{CR} on the basis of total body weight ($R^2 = 0.0652$; $P = 0.182$), the daptomycin CL and CL_{CR} on the basis of ideal body weight ($R^2 = 0.0744$; $P = 0.152$), and the daptomycin CL and CL_{CR} by the use of an adjusted body weight ($R^2 = 0.0761$; $P = 0.148$) were found in our study. Poor correlations were also found between daptomycin CL and the eGFR estimated by using the six-variable MDRD equation ($R^2 = 0.0616$; $P = 0.194$) and the four-variable MDRD equation ($R^2 = 0.0942$; $P = 0.105$) (20). Use of the method of Salazar and Corcoran is recommended for prediction of CL_{CR} in obese patients (28); however, we found a poor correlation between daptomycin CL and CL_{CR} when we used this estimation method for our obese patients ($R^2 = 0.0466$; $P = 0.261$).

Pharmacodynamics. In an in vivo pharmacodynamic study with a neutropenic murine thigh model, the MICs of daptomycin for *S. pneumoniae* ranged from 0.12 to 0.25 μg/ml and the MIC for *S. aureus* was 0.5 μg/ml (27). In the same study, the C_{max}/MIC ratios required for a bacteriostatic effect ranged from 12 to 36 for *S. pneumoniae* and 59 to 94 for *S. aureus* for total (bound and free) daptomycin concentrations. The AUC_{0-24}/MIC ratios for a bacteriostatic effect ranged from 75 to 237 for *S. pneumoniae* and 388 to 537 for *S. aureus* for total (bound and free) daptomycin concentrations. The extent of protein binding is identical between mice and humans; therefore, direct comparisons between total daptomycin plasma concentrations and AUC are possible (7, 27). In our study, all patients achieved the C_{max}/MIC ratios and the AUC_{0-24}/MIC ratios required for a bacteriostatic effect against *S. pneumoniae*. Twenty-seven patients (93%) achieved the C_{max}/MIC ratio required for a bacteriostatic effect against *S. aureus*, and 28 patients (97%) achieved the AUC_{0-24}/MIC required for a bacteriostatic effect against *S. aureus*.

According to the results of the same pharmacodynamic study, free daptomycin concentrations need to average from one to two times the MIC over 24 h to produce a bacteriostatic effect and two to four times the MIC to produce greater than 99% killing (27). All patients achieved these targets for MICs of 0.12 to 0.25 μg/ml. At an MIC of 0.5 μg/ml, the free daptomycin concentrations were two times the MIC in all patients; however, the free daptomycin concentrations were four times the MIC in only 10 of 29 patients (34%). Table 5 shows the values of percent $T >$ MIC during the 24-h dosing interval for MICs of 0.12 to 1.0 μg/ml.

Safety. One study of 120 patients presented in abstract form found that a C_{24} of ≥25.7 mg/liter would have a 14% probability of elevating the CPK level after 1 week of therapy (4). Normal CPK values for adults at the Oregon Health & Science University are 49 to 397 U/liter for males and 38 to 235 U/liter for females. The markedly elevated C_{24} of 29.26 μg/ml observed in one patient resulted in a clinically insignificant elevation in the CPK level of 21 U/liter before the study to 31 U/liter during week 2 of the study. One patient with a C_{24} of 7.39 μg/ml had a CPK level of 101 U/liter before the study, and the level rose to 169 U/liter 2 days after the patient received daptomycin. Another patient with a C_{24} of 7.70 μg/ml had a CPK level of 45 U/liter before the study, and the level rose to 224 U/L on study day 7 and later decreased to 43 U/liter and 45 U/liter on study days 14 and 21, respectively. All patients with elevated CPK levels were asymptomatic. No patients experienced myopathy or discontinued daptomycin due to elevated CPK levels. The daptomycin-related adverse events observed in our study were consistent with those reported in the product information (2), with one patient experiencing a rash and another patient exhibiting mental status changes.

DISCUSSION

The PKs of daptomycin in cancer patients vary from those in healthy subjects. Both C_{max} and $AUC_{0-\infty}$ were reduced and V and total CL were increased. Daptomycin is predominantly cleared renally (~52% of unchanged drug in urine). The current study did not demonstrate a strong linear relationship between daptomycin CL and the estimated CL_{CR} or the eGFR; therefore, the authors assumed that the increase in total CL stems from nonrenal CL. Interestingly, circulating metabolites are not observed in healthy subjects, suggesting the absence of hepatic metabolism of daptomycin (15, 32). It is hypothesized that a significant amount of drug undergoes metabolism in the kidney and is rapidly excreted before it enters the circulation. In vitro studies with animal tissues demonstrated the role of renal tissues in generating metabolites of

TABLE 5. Percent $T >$ MIC

MIC_{90} (μg/ml)	No. of patients with the following $T > MIC_{90}$s[a]:			
	100%	80 to <100%	50 to <80%	<50%
0.12	25	4	0	0
0.25	19	6	4	0
0.5	10	6	10	3
1.0	1	3	10	15

[a] $T >$ MIC is based on the unbound daptomycin concentrations.

daptomycin, giving support to the hypothesis presented above (19). However, it is not clear from the present study whether an induction of renal drug metabolism contributes to the increased total CL.

Daptomycin has the following physicochemical characteristics which limit its distribution to the plasma compartment: high polarity, low lipid solubility, high molecular mass, and a high degree of plasma protein binding (2). In the current study, cancer patients showed 50 to 100% increases in the values of V compared to those for healthy subjects (12, 32). The f_u of a drug markedly affects V for drugs with low levels of V and significantly affects V in the case of drugs with intermediate values of V, such as daptomycin. In the current study, no changes in the f_u of daptomycin were observed. However, an increase in the extracellular fluid volume could raise the values of V of hydrophilic drugs. Our patients received approximately 3 to 5 liters of fluids per day, according to the standard of care, and this may have played a role in increasing the daptomycin V in cancer patients.

The PKs of daptomycin were compared among cancer patients stratified according to their BMIs (based on the Obesity Education Initiative by the National Heart, Lung, and Blood Institute). In corroboration with the findings of studies reported in the literature, AUC and C_{max} increased, total CL decreased, and $t_{1/2}$ did not change with BMI (14, 22). Unlike other studies, the current study did not see a statistically significant increase in V with BMI. However, a trend of an increase in V with BMI was observed. This trend needs to be further examined with larger sample sizes, as the sample size in each of the BMI groups, in comparison to a total sample size of 29, was small and is a limitation of the current study.

In obese subjects, renal CL is generally increased (22, 24). Daptomycin is renally excreted unchanged to a significant degree (~52% of total drug in healthy subjects) in urine, and therefore, in this study, an increase in the renal CL of daptomycin in obese subjects was expected. Contrary to our expectations, we did not see an increase in total CL due to an expected increase in renal CL in obese subjects. It is possible that the interaction between obesity and the disease state (cancer) of a patient might have caused a reverse trend.

Dvorchik et al. (11) did not observe a relationship between CL and comorbidities such as diabetes, hypertension, and congestive heart failure. On the other hand, the current study suggests that patients with a malignancy and significant fluid supplementation have altered daptomycin CL. A population PK study of daptomycin with healthy subjects and subjects with infections (11) related the daptomycin CL to renal function, sex, and body temperature. Together, these three factors accounted for ~22% of the variability in CL. Application of the population PK model for daptomycin CL to our data showed good precision (0.439; 95% confidence interval, 0.328 to 0.550) and a slight but insignificant underprediction of CL (bias = −0.139; 95% confidence interval, −0.307 to 0.029). The small numbers of patients in our study gave us an inadequate power to detect gender differences in daptomycin PK parameters. All of the patients in our study were febrile, neutropenic cancer patients with maximum temperatures ranging from >38.0 to 40.8°C. The higher CLs observed in our study could partially be attributed to the elevated body temperature as well as the fluid therapy used to maintain high urinary flow rates.

The MIC_{90}s of daptomycin are typically ≤1 μg/ml for staphylococci and streptococci and 2 to 4 μg/ml for enterococci, including isolates resistant to vancomycin (8). Free daptomycin concentrations need to average from one to two times the MIC over 24 h to produce a bacteriostatic effect and two to four times the MIC to produce greater than 99% killing (27). The mean accumulation index in our study was 1.18 ± 0.10, which is in agreement with the values reported by Dvorchik et al. (13). Taking this into consideration, the unbound daptomycin concentrations at steady state are unlikely to be within the range of the concentrations needed for 99% killing of more resistant organisms with MICs of 2 to 4 μg/ml.

An in vitro study has shown that the postantibiotic effect of daptomycin was dose dependent and ranged from 1.0 to 6.3 h against *S. aureus* (17). In a murine neutropenic thigh model, postantibiotic effects were 5 and 10 h for *S. aureus* and *S. pneumoniae*, respectively (27). In our study, free plasma daptomycin concentrations were above the MIC of 0.12 to 0.25 μg/ml for 50 to 100% of the dosing interval in all patients. Free plasma daptomycin concentrations were above the MIC of 0.5 μg/ml for 50 to 100% of the dosing interval in 90% of patients. As the MICs increased to 1.0 μg/ml and above, fewer patients had free plasma daptomycin concentrations above the MIC for greater than 50% of the 24-h dosing interval, i.e., >12 h.

Daptomycin exhibits concentration-dependent killing, with efficacy being best correlated with the C_{max}/MIC and the AUC/MIC ratios (29). Despite the achievement of lower daptomycin C_{max} and AUC, all patients achieved these pharmacodynamic target ratios for *S. pneumoniae*, with a majority of patients achieving these targets for *S. aureus*. The median time to defervescence was 3 days from the start of daptomycin therapy (range, 1 to 11 days). Of the 29 study patients with neutropenic fever, 16 patients (55%) had bacteremia which resolved in all but 1 patient while the patients were receiving daptomycin therapy. The patient who was the exception had a line infection that did not clear with daptomycin or vancomycin therapy. Resolution of the infection occurred after the line was removed, followed by linezolid therapy.

The usual daptomycin dose for skin and soft tissue infections is 4 mg/kg administered as a short intravenous infusion every 24 h (2). The data from our PK-pharmacodynamic study show that a higher daptomycin dose of 6 mg/kg administered intravenously every 24 h was effective and well tolerated in the majority of our patients. The higher dose is reasonable in adult oncology patients, when their immunocompromised state, high ratios of institutional pathogen exposure, and concern over the increasing prevalence of resistant organisms are considered. Our results are in agreement with the recent approval of an intravenous daptomycin dose of 6 mg/kg every 24 h for endocarditis. Our pharmacodynamic analysis suggests that higher or possibly more frequent doses may be needed for more resistant organisms with MICs of 2 to 4 μg/ml; however, caution should be exercised when the daptomycin dose is increased beyond 6 mg/kg because of the nonlinear PKs reported at the 8-mg/kg dose level (13).

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