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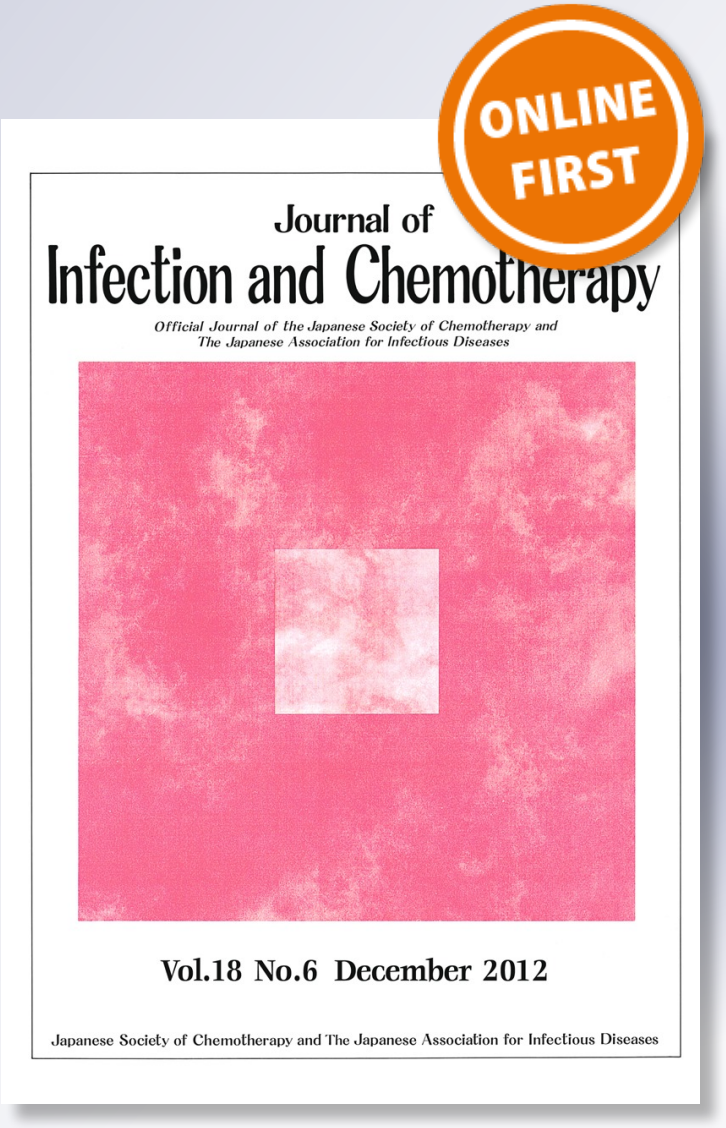
Journal of Infection and Chemotherapy
Official Journal of the Japanese Society of Chemotherapy and The Japanese Association for Infectious Diseases

ISSN 1341-321X

J Infect Chemother
DOI 10.1007/s10156-013-0559-z



Springer

J Infect Chemother
DOI 10.1007/s10156-013-0559-z

ORIGINAL ARTICLE

Variability of pharmacokinetic parameters in patients receiving different dosages of daptomycin: is therapeutic drug monitoring necessary?

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Received: 11 October 2012 / Accepted: 10 January 2013

Abstract Pharmacokinetic studies of daptomycin in septic patients indicate that pharmacokinetic parameters may be altered. The purpose of this clinical investigation is to determine the pharmacokinetics of daptomycin in a population of hospitalized patients with clinically significant gram-positive infections and receiving daptomycin. Daptomycin was measured using an isocratic HPLC technique. Thirty-five patients suffering from gram-positive severe infections and receiving daptomycin were included in the study. Patients were divided into two groups, depending on the dose of daptomycin received: group A, including 24 patients receiving 6 mg/kg/day daptomycin and group B, 11 patients receiving 8 mg/kg/day. Patients receiving a daptomycin dosage of 8 mg/kg/day had significantly higher values of mean C_{max} and AUC_{0-24}. Each group was further divided into three subgroups, according to the creatinine clearance (CrCl) values: (1) patients with a CrCl >80 ml/min, (2) patients with CrCl ranging between 80 and 40 ml/min, and (3) patients with CrCl <40 ml/min. Compared to patients with normal renal function, those with CrCl <40 ml/min had higher mean values of minimum concentration (C_{min}) ($p < 0.001$), AUC_{0-24} ($p = 0.03$), and prolonged plasma half-time ($p < 0.001$). These differences were present both in patients receiving 6 and those with 8 mg/kg/day. However, in each of the three subgroups with different degrees of renal function a marked variability of pharmacokinetics parameters was observed. The factors associated with increased mortality were an infection acquired in the ICU, hypoalbuminemia, and AUC/MIC <666. The marked variability that characterizes daptomycin pharmacokinetics in these patients suggest the monitoring of the main pharmacokinetic parameters in this clinical setting.

Keywords Daptomycin · Pharmacokinetic · Therapeutic drug monitoring · Staphylococcal infections · AUC/MIC

Introduction

Gram-positive pathogens, especially *Staphylococcus aureus* and coagulase-negative staphylococci, are a common cause of nosocomial infection, especially bloodstream infections (BSI) and skin or soft tissue infections (SSTI) [1–6]. Daptomycin, a lipoglycopeptide antibiotic with bactericidal activity against gram-positive organisms, may be prescribed for patients with severe SSTI, BSI, or infectious endocarditis (IE) [7–11].

Hospitalized patients with severe infection usually have many comorbidities, including reduction of renal function, hypoalbuminemia, or obesity; in addition, sepsis can lead to acute kidney injury and the need for renal replacement therapy. Optimal antibiotic dosing ensuring therapeutic concentrations is essential to reduce the risks of therapeutic failure and the development of antibiotic resistance. Considering that sepsis has a high mortality in critically ill patients with acute kidney injury, optimizing antibiotic

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Published online: 30 January 2013

dosing is crucial in this patient population. In these cases, because daptomycin is eliminated primarily by the kidneys, dose adjustments are required [12, 13]. On the other hand, drug accumulation and excessive antibiotic concentrations can result in an increased risk of adverse events, such as creatine kinase elevation with rare cases of rhabdomyolysis.

Daptomycin pharmacokinetics has been extensively studied in animal models and healthy volunteers [14]. However, studies conducted in septic patients with or without chronic kidney disease indicate that pharmacokinetic parameters may be altered [15, 16], especially in some circumstances such as critical illnesses, severe sepsis, or acute kidney injury. The purpose of this clinical investigation is to determine the pharmacokinetics of daptomycin in a heterogeneous population of hospitalized patients with clinically significant gram-positive infections, to correlate PK/PD parameters with the outcome of these patients.

Materials and methods

Patient sample and data collection

The study was carried out in the Policlinico Umberto I of Rome, during a period from November 2009 to December 2010. Thirty-five patients were enrolled; the decision to start daptomycin therapy was based on the personal decision of the attending physician or the infectious diseases consultant. The following parameters were collected for each patient: demographics, clinical and laboratory findings, microbiological data, duration of daptomycin therapy, side effects, and outcome. A written consent from the patient was obtained in all cases. The study was approved by the independent ethics committee or institutional review board of the participating centers.

Inclusion criteria

Patients who fulfilled the following criteria were eligible to participate in this study: (1) they had to be men or women 18 years of age or older, and (2) they had positive blood cultures for gram-positive cocci before final identification or a documented infection with another gram-positive pathogen.

Exclusion criteria

Patients were not eligible for participation in the study if any of the following criteria were met: (1) they had a known allergic reaction to daptomycin or product excipients; (2) they had suspected meningitis or osteomyelitis; (3) 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; (4) they had been treated with daptomycin or other antibiotic agents covering gram-positive organisms in the preceding 7 days; (5) they were pregnant, were positive for serum human chorionic gonadotropin, or were lactating; (6) they were on hemodialysis or continuous ambulatory peritoneal dialysis; (7) they had rhabdomyolysis or a history of rhabdomyolysis; (8) they had documented or suspected pneumonia caused by a gram-positive organism; (9) they had signs and symptoms of myopathy with an elevation of the creatine-phosphokinase (CPK) level (approximately five times the upper limit of normal).

Dosing and sample collection

Daptomycin (Novartis Pharma) was infused intravenously over 30 min. A dosage of 6 or 8 mg/kg every 24 h was based in consideration of patient weight and the type of infection. Blood samples for measurement of plasma daptomycin concentrations were collected before the first administration of the dose (predosing); at 0 min, 30 min (end of infusion), and at the following times after the start of infusion: 1, 2, 4, 8, 12, and 24 h from the first administration.

Pharmacokinetic study

Blood samples (5 ml) were collected in heparinized syringes, separated by centrifugation, kept at −80 °C, and sent to the Department of Pharmacology of University of Florence for further analysis. Concentrations of daptomycin in plasma were determined by a validated high performance liquid chromatography (HPLC) in plasma with a Pinnacle II C8 column (5 μm 250 × 4.6 mm) and measured by UV detection ($l = 220$ nm). The mobile phase consisted of ammonium phosphate (0.5 %) and acetonitrile mixed in a 66:34 (vol/vol) ratio. An injection volume of 100 μl was selected, and the flow rate was maintained at 1.5 ml/min. A standard curve ranging from 1.56 to 50 mg/l was selected, and linearity was confirmed by linear regression ($r^2 = 0.9994$). The intrarun ($n = 6$) coefficients of variation (CVs) were 0.1 mg/l for the low concentration and 50 mg/l for the high concentration.

Quality controls were 6.4 and 2.6 %, respectively. The interrun ($n = 6$) CVs for the low-concentration (0.1 mg/l) and the high-concentration (80 mg/l) quality controls were 2.9 and 2.8 %, respectively. The lower limit of detection was 0.1 mg/l.

Samples were prepared by mixing 500 μl specimen with 1 ml acetonitrile. The samples were mixed and centrifuged

at 14,000 rpm for 10 min. The supernatant was evaporated to dryness, and the residue was reconstituted in 0.5 ml ammonium phosphate (0.5 %); 100 µl was then injected into the HPLC.

A two-compartmental IV infusion model with first-order elimination was selected to fit concentration versus time data for daptomycin. The C_{max} and C_{min} of daptomycin were the observed values. The following pharmacokinetics (PK) parameters were estimated for each patient: volume of distribution (V_d), total clearance (Cl), area under the curve from zero to infinity (AUC_{0-24}), and the terminal elimination half-life ($t_{1/2\beta}$). Individual PK analysis was performed in WinNonlin Professional (Version 5.2.1; Pharsight Corporation, Mountain View, CA, USA).

The pharmacokinetics/pharmacodynamics (PK/PD) target for daptomycin was AUC_{0-24}/MIC (minimum inhibitory concentration) >666; the C_{max}/MIC ratio required range was 59–94.

Statistical analysis

The results obtained were analyzed using a commercially available statistical software package (SPSS, version 17.0; SPSS, Chicago, IL, USA). To detect significant differences between groups, we used the chi square test or Fisher's exact test for categorical variables, and the two-tailed *t* test or Mann–Whitney test for continuous variables, when appropriate. The distribution around the median was expressed by box plot. Statistical significance was established at ≤ 0.05. All reported *p* values are two tailed.

Results

Thirty-five patients suffering from gram-positive severe infections and receiving daptomycin were included in the study. Of these, 19 (54.2 %) had a bacteremia or endocarditis [1 methicillin-resistant *Staphylococcus aureus* (MRSA) endocarditis, 6 MRSA bacteremias, 7 methicillin-resistant *Staphylococcus epidermidis* (MRSE) bacteremias, 2 methicillin-resistant *Staphylococcus haemolyticus* (MRSH) bacteremias, 1 MR *Staphylococcus warnerii* bacteremia, 1 MR *Staphylococcus hominis*, 1 high-level resistant aminoglycosides (HLRA) *Enterococcus faecalis* endocarditis]; 12 (34.2 %) had a skin/soft tissue infection [4 MRSA, 3 MRSE, 1 MRSH, 1 methicillin-susceptible *S. aureus* (MSSA), 1 *Streptococcus pyogenes*, 1 MRSA + *Pseudomonas aeruginosa*, 1 necrotizing fasciitis]; 2 (5.7 %) had an MRSA prosthetic joint infection; and 2 (5.7 %) had an osteomyelitis (1 caused by MRSA and 1 by MRSE). No patients experienced an increase of creatine kinase levels. Clinical characteristics and outcomes of patients are reported in Table 1.

Table 1 Clinical characteristics and outcomes of patients receiving 6 mg/kg or 8 mg/kh daptomycin

Variable	6 mg/kg ($n = 24$)	8 mg/kg ($n = 11$)	*p*
Mean age (years)	61.4	63.4	0.49
Men	15 (62.5 %)	7 (63.6 %)	0.52
COPD	11 (45.8 %)	8 (72.7 %)	0.91
Heart failure	11 (45.8 %)	6 (54.5 %)	0.59
Diabetes mellitus	8 (33.3 %)	6 (54.5 %)	0.28
Neoplasm	1 (4.2 %)	0	1
Chronic liver disease	3 (12.5 %)	3 (27.3 %)	0.67
Type of infection			
Bacteremia-endocarditis	11 (45.8 %)	8 (72.7 %)	>0.05
Skin and soft tissue infections	9 (37.5 %)	3 (27.3 %)	>0.05
Prosthetic joint infection	2 (8.3 %)	0	>0.05
Osteomyelitis	2 (8.3 %)	0	>0.05
Causative pathogens			
MRSA	9 (37.5 %)	5 (45.5 %)	0.95
MRSE	5 (20.1 %)	5 (45.5 %)	0.61
MRSH	3 (12.5 %)	0	0.64
Others microorganisms	7 (29.1 %)	1 (9 %)	0.03
Presence of at least two comorbidities	19 (79.2 %)	9 (81.8 %)	0.73
ICU acquisition of infection	8 (33.3 %)	5 (45.5 %)	0.13
Recent surgery (previous 30 days)	7 (29.1 %)	3 (27.3 %)	0.8
Severe sepsis or septic shock	9 (37.5 %)	5 (45.5 %)	0.59
SOFA score (mean)	2.05	2.85	0.35
Mean duration of antibiotic therapy (days)	20.4	22.2	0.15
Mean length of hospital stay (days)	28.5	33.8	**0.03**
In-hospital mortality	2 (8.3 %)	2 (18.2 %)	**0.04**

Bold values indicate statistically significant *p* values

COPD chronic obstructive pneumonia disease, *MRSA* methicillin-resistant *Staphylococcus aureus*, *MRSE* methicillin-resistant *Staphylococcus epidermidis*, *MRSH* methicillin-resistant *Staphylococcus haemolyticus, ICU* intensive care unit, *SOFA* Sequential Organ Failure Assessment

Patients were divided into two groups, depending on the dose of daptomycin received: group A, including 24 patients, receiving 6 mg/kg/day daptomycin and group B, including 11 patients, receiving 8 mg/kg/day. As shown in Table 2, patients receiving a daptomycin dosage of 8 mg/kg/day had significantly higher values of mean C_{max} and AUC_{0-24}, with a significantly higher AUC/MIC and C_{max}/MIC ratios.

Each group was further divided into three subgroups, according to the renal function of patients: in the subgroups A1 and B1, 9 patients had a value of CrCl >80 ml/min, in the subgroups A2 and B2, 11 patients had a value between 80 and 40 ml/min, and in the subgroups A3 and B3, 15

Table 2 Pharmacokinetics parameters

Parameter (mean ± SD)	6 mg/kg ($n = 24$)	8 mg/kg ($n = 11$)	p
C_{max} (μg/ml)	49 ± 19.8	78 ± 57.2	**0.03**
Calculated $AUC_{0–24}$ (mg h/l)	367.5 ± 163	539.3 ± 244.7	**0.01**
$t_{½}$ (h)	15.22 ± 11.2	11.8 ± 5.14	0.35
Cl (l/h)	0.02 ± 0.03	0.016 ± 0.012	0.68
V_d (l/kg)	0.21 ± 0.1	0.23 ± 0.12	0.59
AUC/MIC	692 ± 210	903 ± 280	**0.01**
C_{max}/MIC	87 ± 31	138 ± 35	**0.02**

Bold values indicate statistically significant p values

C_{max} maximum concentration, *AUC* area under curve, *$t_{½}$* half-time, *Cl* clearance, *V_d* volume of distribution, *MIC* minimum inhibitory concentration

patients had a value <40 ml/min. In Table 3 are compared the pharmacokinetic parameters of patients included in the subgroups A1, A2, and A3; in Table 4 are compared patients in the subgroups B1, B2, and B3. Compared to patients included in the subgroups A1 and A2, those included in the subgroup A3 had significantly higher mean values of minimum concentration (C_{min}) (5.25, 6.3, and 10.5 mg/l, respectively; $p < 0.001$), $AUC_{0–24}$ (406.09, 510.1, and 962.9, respectively; $p = 0.03$), and prolonged plasma half-time (8.75, 8.82, and 22.9, respectively; $p < 0.001$). The total clearance of drug was higher in patients included in the subgroups A1 and A2 than those of the subgroup A3 (18.3, 11 and 6.6, 0.02). There were no significant differences in terms of mean C_{max} values among the three subgroups of patients.

Compared to patients included in the subgroups B1 and B2 receiving 8 mg/kg/day, patients of subgroup B3 had significantly higher values of C_{min} (7.45, 9.21, and 15.9 mg/l; $p = 0.032$), $AUC_{0–24}$ (584.3, 654.5, and 1013.6; $p = 0.01$), and prolonged plasma half-time (8.5, 11.6, and 17.5; $p < 0.001$) than those included in subgroup B3. The total clearance of drug was higher in patients included in the subgroups B1 and B2; there were no significant differences in term of mean C_{max} values. Of importance, the volumes of distribution were similar in both subgroups, patients receiving 6 or 8 mg/kg/day. Figure 1 presents the distribution around the median values of C_{max} and $AUC_{0–24}$ in subgroups A1, A2, and A3; Fig. 2 illustrates the distribution around the median values of C_{max} and $AUC_{0–24}$ in subgroups B1, B2, and B3.

Overall, 4 of 35 patients (11.4 %) died, 2 receiving 6 mg/kg/day and 2 8 mg/kg/day; all patients who died showed an AUC/MIC ratio <666. In Table 5 are compared the pharmacokinetics parameters in patients who survived or died. At univariate analysis, the factors associated with increased mortality were an ICU acquisition of infection,

Table 3 Pharmacokinetics parameters of 24 patients receiving 6 mg/kg daptomycin

Mean values ± SD	Subgroup A1 ($n = 6$)	Subgroup A2 ($n = 7$)	Subgroup A3 ($n = 11$)	p*
C_{max} (mg/l)	55.7 ± 18.6	53 ± 15.2	48.15 ± 16.2	ns
C_{min} (mg/l)	5.25 ± 2.25	6.3 ± 2	10.5 ± 3.9	**<0.001* < 0.001**§
$t_{1/2}$ (h)	8.75 ± 2.1	8.82 ± 1.8	22.9 ± 12.9	**<0.001* < 0.001**§
$AUC_{0–24}$ (mg h/l)	406.09 ± 175.2	510.1 ± 129.3	962.6 ± 225.3	**0.021* 0.036**§
V_d (l/kg)	0.22 ± 0.12	0.20 ± 0.10	0.21 ± 0.1	ns
Cl (ml/h/kg)	18.3 ± 11.8	11 ± 2.6	6.6 ± 1.7	**<0.001* 0.02**§

Bold values indicate statistically significant p values

A1, B1 CrCl >80 ml/min, *A2, B2* CrCl between 80 and 40 ml/min, *A3, B3* CrCl <40 ml/min

* p, A1 vs. A3; $^{§}p$, A2 vs. A3; A1 vs. A2, no statistically significant differences

Table 4 Pharmacokinetics parameters of 11 patients receiving 8 mg/kg daptomycin

Mean values ± SD	Subgroup B1 ($n = 3$)	Subgroup B2 ($n = 4$)	Subgroup B3 ($n = 4$)	p*
C_{max} (mg/l)	85.1 ± 17.2	82.2 ± 15.3	73.9 ± 52.5	ns
C_{min} (mg/l)	7.45 ± 5.4	9.21 ± 3.9	15.9 ± 6.2	**0.032* 0.041**§
$t_{1/2}$ (h)	8.5 ± 1.9	11.6 ± 2	17.5 ± 3.6	**<0.001* < 0.001**§
$AUC_{0–24}$ (mg h/l)	584.3 ± 367.2	654.5 ± 312.7	1013.6 ± 324.9	**<0.001* 0.01**§
V_d (l/kg)	0.25 ± 1.15	0.25 ± 1.1	0.22 ± 0.07	ns
Cl (ml/h/kg)	20.4 ± 14.0	12.2 ± 7.4	8.7 ± 3.6	**0.032* 0.041**§

Bold values indicate statistically significant p values

A1, B1 CrCl >80 ml/min, *A2, B2* CrCl between 80 and 40 ml/min, *A3, B3* CrCl <40 ml/min

* p, B1 vs. B3; §***p***, B2 vs. B3; B1 vs. B2, no statistically significant differences

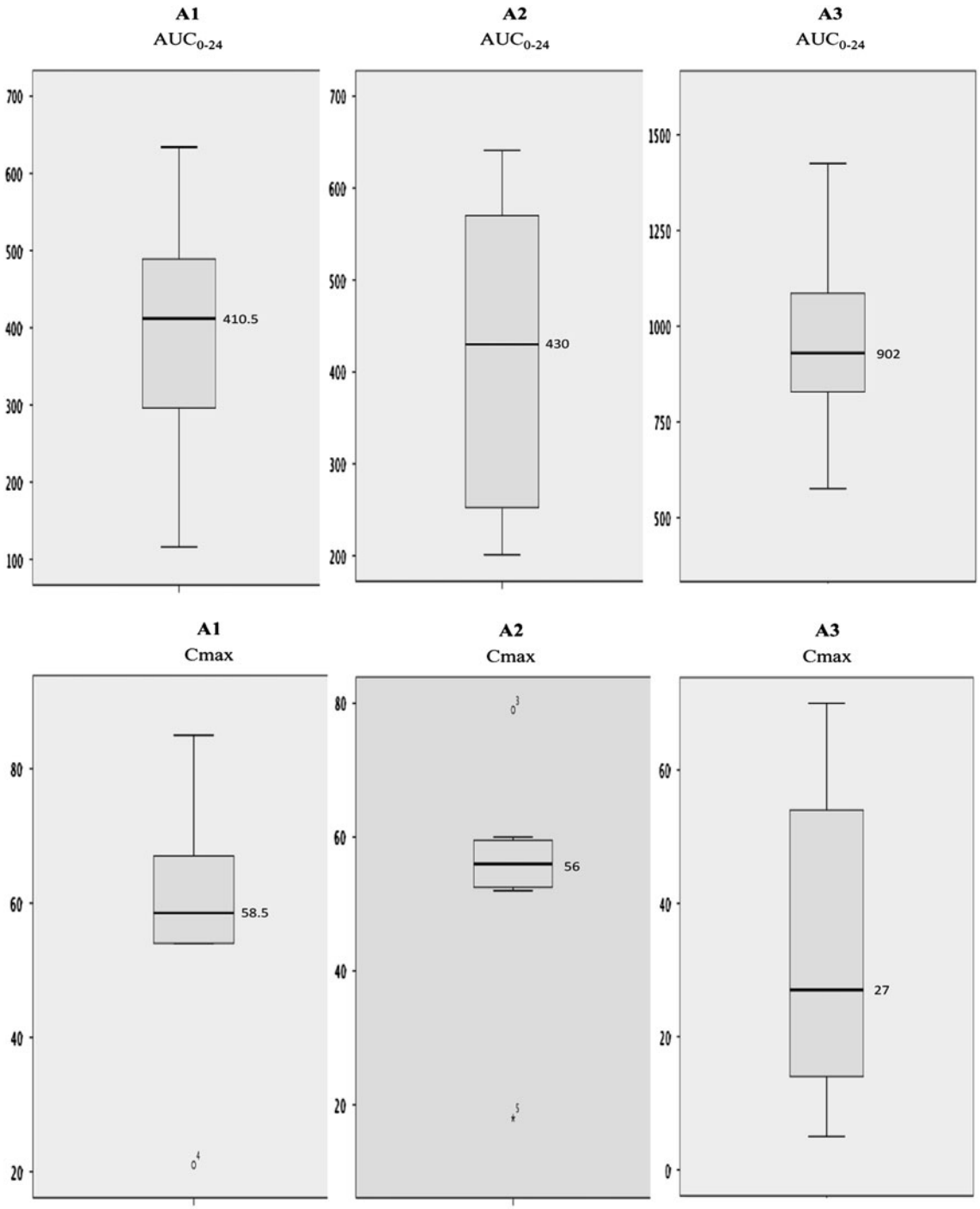

Fig. 1 Distribution around median values of maximum concentration (C_{max}) and area under the curve ($AUC_{0–24}$) in the subgroups of patients receiving 6 mg/kg/day with different renal function

the presence of hypoalbuminemia, and a value of AUC/MIC <666. Multivariate analysis of factors associated with mortality (Table 6) showed that AUC/MIC <666 (OR, 1.24; 95 % CI, 1.18–1.3; p = 0.032), ICU acquisition of infection (OR, 1.93; 95 % CI, 1.48–2.56; p = 0.02), and hypoalbuminemia (OR, 3.82; 95 % CI, 2.21–39.03; p = 0.02) were independently associated with death.

Discussion

The results of our study confirm that daptomycin has a linear and dose-dependent pharmacokinetic profile when administered at doses of 6 or 8 mg/kg/day. Actually, patients receiving 8 mg/kg/day had an increased exposure to the drug, as demonstrated by higher mean AUC and

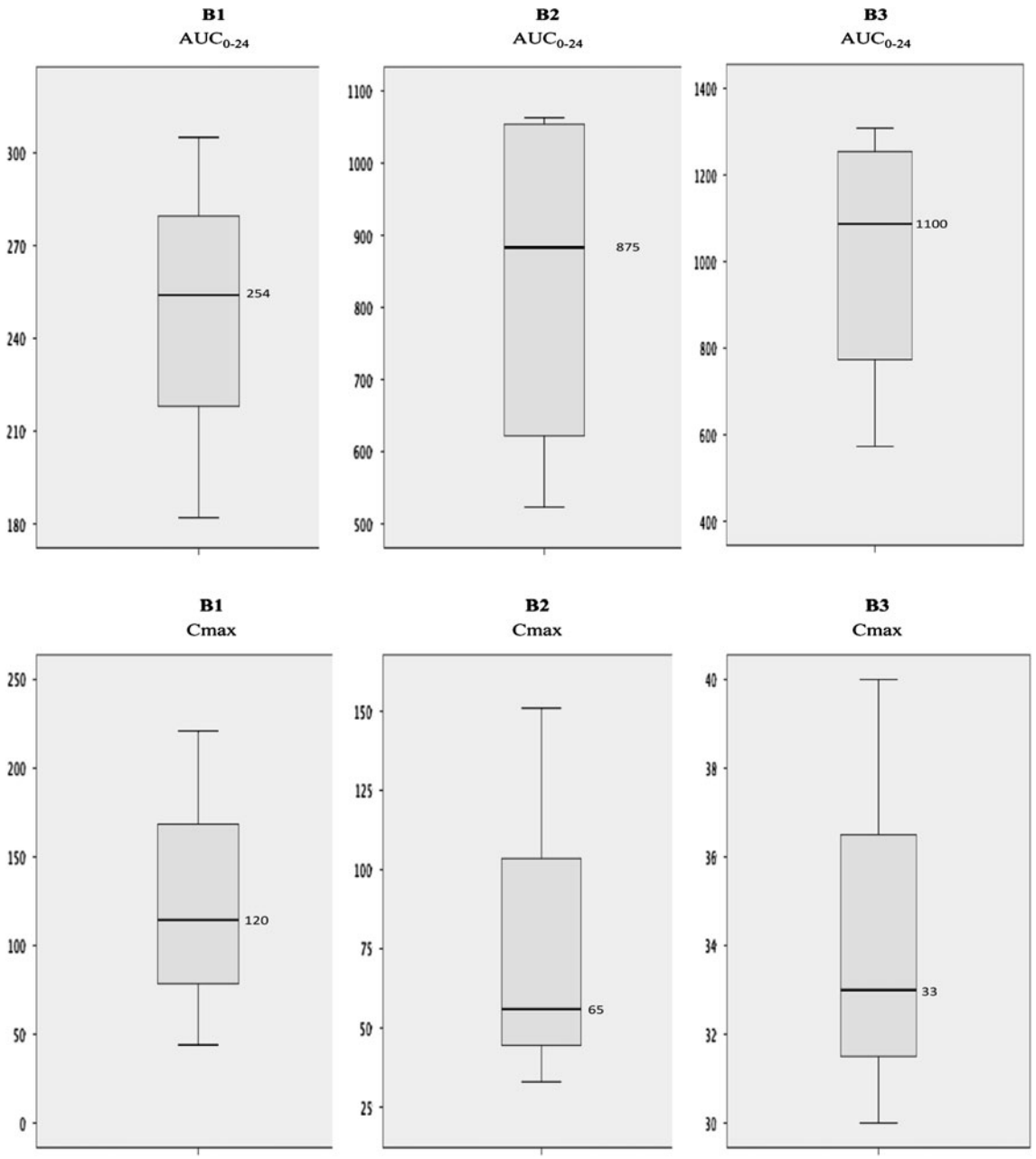

Fig. 2 Distribution around median values of C_{max} and $AUC_{0–24}$ in the subgroups of patients receiving 8 mg/kg/day with different renal function. C_{max} maximum concentration, *AUC* area under curve, *A1, B1* CrCl >80 ml/min, *A2, B2* CrCl between 80 and 40 ml/min, *A3, B3* CrCl <40 ml/min

C_{max} values. The mean C_{max} values observed in our study are similar to those reported in the literature [17–19]. However, patients receiving the same dosage (6 or 8 mg/kg/day) had great variability of C_{max} and AUC values.

The changes observed in the clearance of daptomycin in our patients were primarily caused by renal function; in fact, in all subjects with an efficient renal function (subgroups A1 and B1), the daptomycin clearance was higher compared to data observed in healthy volunteers. These data also agree with those obtained by Woodworth et al. [17], who found a strong correlation between improvement of renal function of patients and increase of drug clearance. A half-life approximately of 9 h justifies the daily administration of the antibiotic (every 24 h). On the other hand, when the renal function of our patients was severely damaged there was a significant reduction in clearance of the drug, with a significantly increased half-life.

However, the value of CrCl was never predictive of the degree of clearance of the antibiotic, and some patients included in the subgroup A3, despite a CrCl <40 ml/min,

Table 5 Univariate analysis of factors associated with poor outcome

Factors	Survived ($n = 31$)	Died ($n = 4$)	p
Daptomycin dosage 6 mg/kg	22	2	0.465
Daptomycin dosage 8 mg/kg	9	2	0.681
ICU acquisition of infection	10	3	**0.002**
Severe sepsis or septic shock	11	3	0.216
AUC/MIC <666	0	4	**<0.001**
Hypoalbuminemia	7	3	**0.002**

Bold values indicate statistically significant p values

ICU intensive care unit, *AUC* area under curve, *MIC* minimum inhibitory concentration

Table 6 Multivariate analysis of factors associated with poor outcome

Variable	p	OR (95 % CI)
AUC/MIC <666	0.032	1.24 (1.18–1.3)
ICU acquisition of infection	0.02	1.93 (1.48–2.56)
Hypoalbuminemia	0.02	3.82 (2.21–39.03)

OR odds ratio, *CI* confidence interval, *ICU* intensive care unit, *AUC* area under curve, *MIC* minimum inhibitory concentration

had high values of daptomycin clearance (15.2 and 17.1 ml/h/kg). This finding is similar to that observed by Bubalo and coworkers [20] in neutropenic patients. This apparent anomaly could be again explained by the patient's clinical condition. All critically ill patients have a strong interindividual variability with regard to the many physiological functions, including renal function, and these patients are subjected to daily changes, with significant variations in a few hours.

Concerning V_d, its value indicates a relatively limited spread of drug in plasma and interstitial fluids. However, in our patients V_d was consistently twice that found in healthy volunteers [16, 17], with values reaching as much as 0.5 l/kg in some patients. These data confirm those obtained by Bubalo et al. [20] in another group of critically ill neutropenic patients. Because a high percentage of our patients (40 %) had severe sepsis or septic shock caused by gram-positive infections, a similar increase of V_d was likely correlated with the septic status of the patient. The severity of sepsis may lead to an imbalance in the volume of body fluids, and this often results in an increased volume of distribution [21].

Roberts and Lipman [21] focused on the need to know all the changes that incur in the pharmacokinetics parameters of critically ill patients to understand their influence on antibiotic efficacy. In general, the most significant changes involve the clearance of the drug and its volume of distribution: changes in volume of distribution are often caused by vascular permeability resulting from bacterial endotoxins with the stimulation of endogenous mediators that alter endothelial permeability, causing an abnormal distribution of antibiotics in body fluids. Other changes of drug clearance may be caused by a possible state of hypoalbuminemia, which characterizes the critically ill patient, especially with regard to hydrophilic antibiotics, and highly binding protein, eliminated by the kidney. Also, liver or kidney failure could lead to a significant increase in the half-life of the antibiotic, resulting in accumulation, which is exactly what happened to our patients with impaired renal function (subgroups A3 and B3), in which the half-life values were significantly increased.

Because daptomycin has a concentration-dependent activity, its therapeutic efficacy is directly related to an adequate concentration in the blood [22]. The parameter that best expresses this relationship is the ratio AUC/MIC. For these reasons, it is advisable to carry out a constant monitoring of therapeutic serum levels of antibiotic and take account of all the pharmacokinetic changes observed in critically ill patients compared to healthy volunteers to predict and improve the therapeutic efficacy of the antibiotic. As shown in our data, especially for patients receiving 6 mg/kg/day, the AUC/MIC ratio is near 666, which is considered the cutoff of efficacy as reported in recent studies [23], with values <666 in some patients; also, however, in four patients receiving 8 mg/kg/day, the AUC/MIC ratio was <666. Of interest, the four patients who died (two receiving 6 mg/kg/day and two 8 mg/kg/day), all showed a AUC/MIC ratio <666. The peak/MIC ratio was 87 ± 31 in patients receiving 6 mg/kg/day and 138 ± 35 in patients receiving 8 mg/kg/day, according to Safdar et al. [15]. It is important to indicate that hypoalbuminemia, AUC/MIC <666, and acquisition of infection in ICU were risk factors independently associated with a poor outcome.

In view of the concentration-dependent activity of daptomycin, a dose of at least 6–8 mg/kg is necessary to ensure the potential effectiveness of the drug in gram-positive infections in critically ill patients. However, standard dosages may be inadequate in septic patients, not only those with impaired renal failure but also in patients with a normal renal function, as confirmed by the great variability of pharmacokinetic parameters.

This study has some limitations. First, because most of our patients were severely ill, daptomycin was administered every 24 h in all patients, including those with Ccr <30 ml/min. Second, the serum levels of daptomycin were measured during the first 24 h but not at the steady state. However, the goal of our study was to evaluate the PK/PD properties of this drug in the early phase of acute infection, when it is more important to reach adequate drug concentrations.

In conclusion, our analysis reveals a marked variation of PK/PD parameters in hospitalized patients receiving daptomycin. This variability suggests the need of therapeutic

drug monitoring, especially in severely ill patients residing in an ICU or those with a sepsis syndrome.

Acknowledgments This study was funded, in part, by the Italian Ministry of Health, Progetto di Ricerca di Interesse Nazionale (PRIN) no MIUR, PRIN 20087SM5HM$_{arucu}$.

Conflict of interest None to declare.

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