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Population pharmacokinetics of daptomycin in patients affected by severe Gram-positive infections

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ABSTRACT

A population pharmacokinetic analysis of daptomycin was performed based on therapeutic drug monitoring (TDM) data from 58 patients receiving doses of 4–12 mg/kg for the treatment of severe Gram-positive infections. At a daily dose of 8 mg/kg, daptomycin plasma concentrations (mean ± S.D.) were 76.9 ± 9.8 mg/L at the end of infusion and 52.7 ± 15.4 mg/L and 11.4 ± 5.4 mg/L at 0.5 h and 23 h after drug administration, respectively. The final model was a one-compartmental model with first-order elimination, with estimated clearance (CL) of 0.80 ± 0.14 L/h and a volume of distribution (V_d) of 0.19 ± 0.05 L/kg. Creatinine clearance (CL_{Cr}) was identified as having a significant influence on daptomycin CL, and a decrease in CL_{Cr} of 30 mL/min from the median value (80 mL/min) was associated with a reduction of daptomycin CL from 0.80 L/h to 0.73 L/h. These results confirm that the presence of severe infection may be associated with an altered disposition of daptomycin, with an increased V_d. MICs were available in 41 patients and results showed that 38 and 31 subjects achieved AUC/MIC values associated with bacteriostatic (>400) and bactericidal effects (>800), respectively. Of note, 31 of these 41 subjects experienced a clinical improvement or were cured. Although daptomycin pharmacokinetics may be influenced by infections, effective AUC/MIC values were achieved in the majority of patients. The present model may be applied in clinical settings for a TDM routine on the basis of a sparse blood sampling protocol.

1. Introduction

Gram-positive bacteria are often responsible for severe and difficult-to-treat infections, characterised by a high mortality rate in hospital settings [1]. The introduction of daptomycin has been a step forward in the treatment of severe infections caused by drug-resistant strains, such as meticillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci [2,3]. Daptomycin has concentration-dependent activity and its effectiveness is best predicted by the ratio of the maximum plasma concentration to the minimum inhibitory concentration (C_{max}/MIC) or the area under the concentration–time curve to the MIC (AUC/MIC) [4].

Daptomycin is characterised by linear pharmacokinetics in healthy volunteers up to doses of 12 mg/kg once daily [5,6], for which effectiveness, safety and tolerability have been documented [7,8]. Furthermore, high drug doses (up to 10 mg/kg) have been safely administered to children [9]. Daptomycin is excreted mainly through the kidneys as an unmodified molecule, and dosage adjustments are recommended in patients with compromised renal function. Biliary excretion accounts for only 3% of an administered dose, but since bile concentrations are high a role for daptomycin in the treatment of biliary tree infections has recently been advocated [10]. The drug displays a limited volume of distribution (V_d), accounting for ca. 0.1–0.2 L/kg of body weight [11]. Although daptomycin has poor penetration into the central nervous system [12], it achieves adequate concentrations in cardiac valve tissues and vegetations [13].

In 2004, the first study investigating the population pharmacokinetics of daptomycin was published based on data in healthy volunteers and patients enrolled in phase 1 and phase 2/3 studies [14]. The trial demonstrated that renal function, dialysis and sex contributed significantly to the interindividual variability in drug clearance (CL). Interestingly, the peripheral V_d was linearly correlated with the patient's body weight and it nearly doubled in the presence of an infection.

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In 2009, Bubalo et al. reported C_{max} values in cancer patients with suspected or confirmed infections compared with those previously measured in healthy volunteers [15], hence further suggesting that the presence of an infection could influence the plasma profile of the drug and possibly reduce treatment effectiveness.

On the basis of those studies, the present work aimed at investigating daptomycin pharmacokinetics in patients affected by severe Gram-positive infections. A therapeutic drug monitoring (TDM) protocol was applied and a population pharmacokinetic (PK) analysis was performed. Specific aims of the study were (a) to monitor peak and trough plasma levels of daptomycin in patients affected by severe infections caused by Gram-positive bacteria, (b) to investigate any possible correlation between daptomycin plasma concentrations and the daily administered dose, (c) to evaluate population pharmacokinetics of the drug, identifying factors able to influence daptomycin disposition and (d) to identify any association of clinical outcome with individual pharmacokinetic/pharmacodynamic parameters (i.e. AUC/MIC).

2. Materials and patients

2.1. Ethics

The Ethics Committee of Azienda Ospedaliero Universitaria Pisana (Pisa, Italy) discussed and approved the study protocol (protocol no. 55945, 24 September 2009).

2.2. Patients

From September 2009 to December 2010, patients admitted to the Infectious Diseases Unit of Azienda Ospedaliero Universitaria Pisana for the treatment of severe Gram-positive infections were enrolled in the present study according to the following inclusion criteria: signed informed consent; administration of daptomycin and measurement of drug plasma concentrations; and full access to clinical records for every subject. Exclusion criteria included age <18 years.

Daptomycin was administered by a 30-min intravenous infusion every 24 h with daily doses ranging from 4 mg/kg up to 12 mg/kg on the basis of infection severity, patient's clinical status, and sensitivity of bacterial strain to daptomycin. Blood samples were withdrawn from a peripheral vein of the forearm at 0.5, 1.0 and 23.5 h after the beginning of the 30-min drug infusion and were collected in heparinised tubes, according to a TDM protocol for daptomycin adopted in this university hospital. In some patients, TDM was performed on more than one occasion, depending on the patient's clinical status and disease severity. Blood samples were then centrifuged and plasma was stored at −20 °C until drug concentrations were measured according to a validated high-performance liquid chromatography (HPLC) method with ultraviolet detection [16]. The HPLC method was characterised by a lower limit of quantitation of 0.78 mg/L as well as intraday and between-day coefficients of variation <10%.

2.3. Pharmacokinetic analysis

A population PK analysis was performed based on values of daptomycin plasma concentrations according to a non-linear mixed-effects modelling approach using NONMEM software v.7.1 [17]. Data set checkout, model diagnostic and covariate testing were performed using Xpose and PsN software [18–20].

One- and two-compartment models with first-order elimination parameterised in terms of drug CL and V_d were evaluated. The residual error was described using additive, proportional or mixed additive and proportional error models. Model development was guided on the basis of goodness-of-fit plots and the plausibility and precision of parameter estimates. The covariates analysed were age, total body weight, serum creatinine, reciprocal serum creatinine, creatinine clearance (CL_{Cr}) (calculated according to the method of Cockcroft and Gault), sex, site of infection, bacterial strain and bacteraemia. Correlations among the covariates were evaluated graphically before the start of the covariate analysis. The relationship between the covariates and the PK parameters was first explored using a generalised additive modelling (GAM) procedure implemented in the Xpose package. Results of the GAM analysis were then evaluated on the basis of the range of the covariate in the data set, its scientific interest and possible mechanistic involvement in drug disposition (i.e. influence of hyperdynamic states on V_d of daptomycin). Based on the results from the GAM analysis, a stepwise covariate model building was performed with forward inclusion and backward exclusion. Non-linear (i.e. piecewise linear, exponential and power) as well as linear models were tested for continuous and categorical covariates, respectively. A decrease in the objective function value (OFV) greater than 3.84 points (i.e. $P < 0.05$) was the criteria used in forward inclusion steps, whilst a decrease in OFV greater than 6.63 points (i.e. $P < 0.01$) was adopted in backward exclusion steps.

The predictive performance of the models was assessed by prediction-corrected visual predictive checks using the PsN and Xpose packages [20]. Using the original data set as template, 1000 data sets were simulated from the final model and the 90% prediction intervals (PIs) were calculated. The 95% confidence intervals for these PIs were computed and superimposed on the observed values. Finally, η- and ε-shrinkage values were calculated using PsN software, and values below the level of 20–30% were considered acceptable [21].

The area under the plasma concentration–time curve from time zero up to infinity ($AUC_{0\rightarrow\infty}$) was calculated from the individual empirical Bayes estimates from the final population PK model as the ratio between total daily dose and CL. These AUC values were then used to calculate the individual value of AUC/MIC when MIC values were available. For AUC/MIC, a cut-off value of 400 was used as the target for a bacteriostatic effect [22], whilst higher cut-off values (i.e. >800) were considered associated with a bactericidal effect [4,22].

2.4. Treatment effectiveness and tolerability

The clinical effectiveness of daptomycin therapy was assessed at the end of treatment as 'cure', 'improvement', 'failure' or 'non-evaluable' [23]. 'Cure' was defined as (a) resolution of clinical signs and symptoms and/or no additional antibiotic therapy required or (b) infection cleared with a negative culture reported at the end of daptomycin therapy. 'Improved' was defined as partial resolution of clinical signs and symptoms and/or additional antibiotic therapy required at the end of daptomycin chemotherapy. The term 'clinical success' was used to describe patients with an outcome of 'cure' or 'improved'. 'Failure' was defined as (a) an inadequate response to daptomycin therapy (resistant, worsening or new/recurrent signs and symptoms), or (b) the need for a change in antibiotic therapy, or (c) a positive culture reported at the end of therapy. 'Non-evaluable' was recorded if there was insufficient information available to make the assessment. Adverse drug reactions observed during daptomycin administration were recorded, including alterations in laboratory examinations.

2.5. Statistical analyses

Data are presented as the mean ± standard deviation (S.D.) or median and range, according to the parameter described, and additional statistical computations (i.e. unpaired Student's *t*-test

Table 1
Demographic characteristics of 58 patients enrolled in the study.

Characteristic	Mean ± S.D. (median)[a]
Patients (*n*)	58
Male	38
Female	20
Age (years)	65.8 ± 14.5 (69)
Weight (kg)	70.6 ± 17.2 (69)
Serum creatinine (mg/dL)	0.99 ± 0.49 (0.90)
Daptomycin	
Total daily dose (mg)	495 ± 126 (500)
Daily dose (mg/kg) [median (range)]	7 (4–12)
Duration (days)	18 ± 8 (16)
Previous chemotherapy before daptomycin (*n*)	
Yes	40
No	18

S.D., standard deviation.
[a] Values are expressed as mean ± S.D. (median), unless otherwise stated.

with Welch's correction, Fisher's exact test) were performed using GraphPad Prism 5.0 (GraphPad Software Inc., La Jolla, CA). *P*-values of <0.05 were considered significant.

3. Results

3.1. Patients

Up to December 2010, 58 patients (38 men and 20 women) were enrolled; relevant demographic and clinical characteristics are reported in Tables 1 and 2. No significant differences were found between men and women. Forty individuals received one or more chemotherapeutic courses before daptomycin administration, including fluoroquinolones (*n* = 13), β-lactams (*n* = 10), glycopeptides (*n* = 9), rifampicin (*n* = 8) and linezolid (*n* = 4). The median daily doses of daptomycin were 525 mg and 513 mg (7 mg/kg and 8 mg/kg), in men and women, respectively, and only 2 and 10 patients received doses <6 mg/kg/day or >8 mg/kg/day, respectively. Plasma daptomycin levels at doses of 6–8 mg/kg/day are reported in Table 3. The median duration of drug administration was 18 days and 16 days in males and females, respectively (Table 1). Total daily doses of daptomycin were increased by 33–50% in four patients because of low C_{max} values. In these patients, a median 27.3% increase in the C_{max}/MIC value was observed after dose adjustment. The majority of patients received daptomycin for the treatment of bone infections (i.e. spondylodiscitis, prosthetic joint infection) and cardiovascular infections (i.e. endocarditis, infection of pacemaker or abdominal aorta prosthesis), followed by skin infections and septicaemia (8 and 7 individuals, respectively) (Table 2). Bacteraemia was diagnosed in 19 patients.

Among the 58 patients, clinical success was achieved in 46 patients (79.3%), of whom 7 subjects experienced clinical cure (12.1%); clinical status worsened during daptomycin administration in only 12 subjects (20.7%) (Table 2).

Severe adverse drug reactions or alterations of blood count and laboratory analyses were not observed in any of the patients. Moreover, abnormalities in markers of muscular toxicity (i.e. increase in serum creatine phosphokinase concentrations) were not reported.

3.2. Pharmacokinetic analysis

One-hundred and fifty-eight values of daptomycin plasma concentrations were available from 58 patients (median number of samples per patient, 2; range 1–7). In all samples the daptomycin concentration was above the limit of quantitation. Among the covariates, weight and serum creatinine were lacking in three and two subjects, respectively, hence they were imputed as median values from the general population of patients according to the individual's sex.

The selected basic model (no covariates included) was a one-compartment model with a mixed additive and proportional residual error model and interindividual variability (IIV) included in CL. A two-compartment structural model and IIV in V_d were tested but they could not be supported due to the sparse TDM sampling scheme.

During model development, covariates were included within the model to evaluate their possible effect on daptomycin pharmacokinetics. CL_{Cr} was identified as a significant covariate, influencing the CL of daptomycin (drop in OFV of 9.354 units), resulting in a decrease in IIV in drug CL from 54.8% to 20.7% and an overall improvement in parameter precision and residual error magnitude. Furthermore, η- and ε-shrinkage values accounted for 22.9% and 6.0%, respectively. Therefore, the final model was as follows: CL

Table 2
Site of infection, bacterial strains and clinical outcome in 58 patients treated with daptomycin.

Site of infection	No. of patients/median MIC (mg/L)				Presence of bacteraemia	Clinical outcome		No. of patients
	Staphylococcus spp.	*Streptococcus* spp.	*Enterococcus* spp.	Other		Success [a]	Failure	
Cardiovascular system	11/0.5	2/0.14	1/1.5	6/0.13	11	17	3	20
Bone	10/0.5	1/0.13	–	8/0.5	2	15	5	20
Skin	4/0.5	–	2/1.25	3/0.5	–	6	2	8
Septicaemia	5/0.38	–	1/3	1/0.13	5	6	1	7
Other	1/0.02	–	1/1.5	1/0.5	1	2	1	3
Total patients [*n* (%)]	31 (53.4)	3 (5.2)	5 (8.6)	19 (32.8)	19 (32.8)	46 (79.3)	12 (20.7)	58

MIC, minimum inhibitory concentration.
[a] Cure and improvement were considered as clinical success.

Table 3
Plasma concentrations of daptomycin measured at time points 0.5 (end of 30-min infusion), 1.0 and 23.5 h after the beginning of administration, according to drug dose levels (6–8 mg/kg).

Dose level (mg/kg/day)	No. of patients	Daptomycin plasma concentration (mg/L) [a]		
		0.5 h	1 h	23.5 h
6	18	35.9[b], 62.9[b]	39.1 ± 12.3 (39.7)	11.2 ± 7.5 (8.4)
7	13	47.1 ± 16.2 (47.5)	47.6 ± 23.2 (46.0)	14.4 ± 7.6 (12.3)
8	15	76.9 ± 9.8 (73.9)	52.7 ± 15.4 (53.1)	11.4 ± 5.4 (10.7)

[a] Values are expressed as the mean ± standard deviation (median) unless otherwise stated.
[b] Individual plasma concentrations of daptomycin.

Table 4
Parameter estimates from the final model together with results from a non-parametric bootstrap of 1000 data sets. The final model is as follows: $CL = THETA_1 \times (CL_{Cr}/80)^{THETA3}$, $V_d = THETA_2$.

Parameter	Final model	Bootstrap	
	Mean (RSE%)	Mean	95% CI
$THETA_1$ (L/h)	0.8016 (4.71)	0.8028	0.7177–0.8735
$THETA_2$ (L)	12.29 (5.41)	12.70	11.00–13.57
Proportional error (%)	36.28 (9.96)	32.27	26.66–41.73
Additive error (mg/L)	1.422 (96.83)	1.932	0.5181–3.035
$THETA_3$	0.2026 (35.46)	0.2184	0.0538–0.3572
IIV_{CL} (%)	20.74 (43.69)	22.24	11.70–30.56

CL, drug clearance; CL_{Cr}, individual creatinine clearance; V_d, volume of distribution; RSE%, relative standard error; 95% CI, 95% confidence interval; IIV_{CL}, interindividual variability in daptomycin clearance.

$(L/h) = 0.8016 \times (CL_{Cr}/80)^{0.2026}$, $V\,(L) = 12.29$, where $(CL_{Cr}/80)$ is the individual creatinine clearance standardised for the corresponding median value calculated in the present patients (Table 4). The mean ± S.D. values (median) of CL and V_d were estimated to be 0.80 ± 0.14 L/h (0.83 L/h) and 0.19 ± 0.05 L/kg (0.18 L/kg).

Furthermore, despite covariates such as patient's body weight, sex and age could be significant covariates for V_d, the introduction of IIV on V_d was highly uninformative and did not improve the model fit, hence it was decided not to further explore covariate effects on V_d. Diagnostic plots confirmed the appropriateness of the model in terms both of fixed and random effects (Figs. 1 and 2). The additive and proportional errors (with their relative standard errors) were estimated to be 1.42 mg/L (96.83%) and 36.28% (9.96%), respectively. Moreover, a decrease in CL_{Cr} of 30 mL/min with respect to the median value of 80 mL/min was associated with a decrease in daptomycin CL from 0.80 L/h to 0.73 L/h.

The C_{max} values were lower than expected on the basis of the previously published population PK model [14], even after accounting for the estimated increase in V_d in patients with an active infection.

3.3. Pharmacodynamics

MIC values were available for calculation of the AUC/MIC parameter in 41 of 58 patients. Although the C_{max} values were lower than expected, the median AUC/MIC value was 1158 [interquartile range (IQR), 824–1580], and 38 of 41 patients actually achieved an AUC/MIC value of >400, which is predictive of a bacteriostatic effect (Fig. 3). Of note, AUC/MIC values associated with 2-log bacterial killing (i.e. >800) were achieved in 31 of 41 patients (Fig. 3). More interestingly, in 23 patients with staphylococcal/streptococcal infections the median AUC/MIC was 1140 (IQR, 751–1548), showing that 20 and 17 subjects actually achieved AUC/MIC values >400 and >800, respectively (Fig. 3).

Of the 41 subjects with MIC values available, 31 experienced a clinical improvement or were cured (Fig. 3). However, eight patients did not receive any therapeutic benefit from chemotherapy even with high AUC/MIC values (>800), whereas clinical improvement was observed in two individuals who had AUC/MIC values <400 (Fig. 3). Finally, univariate and multivariate statistical analysis did not show any significant correlation among clinical outcome (i.e. clinical success versus failure) and the AUC/MIC parameter.

4. Discussion

The present study aimed at evaluating the population pharmacokinetics of daptomycin in patients affected by severe Gram-positive infections. The results demonstrated that daptomycin pharmacokinetics may be altered in patients with severe

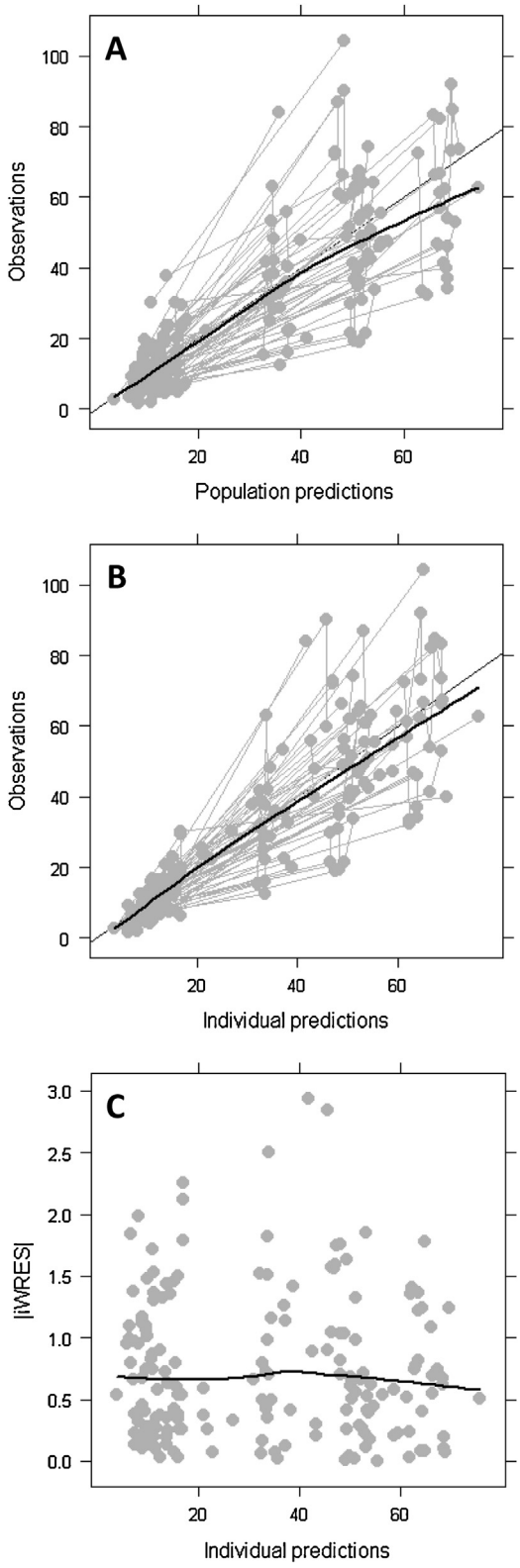

Fig. 1. Diagnostic plots for daptomycin population pharmacokinetic model obtained by simulating 1000 data sets on the basis of the original data set as template: (A and B) Plots of observed versus population (A) and individual (B) predictions; (C) plots of individual weighted residuals (iWRES) versus individual predicted plasma concentrations. Black thin and thick lines indicate lines of identity and linear regression lines, respectively (A and B) or Loess line (C).

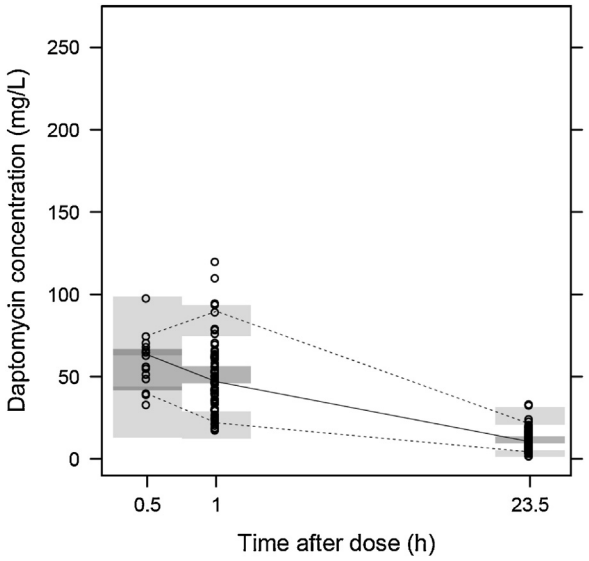

Fig. 2. Prediction-corrected visual predictive checks (90% prediction interval) based on the final population pharmacokinetic model superimposed on prediction-corrected observed daptomycin plasma concentrations. The figure shows the observed data (○), the median (solid line) and 5th and 95th percentiles (dotted lines) of the observed data, and the 95% confidence intervals around the simulated median (dark grey) and 5th and 95th percentiles (light grey).

infections, with evidence of lower plasma concentrations than those described previously in healthy volunteers and patients [14]. It is worth noting that the present study was based on data collected during the application of a TDM protocol, for which an instrumental chromatographic method for the measurement of plasma drug concentrations was available early at our university teaching hospital [16].

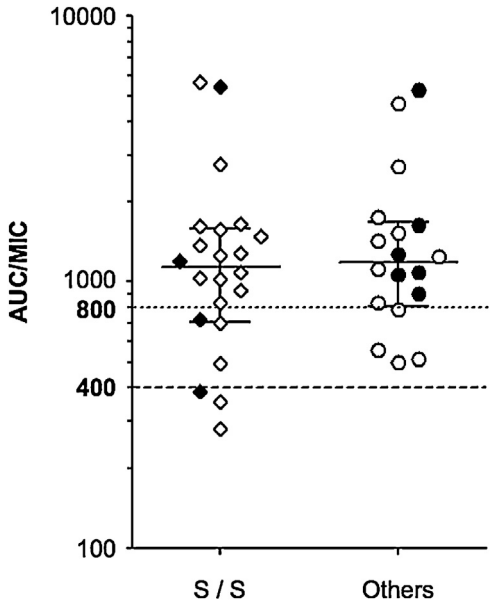

Fig. 3. Graphical representation of the ratio of the area under the concentration–time curve to minimum inhibitory concentration (AUC/MIC) values in 41 patients affected by staphylococcal/streptococcal infections (left, 23 subjects, 1 of them outside higher axis limit; diamonds) and other bacterial species (right, 18 subjects; circles). Lower cut-off values at which daptomycin exerts bacteriostatic (400) or bactericidal (800) effects are indicated by dashed and dotted lines, respectively. Filled symbols represent those 10 patients who were not cured or for whom clinical status did not improve after treatment with daptomycin. Lines and bars, median values and interquartile ranges.

Review of the drug monitoring database showed reduced C_{max} values in agreement with a previous study performed in cancer patients [15] but in contrast to those measured in the early trial including healthy volunteers [14]. Elaboration of a population PK model gave the opportunity to investigate the population pharmacokinetics of daptomycin and the influence of covariates on drug disposition. In comparison with the study of Dvorchik et al. [14], this analysis clearly showed that C_{max} values of daptomycin were lower than expected on the basis of the previous model, and the V_d was increased by ca. 23% with respect to the previous study (after correcting for differences in the covariate distribution between the studies). This suggests that the presence of severe Gram-positive infections is associated with an increase in V_d of daptomycin that is higher than that described by the previous model, despite it included the covariate 'presence of an acute infection'. On the basis of this, the daily dose of daptomycin should be increased up to 8–10 mg/kg to increase the probability of attainment of bactericidal concentrations in some selected patients affected by life-threatening infections.

Hyperdynamic states (i.e. infections) may significantly influence the disposition of daptomycin because of its hydrophilic characteristic. It is worth noting that in neutropenic patients with suspected or confirmed infections, the mean V_d of the drug was nearly identical to the value reported here (0.18 L/kg vs. 0.19 L/kg, respectively) [15]. Similar V_d values have also been recently observed in patients with thermal injuries (0.18 ± 0.05 L/kg) and in critically ill individuals undergoing continuous venovenous haemodialysis (0.20 ± 0.08 L/kg) [24,25]. Therefore, hyperdynamic states may be associated both with altered pharmacokinetics of daptomycin and with lower plasma concentrations that require a TDM-guided dose adjustment [26]. However, other factors may contribute to drug disposition (i.e. fever and sex): e.g., among the present patients, there was an indication that women had a reduced V_d compared with men, in accordance with the former population PK study [14], even if the final model did not take sex into account. However, it must be kept in mind that daptomycin CL is characterised by a non-negligible and unexplained IIV, as demonstrated in the present study (ca. 21%) and in a previous work (21%) [14].

Overall, data from TDM and those from previous PK analyses suggested that some subjects could be at risk of reduced treatment effectiveness. For example, AUC/MIC values were <400 (the threshold associated with a bacteriostatic effect) [22] in only 3 individuals (in agreement with previous results) [15], whilst 10 patients had AUC/MIC values <800, which is considered the minimum value for a 2-log killing effect. The described alteration of drug pharmacokinetics and the high MIC values (≥1 mg/L) of some bacterial strains (including *S. aureus*) could be responsible for these low AUC/MIC values [27,28], despite 19 of these 23 patients experiencing a clinical improvement or cure. The lack of a significant association between AUC/MIC values and clinical outcome in the present population of patients may depend on the wide heterogeneity of the patients, including patient's health status and severity of diseases, previous pharmacological treatments, different daily dosages and length of drug administration. Furthermore, a limitation of this study, as other studies, is the measurement of total rather than free drug concentrations in plasma [14,26].

From a technical point of view, it is worth noting that the present one-compartment model has a better performance with respect to a two-compartment model, and this could depend on the scheme of blood withdrawals adopted at our university hospital for the daptomycin TDM protocol. In fact, measurement of peak and trough plasma concentrations was judged the most informative in terms of treatment effectiveness (in association with MIC values) and tolerability [29,30]. It is likely that a dense sampling schedule could offer better results in terms of model development. However, it is worth noting that the present study achieves similar results with

respect to those previously reported and discussed above, suggesting that population PK analyses may be successfully applied in a clinical context on the basis of a TDM protocol. Future patients who receive daptomycin will be added to the present population in order to increase the model performance and to improve the analysis of covariate effects on drug pharmacokinetics.

In conclusion, patients affected by severe Gram-positive infections may display an altered daptomycin disposition, which is characterised by plasma concentrations lower than those measured in earlier studies. The present population PK analysis has allowed the elaboration of a model that predicts higher V_d with respect to that reported in earlier population PK models. Compared with the available literature, the present results suggest that the observed alteration in daptomycin pharmacokinetics could be due to the presence of infections. Therefore, an increase in daily doses (up to 8–10 mg/kg) should be considered according to the severity of the infection and patient's clinical condition. Finally, the present PK model may be transferred in clinical settings to guide therapies in patients with severe infections.

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Competing interests: None declared.

Ethical approval: The Ethics Committee of Azienda Ospedaliero Universitaria Pisana (Pisa, Italy) approved the study protocol [protocol no. 55945, 24 September 2009]. All of the patients gave their written informed consent before enrolment in the study.

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