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Abstract: Daptomycin has shown activity against a wide range of Gram-positive bacteria, however, the approved dosages usually seem insufficient for critically ill patients. The aim of this study was to develop a population pharmacokinetic model for daptomycin in critically ill patients and to estimate the success of the therapy by applying pharmacokinetic/pharmacodynamic (PK/PD) criteria. Sixteen intensive care unit patients were included, four of whom underwent continuous renal replacement therapies (CRRT). Blood and, when necessary, effluent samples were drawn after daptomycin administration at previously defined time points. A population approach using NONMEM 7.3 was performed to analyse data. Monte Carlo simulations were executed to evaluate the suitability of different dosage regimens. The probabilities of achieving the PK/PD target value associated with treatment success (AUC24/MIC ≥ 666) and to reach daptomycin concentrations linked to toxicity (Cminss ≥ 24.3 mg/L) were calculated. The pharmacokinetics of daptomycin was best described by a one-compartment model. Elimination was conditioned by the creatinine clearance (Clcr) and also by the extra-corporeal clearance when patients were subjected to CRRT. The PK/PD analysis confirmed that 280 and 420 mg/qd dosages would not be enough to achieve high probabilities of target attainment for MIC values ≥ 1 mg/L in patients with Clcr > 60 mL/min or in subjects with lower Clcrs but receiving CRRT. In these patients, higher dosages (560-840 mg/qd) should be needed. When treating infections due to MIC values ≥ 4 mg/L, even the highest dose would be insufficient.

Highlights

1. A population PK model for daptomycin in critically ill patients was performed
2. Drug clearance was conditioned by creatinine clearance and extracorporeal clearance
3. PK/PD analysis showed that, with the approved dosages, patients are often underdosed
4. Dose recommendations should consider renal function and the use of renal replacement therapies

Population pharmacokinetics of daptomycin in critically ill patients

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Abstract

Daptomycin has shown activity against a wide range of Gram-positive bacteria, however, the approved dosages usually seem insufficient for critically ill patients. The aim of this study was to develop a population pharmacokinetic model for daptomycin in critically ill patients and to estimate the success of the therapy by applying pharmacokinetic/pharmacodynamic (PK/PD) criteria. Sixteen intensive care unit patients were included, four of whom underwent continuous renal replacement therapies (CRRT). Blood and, when necessary, effluent samples were drawn after daptomycin administration at previously defined time points. A population approach using NONMEM 7.3 was performed to analyse data. Monte Carlo simulations were executed to evaluate the suitability of different dosage regimens. The probabilities of achieving the PK/PD target value associated with treatment success ($AUC_{24}/MIC \geq 666$) and to reach daptomycin concentrations linked to toxicity ($Cmin_{ss} \geq 24.3$ mg/L) were calculated. The pharmacokinetics of daptomycin was best described by a one-compartment model. Elimination was conditioned by the creatinine clearance (Clcr) and also by the extra-corporeal clearance when patients were subjected to CRRT. The PK/PD analysis confirmed that 280 and 420 mg/qd dosages would not be enough to achieve high probabilities of target attainment for MIC values ≥ 1 mg/L in patients with Clcr > 60 mL/min or in subjects with lower Clcrs but receiving CRRT. In these patients, higher dosages (560-840 mg/qd) should be needed. When treating infections due to MIC values ≥ 4 mg/L, even the highest dose would be insufficient.

Keywords: Daptomycin; pharmacokinetics; critically ill; pharmacokinetic/pharmacodynamic analysis; continuous renal replacement therapies

Abbreviations

SSTI: Skin and soft tissue infection

CRRT: Continuous renal replacement therapies

PK: Pharmacokinetic

PK/PD: Pharmacokinetic/pharmacodynamics

APACHE II: Acute Physiology and Chronic Health Evaluation II

Clcr: Creatinine clearance

HPLC: High Performance Liquid Chromatography

GOF: Goodness of fit

RSE: Relative standard errors

IIV: Inter-individual variability

Sc: Sieving coefficient

CL_{EC}: Extra-corporeal clearance

Qef: Effluent flow

VPC: Visual Predictive Check

SCM: Stepwise covariate model building

CWRES: Conditioned weighted residual errors

IWRES: Individual weighted residual errors

TAD: Time after dose

AUC_{24}: Area under the curve over 24 hours

PTA: Probability of target attainment

CFR: Cumulative fraction of response

CL: Clearance; CL_{NR}: Non-renal clearance; CL_R: Renal clearance

V: Volume of distribution

CPK: Creatinine-phosphokinase

1. Introduction

Daptomycin is a lipopeptide antibiotic with activity against a wide range of Gram-positive microorganisms, including methicillin resistant *Staphylococcus aureus* (MRSA) and vancomycin-susceptible *Enterococcus*. It is currently approved for the treatment of complicated skin and soft tissue infections (SSTI), right-sided infective endocarditis and *S. aureus* bacteraemia [1-3]. Daptomycin is mostly distributed to extracellular fluid and is highly bound to serum proteins (around 90%). Since it is mainly eliminated by the kidneys, dosage adjustment is recommended in patients with renal failure. Additionally, it has demonstrated a linear pharmacokinetic (PK) profile in the dose range of 4-12 mg/kg/qd [3,4].

This antibiotic is commonly used for empirical therapy in the critically ill, as Gram-positive infections are frequent in patients in the intensive care unit (ICU) [5]. The pharmacokinetics of antibiotics, especially hydrophilic ones, is usually altered in these subjects. Some of the changes include increased volume of distribution (V), altered protein binding, augmented renal clearance, impaired renal clearance and hepatic dysfunction. The alteration of the PK behaviour might be due to several pathophysiological changes present during illness [6-8]. Moreover, concomitant treatment used to improve medical outcomes, such as life sustaining devices (e.g. continuous renal replacement therapies, CRRT), may also alter the PK profile.

Therefore, ICU patients often have a high PK variability and selecting the most suitable antimicrobial dosage usually becomes a challenge [8]. In this scenario, building a population PK model is a useful tool to identify and quantify causes of variability and to then determine the optimal posology for each patient by applying pharmacokinetic and pharmacodynamic (PK/PD) analysis. Consequently, the main goal of this research study was to develop a PK model for daptomycin in critically ill patients and to carry out a PK/PD analysis to establish optimal dosages for each subject in order to explain the efficacy and toxicity profiles.

2. Patients and methods

2.1. Study design and settings

An observational multi-centre open-label prospective study was carried out in the ICU at University Hospital Araba (Vitoria-Gasteiz, Spain) and Hospital Clínic (Barcelona, Spain). The Ethics Committees of both institutions approved the study. Written informed consent prior to enrolment was required from all patients, or their legal representatives. Patients were eligible for inclusion if they i) were admitted to the ICU; ii) had an infection probably caused by Gram-positive microorganisms and subsequent treatment with daptomycin; iii) gave informed consent and iv) if it was possible to obtain plasma samples and also effluent samples from the extracorporeal circuit when undergoing CRRT. The exclusion criteria were age < 18 years, pregnancy and hypersensitivity to daptomycin or any of the excipients.

Table 1 shows both demographic and biochemical data of the patient population, together with the APACHE II health score (Acute Physiology and Chronic Health Evaluation II). Creatinine clearance (Clcr) was estimated for each subject using the Cockcroft-Gault equation. For the estimation of the Clcr the actual body weight was used in non-obese patients, whereas the ideal body weight was used in those with BMI $\geq$ 30 kg/m^2 [9].

2.2. Drug administration, sampling procedure and analysis

Daptomycin (Cubicin®) was administered via short intravenous infusion (from 20 to 60 min) at a dose ranging from 350 to 850 mg every 24 or 48 hours. Before starting sample collection, a mean of 4 previous doses was administered. Blood samples were drawn at pre-dose and the end of the infusion. Moreover, one sample was taken within the interval of 4 to 8 h, a second at 10 to 14 h, and another at 24 h and 48 h (when dosed every 48 h). Each sample was immediately centrifuged at 3,000 rpm for 10 min to collect the plasma, which was frozen at -80ºC until analysis. Effluent samples were taken at the same time points and directly stored at -80ºC.

Daptomycin in samples was quantified by a formerly validated High Performance Liquid Chromatography (HPLC) technique with ultraviolet detection. Plasma sample preparation consisted of a protein precipitation step with acetonitrile, where internal standard (propyl 4-hydroxybenzoate) was previously diluted. Afterwards, they were centrifuged (10 min at 12,000 rpm) and the supernatants were injected into the HPLC system. Separation was performed with a Symmetry® C8 column (4.6x150 mm x 5 µm). Linearity in plasma samples was settled over the expected concentration range (2.5-150 µg/mL), whilst for effluent samples, linearity ranged from 0.1 to 20 µg/mL. Intra and inter-day accuracy and precision assays were set at the limits of quantification, as well as at three concentrations in the established range (7, 40 and 120 µg/mL for plasma and 0.3, 2 and 16 µg/mL for the effluent). The calculated concentration never deviated more than 15% from the nominal concentration. The intra-day and inter-day precision, expressed as CV, was always below 15%. The daptomycin standard was kindly provided by Novartis Pharma AG.

2.3. Population pharmacokinetic model

2.3.1. Base model

A population pharmacokinetic model was built using the first-order conditional estimation method with interaction (FOCE-I) utilizing NONMEM 7.3 [10]. The disposition of the total drug plasma concentration was studied using compartmental models. Based on the distribution of the residuals, the data was logarithmically transformed. To evaluate the model, the decrease in objective function value (OFV =-2 log-likelihood), the relative standard errors (RSE) for the parameters and the goodness-of-fit (GOF) plots were considered. The inter-individual variability (IIV) was modelled exponentially and the residual error with an additive model on a logarithmic scale. Moreover, the significance of the off-diagonal elements of the omega variance-covariance matrix was explored.

2.3.2. Covariate selection

The effect of patient characteristics on the pharmacokinetic parameters was studied, in order to minimise the IIV and support a better fit. Thus, demographic and biochemical data was evaluated for inclusion in the model (**table 1**). Moreover, the extracorporeal clearance (CL_{EC}), set as effluent flow (Q_{ef}) multiplied by the sieving coefficient (Sc), was also taken into account. The Sc is defined as the fraction of drug eliminated across the membrane during CRRT, and was estimated as the mean ratio of the daptomycin effluent to plasma concentrations at each time-point. The inclusion of covariates in the model was normalized by the median value of the population studied. The selection of covariates was carried out using stepwise covariate model building procedure (SCM tool in PsN 4.7.0). This is based on a forward inclusion approach followed by a backward deletion. The significance levels used to incorporate the model and to keep a covariate in the model were set to 0.05 and 0.01 in the forward inclusion and backward deletion approaches, respectively. GOF plots were useful to support the covariate selection.

2.3.3. Model evaluation

The model development and evaluation was guided on the basis of plausibility and parameter estimate precision, as well as the following GOF plots: the dependent variable (logarithmic transformation of the observations) against population and individual predictions, conditioned weighted residual errors (CWRES) vs. time after dose (TAD) and the individual weighted residual errors (IWRES) vs. individual predictions. Furthermore, a prediction-and-variability-corrected VPC (pvcVPC) was plotted in order to determine the suitability of the selected model, using xpose4 package in R 3.4.0 [11]. Thereby, using the VPC tool in PsN 4.7.0, data from 1,000 virtual patients was simulated for the daptomycin concentration, based on the final model and the same study design. Both observed and simulated data was divided into 5 bins by ranges of TAD (h) and their 5^{th}, 50^{th} and 95^{th} percentiles were calculated and compared. Moreover, the parameter precision was evaluated by running a 2,000-data set bootstrap (Bootstrap tool in PsN 4.7.0). Pirana v. 2.9.5 software was used to organise the model building and evaluation process [12].

2.4. Monte Carlo simulation

2.4.1. Pharmacokinetic/pharmacodynamic analysis

Probability of Target Attainment (PTA) estimation

PTA is understood as the probability of achieving a specific PK/PD index related to the efficacy of an antibiotic treatment at a certain pathogen susceptibility (minimum inhibitory concentration, MIC). In order to estimate the PTA, 5,000 subject simulations were performed over a range of doubling MICs between 0.25 and 4 mg/L and for different dosage regimens: 280, 420, 560, 700 and 840 mg/qd. These doses would be the equivalent to 4, 6, 8, 10 and 12 mg/kg/qd, respectively, for a standard adult body weight of 70 kg.

As daptomycin shows concentration-dependent activity, the best indicator of its efficacy is the ratio of the area under the plasma concentration-time curve over 24 hours divided by the MIC (AUC_{24}/MIC) [13,14]. High probabilities of success are achieved when total-drug $AUC_{24}/MIC \geq 666$ [15].

In patients without CRRT, different Clcr values (ranging from 10 to 130 mL/min) were evaluated for the calculation of the PTAs. In patients receiving CRRT, Clcr values from 0 to 30 were included and CL_{EC} was also contemplated. The latter, was estimated from the Sc measured in patients (0.2±0.05) and considering 2 different Q_{ef} values (1.5 and 2.5 L/h, close to the lower and upper flows applied to these patients). Simulations were performed using the mlxR package on R 3.4.0 [16].

Calculation of the cumulative fraction of response (CFR)

CFR is defined as the expected population PTA for a specific drug dose and a specific population of microorganisms [17]. It allows us to determine the probability of a favourable outcome for a treatment taking into account the PTA for each MIC value and the MIC distribution of the bacterial population, when the susceptibility of a clinical pathogen is unknown.

Susceptibility data of all isolates from ICU inpatients at the University Hospital Araba from January 2013 to December 2015 was used to calculate CFR values for *Enterococcus faecalis, Enterococcus faecium, Staphylococcus epidermidis, Staphylococcus aureus* and Coagulase negative staphylococci (**table 2**). The susceptibility data was managed with Whonet [18] and the same scenarios as for estimating the PTA were evaluated.

For both PTA and CFR, values greater than or equal to 90% were considered optimal, while values lower than 90% but higher than 80% were linked to moderate probabilities of success [19].

2.4.2. Safety evaluation

Estimation of minimum concentration at steady-state ($Cmin_{ss}$)

The percentage of simulated patients that would reach plasma concentrations considered toxic ($Cmin_{ss} \geq 24.3$ mg/L) [20] was calculated to analyse safety profile by mxlR package in R [16].

3. Results

Sixteen critically ill patients, described in **table 1**, were included in the study (four of them underwent CRRT). Five plasma samples per patient were analysed, six when administering daptomycin every 48 hours. In ~~those~~ patients undergoing CRRT, the same amount of effluent samples were collected. The patients suffered from sepsis (n = 5), SSTI (n = 3), abdominal infections (n = 3), bacteraemia (n = 2) or other infections (n= 3).

The four patients subjected to CRRT underwent continuous venovenous hemodiafiltration. The blood flow rate was maintained between 150 and 180 mL/min and the effluent flow between 1,600 and 2,550 mL/h and replaced as clinically indicated. A negative water balance was maintained, from 50 to 200 mL/h.

3.1. Population pharmacokinetic model

3.1.1. Base model

Plasma concentrations (in log scale) were best described by a one-compartment model, characterized by drug total body clearance (CL) and apparent volume of distribution (V). The fit was verified by GOF plots (**Figure 1**). IIV was included exponentially for total CL and V, and no correlation was detected between them.

3.1.2. Covariate selection

The CL of daptomycin resulted in the sum of a non-renal (CL_{NR}) and a renal clearance (CL_R), dependent on Clcr. In subjects undergoing CRRT, their own CL_{EC} was included in the total CL. The inclusion of Clcr in the CL halved the unexplained IIV in CL (from 75% to 37%). SCM results confirmed these findings. No other covariate turned out to be relevant for inclusion in the model.

3.1.3. Model evaluation

GOF plots (**Figure 1**) showed no relevant trend in CWRES along TAD or IWRES along individual predictions. Likewise, they displayed a good correlation between population or individual prediction against the dependent variable. Moreover, RSE (%) and bootstrap results showed that parameters were accurately estimated (**table 3**). In addition, pvcVPC (**Figure 2**) also demonstrated a good correlation between raw data and data obtained by simulation with the final model.

3.2. Monte Carlo simulation

3.2.1. Pharmacokinetic/pharmacodynamic analysis

Probability of Target Attainment (PTA)

Table 4 shows the probability of achieving the target value for the PK/PD index ($AUC_{24}/MIC \geq 666$) for the simulated scenarios. Overall, the higher the dose and the lower the Clcr, the higher the PTA. For the same Clcr, lower probabilities of success were obtained in patients undergoing CRRT. In all simulated patients, the 280 mg/qd dose appears to be enough to cover infections caused by microorganisms with MICs ≤ 0.25 mg/L. For MICs of 1 mg/L, PTA values greater than 90% were obtained with the highest dose (840 mg/qd), except for patients with Clcrs of 130 mL/min. Infections caused by microorganisms with MICs ≥ 4 mg/L would be never covered by daptomycin.

Cumulative fraction of response (CFR)

Table 5 features calculated CFR values. None of the dosing regimens provided high probabilities of success for infections caused by *E. faecium*. In the case of *E. faecalis,* doses ≥ 560 mg may provide CFR values ≥ 90%, as far as patients show Clcr values ≤ 30 mL/min and they do not undergo CRRT. For the rest of microorganisms,

CFRs would only reach values related to efficacy in some situations, which would depend on the dose, Clcr and, when CRRT are applied, on CL_{EC}.

3.2.2. Safety evaluation

Minimum concentration at steady-state ($Cmin_{ss}$)

Table 6 shows the probability of achieving daptomycin $Cmin_{ss} \geq 24.3$ mg/L, associated with toxicity. For the same Clcr value, the probability of reaching concentrations related to toxic events is much lower in patients undergoing CRRT. It is remarkable that in patients without CRRT and Clcr ≤ 30 mL/min, high probabilities of reaching $Cmin_{ss}$ greater than 24.3 mg/L were obtained even with the lowest dose. In patients undergoing CRRT, the probability of reaching concentrations related to toxicity is considerably higher in subjects with an effluent flow of 1.5 L/h.

4. Discussion

In this study we have developed a population PK model of daptomycin for critically ill patients. This model has been applied to estimate the adequacy of different dosing regimens considering PK and PD criteria. To the best of our knowledge, this is the first population PK model that includes critically ill patients with and without CRRT, allowing for the observation of the effect of these continuous renal techniques on drug PK behaviour.

The PK of daptomycin has been previously described by both one [21-23] and two-compartment models [24-26]. In our study, plasma concentrations vs. time data was entered into a one-compartment model, as no improvement was found when applying a two-compartment model. The daptomycin elimination included both non-renal and renal clearance, the latter being conditioned by patients' Clcr. The influence of Clcr in daptomycin clearance has been widely documented before, and the high intrinsic inter-individual variability obtained in the final model developed for this parameter (IIV_{CL} = 37%) was consistent with studies published previously on critically ill patients [22,27].

Regarding patients undergoing CRRT, their own CL_{EC} value was included in the total body clearance equation, as daptomycin is partially eliminated by CRRT [28]. Mean CL_{EC} observed in the present study (0.43 L/h) was similar to that obtained in previous studies [29,30], which was nearly half of the mean daptomycin total CL shown in healthy volunteers (around 1 L/h) [21]. Therefore, the proportion of drug eliminated by extracorporeal techniques should be considered for dosing optimization.

It is well known that in critically ill patients drug distribution volumes are usually higher than in healthy volunteers, as a consequence of oedema, sepsis, decreased protein binding or liquid overload, to name a few. Moreover, due to the great heterogeneity observed among these patients, high inter-individual variability is detected [7]. In this regard, the distribution volume obtained in this study (12.3 L) is slightly higher than that observed in healthy volunteers and consistent with the distribution volume of daptomycin in critically ill patients reported by Di Paolo et.al [22] and Falcone et.al. [31] (12.9 L and 11.5 L, respectively).

The inclusion of patients' weight as a covariate did not improve the population PK model. This could be due to the small cohort size of the evaluated population, which might be the main limitation of this research paper. However, our findings are in accordance with other studies, where no relationship was found between weight and daptomycin CL or V [22,31].

Integrated PK/PD analysis and Monte Carlo Simulation is a very useful tool that allows us to optimize regimen dosing of antibiotics [32]. Considering the population model and the PK/PD analysis performed in this study, the selection of the most suitable daptomycin dose should be based not only on the susceptibility of the bacteria responsible for the infection, but also on the pharmacokinetic profile.

According to the simulations performed in this study, the approved dosage regimens of daptomycin (4 and 6 mg/kg/qd, which would be equivalent to 280 and 420 mg/qd for a standard adult body weight of 70 kg) would be insufficient to treat infections caused by microorganisms with MICs $\geq$ 4 mg/L, the clinical breakpoint determined for enterococci by the Clinical and Laboratory Standard Institute (CLSI) [33] and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [34]. Moreover, these dose levels would cover infections caused by microorganism with MICs of 1 mg/L (the clinical breakpoint for streptococci and staphylococci) when patients' Clcr is $\leq$ 30 mL/min and are not subjected to CRRT. These results are consistent with previous studies, which conclude that authorized daptomycin dosages usually seem to be insufficient for critically ill patients [22, 25,35]. In fact, in 2011, the Infectious Diseases Society of America (IDSA) guidelines recommended daily doses of daptomycin of 8-10 mg/kg in cases of endocarditis due to *MRSA* or complicated bacteraemia, and 10 mg/kg/qd, in combination with other antimicrobials, for persisting bacteraemia during treatment and/or failing vancomycin treatment [36]. This has been also observed by García de la Maria *et al.* in an experimental rabbit model for methicillin-resistant *Staphylococcus epidermidis* (MRSE) endocarditis [37].

In this study, daptomycin was administered as empirical treatment, and in the majority of the patients, microorganisms susceptible to this antibiotic were not found. This is why, susceptibility data of isolates in University Hospital Araba ICU inpatients was used to calculate CFR values (**table 5**). Daptomycin did not prove to be useful for infections caused by *E. faecium*. For the other microorganisms, the dose required to reach high CFR values would vary, depending on the patients' Clcr or whether they were undergoing CRRT or not. In this regard, we should bear in mind that sensitivity may vary over time and between countries as well as between areas or health centres [31].

Selecting the most favourable dosage for an antimicrobial requires not only maximizing efficacy, but also minimizing side effects or toxicity. For this antibiotic $Cmin_{ss}$ values above 24.3 mg/L have been associated with creatinine-phosphokinase (CPK) elevations, which may precede daptomycin-related muscle toxicity [20]. Therefore, increasing the daptomycin dosage may lead not only to increased efficacy, but also to higher probabilities of achieving toxicity related drug concentrations. However, we should also bear in mind that it is not only dosage that would compromise toxicity, but also the patients' characteristics that influence the drug's PK. As an example, **table 6** shows that the probabilities of reaching $Cmin_{ss} \geq 24.3$ mg/L in critically ill patients are higher when administering 280 mg/qd to patients with Clcr values of 10 mL/min (87%) or 30 mL/min (38%), than in those subjects with a Clcr value of 130 mL/min receiving 840 mg/qd (15%). Based on these results,

simulations considering the administration of daptomycin every 48 h were performed. PTA values higher than 90% for MICs of 1 mg/L were obtained only for patients without CRRT and Clcr ≤ 30 mL/min (data not shown). The results revealed that when administering 560 mg/q48h (if CLcr is 10 mL/min) or 840 mg/q48h (if CLcr is 30 mL/min), the probability of reaching $Cmin_{ss}$ levels ≥ 24.3 mg/L are 65% and 39%, respectively. These values are lower than those obtained for the same daily dose administered in a 24 h regimen (280 and 420 mg/qd), but still compromise safety.

Even though CPK levels are considered to be a sensitive marker of musculoskeletal damage related to daptomycin, it has recently been questioned whether high dosages are related to a greater risk of elevated CPK, as no significant differences were found between standard and higher dosages [34]. Moreover, another study in healthy volunteers concluded that a daptomycin dosage of 12 mg/kg once daily for 14 days was well tolerated, as no evidence of adverse effects were recorded [4]. Although in this study 3 patients had a $Cmin_{ss}$ value ≥ 24.3 mg/L, none of them, nor the other 13, experienced an increase in CPK levels (**table 1**).

According to the results obtained in this study and considering that the MIC values of the majority of isolated bacteria were ≥ 1 mg/L, standard antibiotic dosages would not be appropriate to treat patients with Clcr values ≥ 60 mL/min. Patients with Clcr values between 60 and 90 mL/min would require 700 mg/qd, while 840 mg/qd should be administered to patients with higher Clcr. Although higher probabilities of success are expected in subjects with Clcr ≤ 30 mL/min, probabilities of reaching concentrations of daptomycin linked to toxicity are high. Therefore, the risk-benefit balance of the therapy should be studied. For patients undergoing CRRT, the dosage should be at least 560 mg/qd, although it would depend on the CL_{EC} (conditioned by Sc and Q_{ef}).

It also needs to be taken into consideration that when the MIC value of the bacteria is available or when susceptibility distribution data in a hospital or area is known, dosing regimens should be determined considering this information.

5. Conclusions

A population PK model has been developed for daptomycin in critically ill patients. Logarithmically transformed data best suited a one-compartment model. Drug CL depended on Clcr, and in patients undergoing CRRT, CL was also dependent on the CL_{EC}. The influence of the patient's characteristics on the PK profile was related to differences in the estimated probabilities of success and toxicity. Therefore, individualization of daptomycin therapy is advisable in order to improve the success of therapy and reduce toxicity. The probability of reaching toxic concentrations was highly dependent on the CL, and not only on the dose.

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Declarations

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Competing Interests*:* None

Ethical Approval: The study was carried out in the ICU at University Hospital of Álava (Vitoria-Gasteiz, Spain) and Hospital Clínic (Barcelona, Spain). The Ethics Committees of both institutions approved the study.

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Fig 1. GOF plots obtained for the final model: Population predictions (PRED) [(a)] and individual predictions (IPRED) [(b)] against dependent variable (logarithmic transformation of observed daptomycin plasma concentrations (DV, µg/mL)); conditioned weighted residual errors (CWRES) versus time after dose (h) [(c)] and the individual weighted residual errors (IWRES) versus individual predictions[(d)].

Fig 2. Results from the pvcVPC from 0 to 24 h after dose. Dots correspond to the predicted-corrected observed concentrations (µg/mL). The continuous line represents the median, while the dashed lines correspond to the 5^{th} and 95^{th} observed percentiles. Simulation-based 95% CIs for the median and both 5^{th} and 95^{th} percentiles are displayed by dark and light grey shading, respectively.

Table 1. Hospital, demographic and biochemical data of the 16 patients included in the study and their APACHE II health score. UHA: University Hospital Araba; HC: Hospital Clinic; CRRT: Continuous renal replacement therapies; BMI: Body mass index; Clcr: creatinine clearance; GOT: glutamate oxalacetate transaminase; GPT: glutamate pyruvate transaminase; CPK: creatinine-phosphokinase; CL_{EC}: extracorporeal clearance.

Patient characteristic	**N/N***	**Median (Range)**
Hospital		
UHA (No CRRT/CRRT)	12/2	
HC (No CRRT/CRRT)	0/2	
Demographic data		
Age (years)	-	67 (48-83)
Sex (male/female)	7/9	-
Body weight (kg)	-	84 (52-100)
BMI (kg/m^2)	-	29.6 (20.3-42.2)
Biochemical data		
Creatinine (mg/dL)	-	0.95 (0.6-1.8)
Clcr (mL/min)	-	
No CRRT	-	66 (20-121)
CRRT	-	8 (0-54)
Glucose (mg/dL)	-	197 (106-299)
Haemoglobin (g/dL)	-	9.1 (7.2-11.7)
Haematocrit (%)	-	25.7 (21.0-33.2)
Albumin (g/dL)	-	2.7 (1.7-3.8)
Total proteins (g/dL)	-	5.3 (3.9-6.9)
Bilirubin (mg/dL)	-	0.7 (0.3-2.6)
Leukocytes ($/mm^3$)	-	13,100 (5,500-21,000)
GOT (UI/L)	-	25 (10-200)
GPT (UI/L)	-	38 (6-566)
CPK (U/L)	-	53 (7-520)
APACHE II	-	18 (7-30)
CL_{EC}[a] (L/h)		0.46 (0.32-0.48)

[a] Only for patients undergoing CRRT.

Table 2

Table 2. MIC distributions for daptomycin for *E. faecium, E. faecalis, S. epidermidis, S. aureus* and coagulase-negative staphylococci in the University Hospital Araba from January 2013 to December 2015.

Microorganism	Clinical break point MIC (mg/L) [a]	no. of isolates	% of strains inhibited at a MIC (mg/L) of					
			0.5	1	2	4	8	16
Enterococus faecium	4	18		17	38	39	6	
Enterococus faecalis	4	52	21	60	15	2		2
Staphylococcus epidermidis	1	18		100				
Staphylococcus aureus	1	58	26	74				
Coagulase-negative staphylococci	1	63	2	94	2		2	

[a] According to the Clinical and Laboratory Standard Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

Table 3

Table 3. Base and final population pharmacokinetic models estimates, shrinkage[a] values and bootstrap results for daptomycin after short-term intravenous infusion.

Parameter	Base model	Final model	Bootstrap
	Estimate (RSE (%))	Estimate (RSE (%))	median (5^{th}-95^{th} percentile)
CL (L/h) = CL_{NR} + CL_R+CL_{EC}[b]	0.491 (21) +CL_{EC}		
CL_{NR}		0.16 (54)	0.160 (0.013-0.324)
CL_R = Θ x (Clcr/49)		0.367 (20)	0.366 (0.239-0.527)
V(L)	12.5 (13)	12.30 (13)	12.31 (10.10-15.13)
IIV_{CL} (%)	74.6 (29)	36.7 (30)	32.5 (17.7-54.4)
IIV_{V} (%)	35.4 (25)	27.8 (30)	27.0 (11.9-42.8)
Residual $error\_{additive}$ (log-scale)	0.110	0.123 (17)	0.114 (0.086-0.153)

[a]CLηsh = 30%; VηsH = 10%; εsh = 11%

[b] Only for patients undergoing CRRT.The individual value of CL_{EC} was considered.

CL: Clearance; CL_{NR}: No-renal clearance; CL_R: Renal clearance; CL_{EC}: Extra-corporeal clearance; Clcr: Creatinine clearance; V: Volume of distribution; CRRT: Continuous renal replacement therapies; IIV: Inter-individual variability.

Table 4. PTA values (%) of daptomycin. Bold values represent PTA ≥ 90%. Italics correspond to PTA ≥ 80%.

Dose/day	**Clcr** (mL/min)	**NO CRRT**					**CRRT**									
							Q_{ef} 1.5 (L/h)					**Q_{ef} 2.5** (L/h)				
280 mg	0						**100**	**100**	35	1	0	**100**	*89*	5	0	0
	10	**100**	**100**	**99**	38	5	**100**	**99**	18	0	0	**100**	73	3	0	0
	30	**100**	**100**	61	12	2	**100**	*84*	6	0	0	**100**	40	1	0	0
	60	**100**	*86*	21	4	1										
	90	**100**	52	10	2	1										
	130	**91**	25	5	2	1										
420 mg	0						**100**	**100**	**96**	8	0	**100**	**100**	40	1	0
	10	**100**	**100**	**100**	*83*	18	**100**	**100**	*80*	4	0	**100**	**100**	25	0	0
	30	**100**	**100**	**96**	32	6	**100**	**100**	38	1	0	**100**	**97**	10	0	0
	60	**100**	**100**	55	11	2										
	90	**100**	**93**	26	5	2										
	130	**100**	63	13	3	1										
560 mg	0						**100**	**100**	**100**	35	1	**100**	**100**	*89*	5	0
	10	**100**	**100**	**100**	**99**	38	**100**	**100**	**99**	18	0	**100**	**100**	73	3	0
	30	**100**	**100**	**100**	61	12	**100**	**100**	*84*	6	0	**100**	**100**	40	1	0
	60	**100**	**100**	86	21	4										
	90	**100**	**100**	52	10	2										
	130	**100**	**91**	25	5	2										
700 mg	0						**100**	**100**	**100**	75	3	**100**	**100**	**99**	17	0
	10	**100**	**100**	**100**	**100**	64	**100**	**100**	**100**	47	1	**100**	**100**	**97**	10	0
	30	**100**	**100**	**100**	85	20	**100**	**100**	**99**	18	1	**100**	**100**	*80*	3	0
	60	**100**	**100**	**98**	36	7										
	90	**100**	**100**	80	17	4										
	130	**100**	**99**	43	8	2										
840 mg	0						**100**	**100**	**100**	**96**	8	**100**	**100**	**100**	40	1
	10	**100**	**100**	**100**	**100**	*83*	**100**	**100**	**100**	*80*	4	**100**	**100**	**100**	25	0
	30	**100**	**100**	**100**	**96**	32	**100**	**100**	**100**	38	1	**100**	**100**	**97**	10	0
	60	**100**	**100**	**100**	55	11										
	90	**100**	**100**	**93**	26	5										
	130	**100**	**100**	63	13	3										
MIC (mg/L)		**0.25**	**0.5**	**1**	**2**	**4**	**0.25**	**0.5**	**1**	**2**	**4**	**0.25**	**0.5**	**1**	**2**	**4**

Table 5

Table 5. CFR values (%) of daptomycin for different bacteria taking into consideration frequency distributions of MICs in the University Hospital Araba, from January 2013 to December 2015. Bold values represent CFR ≥ 90%. Italics correspond to CFR ≥ 80%.

		Dose (mg/day) **No CRRT**					**Dose** (mg/day) **CRRT**									
							Q_{ef} 1.5 (L/h)					**Q_{ef} 2.5** (L/h)				
Bacteria	**Clcr** (mL/min)	**280**	**420**	**560**	**700**	**840**	**280**	**420**	**560**	**700**	**840**	**280**	**420**	**560**	**700**	**840**
Enterococcus faecium	0						6	20	31	47	58	1	7	17	24	33
	10	34	57	71	*81*	*89*	3	15	24	36	50	0	4	14	20	27
	30	16	31	46	58	67	1	7	17	24	32	0	2	7	15	20
	60	6	14	25	34	43										
	90	3	7	14	21	28										
	130	2	4	7	11	17										
Enterococcus faecalis	0						42	*80*	*86*	**92**	**96**	22	45	75	*83*	*87*
	10	*86*	**94**	**97**	**97**	**98**	32	70	*83*	*88*	**93**	17	36	65	*81*	*85*
	30	60	*84*	**90**	**94**	**96**	21	44	72	*83*	*87*	9	26	45	69	*81*
	60	31	55	76	*85*	*89*										
	90	17	36	54	70	*81*										
	130	9	21	35	48	61										
Staphylococcus epidermidis	0						35	**96**	**100**	**100**	**100**	5	40	*89*	**99**	**100**
	10	**99**	**100**	**100**	**100**	**100**	18	*80*	**99**	**100**	**100**	3	25	73	**97**	**100**
	30	6	**96**	**100**	**100**	**100**	6	38	*84*	**99**	**100**	1	10	40	*80*	**97**
	60	21	55	*86*	**98**	**100**										
	90	10	26	52	*80*	**93**										
	130	5	13	25	43	63										
Staphylococcus aureus	0						52	**97**	**100**	**100**	**100**	27	56	**92**	**100**	**100**
	10	**99**	**100**	**100**	**100**	**100**	39	*85*	**100**	**100**	**100**	21	44	*80*	**98**	**100**
	30	71	**97**	**100**	**100**	**100**	26	54	*88*	**99**	**100**	11	33	55	*85*	**98**
	60	38	66	**90**	**98**	**100**										
	90	21	44	64	*83*	**95**										
	130	10	26	43	58	73										
Coagulase negative staphylococci	0						36	93	**98**	**98**	**99**	7	40	*86*	**97**	**98**
	10	**96**	**99**	**99**	**99**	**99**	19	78	**97**	**98**	**99**	4	26	72	**95**	**97**
	30	61	**94**	**98**	**99**	**99**	7	38	82	**96**	**98**	2	11	40	78	**94**
	60	22	54	*84*	**96**	**98**										
	90	11	27	52	76	**91**										
	130	5	13	26	43	63										

Table 6. Probability of attaining $Cmin_{ss}$ values ≥ 24.3 mg/L (%).

	Dose (mg/day) **No CRRT**					**Dose** (mg/day) **CRRT**									
						Q_{ef} 1.5 (L/h)					**Q_{ef} 2.5** (L/h)				
Clcr (mL/min)	**280**	**420**	**560**	**700**	**840**	**280**	**420**	**560**	**700**	**840**	**280**	**420**	**560**	**700**	**840**
0						12	45	75	88	94	2	8	21	38	54
10	87	98	99	100	100	6	26	51	72	83	1	4	12	24	38
30	38	67	84	92	96	2	8	21	36	50	0	2	5	10	17
60	12	25	39	52	63										
90	6	11	18	25	33										
130	3	6	9	12	15										

Figure 1

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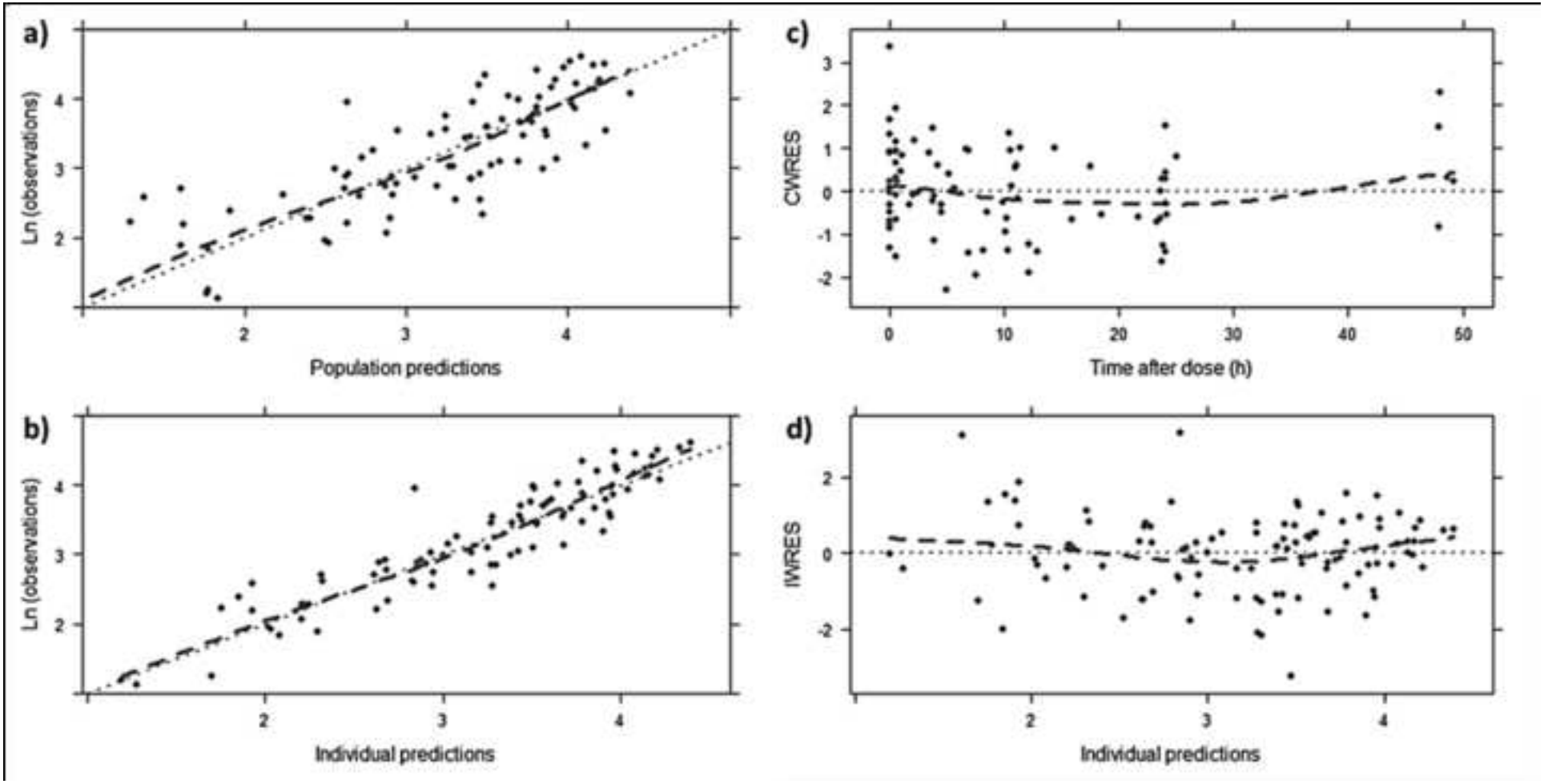

Figure 2

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