British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2017) **83** 498–509 498

PHARMACOKINETICS

Population pharmacokinetics of daptomycin in adult patients undergoing continuous renal replacement therapy

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Received 28 April 2016; **Revised** 22 July 2016; **Accepted** 6 September 2016

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Keywords CRRT, CVVHD, CVVHDF, daptomycin, population pharmacokinetics, renal replacement therapy

AIM

The objective of this population pharmacokinetic (PK) analysis was to provide guidance for the dosing interval of daptomycin in patients undergoing continuous renal replacement therapy (CRRT).

METHODS

A previously published population PK model for daptomycin was updated with data from patients undergoing continuous veno-venous haemodialysis (CVVHD; $n = 9$) and continuous veno-venous haemodiafiltration (CVVHDF; $n = 8$). Model-based simulations were performed to compare the 24 h AUC, C_{max} and C_{min} of daptomycin following various dosing regimens (4, 6, 8, 10, and 12 mg kg^{-1} every [Q] 24 h and Q48 h), with the safety and efficacy exposure references for *Staphylococcus aureus* bacteraemia/right-sided infective endocarditis.

RESULTS

The previously developed daptomycin structural population PK model could reasonably describe data from the patients on CRRT. The clearance in patients undergoing CVVHDF and CVVHD was estimated at 0.53 and 0.94 l h^{-1}, respectively, as compared with 0.75 l h^{-1} in patients with creatinine clearance (CrCl) ≥ 30 ml min^{-1}. Daptomycin Q24 h dosing in patients undergoing CRRT resulted in optimal exposure for efficacy, with AUC comparable to that in patients with CrCl ≥ 30 ml min^{-1}. In contrast, Q48 h dosing was associated with considerably lower $AUC_{24–48h}$ in all patients for doses up to 12 mg kg^{-1} and is therefore inappropriate.

CONCLUSIONS

Q24 h dosing of daptomycin up to 12 mg kg^{-1} provides comparable drug exposure in patients on CVVHD and in those with CrCl ≥ 30 ml min^{-1}. Daily daptomycin use up to 8 mg kg^{-1} doses are appropriate for patients on CVVHDF, but higher doses may increase the risk of toxicity.

DOI:10.1111/bcp.13131

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Daptomycin exhibits concentration-dependent bacterial killing.
- It demonstrates a linear PK profile when administered at once-daily doses of 6–12 mg kg^{-1} and is primarily excreted unchanged by the kidneys.
- Recommendation for dose interval adjustment is available for patients on haemodialysis or continuous ambulatory peritoneal dialysis (Q48 h dosing recommended), but not for patients on CRRT.

WHAT THIS STUDY ADDS

- In contrast to haemodialysis or continuous ambulatory peritoneal dialysis, Q48 h dosing in patients undergoing CRRT is likely to result in exposure levels below the reference range for efficacy every second day and thus be detrimental to patient outcomes.
- Q24 h dosing of daptomycin up to 12 mg kg^{-1} provides drug exposure in patients on CVVHD comparable to that in patients with CrCl $\geq$ 30 ml min^{-1}.
- Daptomycin doses up to 8 mg kg^{-1} Q24 h are appropriate for patients on CVVHDF, but higher doses may increase the risk of toxicity.

Introduction

Acute kidney injury in the hospital setting is a common complication often requiring renal replacement therapy [1, 2]. Among the dialysis modalities available in the intensive care unit (ICU), continuous renal replacement therapy (CRRT) is associated with better efficiency and patient tolerability than peritoneal dialysis or intermittent haemodialysis (HD) and often is a preferred and recommended choice in haemodynamically unstable patients [3–5]. Patients undergoing dialysis are at a 100-fold greater risk for invasive methicillin-resistant *Staphylococcus aureus* infections than the general population, with approximately 85% having invasive devices or catheters at the time of infection [6].

Critically ill patients may show changes in the pharmacokinetic (PK) properties of the drugs being administered, such as clearance, volume of distribution and plasma protein binding [7].

Daptomycin exhibits concentration-dependent bacterial killing, and its 24 h area under the plasma concentration–time curve (AUC) and maximum plasma concentration (C_{max}) are the most relevant parameters that correlate with its *in vivo* efficacy [8]. It demonstrates a linear PK profile when administered at once-daily doses of 6–12 mg kg^{-1} and is primarily excreted unchanged by the kidneys [9]. Therefore, the major factor affecting daptomycin clearance is renal clearance, with decreased renal function resulting in decreased daptomycin clearance.

In general, drugs that are eliminated primarily by the kidneys are efficiently removed during thrice weekly intermittent HD. However, on days without HD, drug elimination is minimal, necessitating dose adjustment. In contrast, CRRT results in removal of drugs and waste products continuously over 24 h and considerably more efficiently than intermittent HD [10, 11]. Therefore, dosing recommendations based on studies conducted in patients receiving conventional intermittent HD are inappropriate for patients undergoing CRRT. Continuous veno-venous HD (CVVHD) removes substances by ultrafiltration through a semipermeable membrane and continuous veno-venous haemodiafiltration (CVVHDF) by diffusion. The main determinants of drug clearance in CRRT are ultrafiltration flow rate (CVVHD), dialysate flow rate (CVVHDF) and filter membrane types (CVVHD and CVVHDF). Variations in these factors could explain differences in drug clearance and dosing recommendations [12].

Daptomycin is approved for use in complicated skin and skin structure infections at a dose of 4 mg kg^{-1} every 24 h (Q24 h) and in *S. aureus* bloodstream infections (*S. aureus* bacteraemia [SAB]), including right-sided infective endocarditis (RIE), at a dose of 6 mg kg^{-1} Q24 h [13, 14]. The same dose at a reduced frequency of every 48 h (Q48 h) is recommended for patients with a creatinine clearance (CrCl) $<$ 30 ml min^{-1} (with or without HD or continuous ambulatory peritoneal dialysis [CAPD]), but no formal recommendations have been approved in critically ill patients undergoing CRRT [14, 15]. This analysis aimed to estimate the clearance of daptomycin and to provide guidance for the dosing frequency of daptomycin in critically ill patients undergoing CRRT. Modifications to a previously published population PK model [15] for daptomycin are reported, with additional covariates of two CRRT subtypes (CVVHD and CVVHDF) according to the protocols applied in the respective studies [16, 17]. Simulations were performed using this updated model to assess the optimal daptomycin dosing frequency for critically ill patients undergoing CRRT, and the results were compared with those of previous studies [15–17].

Methods

Patients

In this analysis, demographic and daptomycin PK data from patients on CVVHD (n = 9) or CVVHDF (n = 8) included in two published studies by Corti *et al*. [16] and Khadzhynov *et al*. [17] were pooled with the PK database of the base model for daptomycin [15], which had been updated from a previously published and validated PK model for daptomycin [18]. In the base model [15], subjects were categorized as having CrCl $\geq$ 30 ml min^{-1} (n = 374), CrCl $<$ 30 ml min^{-1} but not-on-dialysis (n = 11), end-stage renal disease on HD Q48 h or thrice weekly (n = 40), and end-stage renal disease on CAPD (n = 14). This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

CRRT procedures

CVVHD and CVVHDF were performed using a Multifiltrate system (Fresenius Medical Care, Bad Homburg, Germany) with capillary haemofilter AV 1000s (polysulphone; surface area, 1.8 m^2) or a Prismaflex ST150 system (Gambro AB, Lund, Sweden) with capillary haemofilter AN69 ST (acrylonitrile-sodium-methyl sulphonate; surface area, 1.5 m^2) [16], or a Multifiltrate system (Fresenius Medical Care, Bad Homburg, Germany) with a high-flux dialyser (PF140H; surface area, 1.4 m^2; Gambro Dialysatoren GmbH, Hechingen, Germany) and using citrate as the anti-coagulation agent [17]. In the Corti *et al*. study, where possible, total combined filtration and dialysate rates were maintained between 30 and 40 ml kg^{-1} h^{-1} [16]. Unless prefilter substitution was necessary, the substitute solutions were supplied after the filter. Blood flow rates were set between 100 and 200 ml min^{-1} [16]. In the study by Khadzhynov *et al*., average blood and dialysate flow rates of 100 ml min^{-1} and 2000 ml h^{-1}, respectively, were targeted to achieve a dialysis dose > 30 ml kg^{-1} h^{-1} [17].

Population PK model

Population PK and PK-pharmacodynamic (PD) analyses for repeated-measures endpoints were conducted via the nonlinear mixed-effects modelling with a qualified installation of the nonlinear mixed effects modelling (NONMEM) software, version 7.2.0 (ICON Development Solutions, Hanover, MD, USA). Models were developed on a computer grid with multiple computer nodes. Each node runs the Linux operating system and utilizes the Intel® Fortran Compiler, version 12.0. The first-order conditional estimation with η–ε interaction (FOCEI) was employed for all model runs. Initial modelling was conducted using a PK model originally developed by Dvorchik *et al*. [18]; this model was thereafter updated by Chaves *et al*., with daptomycin PK data from patients with renal impairment [15]. The Chaves model was used as a framework for the analysis that is presented in this article [15]. PK data from the CRRT patients [16, 17] were added to the original dataset (that was used to develop the Chaves model), and the model was updated to describe the PK of daptomycin in patients undergoing CRRT.

The two-compartment, disposition model was parameterized in terms of total clearance (*CL*), central volume of distribution (V_c), peripheral volume of distribution (V_p), and inter-compartmental clearance (Q_2). Inter-individual variability of the parameters was described using an exponential error model or log-normal parameter distribution. The residual error was described using an additive model.

Although the focus of this analysis was to describe the PK of daptomycin in patients undergoing CRRT, the base model reported by Chaves *et al*. is briefly outlined [15]. This model included the following covariates on clearance: on dialysis, not-on-dialysis, temperature, CrCl, gender, high-/low-flux membrane, and disease subtypes (complicated/uncomplicated bacteraemia, complicated/uncomplicated RIE or left-sided infective endocarditis [LIE]) [15]. It also included covariates of body weight on V_p and Q_2 and infection on V_p. The base model could adequately describe the new data from patients on CRRT added to the database in the stage of subsequent model development; hence, no evaluation of the other structural models was carried out. A graphical evaluation of covariate-parameter relationships supported retaining the previous covariates from the base model, and no formal covariate search or backward elimination step on previously included covariates was undertaken.

In this analysis, CVVHD and CVVHDF were included as individual covariates on *CL*, V_c, V_p, and Q_2 to reflect the effect of the dialysis types on daptomycin PK.

The final model comprised separate equations (1)–(5), with some shared covariate effects (e.g. *CL* in different dialysis types); other equations were applied to all populations.

$$CL_{\text{Dialysis}i} = \theta_{\text{CL}}\left\{\frac{\text{Temp }(^{\circ}\text{C})}{37(^{\circ}\text{C})}\right\}^{\theta 9}\cdot\theta_8^{\text{Sex[Female]}}\cdot\theta_{13}^{DIAM[Low\ \ flux]}\cdot\theta_{14}^{DIAM[High\ \ flux]}\cdot\theta_{15}^{IEAC[IEAC\ 1]}\cdot \\ \cdot\ \theta_{16}^{\text{IEAC[IEAC 2]}}\cdot\theta_{17}^{\text{IEAC[IEAC 3]}}\cdot\theta_{18}^{\text{IEAC[IEAC 4]}}\cdot\theta_{19}^{\text{IEAC[IEAC 5]}}\cdot e^{\eta_{CLi}} \quad (1)$$

where θ_{CL} is θ_1, θ_{20}, θ_{21}, θ_{22}, and θ_{23} for patients on unknown dialysis, HD, CAPD, CVVHD and CVVHDF, respectively.

$$Vc_i = \theta_{vc}\cdot e^{\eta_{Vci}} \quad (2)$$

where θ_{Vc} is θ_{24}, θ_{25} and θ_2 for CVVHD, CVVHDF and all other patients, respectively.

$$\theta_i = \theta_{Q2}\left\{\frac{WT\ (kg)}{70\ (kg)}\right\}^{\theta_{10}}\cdot e^{\eta_{Qi}} \quad (3)$$

where θ_{Q2} is θ_{26}, θ_{27} and θ_3 for CVVHD, CVVHDF and all other patients, respectively.

$$V_{Pi} = \theta_{Vp}\cdot\left\{\frac{WT\ (kg)}{70\ (kg)}\right\}^{\theta_{11}}\cdot\theta_{12}^{INFN[INFN]}\cdot e^{\eta_{Vpi}} \quad (4)$$

where θ_{Vp} is θ_{28}, θ_{29} and θ_4 for CVVHD, CVVHDF and all other patients, respectively.

$$D1 = \theta_5 \quad (5)$$

$$CL_{\text{Not-on-dialysis}} = \theta_6 \left\{ \frac{CLC_0\ (\text{ml min}^{-1})}{80\ (\text{ml min}^{-1})} \right\}^{\theta 7} \cdot \left\{ \frac{\text{Temp (°C)}}{37(\text{°C})} \right\}^{\theta 9} \theta_8{}^{Sex[Female]} \cdot \theta_{15}{}^{\text{IEAC[IEAC 1]}} \cdot \theta_{16}{}^{\text{IEAC[IEAC 2]}} \cdot \cdot \theta_{17}{}^{\text{IEAC[IEAC 3]}} \cdot \theta_{18}{}^{\text{IEAC[IEAC 4]}} \cdot \theta_{19}{}^{\text{IEAC[IEAC 5]}} \cdot e^{\eta_{CLi}} \quad (6)$$

$$Cp_i = \frac{A1_i}{Vc_i} \quad (7)$$

The symbols represent the following parameters: η, NONMEM inter-individual error; θ, NONMEM fixed-effect parameter; *A*1, amount in central compartment (mg); *CL*, clearance; CL_{Dialysis}, clearance in dialysis patients (l h^{-1}); $CL_{\text{Not-on-dialysis}}$, clearance in not-on-dialysis patients (l h^{-1}); CLC_0, creatinine clearance at baseline (ml min^{-1}); *CP*, concentration in the central compartment (mg l^{-1}); *DIAM*, dialysis membrane; *D*1, duration of zero order infusion (h); *i*, individual; *INFN*, presence of Gram-positive infection; *TEMP*, temperature (°C); *WT*, weight at baseline (kg). IEAC, independent external adjudication committee (1 = LIE, 2 = complicated RIE, 3 = uncomplicated RIE, 4 = complicated bacteraemia and 5 = uncomplicated bacteraemia).

Simulations and references for drug exposure

As the number of patients was small in the CRRT subpopulations, a practical parametric bootstrap approach was used in the simulations. A set of individual parameters from the final model (MAP Bayes parameter estimates) with the same number of patients in the original study were sampled (with replacements). The mean $C_{\min}$, $C_{\max}$, AUC_{0-24}, and AUC_{24-48} were computed for each set, following different dosing regimens (4, 6, 8, 10, and 12 mg kg^{-1} Q24 h or Q48 h) in patients undergoing CVVHD or CVVHDF dialysis. Overall, 100 sets of parameters were drawn to calculate the variability in the PK summary parameters. The simulations were performed in R version v3.3 using the package RxODE v0.5 [19]. Simulated data were presented as means with 95% confidence intervals around the means.

Exposure references for efficacy and safety were derived from controlled clinical trials of daptomycin that demonstrated its efficacy in SAB [20] and tolerability at daily doses up to 12 mg kg^{-1} [9], as previously published [15]. Daptomycin exposure in patients representative of those in the pivotal IE/bacteraemia study [20], that is patients with SAB/RIE and CrCl > 30 ml min^{-1} treated with 6 mg kg^{-1} once daily, served as the efficacy exposure reference (AUC_{0-24h} of 465–761 μg h ml^{-1} and $C_{\max}$ of 66–112 μg ml^{-1}) [15]. The reference for safety threshold (AUC_{0-24h} of 1422 μg h ml^{-1} and $C_{\max}$ of 197 μg ml^{-1}) was the 75th percentile of the steady state AUC_{0-24h} reported in healthy volunteers with normal renal function who received daptomycin at 12 mg kg^{-1} Q24 h, the highest well-tolerated dose used in controlled clinical trials [9, 15]. From a clinical point of view, any individual patient with 24 h AUC or $C_{\max}$ above the upper efficacy boundary, but not exceeding the safety threshold, may achieve more clinical benefit without increased relevant safety risk. As $C_{\min} > 24.3$ μg ml^{-1} may be associated with elevated creatine phosphokinase (CPK) [21], $C_{\min}$ was used as an additional safety threshold in this investigation.

Results

Population PK model in patients on CRRT

Data from 459 adult patients from the Chaves *et al*. [15], Corti *et al*. [16] and Khadzhynov *et al*. [17] studies were included in the present population PK model. Of these patients, 385 had CrCl ≥ 30 ml min^{-1}, 40 were on HD, 14 were on CAPD, and 17 were on CRRT (CVVHD, 9; CVVHDF, 8). Three patients with unknown dialysis status were excluded from the analysis. A summary of the subject demographic and baseline characteristics of the final pooled dataset is presented in Table 1. Detailed demographic and baseline characteristics of the patients on CVVHD and CVVHDF are presented in supplementary Table S1. A concentration–time profile of 24 h after first dose administration in patients on CVVHD and CVVHDF was co-plotted with all the other patients in the pooled dataset in Figure 1.

The final model and parameter estimates were investigated using a predictive check method, with the basic premise that a model and parameters derived from an observed dataset should produce simulated data that are similar to the original observed data. The model evaluation results provided evidence that both the fixed- and random-effects components of the final model were reflective of the observed data. This CRRT final model, which included CVVHD and CVVHDF as covariates, describes the effect of renal clearance and dialysis type on the daptomycin PK parameters: *CL*, V_c, V_p, and Q_2. The model described the daptomycin concentration–time data reasonably well, allowing an estimation of the PK parameters and covariates affecting the PK properties of daptomycin. Plots of the observed *vs*. predicted concentrations (both individual and population) and of the conditional weighted residuals *vs*. time and *vs*. predicted values were well centred, with relatively few outliers (Figure 2). All final population model parameters are provided in supplementary Table S2.

Model-predicted vs. observed concentrations of daptomycin in patients undergoing CVVHD and CVVHDF

The final model describes the daptomycin concentration–time data, allowing estimation of the PK parameters and covariates affecting the PK profile of daptomycin. The

Table 1

Summary of patient demographic and baseline characteristics – pooled dataset

Characteristic	All subjects (*n* = 459)	CVVHD (*n* = 9)	CVVHDF (*n* = 8)
Body weight, kg			
Median (range)	75 (42.0–152.8)	74 (42, 100)	82 (63, 120)
Gender, *n* (%)			
Male	272 (59)	8 (89)	6 (75)
Female	187 (41)	1 (11)	2 (25)
Infection, *n* (%)			
Yes	273 (59)	9 (100)	8 (100)
No[a]	186 (41)	0 (0)	0 (0)
Body temperature, °C			
Median (range)	37.1 (35.1–40.1)	37.2 (36.5–38.3)	36.8 (35.8–37.9)
Dialysis membrane, *n* (%)			
Low flux	7 (2)	1 (11)	0 (0)
High flux	28 (6)	2 (22)	8 (100)
Not available	424 (92)	6 (67)	0 (0)
IEAC diagnosis, *n* (%)			
LIE	9 (2)	1 (11)	0 (0)
Complicated RIE	13 (3)	1 (11)	0 (0)
Uncomplicated RIE	5 (1)	0 (0)	0 (0)
Complicated bacteraemia	58 (13)	4 (45)	2 (25)
Uncomplicated bacteraemia	37 (8)	1 (11)	5 (63)
Not available	337 (73)	2 (22)	1 (12)

[a]Dataset included healthy volunteers and some subjects suspected of having infections.
Note: Three patients in whom it was unknown whether or not they were on dialysis were excluded from this analysis. IEAC, independent external adjudication committee; LIE, left-sided infective endocarditis; RIE, right-sided infective endocarditis.

individual and population predicted *vs*. observed concentrations of daptomycin in individual patients on CVVHD (*n* = 9; NONMEM ID, 5001–5009) and CVVHDF (*n* = 8; NONMEM ID, 6001–6005 and 6007–6009) are shown in Figure 3. In general, the population and individual predictions superimposed the observed data except for one subject (6003), where the model appeared to slightly overpredict the data on Day 1 but not on Days 3 and 5, most likely due to an experimental error on Day 1.

Model-predicted PK parameters of daptomycin in patients undergoing CVVHD and CVVHDF

The PK parameter values for a typical subject (70 kg male with CrCl ≥ 30 ml min^{-1}) were $CL_{\text{Not-on-dialysis}}$ = 0.75 l h^{-1}, V_c = 4.86 l, V_p = 3.20 l, and Q_2 = 3.69 l h^{-1} (Table 2). These point estimates of the parameters and the estimates of unexplained inter-individual variability were consistent with those estimated previously in the base model without the patients on CRRT shown in Table 2 (e.g. 11.4 ml h^{-1} kg^{-1}, or 0.80 l h^{-1} at 70 kg) [15]. This similarity was also noted for patients on HD (0.22 l h^{-1} *vs*. 3.43 ml h^{-1} kg^{-1} or 0.24 l h^{-1} at 70 kg) and CAPD (0.24 l h^{-1} *vs*. 2.98 ml h^{-1} kg^{-1} or 0.21 l h^{-1} at 70 kg) when compared with the base model [15]. These results increase the confidence in the estimation of the PK parameters for the CRRT patients.

Table 2 and Figure 4 show the model-predicted typical total *CL* of daptomycin in patients undergoing different dialysis methods *vs*. patients not on dialysis. In patients undergoing CVVHD, the *CL* (0.94 l h^{-1}) was 1.25-fold greater than that in patients with CrCl ≥ 30 ml min^{-1} (0.75 l h^{-1}) and was approximately 4.3 and 3.9-fold greater than that in patients on typical HD (0.22 l h^{-1}) and CAPD (0.24 l h^{-1}), respectively. The total *CL* in patients undergoing CVVHDF (0.53 l h^{-1}) was 29% lower than the estimated total *CL* in patients with CrCl ≥ 30 ml min^{-1} and was slightly more than 2-fold greater than that in typical HD and CAPD patients.

Interestingly, both V_c and V_p in both CVVHD and CVVHDF patients were higher than those of the not-on-dialysis patients. The Q_2 value in CVVHD was much higher than that of the not-on-dialysis patients; however, in CVVHDF, it was lower than that of the not-on-dialysis patients (Table 2). Individual estimated daptomycin PK parameters for CVVHD and CVVHDF patients are

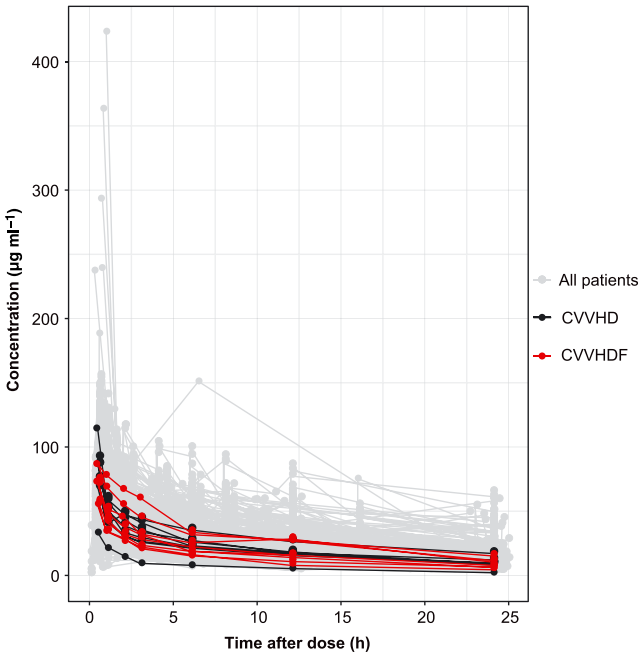

Figure 1

Concentration–time profile of 24 h post first-dose in patients on CVVHD and CVVHDF. CVVHD, continuous veno-venous haemodialysis; CVVHDF, continuous veno-venous haemodiafiltration

summarized in supplementary Table S3. Shrinkage between subject variability for CL, V_c, Q_2 and V_p was 10.0%, 7.52%, 28.5% and 40.9%, respectively. The residual inter-subject error was 11%.

Simulations of AUC in patients undergoing CVVHD and CVVHDF

The predicted means with 95% confidence intervals of the AUC at steady state (AUC_{ss}), C_{max} and C_{min} for Q24 h and Q48 h dosing in patients undergoing CRRT are summarized in Table 3.

Daptomycin dosing Q24 h at 4–12 mg kg^{-1} resulted in mean systemic exposures of 335–999 μg h ml^{-1} and 508–1475 μg h ml^{-1} in patients undergoing CVVHD and CVVHDF, respectively. If dosed at 4–12 mg kg^{-1} Q48 h, the mean systemic exposure was 272–799 μg h ml^{-1} on the first day after dosing and 63–182 μg h ml^{-1} on the second day in CVVHD patients, and the mean systemic exposure was 383–1129 μg h ml^{-1} and 126–361 μg h ml^{-1} on the first and second days, respectively, in CVVHDF patients.

The mean AUC_{ss} was predicted to be above the lower boundary of the efficacy threshold for SAB/RIE but below the safety threshold following a Q24 h dose in CVVHD (at 6–12 mg kg^{-1}) and CVVHDF (at 4–10 mg kg^{-1}) patients, without a potentially increased risk of toxicity. With a 95% CI, this holds true that, except for some CVVHDF patients receiving 10 mg kg^{-1} Q24 h may achieve higher AUC_{ss} than the safety threshold of 1422 μg h ml^{-1}.

In contrast, following Q48 h dosing, mean AUC_{ss} levels were expected to be above the lower boundary of the efficacy threshold for SAB/RIE but below the safety threshold in CVVHD (at 8–12 mg kg^{-1}) and CVVHDF (at 6–12 mg kg^{-1}) patients during the first day, but fall below the lower boundary of the efficacy threshold on the second day at all dose levels (4–12 mg kg^{-1}).

Simulations of C_{max} and C_{min} in patients undergoing CVVHD and CVVHDF

Daptomycin dosing Q24 h at 4–12 mg kg^{-1} resulted in a mean C_{max} of 46–137 μg ml^{-1} and 57–169 μg ml^{-1} in patients undergoing CVVHD and CVVHDF, respectively. With Q48 h dosing, daptomycin at 4–12 mg kg^{-1} resulted in a mean C_{max} of 42–124 μg ml^{-1} and 49–147 μg ml^{-1} in patients undergoing CVVHD and CVVHDF, respectively (Table 3). The mean C_{max} in the CVVHD (at 6–12 mg kg^{-1} Q24 h or at 8–12 mg kg^{-1} Q48 h) patients was above the lower boundary of the efficacy threshold for SAB/RIE, but below the safety threshold. Regardless of Q24 h or Q48 h dosing, CVVHDF (at 6–12 mg kg^{-1}) patients achieved mean C_{max} above the lower boundary of the efficacy threshold for SAB/RIE but below the safety threshold. Daptomycin dosing Q24 h at 4–12 mg kg^{-1} resulted in a mean C_{min} of 6.2–18.0 μg ml^{-1} and 11.0–32.2 μg ml^{-1} in patients undergoing CVVHD and CVVHDF, respectively. With Q48 h dosing, daptomycin at 4–12 mg kg^{-1} resulted in a mean C_{min} of 1.2–3.5 μg ml^{-1} and 3.1–8.8 μg ml^{-1} in patients undergoing CVVHD and CVVHDF, respectively (Table 3). Although the mean C_{min} is below 24.3 μg ml^{-1} in patients undergoing CVVHDF who received 6–8 mg kg^{-1} Q24 h, some patients will have a $C_{min} > 24.3$ μg ml^{-1} based on 95% CI. With Q24 h dosing, daptomycin at 10–12 mg kg^{-1} resulted in a mean $C_{min} > 24.3$ μg ml^{-1} in patients undergoing CVVHDF. All patients on CVVHD and CVVHDF receiving 4–12 mg kg^{-1} of daptomycin maintained a $C_{min} < 24.3$ μg ml^{-1} with daptomycin dosing Q48 h.

Discussion

A previously reported population PK model for daptomycin was used as a framework to analyse the PK profiles in patients undergoing CRRT. The present population PK model reasonably describes daptomycin concentration profiles in patients undergoing CVVHD or CVVHDF.

Our analysis suggests that the clearance in CVVHDF patients was 29% lower, while the clearance in CVVHD patients was 25% higher than that in patients with CrCl ≥ 30 ml min^{-1}. This finding was consistent with the reports of Churchwell *et al.* [22] and Clark *et al.* [23]. In the Churchwell *et al.* report [22], continuous haemofiltration and CVVHD led to higher daptomycin clearance compared with HD in a bovine model. The main factors affecting clearance were filter surface and ultrafiltrate and dialysis flow rates. In the Clark *et al.* report [23], drug clearance was significantly reduced in continuous haemofiltration by prefilter fluid replacement. This could possibly explain the lower daptomycin clearance observed in CVVHDF patients compared with those in CVVHD patients in the present analysis. In the study by Corti *et al.*, higher flow rates were used in CVVHD patients compared with those in CVVHDF patients, resulting in higher clearance in these patients [16]. Furthermore, prefilter solute substitution in four of their patients could also account for decreased

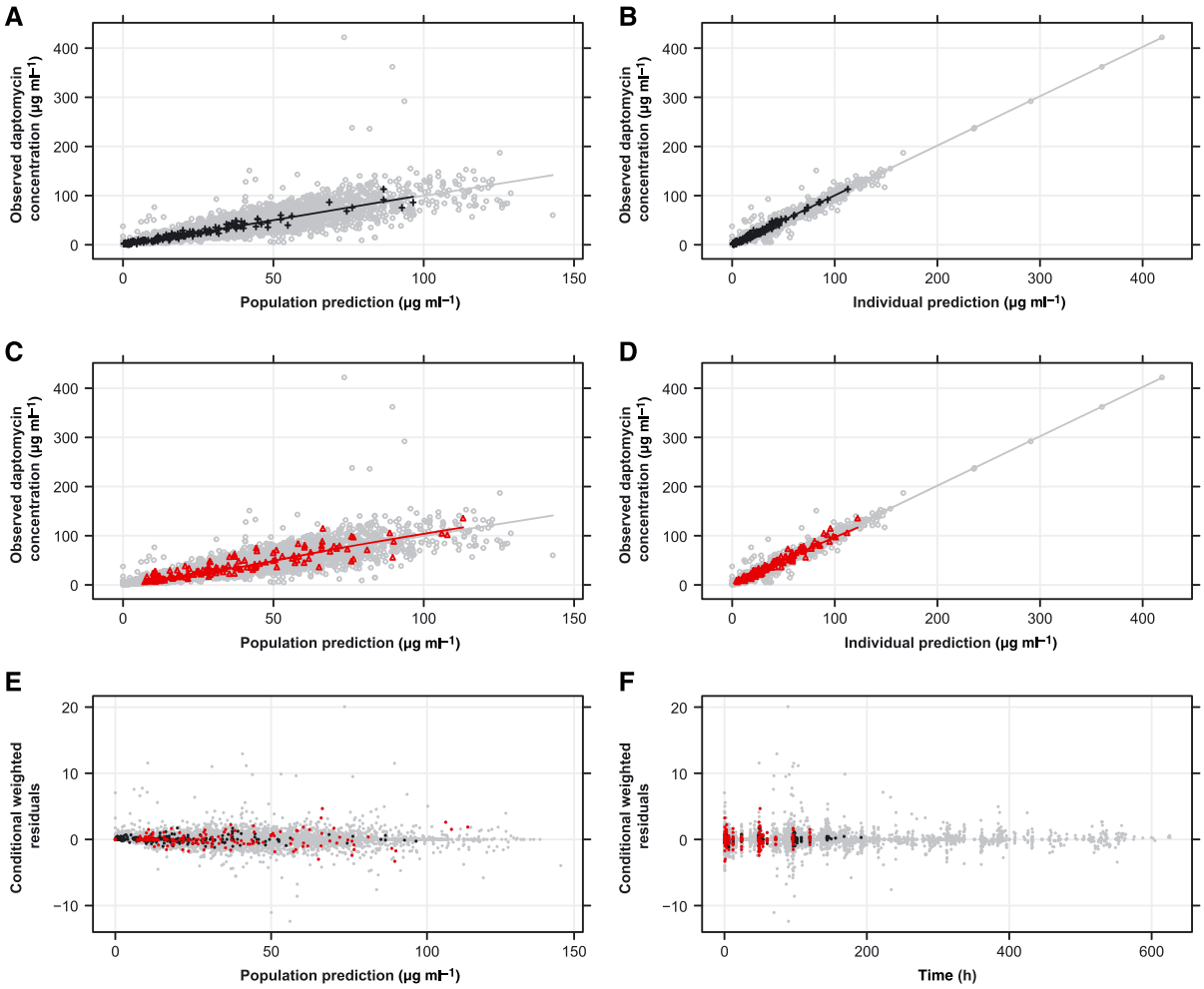

Figure 2

Goodness-of-fit diagnostic plots: A) DV *vs.* PRED for CVVHD patients; B) DV *vs.* IPRED for CVVHD patients; C) DV *vs.* PRED for CVVHDF patients; D) DV *vs.* IPRED for CVVHDF patients; E) Weighted residuals *vs.* PRED; F) Weighted residuals *vs.* time in h. Black cross, CVVHD patients; grey circle, all other patients in parts A & B. Red triangle, CVVHDF patients; grey circle, all other patients in parts C & D. Black circle, CVVHD patients; red circle, CVVHDF patients; grey circle, all other patients in parts E & F. CVVHD, continuous veno-venous haemodialysis; CVVHDF, continuous veno-venous haemodiafiltration; DV, observation; IPRED, individual prediction; PRED, population prediction

filter clearance. Although these results should be interpreted with caution due to the small sample size, the overall estimated higher clearance of daptomycin in CRRT patients is consistent with the CRRT procedure, wherein drugs and waste products are removed more efficiently on a continuous basis than with thrice-weekly intermittent HD [10, 11]. Previous studies have also shown that clearance of daptomycin by CRRT accounted for approximately 40–50% of the total drug clearance [16, 17, 24], which is comparable to the amount of drug cleared by the kidneys in patients with normal renal function (34–54%) [25].

With Q24 h dosing, mean AUC_{ss} in patients on CVVHD (at 6–12 mg kg^{-1}) and CVVHDF (at 4–10 mg kg^{-1}) was above the lower boundary of the efficacy threshold for SAB/RIE but below the safety threshold every day. Q48 h dosing resulted in appropriate drug levels in a similar proportion of patients in the first 24 h ($AUC_{0–24h}$); however, all patients receiving doses up to 12 mg kg^{-1} Q48 h had AUC below the reference range for efficacy in SAB/RIE every second day ($AUC_{24–48h}$). Drug concentrations decrease over time and are markedly lower on the second day after Q48 h dosing. Adequate efficacy is at risk every second day after Q48 h dosing.

Results of this analysis show that the difference in mean C_{max} following Q24 h and Q48 h dosing in patients undergoing the same CRRT method is < 15%. CVVHD (at 6–12 mg kg^{-1} Q24 h and at 8–12 mg kg^{-1} Q48 h) patients achieved C_{max} above the lower boundary of the efficacy threshold for SAB/RIE but below the safety threshold. Regardless of Q24 h or Q48 h dosing, CVVHDF (at 6–12 mg kg^{-1}) patients achieved mean C_{max} above the lower boundary of the efficacy threshold but below the safety threshold. Similarity in C_{max} between the Q24 h and Q48 h dosing regimens in this simulation is expected at the same dose level. However, the clinical relevance of 'missing' C_{max} every second day, which is associated with Q48 h dosing, has not been well investigated and its potential impact remains unclear. Nevertheless, Q24 h dosing of

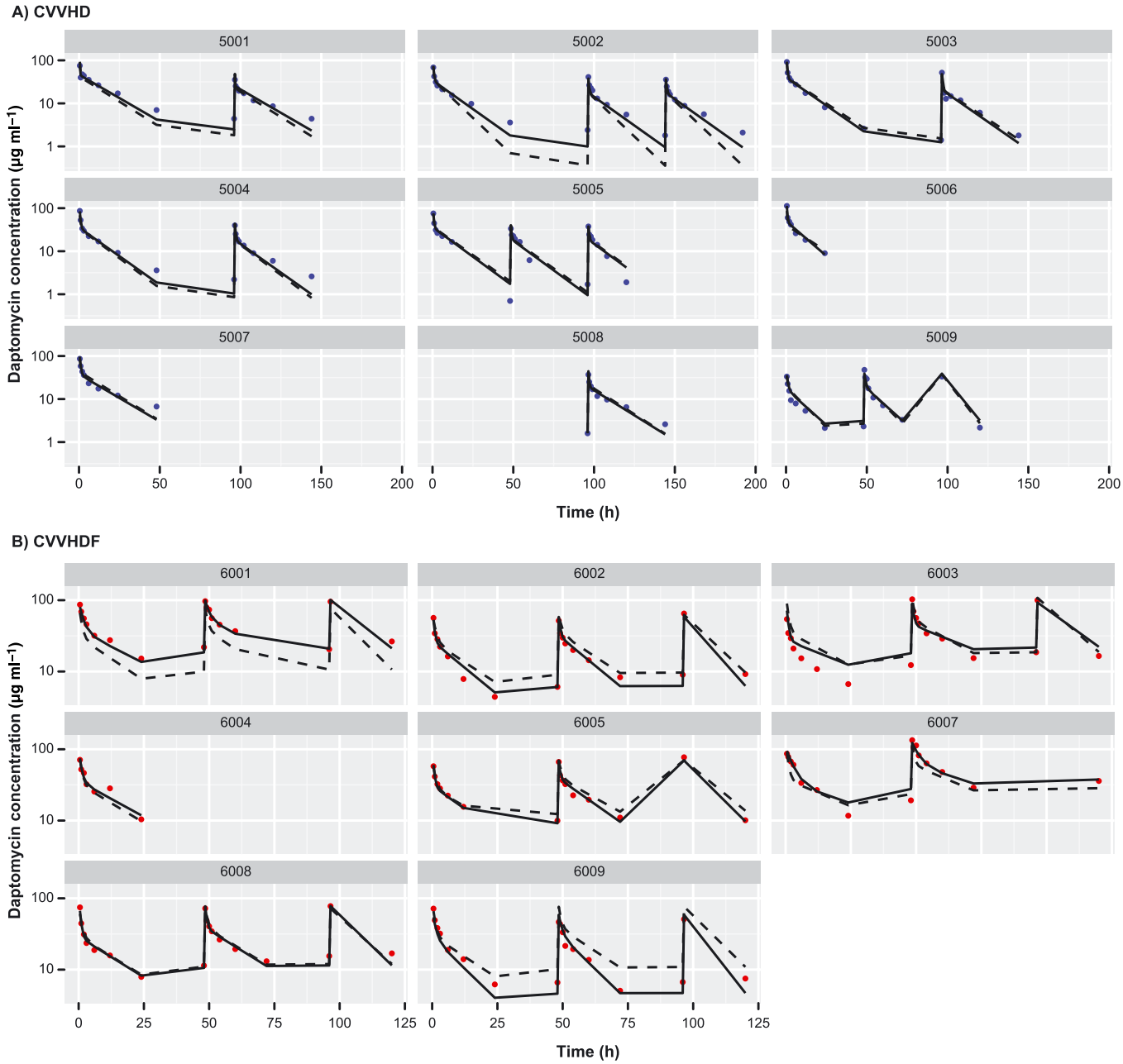

Figure 3

Model-predicted *vs.* observed daptomycin concentrations in patients undergoing CVVHD and CVVHDF. Solid line, individual prediction; dashed line, population prediction; blue dots in part A, observed data from the Khadzhynov *et al.* [17] (5001–5008) and Corti *et al.* [16] (5009) studies; red dots in part B, observed data from the Corti *et al.* study [16]. CVVHD, continuous veno-venous haemodialysis; CVVHDF, continuous veno-venous haemodiafiltration

daptomycin in CRRT patients provided comparable systemic exposure (AUC) to that with Q24 h dosing in patients with CrCl ≥ 30 ml min^{-1}. In contrast, daptomycin dosing Q48 h was associated with a high risk of considerably low systemic exposure every second day after dosing in CRRT patients and thus may be detrimental to clinical outcomes. This is valid for all daptomycin doses evaluated in controlled clinical trials – up to 12 mg kg^{-1}.

Excessive drug exposure may be a safety concern. The AUC and C_{max} results obtained indicate that doses up to 12 mg kg^{-1} in patients undergoing CVVHD do not exceed the defined safety threshold in randomized clinical trials, regardless of the dosing interval. Additionally, the mean C_{min} of doses up to 12 mg kg^{-1} in CVVHD also remain clearly below the safety threshold (> 24.3 µg ml^{-1}), which may be associated with a higher risk of CPK elevation in plasma.

Table 2

Daptomycin typical PK parameters by dialysis type

Dialysis type	Estimated parameters from final model				Estimated parameters from base model [15]			
	CL (l h^{-1}) (SE)	V_c (l) (SE)[a]	Q_2 (l h^{-1}) (SE)[a]	V_p (l) (SE)[a]	CL (l h^{-1}) (%CV)	V_c (l) (%CV)	Q_2 (l h^{-1}) (%CV)	V_p (l) (%CV)
Not-on-dialysis	0.75 (0.03)				0.75 (3)			
HD	0.22 (0.06)	4.86 (0.04)	3.69 (0.06)	3.20 (0.03)	0.24 (1)	4.89 (3%)	3.64 (4%)	3.19 (3%)
CAPD	0.24 (0.08)				0.21 (1)			
CVVHD	0.94 (0.06)	5.74 (0.08)	7.11 (0.15)	4.89 (0.07)	–	–	–	–
CVVHDF	0.53 (0.14)	6.53 (0.06)	2.88 (0.35)	3.85 (0.16)	–	–	–	–

[a]V_c, V_p and Q_2 were estimated separately for CVVHD and CVVHDF.
CAPD, continuous ambulatory peritoneal dialysis; CL, clearance; CVVHD, continuous veno-venous haemodialysis; CVVHDF, continuous veno-venous haemodiafiltration; HD, haemodialysis; PK, pharmacokinetics; Q_2, inter-compartmental clearance; SE, standard error; V_c, central volume of distribution; V_p, peripheral volume of distribution.

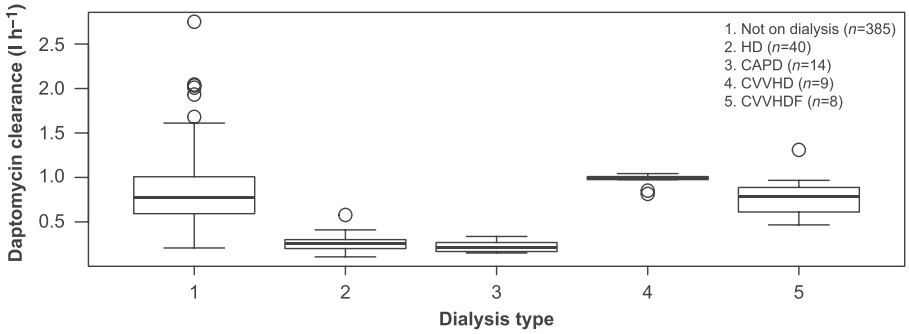

Figure 4

Model-predicted total clearance of daptomycin in different patient populations. Note: Three patients in whom it was unknown whether or not they were on dialysis were excluded from this analysis. Boxplot: whiskers (5th and 95th percentiles); box (25th and 75th percentiles); line (median). CAPD, continuous ambulatory peritoneal dialysis; CVVHD, continuous veno-venous haemodialysis; CVVHDF, continuous veno-venous haemodiafiltration; HD, haemodialysis

However, the mean AUC and C_{max} results in patients undergoing CVVHDF and receiving doses of 10–12 mg kg^{-1} Q24 h are close to or above these safety thresholds. Therefore, careful safety monitoring in patients undergoing CVVDHF is indicated, especially in clinical situations demanding the use of high daptomycin doses (≥10 mg kg^{-1}) once daily, as suggested in recent treatment guidelines and expert recommendations in Europe and the USA [26–31]. CPK levels in the blood are a sensitive marker of daptomycin-related muscle toxicity, and regular monitoring during therapy is recommended in all patients with renal impairment regardless of the dose regimen.

Other authors have also shown that Q24 h dosing is a more appropriate dosing strategy in patients undergoing CRRT without the risk of exposure above the target ranges [32, 33]. Preiswerk *et al.* [32] showed that daptomycin exposure in critically ill patients undergoing CRRT after once-daily dosing was similar to that in ICU patients with normal renal function. In the study by Rudiger *et al.* [33], nine critically ill patients undergoing CVVHDF were administered 4–6 mg kg^{-1} of daptomycin in a once-daily dosing regimen (effluent flow 30–40 ml kg^{-1} h^{-1}). No daptomycin accumulation was seen in any of the patients. The C_{max} and C_{min} were rather variable, and ranged between 24.7–69.7 μg ml^{-1} and 2.7–11.9 μg ml^{-1}, respectively, with the 4 mg kg^{-1}/day dose (n = 4); between 34.7–35.7 μg ml^{-1} and 3–3.7 μg ml^{-1}, respectively, with the 5 mg kg^{-1}/day dose (n = 2); and between 20.5–61.7 μg ml^{-1} and 1.5–15.9 μg ml^{-1}, respectively, with the 6 mg kg^{-1}/day dose (n = 2). Based on these findings, the authors concluded that 6 mg kg^{-1} Q24 h could be insufficient in patients undergoing CVVHDF compared with the plasma concentrations attained in healthy volunteers. Overall, our results are largely consistent with those from Preiswerk *et al.* [32] and Rudiger *et al.* [33], who also concluded that daily-dosing regimens with daptomycin are more appropriate than dosing every second day in CRRT patients.

Contrary to the aforementioned Q24 h dosing recommendations, a few authors have recommended Q48 h dosing

Table 3

Simulation of AUC, C_{max} and C_{min} in patients on CVVHD and CVVHDF using Q24 h and Q48 h dosing frequencies

Dose (mg kg^{-1})	4	6	8	10	12
Q24 h dosing					
CVVHD					
Mean AUC_{ss}, μg h ml^{-1}	335 (285, 387)	498 (412, 563)	673 (563, 750)	839 (717, 942)	999 (854, 1146)
Mean C_{max}, μg ml^{-1}	46 (40, 51)	69 (61, 75)	92 (81, 101)	115 (102, 130)	137 (122, 157)
Mean C_{min}, μg ml^{-1}	6.2 (4.8, 7.6)	9.0 (6.9, 10.9)	12.0 (9.6, 14.8)	15.4 (12.4, 17.9)	18.0 (14.6, 22.5)
CVVHDF					
Mean AUC_{ss}, μg h ml^{-1}	508 (359, 681)	712 (527, 1017)	1000 (671, 1289)	1203 (819, 1813)	1475 (1082, 1896)
Mean C_{max}, μg ml^{-1}	57 (46, 69)	82 (68, 103)	113 (90, 133)	139 (112, 180)	169 (142, 196)
Mean C_{min}, μg ml^{-1}	11.0 (6.7, 16.5)	15.4 (9.6, 24.8)	21.7 (12.1, 30.7)	26.5 (14.8, 45.3)	32.2 (20.0, 44.3)
Q48 h dosing					
CVVHD					
Mean $AUC_{0–24h}$, μg h ml^{-1}	272 (235, 307)	404 (354, 450)	542 (460, 607)	684 (571, 761)	799 (692, 899)
Mean $AUC_{24–48h}$, μg h ml^{-1}	63 (47, 77)	93 (74, 113)	126 (95, 161)	158 (118, 194)	182 (141, 222)
Mean C_{max}, μg ml^{-1}[a]	42 (36, 48)	62 (55, 68)	82 (72, 92)	104 (89, 117)	124 (108, 142)
Mean C_{min}, μg ml^{-1}[b]	1.2 (0.9, 1.6)	1.8 (1.4, 2.3)	2.4 (1.7, 3.3)	3.1 (2.1, 3.9)	3.5 (2.5, 4.5)
CVVHDF					
Mean $AUC_{0–24h}$, μg h ml^{-1}	383 (278, 493)	558 (439, 708)	759 (574, 997)	936 (751, 1243)	1129 (891, 1479)
Mean $AUC_{24–48h}$, μg h ml^{-1}	126 (63, 182)	180 (102, 267)	244 (132, 387)	304 (183, 466)	361 (212, 567)
Mean C_{max}, μg ml^{-1}[a]	49 (41, 57)	73 (63, 85)	98 (83, 117)	121 (107, 145)	147 (126, 174)
Mean C_{min}, μg ml^{-1}[b]	3.1 (1.3, 5.0)	4.5 (2.0, 7.3)	6.1 (2.6, 10.6)	7.8 (3.7, 12.7)	8.8 (4.3, 15.7)

[a]Apply for the first day.
[b]Apply for the second day.
Efficacy exposure reference is $AUC_{0–24h}$ of 465–761 μg h ml^{-1} and safety threshold is $AUC_{0–24h}$ of 1422 μg h ml^{-1}. Data are presented as mean (95% CI). AUC, area under the plasma concentration–time curve; AUC_{ss}, area under the plasma concentration–time curve at steady state; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; CVVHD, continuous veno-venous haemodialysis; CVVHDF, continuous veno-venous haemodiafiltration; Q24 h, every 24 h; Q48 h, every 48 h.

frequency [24, 34, 35]. Although the PK simulation results from the Vilay *et al*. [24] study are generally consistent with previously published results, the authors used $AUC_{0–48h}$ as an exposure indicator without considering that daptomycin concentration decreases over time and is markedly lower in patients on dialysis the second day after Q48 h dosing, as demonstrated by our results and those of others [15, 36]. The use of $AUC_{0–48h}$ as an exposure indicator does not accurately indicate the needed exposure to ensure efficacy at every 24 h interval. The same limitation applies to the reports by Falcone *et al*. [35] and Wenisch *et al*. [34], in which Q48 h dosing was used.

Since the mean time for clearance of methicillin-resistant *S. aureus* infection with daptomycin therapy in patients with IE/bacteraemia is > 1 week [20], exposure to suboptimal antimicrobial concentrations on any day of treatment could be associated with treatment failure and the development of antimicrobial resistance [15]. The risk of suboptimal antimicrobial concentrations and resistance also increases with the occurrence of biofilms on the surfaces of catheters and foreign devices that are frequently used in CRRT patients [37]. Hence, appropriate systemic exposure every day is crucial to avoid detrimental effects in patients.

The Q24 h dosing interval recommendation based on this investigation is applicable to comparable CVVHD and CVVHDF procedures (e.g. high-flux filter with 1.4–1.8 m^2 surface, blood flow of 100–200 ml min^{-1} and target dialysis flow rate of 30–40 ml kg^{-1} h^{-1}). Although this represents common practice in the ICU, cases may exist wherein the dialysis procedure could differ largely from this procedure and therefore the dose recommendation will possibly not be applicable under those conditions. Regardless of the daptomycin dose, frequent monitoring of blood CPK levels is indicated in all patients with renal impairment to ensure that this drug is used safely.

In conclusion, the clearance of daptomycin in patients undergoing CRRT is similar to that in patients with normal renal function (CrCl ≥ 30 ml min^{-1}). The final model predicts that administration of daptomycin Q24 h will result in exposure levels to achieve adequate efficacy, generally without the risk of increased toxicity (except for doses ≥ 10 mg kg^{-1} in CVVHDF). In contrast, Q48 h dosing in patients undergoing

CRRT is likely to result in exposure levels below the efficacy requirement every second day and thus be detrimental to patient outcomes.

Competing Interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: X.X., K.H. and M.L. are employees of Novartis Pharmaceuticals Corporation and R.L.C. is an employee of Novartis Pharma AG; these authors may thus be eligible for Novartis stock and stock options. HP has received research funding and lecture honoraria from Novartis and Fresenius Medical Care AG & Co. N.C. has been a member of the advisory board of Novartis and has received travel and accommodation grants from Novartis. D.K. has no disclosures to provide.

The analysis was sponsored by Novartis Pharma AG, Basel, Switzerland. This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

The authors acknowledge Geetanjali Tonpe and Anupama Tamta (Novartis Healthcare Pvt. Ltd., Hyderabad, India) for providing medical writing assistance for this manuscript.

Contributors

All authors had full access to all data and take responsibility for the integrity of the data and accuracy of analyses. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors. D.K., H.P. and N.C. had collected data from patients undergoing CVVHD and CVVHDF in two previous studies. X.X., K.H. and M.L. planned the update of a previously published population PK model. X.X. and M.L. updated the model. All authors actively participated in the preparation of the manuscript and provided critical review at each step. All authors read and approved the final manuscript.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

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Table S1 Detailed patient demographic and baseline characteristics – CVVHD and CVVHDF populations
Table S2 All population model parameter estimates of the final model
Table S3 Daptomycin individual estimated PK parameters in CVVHD and CVVHDF patients