J Antimicrob Chemother 2012; **67**: 977–983
doi:10.1093/jac/dkr551 Advance Access publication 29 December 2011

Journal of Antimicrobial Chemotherapy

Multiple-dose pharmacokinetics of daptomycin during continuous venovenous haemodiafiltration

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Received 17 August 2011; returned 13 October 2011; revised 22 November 2011; accepted 1 December 2011

Objectives: Daptomycin is bactericidal against Gram-positive bacteria, with peak-dependent effect but trough-dependent toxicity. This study was performed to develop dosing recommendations in continuous venovenous haemodiafiltration (CVVHDF).

Patients and methods: Nine critically ill patients in intensive care units of the Medical University Hospital of Vienna, requiring CVVHDF due to acute renal failure and antimicrobial treatment, were included. Blood and effluent samples were collected over 72 h to determine daptomycin concentrations by HPLC. Pharmacokinetic parameters were based on 10 sampling timepoints during the first 24 h, and peak and trough samples thereafter. An open two-compartment model was fitted to each subject's plasma concentration–time data. Simulations of serum concentration–time profiles after different doses and intervals were performed using ADAPT 5.

Results: Peak plasma concentrations with 6 mg/kg daptomycin were 62.2 ± 16.2, 66.1 ± 17.3 and 78.5 ± 22.1 mg/L on days 1, 2 and 3, respectively. The total clearance was 6.1 ± 4.9 mL/min, and the elimination half-life was 17.8 ± 9.7 h. Daptomycin was filtrated and could therefore be measured in the effluent. Protein binding was lower than that seen in healthy volunteers. The unbound fraction was 16 ± 4.5%. All subjects maintained trough serum concentrations above 4 mg/L, at which relevant pathogens are considered daptomycin-susceptible. Accumulation resulted when daptomycin was given every 24 h. Simulation of 8 mg/kg daptomycin given every 48 h resulted in adequate levels without accumulation.

Conclusions: We recommend 8 mg/kg daptomycin every 48 h in patients on CVVHDF and therapeutic drug monitoring, if possible.

Keywords: renal replacement therapy, antimicrobial therapy, acute renal failure

Introduction

Daptomycin is the first approved member of a new class of antibiotics, the cyclic lipopeptides. It has rapid bactericidal activity against Gram-positive pathogens and acts by penetrating the bacterial cell wall, resulting in formation of pores, loss of membrane electrical potential and inhibition of peptidoglycan synthesis.[1] Its activity against resistant pathogens makes the substance attractive for empirical therapy in critically ill patients. Gram-positive bacterial infections are higher in intensive-care patients due to risk factors such as mechanical ventilation, the use of steroids and other kinds of immunosuppressants, central venous catheter and renal replacement therapy. Also, bloodstream infections with Gram-positive pathogens can result in acute renal failure and the need for renal replacement therapy, and can contribute to morbidity and mortality in intensive care units (ICUs).[2,3]

Daptomycin has a large molecular weight (1621 Da) and high plasma protein binding (90%–96%).[4–7] Elimination is primarily by renal excretion (78%), which occurs to a great extent unmetabolized (52%). The renal excretion seems to be by glomerular filtration without significant tubular secretion or reabsorption. Therefore, renal clearance of daptomycin roughly corresponds to the glomerular filtration of the free plasma concentration.[4,5] Daptomycin shows peak-dependent killing,[8–10] but trough-dependent toxicity.[11] The MICs at which 90% of tested

pathogens were inhibited was 1 mg/L, with the exception of enterococci (2–4 mg/L).[9,12] Daptomycin has limited distribution, as most of the drug remains in the vasculature. Therefore, we considered removal of daptomycin by continuous venovenous haemodialysis (CVVHD) as feasible, despite its high protein binding and large molecular weight.

Although dose adjustments are recommended in renal insufficiency, only limited data exist about daptomycin dosing during continuous renal replacement therapy. Current recommendations are based on *in vitro* data, including one *in vivo* CVVHD study following a single-dose administration of 8 mg/kg.[13,14] Upon estimating a CVVHDF creatinine clearance of 35 mL/min, we followed the manufacturer's daptomycin dosing recommendations for bacteraemia in patients with a creatinine clearance >30 mL/min: 6 mg/kg every 24 h, to prevent underdosing. In healthy volunteers the recommended dose (6 mg/kg every 24 h) resulted in a mean C_{max} of 86.4 ± 7.1 mg/L on day 1. C_{max} values in patients with mild to moderate renal impairment were similar to those in patients with normal renal function.[15] We therefore expected C_{max} in the current study to be similar to that in persons with normal renal function. These levels were considered adequate, considering the concentration-dependent activity of daptomycin[10,16,17] and the need for relatively high peak levels in critically ill patients.

The purpose of this study was to determine the pharmacokinetics of 6 mg/kg daptomycin and the concentration–time profiles after several doses in critically ill patients during CVVHDF, and to compare the results with recent literature data to develop robust dosing recommendations for this specific patient population.

Methods

Patients

From March to November 2010 patients of the ICU of the Medical University Hospital of Vienna requiring CVVHDF due to acute renal failure were screened for eligibility. It was planned to include ten critically ill patients on CVVHDF with suspected or proven systemic bacterial infection. Patients had to be anuric (urine production <400 mL per 24 h) and without need of albumin substitution. Patients with known hypersensitivity to daptomycin or glycopeptides were not eligible. In patients diagnosed with osteomyelitis, meningitis, enterococci infection or pneumonia, daptomycin was only allowed in combination with other antimicrobials. Pregnant patients and patients below the age of 18 years were not eligible. The study protocol was approved by the local Ethics Committee (EK871/2009, EudraCT number 2009-016092-30), and informed consent forms were available. For subjects unable to consent due to reduced vigilance, the Ethics Committee waived the need for patient consent. The patients were informed of their inclusion by letter, including details of the study purpose and procedures, contact details of the study investigators, as well as the study insurance details. The demographics and severity scores of the included patients are given in Table 1.

CVVHDF

CVVHDF was done by the Prismaflex system M100 set (Gambro Lundia AB, Lund, Sweden), using an acrylonitrile hollow-fibre filter with a surface area of 0.9 m^2. CVVHDF was performed by using pre-dilution fluid infusion at a standard rate of 1 L/h and at a dialysate flow rate of 1 L/h. Fluid balance was adjusted according to clinical requirements. Mean blood flow rate was 150 ± 48 mL/min. The scheduled duration of CVVHDF was 72 h without filter changes. In three patients (#8, 9 and 11), filter changes were necessary during the study period (at 4, 49 and 23 h, respectively) although this did not influence measured daptomycin levels. The overall duration of CVVHDF was less than 72 h in patients #6, 7 and 8 (48, 48 and 35 h, respectively) due to regain of urine production >400 mL or to CVVHDF pauses for interventions and surgical procedures.

Drug administration and sampling

Daptomycin (Cubicin, Novartis, Vienna, Austria) was given as a single daily infusion over 30 min at a dose of 6 mg/kg, as recommended for bacteraemia,[15] into a venous catheter, separate from the venous catheter used for CVVHDF. Blood samples were drawn on day 1 from the arterial and venous line of the extracorporeal circuit before, and at 0.5, 1, 2, 4, 6, 8, 10, 12 and 24 h after the start of the infusion. After the

Table 1. Patient demographics

Patient	Sex	Age (years)	BMI (kg/m^2)	Protein (g/L)	Albumin (g/L)	Norepinephrine (μg/kg/min)	SAPS II	Diagnosis
1	female	57	29	48.6	22.1	0	82	aspiration, ARDS, severe sepsis
2	male	68	27	64.8	20.1	0.052[a]	111	sepsis with *Streptococcus pneumoniae*, myeloma
3	male	44	20	50.7	25.1	0.033	54	double lung transplantation, severe sepsis
6	female	69	27	45.9	27.4	0	79	colon perforation after chemotherapy, VRE
7	male	64	20	48.9	28.3	0.321[a]	62	Child C cirrhosis, urosepsis, septic shock
8	male	65	32	46.7	22.2	0.392	77	COPD exacerbation, CMP, sepsis
9	male	73	25	52.7	26.2	0	43	septic shock, ARDS, AVR
10	female	44	23	47.3	23.9	0.716[a]	74	MVR, right ventricular failure, sepsis
11	female	67	52	65.8	20.1	0	63	infected diabetic ulcer, sepsis
Mean ± SD	—	61 ± 11	28 ± 10	52.4 ± 7.6	23.9 ± 3.0	0.168 ± 0.255	72 ± 20	
Median (QR)	—	65 (11)	27 (6)	48.9 (5.4)	23.9 (4.1)	0.033 (0.321)	74 (17)	

ARDS, adult respiratory distress syndrome; VRE, vancomycin-resistant *Enterococcus*; COPD, chronic obstructive pulmonary disease; CMP, cardiomyopathy; MVR, mitral valve replacement; AVR, aortic valve replacement; QR, quartile range.
[a]These patients additionally received vasopressin and/or dobutamine.

first day, peak and trough levels were measured before the start and at the end of each daptomycin infusion, up to 72 h. As described previously,[18] blood and effluent samples, collected from the outlet of the dialysate compartment of the haemofilter, were taken at corresponding times. Blood samples were collected in heparin-anticoagulated evacuated tubes (Vacutainer, Becton Dickinson, Vienna, Austria). Plasma was separated immediately by centrifugation at 3000 **g** for 15 min and stored together with the ultrafiltration samples in cryotubes (Nunc GmbH & Co. KG, Langenselbold, Germany) at −80°C until batch analysis. Patients with only one day of analysis, for example due to shorter duration of CVVHDF, were followed for their single-dose pharmacokinetic profile.

Drug assay

The concentrations of daptomycin in plasma and ultrafiltrate were determined using a validated HPLC method with UV detection.[19] In short, chromatographic separation was achieved on a ZORBAX Eclipse XDB-C8 column (4.6×150 mm; 5 μm particle diameter) using a Waters 717plus autosampler, two 515 HPLC pumps and a Waters 2487 absorbance detector at 224 nm. The sample preparation consisted of a protein precipitation step with methanol followed by centrifugation, and the clear supernatants were injected into the HPLC apparatus. The calibration function was linear over 3.5–350 mg/L. The accuracy of quality control samples was better than 2.5%, and the inter-day relative standard deviation was better than 5.3%.

Daptomycin protein binding was determined using a Centrifree Ultrafiltration Device according to the manufacturer's package insert (Millipore Corporation). The level of protein binding was calculated using the following equation: % protein binding = $100-(100\times C_{ultrafiltrate}/C_{plasma})$.

Pharmacokinetic analysis

An open two-compartment model was fitted to each subject's plasma concentration–time data. The pharmacokinetic parameters were apparent volume of distribution in the central compartment, apparent volume of distribution in the peripheral compartment and distribution clearance. These were estimated using ADAPT 5 (Biomedical Simulations Resource, University of Southern California, Los Angeles, CA, USA).

The fitted pharmacokinetic parameters obtained by this model were used to calculate apparent steady-state volume of distribution (the sum of apparent volume of distribution in the central compartment and volume of distribution in the peripheral compartment) and other pharmacokinetic parameters by standard methods. Non-compartmental pharmacokinetic (PK) parameters were estimated with the R package PK.[20] AUC was calculated using the linear trapezoidal rule. Fitting was done with Model 2COMPCL of ADAPT 5, parameterized using clearances with the 'weighted least squares' (WLS) estimation procedure and weighting option 1 (general). The sieving coefficient was determined by $C_{effluent}/C_{post\text{-}filter}$ ratios. Demographic calculations and Friedman ANOVA for peak and trough concentrations were done using Statistica 6.0. (StatSoft, Tulsa, OK, USA).

Serum concentration–time profiles were simulated with ADAPT 5 using the means of the individual pharmacokinetic parameters. Concentration–time curves were simulated in a person of 70 kg on CVVHDF at 6 mg/kg daptomycin every 24 h (three doses), and every 48 h (4 doses); concentration–time curves for 8 mg/kg daptomycin were simulated for a person of 70 kg on CVVHDF every 48 h (2 or 4 doses).

Results

Tested from March to November 2010, initially ten critically ill patients with acute renal failure on daptomycin treatment were included. One of the patients (#4) died during the study due to the disease, and was replaced because of insufficient pharmacokinetic data (additional patient #11). In another patient (#5), daptomycin was stopped prematurely due to the occurrence of rhabdomyolysis, which was diagnosed as potentially drug-related by the investigators. This patient was excluded without replacement. In the other patients, daptomycin was well tolerated.

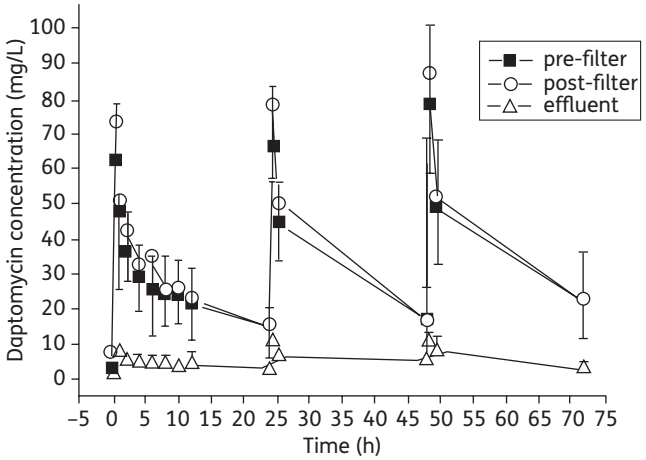

Figure 1. Concentration–time profiles of the study population. Daptomycin concentrations after intravenous infusions of 6 mg/kg on days 1–3, sampled from the pre-filter, post-filter and the effluent ports during 72 h of CVVHDF. Data are presented as mean ± SD.

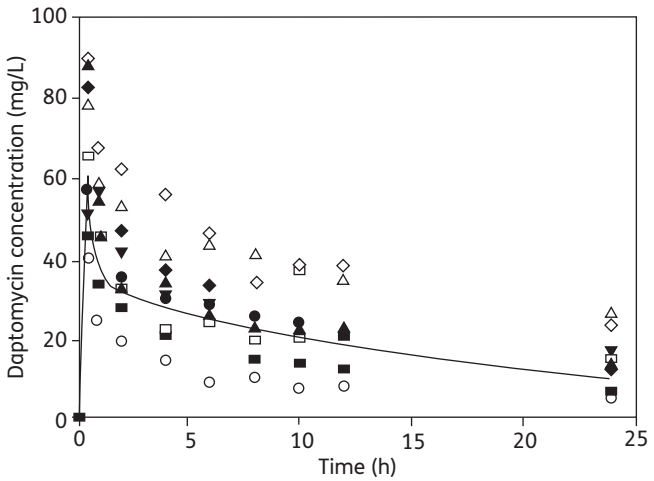

Figure 2. Individual values and calculated time–concentration curve in the first 24 h. Plasma concentrations of daptomycin after intravenous administration of 6 mg/kg; individual values and calculated curve (pre-filter port measurements).

Nine patients (5 male, 4 female) remained for analysis. Table 1 summarizes the demographic findings in the study population. The population concentration–time profile is illustrated in Figure 1 and the individual profiles for the first 24 h are shown in Figure 2.

Plasma concentrations were at their highest directly after infusion, and reached their maxima on the third treatment day. Peak plasma concentrations after infusion of 6 mg/kg daptomycin were 62.2 ± 16.2, 66.1 ± 17.3 and 78.5 ± 22.1 mg/L at

Table 2. Pharmacokinetic parameters, two-compartment model, AUC in the first 24 h, non-compartmental calculation

	Model-derived parameters				Calculated parameters							
Patient	V_p (L)	V_c (L)	CL_d (mL/min)	CL_t (mL/min)	V_{ss} (L/kg)	CL_t (mL/min/kg)	$t_{1/2}$ (h)	fraction unbound (%)	median sieving coefficient	AUC pre-filter (mg·h/L)	AUC venous (mg·h/L)	AUC haemo-filtrate (mg·h/L)
1	2.7	3.3	36	4.3	0.08	0.059	16.4	11	0.15	549	558	88
2	6.7	4.6	90.0	17.3	0.14	0.214	8.1	22	0.21	225	245	51
3	3	3.4	9.2	2.4	0.1	0.036	33.4	12	0.11	587	690	80
6	1.2	2.9	10.8	1.8	0.06	0.027	26.6	13	0.14	880	1088	156
7	2.4	3.0	49.2	7.1	0.09	0.124	9.0	19	0.18	353	335	69
8	6.2	3.3	42.6	3.8	0.11	0.044	30.1	14	0.17	511	500	95
9	4.3	0.3	208.5	5.8	0.06	0.072	9.3	12	0.16	605	597	115
10	2.3	0.5	175.7	2.7	0.04	0.041	12.4	22	0.07	939	767	45
11	7.9	3.8	79.8	9.5	0.08	0.063	14.9	16	0.17	555	405	161
Mean	4.1	2.8	78.0	6.1	0.09	0.076	17.8	16	—	578	576	96
SD	2.3	1.4	70.6	4.9	0.03	0.059	9.7	4.5	—	224	254	41
Median	3	3.3	49.2	4.3	0.08	0.059	14.9	14	—	555	558	88
QR	3.8	0.5	54.0	4.4	0.04	0.031	17.3	7	—	94	285	46

V_p, apparent volume of distribution in the peripheral compartment; V_c, apparent volume of distribution in the central compartment; CL_d, distribution clearance between the central and the peripheral compartment; CL_t, total clearance; V_{ss}, apparent volume of distribution at steady-state; $t_{1/2}$, half-life; QR, quartile range.

the pre-filter port on days 1, 2 and 3, respectively (accumulation 19%, $P=0.03$; Figure 1). Mean trough levels also increased with time: 14.0 ± 6.3 mg/L, 17.2 ± 8.8 mg/L and 22.4 ± 13.8 mg/L at 24, 48 and 72 h, respectively (accumulation 60%, $P=0.04$). Daptomycin was filtered and peak levels in the ultrafiltrate were measured directly after infusion, i.e. at the times that levels peaked in plasma. Maximum levels were 9.3 ± 2.2, 10.4 ± 2.2 and 10.5 ± 2.2 mg/L on days 1, 2 and 3, respectively (Figure 1).

The apparent volume of distribution of daptomycin in the peripheral and central compartments, the distribution clearance and total clearance for the two-compartment model, as well as the elimination half-lives are summarized in Table 2. The individual and population AUCs of daptomycin during the first 24 h are also summarized. Protein binding was lower than that seen in healthy volunteers. The unbound fraction was 16 ± 4.5%, and median individual sieving coefficients ranged from 0.07–0.21. The median sieving coefficients were lower at peak (0.12–0.13) and higher at trough levels (0.15–0.22).

There was no significant difference in AUC between the pre- and post-filter port measurements (Table 2). Although substance loss occurred, overall accumulation resulted from the dose regimen (6 mg/kg every 24 h, Figure 1).

A 3 day concentration–time profile was simulated in a critically ill person of 70 kg on CVVHDF with 6 mg/kg daptomycin every 24 h (Figure 3).

Administration of 6 mg/kg every 48 h for 8 days was also simulated. Infusions of 30 min duration were simulated at 0, 48, 96 and 144 h. After the fourth infusion (i.e. at 144.5 h) C_{max} was 55.72 mg/L; thereafter, the concentration fell below 4 mg/L at 184 h, and reached C_{min} (2.68 mg/L) 8 h later (i.e. at 192 h).

A simulation of 8 mg/kg daptomycin given every 48 h (Figures 3 and 4) resulted in a C_{max} of 74.29 mg/L after 144.5 h. The concentration fell below 4 mg/L after 190 h and reached C_{min} (3.58 mg/L) at 192 h. In the models employing 48 h intervals, no accumulation was observed.

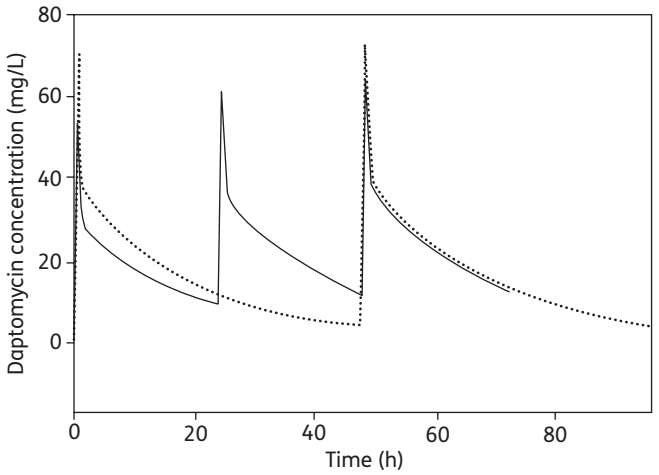

Figure 3. Daptomycin at 6 mg/kg every 24 h (continuous line) and 8 mg/kg every 48 h (broken line), for 3 days. Simulated concentrations of daptomycin after repeated administration in a person of 70 kg for 3 days. Infusions of 30 min duration were simulated at 0, 24 and 48 h. At 6 mg/kg every 24 h, slight increases in peak and trough levels can be observed over 72 h.

Discussion

To the best of our knowledge, this is the first study describing the pharmacokinetics and concentration–time profiles after multiple doses of daptomycin in critically ill patients on CVVHDF. Our data

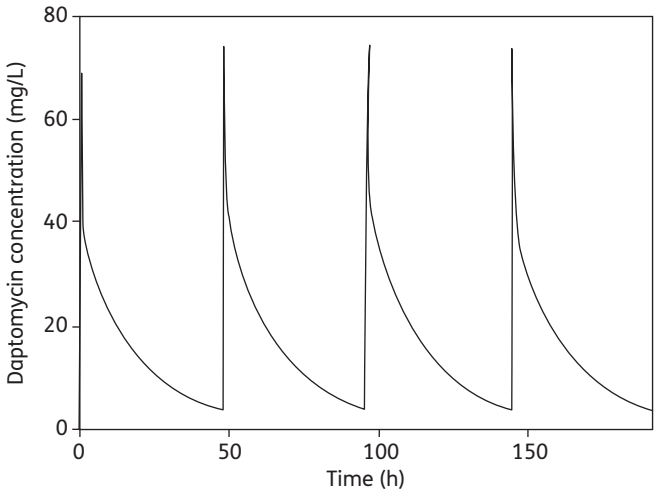

Figure 4. Daptomycin at 8 mg/kg every 48 h for 8 days. Simulated repeated administration in a person of 70 kg for 8 days. An infusion of 30 min duration was simulated every 48 h. After the last 560 mg infusion (i.e. at 144.5 h) C_{max} was 74.29 mg/L; the concentration fell to below 4 mg/L after 190 h, and reached C_{min} (3.58 mg/L) at 192 h.

show that daptomycin can be found in the effluent during CVVHDF and is therefore removed, as occurs for other substances with similar high protein-binding properties or molecular weight.[21,22] However, substance loss seemed to be compensated for by accumulation of daptomycin at 6 mg/kg every 24 h, as revealed by small but rising peak and trough levels of daptomycin (Figure 1). This was not surprising taking into account that daptomycin is primarily eliminated via the kidneys, and that an accumulation factor [1.2, indicating minor (20%) drug accumulation] was previously described with once-daily dosing, even in patients with normal renal function.[5]

The study of Vilay *et al.*[13] evaluated single-dose daptomycin in CVVHD at 8 mg/kg. The patients had similar body mass index (BMI) and dialysate flow, but were younger (51 ± 14 years) and had higher blood flow rates (181 ± 26 mL/min) than those in our study. Although the C_{max} reached after a single dose of 8 mg/kg was lower than the target (100 mg/L), it was higher than with 6 mg/kg in the first 24 h of our study. However, the mean C_{max} on day 3 in this study (78.5 ± 22.1 mg/L) was comparable with that seen after a single dose of 8 mg/kg (82.3 ± 17.9 mg/L). Several studies have claimed that daptomycin's concentration-dependent activity suggests a desirability for higher C_{max} values.[8,9] The target peak concentration has to be chosen carefully for each patient, based on C_{max}, C_{min} and dosing intervals. C_{max}/MIC and AUC/MIC ratios are the most relevant pharmacokinetic/pharmacodynamic parameters regarding clinical efficacy.[23–26] In bacteraemic patients with normal renal function, the currently recommended dose is 6 mg/kg every 24 h. In healthy volunteers this dose resulted in a mean C_{max} of 86.4 ± 7.1 mg/L on the first day of treatment,[5] which was higher than in our study. In patients on haemodialysis[27] a C_{max} of 61.1 ± 7.6 mg/L was regarded as sufficient. However, longer dose intervals, due to higher AUC and periods without dialysis, have to be taken into account in these patients. Nonetheless, we share the concern of Vilay *et al.*[13] that 4 mg/kg every 48 h (C_{max} 41 mg/L) could be too low in bacteraemic, critically ill patients.

The mean free drug fraction ($16 \pm 4.5\%$) was higher in our critically ill patients with acute renal failure than in healthy volunteers (fraction unbound: 4%–10%).[4–7] The higher free fraction is consistent with the results for the CVVHD patients of Vilay *et al.*[13] ($17.5 \pm 5\%$), and has also been described in patients with end-stage renal disease and haemodialysis.[28] Since the unbound substance is relevant for exertion of the drug's effect, a higher free fraction is beneficial in critically ill patients, as it might be associated with sufficient free daptomycin concentrations despite lower C_{max}. However, caution is advisable in patients with profound hypoalbuminaemia; they might reach lower C_{max} levels but have unpredictable high free fractions.[13] Median sieving coefficient and free fraction seemed to correlate in most patients (with the exception of subject #10; Table 2).

Although high peak concentrations are desirable in respect of antimicrobial efficacy, the disadvantage of higher peaks is the associated higher trough concentrations. Bhavnani *et al.*[11] demonstrated that the probability of daptomycin-induced creatine phosphokinase (CPK) elevation is associated with C_{min} rather than with C_{max}. In long-term treated patients with endocarditis, the authors found that a prolonged daptomycin C_{min} of 24.3 mg/L or higher was associated with an increased probability of elevated CPK after 5 to 20 days of treatment. In the CVVHDF patients, only one had trough levels above 25 mg/L, but did not show CPK elevation. In our patient who was excluded due to rhabdomyolysis, the CPK elevation became evident on the first day of treatment, which makes a direct relationship with daptomycin administration rather unlikely. Furthermore, this particular patient had a prior episode of CPK elevation several days before. Both his clinical condition and multiple drug use were potential causes. For safety reasons, daptomycin was discontinued and the patient was excluded due to incomplete pharmacokinetic data. However, his daptomycin C_{max} was not higher than those of other patients on the first treatment day.

Studies in dogs receiving daptomycin (75 mg/kg daily for 20 days) demonstrated decreased skeletal myopathy and CPK elevation when the dose was administered once daily, compared with 25 mg/kg every 8 h.[29] These studies led to human studies resulting in the currently recommended once daily dosing regimens. It has not been investigated whether even wider dosing intervals would further reduce the risk of myopathy, which is conceivable.

Based on our findings with 6 mg/kg every 24 h, a simulation of a critically ill person of 70 kg on CHHHDF was performed for 6 mg/kg and 8 mg/kg every 48 h for 8 days of treatment. In the case of 8 mg/kg daptomycin, this resulted in an effective C_{max} (74.29 mg/L) and lower C_{min} without accumulation (Figures 3 and 4). With 6 mg/kg of daptomycin every 24 h all subjects maintained trough serum concentrations above 4 mg/L (the lowest individual C_{min} was 4.6 mg/L), which is higher than the concentrations at which *Staphylococcus aureus* (≥1 mg/L) and *Enterococcus faecalis* (≥4 mg/L) isolates are considered daptomycin susceptible.[9,12] When daptomycin administration every 48 h was simulated, the level fell below 4 mg/L for a period of 8 h (6 mg/kg daptomycin) or 2 h (8 mg/kg) (Figure 4). Especially concerning the 8 mg/kg dose, the authors believe that this short period is without clinical relevance. Still, regarding the longer intervals between peak concentrations, we cannot

entirely be sure that the post-antibiotic effect would last long enough to effectively treat bacteraemias of intermediate susceptibility, which might be of importance in neutropenic patients.

In summary, the findings suggest that wider dosing intervals would be preferable in CVVHDF to avoid accumulation and high trough levels, which may help to reduce the risk of CPK elevation. Following our simulation model it might be necessary to increase the dose from 6 mg/kg to 8 mg/kg to achieve effective treatment levels in bacteraemic patients.

Limitations

Our pharmacokinetic results in CVVHDF show great variability (Figure 2) and may therefore not be applicable to every ICU patient. In particular, different CVVHDF settings, for example different flow rates and filters, may achieve diverging pharmacokinetic results. If possible, therapeutic drug monitoring should be established to guide treatment and optimize individual pharmacokinetics of daptomycin for each individual patient on CVVHDF.

Conclusions

Daptomycin at 6 mg/kg every 24 h resulted in good drug exposure and achieved high peak concentrations to maximize daptomycin's concentration-dependent activity during CVVHDF. Although peak concentrations were favourable with 6 mg/kg, lower trough levels and prevention of accumulation could be achieved with higher doses at greater dose intervals. We therefore recommend 8 mg/kg daptomycin every 48 h for patients on CVVHDF, and therapeutic drug monitoring if possible.

Acknowledgements

We thank the staff of the intensive care units of the Medical University of Vienna, Austria, for their cooperation in this study.

Funding

This study was carried out as part of our routine work and was supported by internal funding.

Transparency declarations

F. T. has received unrestricted research grants from Pfizer, Novartis and Janssen. All other authors: none to declare.

References

1 Sauermann R, Rothenburger M, Graninger W *et al*. Daptomycin: a review 4 years after first approval. *Pharmacology* 2008; **81**: 79–91.

2 Cotterill S. Antimicrobial prescribing in patients on haemofiltration. *J Antimicrob Chemother* 1995; **36**: 773–80.

3 Vincent JL, Rello J, Marshall J *et al*. International study of the prevalence and outcomes of infection in intensive care units. *JAMA* 2009; **302**: 2323–9.

4 Woodworth JR, Nyhart EH Jr, Brier GL *et al*. Single-dose pharmacokinetics and antibacterial activity of daptomycin, a new lipopeptide antibiotic, in healthy volunteers. *Antimicrob Agents Chemother* 1992; **36**: 318–25.

5 Dvorchik BH, Brazier D, DeBruin MF *et al*. Daptomycin pharmacokinetics and safety following administration of escalating doses once daily to healthy subjects. *Antimicrob Agents Chemother* 2003; **47**: 1318–23.

6 Benvenuto M, Benziger DP, Yankelev S *et al*. Pharmacokinetics and tolerability of daptomycin at doses up to 12 milligrams per kilogram of body weight once daily in healthy volunteers. *Antimicrob Agents Chemother* 2006; **50**: 3245–9.

7 Liang SH, Sheng WH, Huang YT *et al*. Pharmacokinetics and safety of multiple intravenous doses of daptomycin in a Taiwanese adult population. *Chemotherapy* 2009; **55**: 91–6.

8 Carpenter CF, Chambers HF. Daptomycin: another novel agent for treating infections due to drug-resistant gram-positive pathogens. *Clin Infect Dis* 2004; **38**: 994–1000.

9 Rybak MJ, Hershberger E, Moldovan T *et al*. In vitro activities of daptomycin, vancomycin, linezolid, and quinupristin-dalfopristin against Staphylococci and Enterococci, including vancomycin-intermediate and -resistant strains. *Antimicrob Agents Chemother* 2000; **44**: 1062–6.

10 Vance-Bryan K, Larson TA, Rotschafer JC *et al*. Investigation of the early killing of *Staphylococcus aureus* by daptomycin by using an in vitro pharmacodynamic model. *Antimicrob Agents Chemother* 1992; **36**: 2334–7.

11 Bhavnani SM, Rubino CM, Ambrose PG *et al*. Daptomycin exposure and the probability of elevations in the creatine phosphokinase level: data from a randomized trial of patients with bacteremia and endocarditis. *Clin Infect Dis* 2010; **50**: 1568–74.

12 Hanberger H, Nilsson LE, Maller R *et al*. Pharmacodynamics of daptomycin and vancomycin on *Enterococcus faecalis* and *Staphylococcus aureus* demonstrated by studies of initial killing and postantibiotic effect and influence of Ca2+ and albumin on these drugs. *Antimicrob Agents Chemother* 1991; **35**: 1710–6.

13 Vilay AM, Grio M, Depestel DD *et al*. Daptomycin pharmacokinetics in critically ill patients receiving continuous venovenous hemodialysis. *Crit Care Med* 2011; **39**: 19–25.

14 Wagner CC, Steiner I, Zeitlinger M. Daptomycin elimination by CVVH in vitro: evaluation of factors influencing sieving and membrane adsorption. *Int J Clin Pharmacol Ther* 2009; **47**: 178–86.

15 Cubicin Prescribing Information. 2010. http://www.cubicin.com/pdf/PrescribingInformation.pdf (21 December 2011, date last accessed).

16 Flandrois JP, Fardel G, Carret G. Early stages of in vitro killing curve of LY146032 and vancomycin for *Staphylococcus aureus*. *Antimicrob Agents Chemother* 1988; **32**: 454–7.

17 Rose WE, Rybak MJ, Kaatz GW. Evaluation of daptomycin treatment of *Staphylococcus aureus* bacterial endocarditis: an *in vitro* and *in vivo* simulation using historical and current dosing strategies. *J Antimicrob Chemother* 2007; **60**: 334–40.

18 Leitner JM, Meyer B, Fuhrmann V *et al*. Multiple-dose pharmacokinetics of anidulafungin during continuous venovenous haemofiltration. *J Antimicrob Chemother* 2011; **66**: 880–4.

19 Martens-Lobenhoffer J, Kielstein JT, Oye C *et al*. Validated high performance liquid chromatography-UV detection method for the determination of daptomycin in human plasma. *J Chromatogr B Analyt Technol Biomed Life Sci* 2008; **875**: 546–50.

20 Jaki T, Wolfsegger MJ. Estimation of pharmacokinetic parameters with the R package PK. *Pharmaceutical Statistics* 2011; **10**: 284–8.

21 Meyer B, Ahmed el Gendy S, Delle Karth G *et al*. How to calculate clearance of highly protein-bound drugs during continuous venovenous hemofiltration demonstrated with flucloxacillin. *Kidney Blood Press Res* 2003; **26**: 135–40.

22 Meyer B, Traunmüller F, Hamwi A *et al*. Pharmacokinetics of teicoplanin during continuous hemofiltration with a new and a 24-h

used highly permeable membrane: rationale for therapeutic drug monitoring-guided dosage. *Int J Clin Pharmacol Ther* 2004; **42**: 556–60.

23 Louie A, Kaw P, Liu W *et al*. Pharmacodynamics of daptomycin in a murine thigh model of *Staphylococcus aureus* infection. *Antimicrob Agents Chemother* 2001; **45**: 845–51.

24 Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. *Clin Infect Dis* 1998; **26**: 1–10.

25 Tally FP, Zeckel M, Wasilewski MM *et al*. Daptomycin: a novel agent for Gram-positive infections. *Expert Opin Investig Drugs* 1999; **8**: 1223–38.

26 Safdar N, Andes D, Craig WA. In vivo pharmacodynamic activity of daptomycin. *Antimicrob Agents Chemother* 2004; **48**: 63–8.

27 Salama NN, Segal JH, Churchwell MD *et al*. Single-dose daptomycin pharmacokinetics in chronic haemodialysis patients. *Nephrol Dial Transplant* 2010; **25**: 1279–84.

28 Salama NN, Segal JH, Churchwell MD *et al*. Intradialytic administration of daptomycin in end stage renal disease patients on hemodialysis. *Clin J Am Soc Nephrol* 2009; **4**: 1190–4.

29 Oleson FB Jr, Berman CL, Kirkpatrick JB *et al*. Once-daily dosing in dogs optimizes daptomycin safety. *Antimicrob Agents Chemother* 2000; **44**: 2948–53.