

## Original Article

## Dosing of daptomycin in intensive care unit patients with acute kidney injury undergoing extended dialysis—a pharmacokinetic study

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### Abstract

**Background.** Daptomycin is a new intravenous cyclic lipopeptide antibiotic, licensed for the treatment of complicated skin and soft tissue infections caused by Gram-positive organisms including both susceptible and resistant strains of *Staphylococcus aureus* and for the treatment of various infections due to susceptible organisms, including serious and life-threatening Gram-positive infections, vancomycin-resistant enterococcal infections and right-sided endocarditis with associated bacteremia. Currently, no dosing recommendations exist for this drug for patients with acute kidney injury (AKI) undergoing renal replacement therapy. The aim of this study was to evaluate pharmacokinetics of daptomycin in critically ill patients with AKI undergoing extended dialysis (ED), a frequently used mean of renal replacement therapies in intensive care units (ICUs) around the world.

**Patients and methods.** A prospective, single-dose pharmacokinetic study was performed in the medical and surgical ICUs of a tertiary care center. The aim was to investigate critically ill patients with anuric AKI being treated with ED and receiving daptomycin ( $n = 10$ ). Daptomycin (6 mg/kg) was administered 8 h before ED was started.

**Results.** Key pharmacokinetic parameters like half-life in critically ill patients treated with ED were comparable to healthy controls. The dialyser clearance for daptomycin was  $63 \pm 9$  ml/min. Based on the amount of the drug recovered from the collected spent dialysate, the mean fraction of the drug removed by one dialysis treatment was 23.3%.

**Conclusion.** Our data suggest that patients treated with ED using a high-flux dialyzer (polysulphone, 1.3 m<sup>2</sup>; blood and dialysate flow, 160 ml/min; ED time, 480 min) and employing current dosing regimen, 6 mg/kg daptomycin every 48 h, run the risk of becoming significantly under dosed if one adheres to a twice daily dosing schedule that is recommended for patients on maintenance haemodialysis.

Our data suggest that a daily dose of 6 mg/kg daptomycin is necessary in this special patient population to avoid under dosing, which may have detrimental effects in critically ill patients suffering from life-threatening infections.

**Keywords:** acute kidney injury; daptomycin; extended dialysis; pharmacokinetics

### Introduction

A recent multinational study in intensive care patients showed that more than 50% of patients suffer from acute kidney injury (AKI) due to sepsis, followed by drug-induced renal failure. Hence, appropriate dosing of antibiotics is essential in this setting to treat the underlying infection effectively and to avoid renal toxicity of drugs [1]. Daptomycin belongs to a class of new cyclic lipopeptide antibiotics that has been licensed in the USA and Europe for the treatment of complicated skin and soft tissue infections caused by Gram-positive organisms including both susceptible and resistant strains of *Staphylococcus aureus*. It is also licensed for the treatment of various infections due to susceptible organisms, including serious and life-threatening Gram-positive infections, vancomycin-resistant enterococcal infections and right-sided endocarditis with associated bacteraemia. As the percentage of the drug excreted intact in urine is about 54%, extending the dosing interval has been advocated for patients with renal failure [2]. These dosing recommendations are however based on scarce data [3], even though the drug seems to be promising such as for the treatment of vancomycin-resistant enterococcus peritonitis in peritoneal dialysis patients [4] or as catheter lock solution [5]. A single report from a patient with AKI suggests that higher doses might be necessary for septic patients treated with extend-

ed dialysis (ED) as compared to intermittent haemodialysis (IHD) in the outpatient setting [6]. ED represents an important extracorporeal renal replacement therapy that is frequently used in intensive care units (ICUs) throughout Europe, the USA and Brazil [7–10]. This treatment modality could remove drugs to a much different degree than standard IHD three times a week or continuous renal replacement therapy [11]. The slowly growing data on the effect of ED on the elimination of frequently used antibiotics in critically ill patients with renal failure support this notion [5,12–16]. The aim of our study was to investigate the pharmacokinetics of daptomycin in anuric critically ill patients with AKI undergoing ED as a basis to guide dosing recommendations in this patient population.

## Materials and methods

### Patients and study protocol

The study protocol was approved by the Medical School Hannover Ethics Committee (project # 4709) and was conducted in accordance with the declaration of Helsinki and German federal guidelines. Adult intensive care patients with anuric AKI being treated with ED and having a clinical cause for the administration of daptomycin received a single dose of the drug on top of a preexisting antibiotic treatment. This was the requirement of the ethics committee that approved the study only in its current form as the previous case report had already suggested substantial removal of daptomycin by ED, to decrease the risk of treatment failure by the currently recommended 48-h dosing interval [6]. The patient described in our case report [6] was not included in the current analysis. Patients were included in the study after informed consent had been obtained from the patient or the patient's legal representative. Daptomycin (6 mg/kg), based on actual body weight, was infused intravenously in 10 patients over a period of 30 min using a perfusion pump. This was done 8 h before ED was started, to study the pharmacokinetics of the drug off and on dialysis in the same patient whilst avoiding inter-day variability.

ED was performed using the GENIUS<sup>®</sup> batch dialysis system (Fresenius Medical Care, Bad Homburg, Germany) with a polysulfone high-flux dialyser [F60S (surface area, 1.3 m<sup>2</sup>), Fresenius Medical Care, Bad Homburg, Germany] as described previously [12]. The technical details of the system are explained elsewhere [17]. In brief, sterile bicarbonate dialysate is filled into a 75- or 90-l tank and is thereafter circulated in a closed loop circuit. During dialysis, fresh dialysate is taken from the top of the tank, while the spent dialysate flows back to the bottom [18]. Thus, complete collection of spent dialysate in the same tank after the dialysis session permits estimation of the total amount removed of a substance assuming that adsorption of the substance to the dialyser system is negligible. The average dialysis time during the study was 456 ± 13 min, and mean blood

and counter current dialysate flow was 166 ± 5 ml/min. ED started 8 h after the end of the daptomycin infusion. Vascular access in all patients was achieved by a double-lumen catheter either inserted into the internal jugular or the femoral vein.

### Sampling and analysis

Blood samples (5 ml) were collected via an arterial catheter before intravenous daptomycin infusion and 0.5, 1, 1.5, 2, 4, 6, 8, 8.25, 9, 10, 12, 14, 16, 16.5, 18 and 24 h after the start of infusion. Samples were centrifuged at 1300 g for 10 min at 4°C. Plasma was separated and stored at -80°C until analysis. Additional blood samples were drawn pre- and post-dialyser, i.e. from the afferent 'artery' and efferent 'venous' dialyser blood tubing 15 min after the start of ED in order to calculate the dialyser clearance from the pre- and post-dialyser concentration difference. For the collection of the pre- and post-dialyser samples, ultrafiltration was stopped.

### Chemical assays

Daptomycin was determined by an HPLC method with UV detection described previously [19]. Shortly, sample preparation consists only of protein precipitation with methanol. Chromatographic separation was achieved on a Zorbax Eclipse XDB-C8 column, and daptomycin was detected at 224 nm. The calibration function was linear over the range from 3.5 to 350 mg/l. The relative standard deviations (SD) were <2% in the intra-day and <6% in the inter-day measurements. The accuracy was always better than 7%.

### Pharmacokinetic calculations

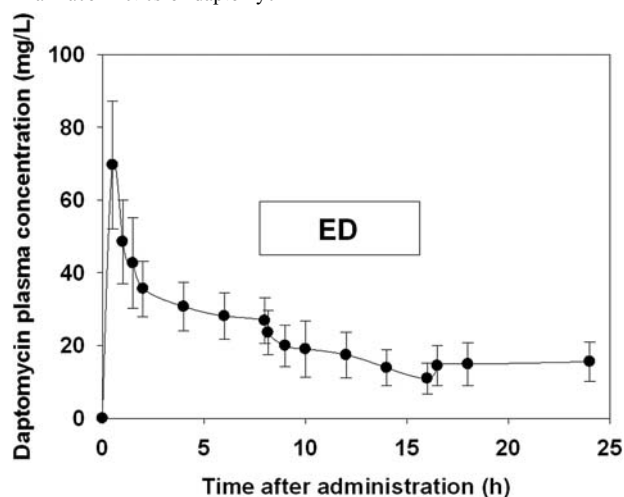
Noncompartmental pharmacokinetic analysis for the data was performed using WinNonlin software program (WinNonlin version 3.1, Pharsight Corporation, Mountain View, CA, USA). The maximum concentration in plasma ( $C_{max}$ ) and time to reach  $C_{max}$  ( $T_{max}$ ) after drug administration were obtained directly by visual examination of concentration–time data. The area under the plasma concentration–time curve from time 0 to infinity ( $AUC_{0-inf}$ ) was calculated by the log-linear trapezoidal rule until the time of last quantifiable plasma concentration and then extrapolated to infinity by using the quotient of the last measurable concentration ( $C_{last}$ ) to the terminal phase rate constant ( $\beta$ ). The terminal elimination rate constant ( $\beta$ ) was estimated from the slope of terminal exponential phase of the logarithmic plasma concentration–time profile using at least three data points. The elimination half life ( $t_{1/2\beta}$ ) was determined as  $0.693/\beta$ . Total body clearance ( $CL_{tot}$ ) was determined as  $dose/AUC_{0-inf}$ . The apparent volume of distribution during the terminal phase ( $V_z$ ) was calculated as  $dose/(AUC_{0-inf} \cdot \beta)$ . For all variables, arithmetic mean values, SD, median, minimum and maximum values were calculated, with the exception of  $T_{max}$ , for which median and minimum–maximum ranges are given.

The dialyser clearance was estimated from concentrations before ( $C_{in}$ ) and directly after ( $C_{out}$ ) the dialysis membrane as  $CL_{dial} = (Fl_{in} \cdot C_{in} - Fl_{out} \cdot C_{out}) / C_{in}$ , where the plasma flow in ( $Fl_{in}$ ) and out ( $Fl_{out}$ ) of the

**Table 1.** Critically ill patients treated with a single dose daptomycin and undergoing extended dialysis

#	Sex	Age (years)	Diagnosis	Weight (kg)	Height (cm)	BMI	APACHE II	Albumin (g/l)	UF volume (ml)
1	f	47	Liver Tx	94	155	39.1	32	25	4000
2	f	66	Lung Tx	53.7	163	20.3	39	41	2910
3	m	62	Sepsis	85	175	27.8	40	18	3000
4	m	50	Sepsis	95	190	26.3	37	15	70
5	m	62	Lung Tx	71	167	25.5	36	21	70
6	m	43	Sepsis	70	176	22.6	30	13	2400
7	f	49	AKI	50	165	18.4	37	23	3500
8	m	59	Lung Tx	72	182	21.7	39	14	970
9	m	21	ARDS	85	185	24.8	31	16	2350
10	m	43	Endocarditis	68	181	20.8	29	17	500
Mean		50.2		74.4	173.9	24.7	35.0	20.3	1977
SEM		4.1		4.8	3.5	1.8	1.3	2.6	455

BMI, body mass index; UF, ultrafiltration; Liver Tx, liver transplantation; Lung Tx, lung transplantation; ARDS, acute respiratory distress syndrome; AKI, acute kidney injury.



**Fig. 1.** Average concentrations of daptomycin in plasma of critically ill patients ( $n = 10$ ) with AKI undergoing ED (duration depicted by box size) after a single intravenous dose of 6 mg/kg body weight. Infusion period, 30 min. ED started 8 h after the end of the daptomycin infusion. Values are arithmetic means  $\pm$  SD,  $n = 10$ .

dialyser was estimated using the blood flow, haematocrit and ultrafiltration rate. In addition, total drug removal was estimated by measuring drug concentration in the spent dialysate, since the GENIUS-system permits easy access to the entire amount of substances that had been removed during a dialysis session. In contrast to other published studies with the GENIUS-system in which the amount of removed substances were measured, we did not take samples from the collected ultrafiltration fluid [17,18] but instead took samples from the total spent dialysate after it was mixed by air insufflations.

## Results

There was a significant rebound of 31% comparing daptomycin concentrations at the end of ED and 30 min thereafter (clinical information is given in Table 1). Average serum concentration–time data for daptomycin are shown in Figure 1. The dialyzer clearance for daptomycin was  $63 \pm 9$  ml/min at a plasma flow rate of  $120 \pm 5$  ml/min. The average total amount of daptomycin in the collected spent dialysate was  $116 \pm 27$  mg which equals 23.3% of the administered dose of daptomycin. Table 2 summarizes all pharmacokinetic data and compares them to literature data for IHD in an outpatient's setting as well as to normal controls without renal impairment. There were no adverse effects attributable to the use of daptomycin in our patients.

## Discussion

Our study provides the first systematic pharmacokinetic data of daptomycin in critically ill patients with anuric AKI. The pharmacokinetic data obtained in the present prospective study in patients undergoing ED document that (i) daptomycin is eliminated by ED and that (ii) current dosing recommendations from patients undergoing IHD (6 mg/kg every 48 h) would cause a significant under dosing of the drug in patients treated with ED.

**Table 2.** Comparison of daptomycin pharmacokinetic data obtained in critically ill patients with acute renal failure undergoing ED with data of patients on normal hemodialysis and healthy young volunteers previously reported

	Patients on ED	Patients on IHD [3]	Healthy volunteers [2]
$C_{\max}$ (mg/l)	$69.6 \pm 17.7$	–	$86.4 \pm 7.1$
$T_{\max}$ (h)	0.5 (0.5)	–	0.5 (0.5)
$AUC_{0-\infty}$ (mg h/l)	$531.1 \pm 177.4$	1205.6	$705 \pm 67$
$T_{1/2ON}$ (h)	$8.0 \pm 1.8$	29.3	–
$T_{1/2OFF}$ (h)	$27.7 \pm 4.3$	–	$7.8 \pm 1.0$
$V_z$ (l)	$11.4 \pm 2.9$	6.0	–
$V_z$ (l/kg)	$0.161 \pm 0.057$	–	$0.096 \pm 0.009$
$CL_{\text{tot}}$ (l/h)	$1.03 \pm 0.29$	0.24	–
$CL_{\text{tot}}$ (ml/h/kg)	$14.4 \pm 4.9$	–	$8.6 \pm 0.8$

The pharmacokinetic and pharmacodynamic properties of daptomycin should allow for once daily dosing. Daptomycin (1620.67 Da) has 92% plasma protein binding *in vitro*. In healthy adult humans, daptomycin has a volume of distribution of 0.1 l/kg and a plasma elimination half life of 7.8 h and is primarily excreted unchanged by the kidneys. Patients with a creatinine clearance  $<30$  ml/min exhibit mean area under the curve (AUC) values twice those of patients with normal renal function; patients on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD) had mean AUC values three times that of those with normal renal function. Daptomycin is removed by haemodialysis; 15% of an administered dose is eliminated in a 4-h hemodialysis session and 11% after 48 h of CAPD [3]. Therefore, in patients with reduced renal function, including those receiving haemodialysis and peritoneal dialysis, the recommended dosing interval is 48 h. There are major limitations in the study by Dvorchik. It was not aimed to specifically study patients on dialysis, therefore most of the essential coordinates of the dialysis procedure itself are missing, such as blood and dialysate flow, type and surface area of dialyser used. These specifics are however of utter importance as data from an *in vitro* model of haemodialysis have recently shown [20]. In the *in vitro* study by Churchwell, the clearance of daptomycin varied with the filter type, dialysate flow and ultrafiltration rate used, important information that is not reported in the study by Dvorchik *et al.* [3]. The lower  $AUC_{0-\infty}$  in our patients and higher total clearance of daptomycin in our patients as compared to healthy volunteers can be attributed to several causes. Firstly, volume of distribution in our critically ill patients was considerably higher than reported for patients on regular IHD. Moreover, our patients had a low serum protein, facilitating the removal of daptomycin by dialysis as the drug is protein bound up to 92%. Interestingly, there was a significant rebound with a 31% increase in daptomycin levels comparing the end of ED levels with those 30 min after the end of ED. We consider this rebound to be a result of a disequilibrium of daptomycin distribution within different body pools, as well as caused by the intensity of ED. During ED, there is most likely a concentration gradient between the intracellular and extracellular spaces, which leads to rebound of daptomycin from the intracellular

space after the end of ED. We do not think that this rebound has any clinical relevance as it would be the case for vancomycin in which the rebound is important for the timing of trough levels after renal replacement therapy.

#### *Why are these results of clinical importance?*

A recent multi-centre trial evaluating the outcome of different intensities of renal replacement therapy including ED, found that hypophosphataemia developed in 17.6% of patients in the intensive-therapy group as compared to 10.9% in the group undergoing less-intensive therapy [21]. The obvious failure to adapt phosphate supplementation to the increased dialysis dose suggests that the dosing of antibiotics, which in many instances had to be increased considerably in parallel to intensified renal support [11], was even worse, leading to under dosing of these important drugs. This is aggravated by the fact that therapeutic drug monitoring is only available for a few antibiotics. The dilemma of under dosing antibiotics could in part explain why especially septic patients, i.e. those patients in whom therapeutic drug levels of antibiotics are of vital importance, tended to have an even higher mortality with intensive renal support in the trial. Hence, pharmacokinetic data in intensive care patients with an increased volume of distribution and low albumin concentration are of utter importance to guide dosing in these patients.

We wish to point out some important limitations of our study. Although the half-life of daptomycin in our patients was comparable to that of controls reported in the literature, repeated dosing could theoretically still lead to accumulation of daptomycin. Moreover, as the specifics of ED vary between centres, our dosing recommendation holds only true for the specifics of the ED procedure reported here; however, key characteristics (low dialysate and blood flow as well as long treatment hours) are in a rather narrow range all over the world [8]. Furthermore, the timing of the start of ED, i.e. 8 h after the end of the daptomycin infusion, had a considerable influence on the  $AUC_{0-inf}$  and daptomycin removal. The earlier the ED with respect to drug administration, the lower the  $AUC_{0-inf}$  and the higher the resulting total body clearance. Thus, once daily dosing of 6 mg/kg would be considered safe and necessary if ED starts within 8 h after the administration of daptomycin. An ED treatment starting later will have a less marked effect on daptomycin removal. Lastly, the size and the purpose of our trial do not allow the drawing of any conclusion on the efficacy of daptomycin in patients with AKI undergoing ED.

In summary, our data suggest that ED—by definition an intermittent mode of renal replacement therapy—eliminates daptomycin effectively and to a larger extent than regular IHD. Thus, dosing daptomycin every 48 h, as recommended for regular haemodialysis, would result in a significant under dosing, which could be associated with a substantial risk, especially in septic patients in the ICU.

*Acknowledgements.* This study was supported by an unrestricted grant from Novartis Germany. Dr Kielstein is supported by a grant of the Else-Kröner-Fresenius Foundation (P63/06/EKMS 06/03).

*Conflict of interest statement.* C.J. is acting as an independent consultant/speaker for pharmaceutical companies. J.T.K. has received funds for speaking at symposia organized on behalf of Fresenius Medical Care and has also received funds for research from Fresenius Medical Care. All other authors have nothing to declare.

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*Received for publication: 6.4.09; Accepted in revised form: 25.11.09*