

A simplified three-times weekly daptomycin dosing regimen for chronic hemodialysis patients

Expert Rev. Anti Infect. Ther. 8(1), 11–14 (2010)

**Olaf Burkhardt and
Jan T Kielstein[†]**

[†]Author for correspondence
Department of Nephrology and
Hypertension, Medical School
Hannover, Carl-Neuberg-
Strasse 1, 30625 Hannover,
Germany
Tel.: +49 511 532 6319
Fax: +49 511 532 4005
kielstein@yahoo.com

Evaluation of: 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.* 4, 1190–1194 (2009).

Approximately 2.3 million patients worldwide are undergoing chronic renal replacement therapy. In that population, acute infections substantially contribute to the excessive morbidity and mortality. The risk for invasive methicillin-resistant *Staphylococcus aureus* infections in this population is approximately 100-fold higher than in the general population, therefore dialysis patients currently account for up to approximately 15% of all invasive methicillin-resistant *Staphylococcus aureus* infections. A simplified three-times weekly dosing regimen for hemodialysis patients now allows for practical, hassle-free and effective treatment with daptomycin, which is licensed for the treatment of complicated skin and soft tissue infections including resistant strains of *Staphylococcus aureus* and life-threatening Gram-positive infections, vancomycin-resistant enterococcal infections and right-sided endocarditis.

KEYWORDS: daptomycin • dialysis • end-stage renal disease • infection • pharmacokinetics

Salama and coworkers provide a simplified three-times weekly dosing regimen for hemodialysis patients allowing a practical, hassle free and effective treatment with daptomycin [1]. The number of patients undergoing renal replacement therapy for chronic and acute renal failure worldwide has been increasing dramatically. Approximately 2.3 million patients worldwide are undergoing chronic dialysis treatment [2]. Infections are among the most frequent causes of mortality in end-stage renal disease (ESRD) patients on dialysis. In this patient population infections account for about a quarter of all deaths [3]. The annual mortality rates in the dialysis population are increased by tenfold for pneumonia [4] and 100-fold for sepsis compared with the general population [5]. Salama and coworkers [1] investigate the feasibility of intradialytic administration of daptomycin in hemodialysis (HD) patients, as the current package insert only advises doctors to dose daptomycin every 48 h – a regimen that is neither practical nor sensible in patients who undergo

dialysis three-times weekly. Their study indicates that intradialytic daptomycin, given in the last 30 min of dialysis at a dose up to 30% higher than the recommended dose, may be an appropriate dosing strategy for HD units. This practical approach is not only convenient for the dialysis staff, but also for the patient.

Summary of methods & results

Salama and coworkers used a nonblinded, prospective, crossover design to study the pharmacokinetics of daptomycin in nine otherwise healthy adults with ESRD [1]. Only seven out of the nine patients completed all three study arms. In arm A, patients received a single dose of daptomycin according to the recommendations of the manufacturer – a dose of 6 mg/kg daptomycin was infused intravenously after the end of the dialysis session. In arm B, the patients received daptomycin (6 mg/kg) in the last 30 min of a dialysis session using a low-flux polysulfone membrane (F-8; surface area 1.8 m²). In arm C, patients received the same

dose also during the last 30 min of the dialysis session; however, a high-flux membrane (F-200 NR; surface area 2.0 m²) was used. Throughout the study, the other coordinates of the dialysis procedure such as blood flow (on average 400 ml/min) and dialysate flow (on average 700 ml/min) were not changed. In all study arms, blood samples were taken at regular intervals to measure daptomycin using liquid chromatography/mass spectrometry. Noncompartmental analysis was used to evaluate the elimination rate constant and half-life for each of the seven patients. Daptomycin serum concentrations were calculated at 45 h, and the area under the serum concentration–time curve up to 45 h (AUC) was calculated by the linear trapezoidal rule. C_{max} and T_{max} were determined on the basis of observed data. Intradialytic daptomycin administration resulted in reduced maximum serum concentration and AUC values that were approximately 12–20% lower when administered during HD with low-flux dialyzers and approximately 35% lower with high-flux dialyzers. Thus, intradialytic daptomycin administration during the last 30 min of HD is feasible but the dose has to be increased to compensate for intradialytic drug loss, which varies dramatically with the type of dialyzer used. On the basis of their findings, intradialytic doses of approximately 7 mg/kg for low-flux membranes and 9 mg/kg for high-flux membranes, that is, up to 30% higher than the dose recommended by the manufacturer, have to be administered if the intradialytic application of the drug is chosen over the postdialysis administration (TABLE 1).

Discussion

Recent data from the US renal data system indicate that in 2008, 545,753 people received renal replacement therapy, most of whom were receiving maintenance dialysis [10]. Second only to cardiovascular events, acute infections contribute substantially to the excessive morbidity and mortality of this patient population, which is 20% in the first year after the start of dialysis treatment [6]. Moreover, the relative proportion of infection-related hospitalizations has increased. In a US cohort of incident dialysis patients between 1996 and 2001, the 1-year incidence of infection-related hospitalizations was 32% for those who received

HD and 24% for those who received peritoneal dialysis; the 3-year incidence exceeded 50% in both groups [7]. The progressive spread of methicillin-resistant *Staphylococcus aureus* (MRSA) makes the treatment of those patients even more problematic. While approximately 30% of patients on dialysis in Europe are colonized with MRSA, this value increases up to 60% in the USA. Furthermore, US data indicate that the risk for invasive MRSA infections is 100-fold higher in dialysis patients than in the general population (45.2/1000 vs 0.2–0.4/1000) [8]. Dialysis patients currently account for up to 15.4% of all invasive MRSA infections [8]. The majority (86%) of these infections were bloodstream infections, identified via positive blood culture. Approximately 85% of dialysis patients in this report had an invasive device or catheter in place at the time of infection, and approximately 90% required hospitalization. The in-hospital mortality rate for MRSA-related hospitalization was 17%. Therefore, the need for a bactericidal easy-to-dose MRSA antibiotic with excellent penetration into biofilm is more important than ever. 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 *S. 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. On bloodstream *S. aureus* isolates from HD patients, daptomycin has been shown to be four-to-eight-fold more potent than linezolid and vancomycin [9]. Daptomycin has also been shown to prevent biofilm building both in initial and mature biofilms on a plastic support [10].

The pharmacokinetic and pharmacodynamic properties of daptomycin should allow for once-daily dosing. Daptomycin (1620.67 Da) has 92% plasma protein binding *in vitro*. As the percentage of the drug excreted intact in urine is approximately 54%, extending the dosing interval has been advocated for patients with renal failure [11]. These dosing recommendations are, however, based on scarce data [12]. Data from patients with acute kidney injury undergoing extended dialysis indicate that the half-life is comparable to healthy controls, hence daily dosing is necessary [13]. There are major limitations in the study by Dvorchik, which was not aimed to specifically study patients on dialysis, most of all being that essential coordinates of the dialysis procedure itself are missing, such as blood and dialysate flow, type and surface area of dialyzer used [12]. These specifics are of utmost importance as data from an *in vitro* model of continuous hemofiltration and HD by Churchwell *et al.* have shown recently [14]. In their study, the clearance of daptomycin varied with the filter type, dialysate flow and ultrafiltration rate used, important

Table 1. Three-times weekly daptomycin dosing: differences depending on the dialyzer used.

Flux	Recommended dose three-times weekly*	Dialyzer	Blood flow/dialysate flow	Treatment time
Low flux	7 mg/kg bodyweight	F-8 1.8 m ² Kuf 11 ml/h per mmHg polysulfone	400 ml/700 ml	?
High flux	9 mg/kg bodyweight	F-200NR 2.0 m ² Kuf 62 ml/h per mmHg polysulfone	400 ml/700 ml	?

*Infused over the last 30 min of the dialysis session.
Kuf: Ultrafiltration coefficient.
Data taken from [1].

information that is not reported in the study by Dvorchik *et al.* [12]. Salama and coworkers now extend these *in vitro* data to the real world [1]. Intradialytic daptomycin administration during the last 30 min of HD is feasible, provided that larger dosages are used to compensate for intradialytic drug loss. On the basis of the findings, intradialytic doses of approximately 7 mg/kg (for a low-permeability dialyzer) or approximately 9 mg/kg (for a high-permeability dialyzer) should theoretically be bioequivalent to 6 mg/kg infused after HD. The calculated dosages are mathematically driven and must be validated in prospective clinical trials.

Expert commentary

In the fast-growing population of patients with ESRD on dialysis, which is frequently suffering from multidrug-resistant, Gram-positive pathogens, daptomycin is a viable alternative to vancomycin and linezolid. Several studies on the pharmacokinetics of daptomycin in patients undergoing different renal replacement therapy enable us to set the coordinates for dosing [1,13,15,16]. The study by Salama and coworkers allows rather formal recommendations for outpatient HD patients [1]. In US-based institutions, where the 2-min injection is not approved, it is feasible to give daptomycin at a dose of 7 mg/kg three-times weekly for patients undergoing low permeability/flux dialysis and 9 mg/kg three-times weekly for patients undergoing high permeability/flux dialysis. Deductive reasoning would suggest that in Europe, where the

2-min injection is approved, a 6 mg/kg dose three-times weekly after dialysis is an adequate dose. However, studies supporting this assumption are missing. In contrast to vancomycin, in which therapeutic drug monitoring is mandatory [17], daptomycin levels do not have to be checked, making outpatient treatment even more feasible.

Five-year view

The number of patients on renal replacement therapy receiving daptomycin will rise in parallel to the spread of MRSA and with the increasing number of patients being treated with permanent dialysis catheters. In outpatients on HD with a three-times weekly treatment schedule, a three-times weekly daptomycin dose will become the standard of care. This regimen must not be applied to intensive care patients undergoing extended daily dialysis or chronic veno-venous hemofiltration.

Financial & competing interests disclosure

Olaf Burkhardt has received travel grants from Novartis (Germany). Jan T Kielstein has received an unrestricted grant from Novartis, has received funds for speaking at symposia organized on behalf of Novartis, and has also received funds for research from Novartis. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Key issues

- The number of dialysis patients is rising, doubling every 10 years.
- Dialysis patients have a high rate of methicillin-resistant *Staphylococcus aureus* infections and high mortality due to infection.
- Daptomycin is a viable alternative to vancomycin and linezolid.
- Three-times weekly administration of daptomycin in the last 30 min of dialysis is feasible and safe in chronic hemodialysis patients.
- The dose of daptomycin has to be adapted to the efficiency of dialysis, that is, mainly to flux and permeability of the dialyzer.

References

- 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.* 4, 1190–1194 (2009).
- Lysaght MJ. Maintenance dialysis population dynamics: current trends and long-term implications. *J. Am. Soc. Nephrol.* 13(Suppl. 1), S37–S40 (2002).
- Amann K, Wanner C, Ritz E. Cross-talk between the kidney and the cardiovascular system. *J. Am. Soc. Nephrol.* 17, 2112–2119 (2006).
- Sarnak MJ, Jaber BL. Pulmonary infectious mortality among patients with end-stage renal disease. *Chest* 120, 1883–1887 (2001).
- Sarnak MJ, Jaber BL. Mortality caused by sepsis in patients with end-stage renal disease compared with the general population. *Kidney Int.* 58, 1758–1764 (2000).
- Dalrymple LS, Go AS. Epidemiology of acute infections among patients with chronic kidney disease. *Clin. J. Am. Soc. Nephrol.* 3, 1487–1493 (2008).
- Chavers BM, Solid CA, Gilbertson DT, Collins AJ. Infection-related hospitalization rates in pediatric versus adult patients with end-stage renal disease in the United States. *J. Am. Soc. Nephrol.* 18, 952–959 (2007).
- CDC. Invasive methicillin-resistant *Staphylococcus aureus* infections among dialysis patients – United States, 2005. *MMWR Morb. Mortal. Wkly Rep.* 56, 197–199 (2007).
- Sader HS, Fritsche TR, Jones RN. Antimicrobial activity of daptomycin and selected comparators tested against bloodstream *Staphylococcus aureus* isolates from hemodialysis patients. *Int. J. Infect. Dis.* 13, 291–295 (2009).
- Roveta S, Marchese A, Schito GC. Activity of daptomycin on biofilms produced on a plastic support by *Staphylococcus* spp. *Int. J. Antimicrob. Agents* 31, 321–328 (2008).
- Dvorchik BH, Brazier D, DeBruin MF, Arbeit RD. Daptomycin pharmacokinetics and safety following administration of escalating doses once daily to healthy subjects. *Antimicrob. Agents Chemother.* 47, 1318–1323 (2003).
- Dvorchik B, Arbeit RD, Chung J, Liu S, Knebel W, Kastrissios H. Population pharmacokinetics of daptomycin. *Antimicrob. Agents Chemother.* 48, 2799–2807 (2004).
- Kielstein JT, Oye C, Bode-Boeger SM *et al.* Dosing of daptomycin in intensive care unit patients with acute kidney injury undergoing extended dialysis – a pharmacokinetic study. *Nephrol. Dialysis Transplant.* DOI: 10.1093/ndt/gfp704 (2009) (Epub ahead of print).

- 14 Churchwell MD, Pasko DA, Mueller BA. Daptomycin clearance during modeled continuous renal replacement therapy. *Blood Purif.* 24, 548–554 (2006).
- 15 Goedecke VA, Clajus C, Burkhardt O *et al.* Pharmacokinetics and dialysate levels of daptomycin given intravenously in a peritoneal dialysis patient. *Scand. J. Infect. Dis.* 41, 155–157 (2009).
- 16 Huen SC, Hall I, Topal J, Mahnensmith RL, Brewster UC, Abu-Alfa AK. Successful use of intraperitoneal daptomycin in the treatment of vancomycin-resistant enterococcus peritonitis. *Am. J. Kidney Dis.* 54, 538–541 (2009).
- 17 Kielstein JT, Czock D, Schopke T *et al.* Pharmacokinetics and total elimination of meropenem and vancomycin in intensive care unit patients undergoing extended daily dialysis. *Crit. Care Med.* 34, 51–56 (2006).

Website

- 101 United States Renal Data System
www.usrds.org

Affiliations

- Olaf Burkhardt
Department of Pulmonary Medicine,
Medical School Hannover, Germany
Tel.: +49 364 585 41511
Fax: +49 511 532 3353
burkhardt.olaf@mh-hannover.de
- Jan T Kielstein, MD, FASN
Department of Nephrology and
Hypertension, Medical School Hannover,
Carl-Neuberg-Strasse 1, 30625 Hannover,
Germany
Tel.: +49 511 532 6319
Fax: +49 511 532 4005
kielstein@yahoo.com