

Intradialytic Administration of Daptomycin in End Stage Renal Disease Patients on Hemodialysis

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Background and objectives: Infusion of intravenous antibiotics after hemodialysis (HD) may delay initiation of treatment for the next HD shift. Intradialytic administration of drugs such as vancomycin during the final hour of HD obviates these delays. Daptomycin has potent activity against Gram-positive bacteria, but the manufacturer recommends that the dose be infused after HD ends. This study determined the pharmacokinetics of intradialytically dosed daptomycin in patients with ESRD.

Design, setting, participants, & measurements: This prospective crossover study compared single-dose daptomycin (6 mg/kg, 30-min intravenous infusion) pharmacokinetics administered after HD *versus* during the last part of HD with high-permeability (HP) and low-permeability (LP) dialyzers to seven patients who had ESRD and were on thrice-weekly HD. Serial blood samples were collected to determine daptomycin serum concentrations and protein binding. Statistical analysis was done using linear mixed model analysis.

Results: The maximum serum concentration observed with a 6 mg/kg post-HD dose was 61.1 ± 7.6 $\mu\text{g/ml}$ with a mean protein binding of 89.2%. Intradialytic daptomycin administration resulted in reduced maximum serum concentration and area under the curve values that were approximately 12 to 20% lower when administered during HD with LP dialyzers and approximately 35% lower with HP dialyzers.

Conclusions: 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 our findings, intradialytic doses of approximately 7 mg/kg (LP) or approximately 9 mg/kg (HP) theoretically should be bioequivalent to 6 mg/kg infused after HD. The calculated dosages are mathematically driven and must be validated in prospective clinical trials.

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Daptomycin is an antibiotic that exhibits rapid concentration-dependent bactericidal activity against a broad range of Gram-positive bacteria, including methicillin- and vancomycin-resistant *Staphylococcus aureus*. Infections with Gram-positive organisms constitute a substantial cause for morbidity and mortality in patients who are on hemodialysis (HD) (1). The minimum inhibitory concentration (MIC_{90}) for *Staphylococcus aureus* and *Enterococcus faecalis* isolates that are daptomycin susceptible are ≤ 1 and ≤ 4 $\mu\text{g/ml}$, respectively (2). Daptomycin is renally eliminated and is administered every 48 h to patients with renal impairment (creatinine clearance < 30 ml/min) or patients who are on HD (2). For those patients, the drug is infused over 30 min after HD ends (2); however, this infusion time is inconvenient for patients and often delays treatment of patients on the next HD

shift, creating an additional burden. Vancomycin, another antibiotic used for Gram-positive bacterial infections, was originally infused after HD ended, causing a similar disruption to the HD treatment schedule. Studies by our group (3) and others (4–6) found that infusion of vancomycin during the final 60 to 90 min of HD can achieve therapeutic serum concentrations while alleviating the delay caused by infusions extending beyond the HD session. Intradialytic vancomycin is now the standard treatment at most HD centers, although larger vancomycin dosages must be administered to compensate for the intradialytic drug removal. The necessary vancomycin dosage increase depends on the dialyzer permeability (3).

An advantage of daptomycin compared with vancomycin is that it is not associated with infusion-related adverse effects or large infusion volumes. The large molecular weight of daptomycin (1621 Da) suggests that it could also be administered near the end of HD, similar to vancomycin. The purpose of this study was to compare daptomycin pharmacokinetics when administered after HD *versus* during the last 30 min of HD with high-permeability (HP) and low-permeability (LP) dialyzers.

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We evaluated the extent of daptomycin dialytic removal and protein binding in patients with ESRD.

Materials and Methods

Study Design

This study was a nonblinded, prospective, crossover trial in otherwise healthy adults with ESRD. Patients who were receiving thrice-weekly outpatient hemodialysis at the University of Michigan outpatient dialysis clinics were recruited. Patients were considered for inclusion into the study when they were ≥ 18 yr of age, had ESRD and had been on maintenance HD for at least 6 mo, were within 40% of ideal body weight and >40 kg, had no acute concurrent illness or evidence of infection, and were compliant with their thrice-weekly HD schedule. Medical records were reviewed to ensure that patients had not received daptomycin within the past month before study enrollment. Exclusion criteria were prestudy hemoglobin <11 g/dl, plasma albumin <2.5 g/dl, unstable BP control, need for routine large HD fluid removal (>4 L), and elevated creatine phosphokinase >600 U/L or more than three times the upper limit of normal. Patients who were pregnant; were already enrolled in other investigational drug studies; were allergic to daptomycin; or had liver disease (Child Pugh C) or HIV or experienced any signs and symptoms of myopathy (muscle pain or weakness) were excluded. The study protocol was approved by the University of Michigan institutional review board and adhered to the Declaration of Helsinki. The study was conducted at the University of Michigan Hospital's Hemodialysis Unit and General Clinical Research Center (GCRC).

Patients who met the inclusion/exclusion criteria were invited to participate in this study, and informed consent was obtained. At baseline, all patients underwent a routine physical examination, and pertinent laboratory values as described in the inclusion/exclusion criteria were assessed. The initial patient interview documented the study patient's medical history, current drug therapy, and history of allergy(ies) and included age, gender, weight, and race. No women of child-bearing age were enrolled in this study.

This study was composed of three treatment arms, and patients served as their own controls by completing all three study arms. Patients completed study arm 1 first (control arm) and then were randomly assigned to either study arm 2 (LP HD) or arm 3 (HP HD) next. Upon completion of the second portion of the study, the patient then completed the third and final arm. Study arms were separated by at least a 7-d washout. Blood (average 400 ml/min) and dialysate (average 700 ml/min) flow rates used in every study arm were the same ones used at each patient's usual dialysis session. Daptomycin doses were prepared by the University of Michigan Investigational Drug Service on the day of the study according to the manufacturer's recommendations.

Control Arm (Study Arm 1)

Patients received their usual HD session using a F200NR (Fresenius Medical Corp., Waltham, MA) hemodialyzer in the hospital dialysis unit. Once HD ended, patients were transported to the GCRC, where they received a 6-mg/kg (based on dry body weight) daptomycin dose infused intravenously over 30 min. Serial blood samples (5 ml per sample) were obtained before infusion; at end of infusion; and at 1, 2, 3, 4, 24, and 44 h (time next dialysis session started) from the start of infusion to determine daptomycin pharmacokinetics when no HD was occurring.

LP Arm (Study Arm 2) and HP Arm (Study Arm 3)

After at least a 7-d washout period from the previous study arm, patients received their standard HD session at their normally scheduled

time. The hemodialyzer used in this session was either a new LP polysulfone membrane (F-8; SA 1.8 m², ultrafiltration coefficient (Kuf) 11 ml/h per mmHg; Fresenius) for arm 2 or a new HP polysulfone membrane (F-200NR; SA 2.0 m², Kuf 62 ml/h per mmHg; Fresenius) for arm 3. During the final 30 min of HD, a 6-mg/kg (based on dry body weight) daptomycin dose was infused intravenously over 30 min. Dialysis ended at the same time as the daptomycin infusion ended. Serial blood samples (5 ml per sample) were obtained before infusion; at the end of the infusion; and at 1.0, 1.5, 2.5, 3.5, 4.5, 24.0, and 45.0 h from the start of the infusion, to determine the pharmacokinetics of daptomycin when it is administered during LP (arm 2) and HP (arm 3) hemodialysis.

After HD, one of the dialysis needles remained in the patient's access for venous blood sampling. After the blood samples for the first 4 h were obtained, the venous access needle was removed and the patient was discharged home. The patient returned the next day to the GCRC for the 24-h blood draw, obtained *via* standard venipuncture. The last blood sample (approximately 45 h) was obtained at the HD unit before initiation of the next HD session from the dialysis needle that was already placed for the impending dialysis session.

Liquid Chromatography/Mass Spectrometry Assay Method

Serum was separated by centrifugation, and daptomycin concentrations were analyzed by a liquid chromatography/mass spectrometry (LC/MS/MS) method. A daptomycin analogue, CB-183253, was used as internal standard, which, along with the daptomycin analytical reference standard, were provided by Cubist Pharmaceuticals Inc. Human serum purchased from Bioreclamation Inc. (Liverpool, NY) was used as a matrix blank to build the calibration standard curve. Other instrumentation included an Applied Biosystem API-3000 coupled with an Agilent 1100 Quaternary Pump and a Leap CTC Autosampler. The calibration standard curve ranged from 1.0 to 100.0 μ g/ml. A 5% CHAPS (3-[(3-cholamidopropyl)-dimethylammonio]-1-propane-sulfonate) solution (50 mM in 0.1% formic acid) was added to calibration standards, quality control samples, and study samples. The 50- μ l serum samples were mixed with 400- μ l internal standards CB-183253 5.0 μ g/ml in 0.1% trifluoroacetic acid in acetonitrile solution. The mixture was vortexed for 10 min and then centrifuged at 3000 rpm for 10 min at 4°C. The 250- μ l supernatant was dried under nitrogen gas and reconstituted with 100 μ l of 5 mM CHAPS in 0.1% formic acid water solution and analyzed by LC/MS/MS. Multiple ions Reactions Monitor transitions on mass spectrometer of 811 to 159 and 837 to 365 were used to monitor daptomycin and internal standards, respectively.

Protein Binding Determination

Because the extent of daptomycin protein binding has not been published in patients with ESRD, an additional 10-ml blood sample was obtained at 1.5, 24.0, and 44.0 h after the end of the infusion in the control arm to determine protein binding. The blood sample was allowed to clot for at least 30 min and was then centrifuged (2000 \times g, 10 min, 4°C). The resultant serum was collected for protein-binding analysis.

The percentage of protein-bound daptomycin in serum and the percentage of free fraction (F_u) were determined by equilibrium dialysis. The generated serum side samples and buffer side samples were subsequently analyzed by LC/MS/MS method (described in previous section). The percentage of daptomycin-free fraction was calculated on the basis of the buffer side sample concentration divided by the serum side sample concentration, which represents total daptomycin concentrations. Equilibrium dialysis was performed in dialysis cells made from Teflon compartment volumes of 1.0 ml. Diachema dialysis membranes (Amika, Columbia, MD) with 10,000 molecular weight cutoff were used. One milliliter of the isotonic 200 mM phosphate buffer (pH 7.4) was used to dialyze against 1.0

ml of human serum samples. The dialysate chamber was incubated for 3 h at 37°C. The drained serum samples and buffer samples were stored at –20°C until analysis by LC/MS/MS.

Pharmacokinetic Analysis

Noncompartmental analysis was used to evaluate the elimination rate constant and half-life for each of the seven patients (Table 1). 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 linear trapezoidal rule. The maximum serum concentrations (C_{max}) and time to maximum serum concentration (T_{max}) were determined on the basis of observed data. The relative bioavailability (F), using C_{max} or AUC, for each patient was calculated according to the following formula:

$$F = ([\text{HD}/\text{control}] \times 100\%)$$

HD = hemodialysis arm 2 or arm 3

Statistical Analysis

Given the lack of balance in the data set as a result of the presence of missing data (patient 7 in control arm), a two-way repeated measures ANOVA was performed using the MIXED procedure in SPSS 15 (SPSS, Chicago, IL; designed for unbalanced repeated measures data sets), where errors associated with observations on the same patient had a compound symmetry or unstructured covariance structure. The best-fitting covariance structure was determined by comparing model fit criteria (Akaike information criterion, Bayesian information criterion) between competing models with a fully specified mean structure (including the interaction between arm and sequence). Nonsignificant interactions were dropped to examine main effects. No adjustments were made for multiple comparisons between the study arms to maintain the power of the study design. Statistical significance was considered to be $P < 0.05$ for all comparisons.

Sample Size Calculation

Power analysis showed that a sample size of six patients would be sufficient to detect a $\geq 25\%$ difference in the daptomycin AUC when daptomycin is administered during dialysis with a high-flux hemodialyzer (arm 3), compared with when it is infused after dialysis (arm 1). Our previous work found a difference of 26.3% in this comparison using vancomycin, another drug with a large molecular weight. This calculation assumed a 10% SD with a power of 0.9 and a significance level of $P < 0.05$. We recruited nine patients for this study because of the potential for patient dropout.

Results

Nine otherwise healthy patients who had ESRD and were on long-term HD were recruited, and seven (age 56 ± 15 yr; three female; weight 64.1 ± 14.1 kg; four black, two white, one Native American; body mass index 22.5 ± 3.3 kg/m²) completed all three arms of the trial. One patient elected to discontinue participation after receiving the drug on day 1. A second patient was enrolled but was found to be ineligible because of a recent hospitalization before receiving daptomycin. Study patients who completed the trial continued all of their usual maintenance medications while on this study. All patients scored below the minimum class A Child Pugh score and had serum albumin concentrations >3.8 g/dl during the month in which we conducted their trial. The causes of underlying renal failure were diabetes (two patients), hypertension (two patients), and glomerulonephritis (three patients). The length of time the patients received long-term HD before the study ranged from 8 to 331 mo. The average ultrafiltration volume was 2.8 ± 1.4 L. Patients received their HD *via* arteriovenous fistula (three patients), arteriovenous graft (two patients), and tunneled catheter (two patients). During the study, none of the patients experienced elevated creatine phosphoki-

Table 1. Daptomycin (6 mg/kg) pharmacokinetic parameters after 30-min intravenous infusion when administered (1) after HD *versus* (2) infused during the last part of HD with LP and (3) HP dialyzers in seven patients who had ESRD and were receiving thrice-weekly HD^a

Parameter	Study Arm		
	Control, after HD (n = 6)	LP, HD (n = 7)	HP, HD (n = 7)
C _{max} (μg/ml)			
mean ± SD	61.1 ± 7.6	51.4 ± 8.9	39.7 ± 7.6 ^{b,c}
F (%)		87.7 ± 18.4	67.3 ± 18.6
Calculated AUC (0 to 45 h; μg* h per ml)			
mean ± SD	1076.4 ± 87.7	876.3 ± 86.4 ^b	711.5 ± 125.9 ^{b,c}
F (%)		80.6 ± 8.0	64.6 ± 12.8
Half-life (h)			
mean ± SD	45.5 ± 22.8	29.0 ± 7.8	34.1 ± 14.8
range	27.5 to 90.4	14.8 to 39.6	13.9 to 59.8
T _{max} (h)	0.5	0.5	0.5
Calculated serum concentration at 45 h (μg/ml)	15.27 ± 2.60	10.15 ± 3.30 ^b	9.64 ± 3.80 ^b

^aAUC, area under the curve; C_{max}, maximum serum concentrations; F, relative bioavailability; HD, hemodialysis; HP, high-permeability; LP, low-permeability; T_{max}, time to maximum serum concentration.

^b $P < 0.05$ *versus* control.

^c $P < 0.05$ *versus* LP.

nase plasma concentrations, reported symptoms of myopathy, including muscle weakness or pain, or any other adverse effects. In the control arm only, the mean pharmacokinetic data (Table 1) excluded information from one patient whose daptomycin serum profile did not allow us to calculate valid pharmacokinetic parameters.

The mean (\pm SD) daptomycin serum concentrations observed in the three study arms are displayed in Figure 1. All daptomycin serum concentrations before infusion were below the level of assay quantification (<1.0 $\mu\text{g}/\text{ml}$) indicating sufficient washout. The pharmacokinetic parameters are displayed in Table 1. Daptomycin half-life did not differ between study arms ($P = 0.1$). The variability associated with this parameter may have contributed to this finding. The percentage of unbound daptomycin in the control arm at 1.5, 24.0, and 44.0 h was 10.7 ± 1.5 , 10.6 ± 1.9 , and $11.1 \pm 2.6\%$, respectively. In the control arm, the apparent volume of distribution was 0.18 ± 0.02 L/kg and apparent clearance was 0.21 ± 0.08 L/h.

The mean observed C_{max} (\pm SD) in the control arm was 61.1 ± 7.6 $\mu\text{g}/\text{ml}$ (range 52.2 to 69.6 $\mu\text{g}/\text{ml}$). The mean C_{max} in the HP arm of 39.7 ± 7.6 $\mu\text{g}/\text{ml}$ was lower than the control arm ($P = 0.001$). There was a trend toward lower C_{max} values in the LP arm (51.4 ± 8.9 $\mu\text{g}/\text{ml}$; $P = 0.059$) when compared with the control arm. In addition, the mean C_{max} observed in the HP arm was significantly ($P = 0.021$) lower than the LP C_{max} . Similarly, AUC was significantly ($P < 0.005$) lower in the LP and HP arms compared with the control arm. The AUC was lowest in the HP arm compared with control and LP arms. Furthermore, AUC observed in the HP arm was significantly ($P = 0.003$) lower than the LP AUC. The relative bioavailability parameters, C_{max} and AUC,

were lower in the LP and HP arms, when compared with control. The mean relative bioavailability for AUC (64.6%) and C_{max} (67.3%) were lower in the HP arm compared with those calculated for the LP arm (80.6 and 87.7% for AUC and C_{max} , respectively).

Discussion

This is the first study to assess the feasibility of administering daptomycin intradialytically. Because of its spectrum of activity against Gram-positive organisms, daptomycin use in HD units is likely to grow. Intradialytic daptomycin administration may improve the efficiency of nursing and patient time by not requiring patients to remain in the unit for an extra 30 min to receive the drug.

In our trial, intradialytic daptomycin administration resulted in C_{max} and AUC values substantially lower than those obtained when daptomycin was administered after HD. As a result, larger daptomycin doses are needed to compensate for the intradialytically removed drug, the extent of which depends on the dialyzer permeability. We quantified this difference by using the concept of relative bioavailability (F). The ratio of $1/F$ calculates the higher dosage necessary to reach the same C_{max} and AUC values as were achieved with the 6-mg/kg post-HD dose. For the LP arm, F was $87.7 \pm 18.4\%$ (range 62.9 to 111.9%) and $80.6 \pm 8.0\%$ (range 68.1 to 90.2%) when calculated with C_{max} and AUC, respectively. Consequently, the LP dosage increase should range from 6.8 (6 mg/kg/0.877) to 7.4 mg/kg (6 mg/kg/0.806). Similarly, the dosage increase for the HP arm ranges from 8.9 to 9.3 mg/kg when considering F calculated with C_{max} (range 49.5 to 92.3%) and AUC (range 43.0 to 78.8%) parameters, respectively. Collectively, we hypothesize intradialytic dosages of approximately 7 mg/kg

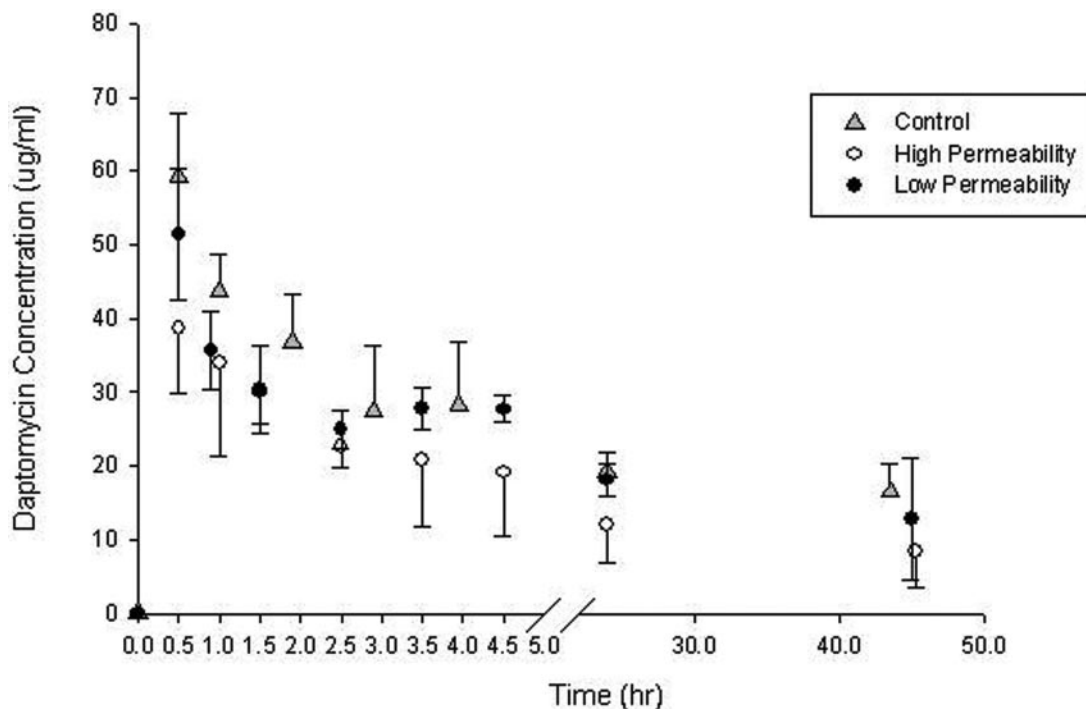


Figure 1. Mean \pm SD daptomycin (6 mg/kg) serum concentrations versus time profile after 30-min intravenous infusion when administered (1) after hemodialysis (HD; \triangle) versus (2) infused during the last part of HD with high-permeability (\circ) and (3) low-permeability (\bullet) dialyzers to seven patients who had ESRD and were on thrice-weekly HD.

(LP) or approximately 9 mg/kg (HP) should be bioequivalent to 6 mg/kg infused after HD; however, these estimated dosages are theoretical, based on relative bioavailability calculations, and must be validated in prospective pharmacokinetic studies before implementation, given the relatively wide ranges seen in observed AUC and C_{max}.

Daptomycin efficacy may be correlated with C_{max}/MIC and AUC/MIC (7–9). In previously published pharmacokinetic trials of healthy volunteers, once-daily administration of daptomycin (6 mg/kg) yielded C_{max} of approximately 88 μg/ml, half life of approximately 8 h, and volume of distribution of approximately 0.11 L/kg (10–12). In the control arm of our study, in which a 6-mg/kg dose was administered after HD, we observed lower C_{max} (61.1 ± 7.6 μg/ml), longer half-life (45.5 ± 22.8 h), and higher apparent volume of distribution (0.18 ± 0.02 L/kg). Previous reports also suggested that patients with kidney disease have higher volume of distribution compared with healthy volunteers (13). Other studies suggested a mean apparent volume of distribution of 0.13 ± 0.03 L/kg, a half-life of 28.03 ± 6.22 h, and a C_{max} of 69.00 ± 11.01 μg/ml after administration of 6 mg/kg daptomycin after HD (unpublished Cubist data, David P. Benziger, Ph.D., Cubist Pharmaceutical, Inc., Lexington, MA, personal communication, November 19, 2008), similar to our findings. Sica *et al.* (14) reported daptomycin half-life of 36.7 ± 7.4 h and volume of distribution of 0.154 ± 0.040 L/kg in patients with ESRD (*n* = 13) after 4 mg/kg daptomycin dosing after HD. Similar to our findings, they reported achieving lower C_{max} values in patients with ESRD than in healthy volunteers. In addition, the percentage of protein binding that we measured (mean unbound fraction 10.8%) was similar to that reported in healthy volunteers (approximately 10%) (10,11) and in patients who were receiving HD (10.70 ± 1.84%; unpublished Cubist data, David P. Benziger, Ph.D., Cubist Pharmaceutical, Inc., Lexington, MA, personal communication, November 19, 2008). The clinical significance of a larger volume of distribution in patients with ESRD and the resultant lower C_{max} compared with those achieved in healthy volunteers has yet to be determined.

Conclusions

Our study indicates that intradialytic daptomycin may be an appropriate dosing strategy for HD units. As is routinely done with vancomycin, the advantages of convenience to the unit, HD staff, and patients as well as reduction in personnel expenses may outweigh the cost associated with the larger daptomycin dosage needed to offset intradialytic loss.

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Disclosures

B.A.M., the principal investigator of this trial, serves on Cubist speaker bureau.

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