Antibiotic Dosing in Slow Extended Daily Dialysis

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Slow extended daily dialysis (SLEDD) is the newest form of dialysis that is being used increasingly to replace continuous venovenous hemodialysis (CVVHD) for critically ill patients; it is less expensive to administer and has similar safety for patients who are prone to hemodynamic instability. Unfortunately, there are limited data regarding the appropriate dosing of antimicrobial agents for patients undergoing SLEDD. Furthermore, many nonnephrologists are not familiar with the differences between SLEDD, other continuous renal replacement therapies—for example, CVVHD—and routine hemodialysis. Thus, there is potential for inaccurate and, at worst, inadequate dosing of critical antimicrobial agents for this patient population. We review the available pharmacokinetic data on SLEDD and give preliminary recommendations for how to approach dosing in this situation.

OVERVIEW OF DIALYSIS MODALITIES IN THE INTENSIVE CARE UNIT

A variety of hemodialysis modalities are available for the treatment of acute kidney failure, ranging from conventional intermittent hemodialysis to continuous treatment [1]. These vary widely in the length of time undergoing dialysis and their efficiency of solute removal. The proliferation of dialysis methods has generated a panoply of acronyms, as well as confusion, especially among nonnephrologists, about what is being accomplished during each of these procedures (Table 1).

The original extended dialysis modality was continuous arteriovenous hemofiltration (CAVH). It was introduced to afford improved hemodynamic stability over that achieved with conventional intermittent hemodialysis. During CAVH, removal of solutes is accomplished by filtration of blood across a membrane, producing an ultrafiltrate of plasma under the pressure of the patient’s own arterial pressure—no blood pump is used. Solute removal is thus a function of the total amount of filtrate produced and solute permeability. For instance, if 1 L of ultrafiltrate per hour is produced, then for a freely permeable solute, removal is 24 L/day (ignoring factors such as predilution). To put this in context, the normal glomerular filtration rate is ∼120 mL/min or 180 L/day. Thus, the effectiveness in this instance would be ∼13% of normal. Because antibiotics have a molecular weight that is generally <2000 Daltons, if they are not protein bound, then they are readily filtered at the glomerulus. They are also reasonably well filtered by modern dialysis and ultrafiltration membranes. In this example, they would be filtered at a rate of ∼24 L/day. In CAVH, some control of ultrafiltration rate could be achieved by placing a pump on the ultrafiltrate side; however, because no blood pump was used, ultrafiltrate rates were determined by peripheral blood pressure and resistance at the filter. Initial high filtration rates relative to blood flow often caused sludging of blood on the venous side of the hollow fibers, increasing resistance to flow with reduced filtration rate. Historically, addition of blood pumps and dialysis baths increased the complexity but allowed more versatility. The addition of a blood pump allows venous catheters to be placed instead of arterial catheters and allows the blood flow rates to increase (in continuous venovenous hemofiltration [CVVH]), thus achieving clearances of at least 35 mL/kg/h. This clearance is ∼30% of normal and is reflected in the tables for antibiotic use in such references as The Sanford Guide to Antimicrobial Therapy [2]. Addition of a dialysis bath permits the use of dialysis alone or in combination with ultrafiltration (in continuous venovenous hemodialysis [CVVHD]).

In recent years, slow extended daily dialysis (SLEDD) has become an alternate modality to CVVH [3–5]. It represents a “hybrid” that uses conventional dialysis machines but at some-
what lower efficiency (than conventional dialysis). The nomenclature is confusing because a variety of terms have been applied to this therapy, the efficiency is not very low, and the dialysis may not always be provided daily. It differs from the original continuous therapies in that, during the time of dialysis, clearances for small molecules are generally higher per hour than they are in CVVH or CVVHD; however, SLEDD is generally used for only 6–12 h per day (although some people use it continuously). As with continuous therapies, hemodynamic stability in SLEDD is better than in intermittent hemodialysis because it is still less efficient and runs for a longer time. Conventional dialysis machines are used; thus, no additional equipment is needed, and the machine can be used for intermittent hemodialysis. The dialyzers are also relatively inexpensive. Routine dialysate concentrate is used, rather than specialized dialysate and ultrafiltrate replacement solutions. Overall, the operating expenses are considerably less than those for CVVH [6]. Furthermore, anticoagulation is not generally necessary for SLEDD [7]. There was less removal of “middle molecules” in the size range 1000–10,000 Daltons than with CVVH, because the membranes are generally less leaky, and this may be a disadvantage.

Dialysis efficiency is related to the rates of dialysate and blood flow. With use of current dialyzers, the diffusion of small molecules is high enough that, at relatively low flow rates, the dialysate and blood nearly equilibrate. For example, at a dialysate flow of 100 mL/min, a typical flow rate for SLEDD (as opposed to a rate of 500–800 mL/min for routine intermittent dialysis), and a blood flow rate of 200 mL/min, in vitro urea clearances with use of a Fresenius AV600 polysulfone hemodialyzer (surface area, 1.4 m²) were 82–98 mL/min (T. Folden, Fresenius Medical Care, personal communication). Thus, clearance was limited in this case by dialysate flow rate. Modeling of SLEDD on the basis of actual in vivo clearances using similar parameters (dialysate flow rate, 100 mL/min; blood flow rate, 250–300 mL/min) predicted a urea clearance of 78 mL/min [8]. As in this example, in actual practice, the clearance will vary from the theoretical 100 mL/min because of factors such as recirculation, use of a prefilter dilution fluid, and variances in dialysate and blood pump rates. Nevertheless, if one simply assumed a clearance of 100 mL/min as an estimate of clearance, then this would lead to a modest overdosing of antibiotic. On the other hand, simply using dosing tables designed for CVVH would suggest a clearance of 30 mL/min, which would lead to underdosing, at least during the time of dialysis. Some centers use dialysate flow rates of 300 mL/min. Clearances in the laboratory at this flow rate and a blood flow rate of 200 mL/min are ~170 mL/min (T. Folden, personal communication). In this case, clearances are limited by blood flow rate. Again, although clearances in the clinical setting would likely be lower, they would still be generally higher than that of normal kidneys. During the procedure, depending on the antibiotic used, the dose could be that used for patients with normal kidneys and then, when dialysis is not being administered, it could be the anephric dose.

LITERATURE REVIEW

Vancomycin

Two studies have examined the pharmacokinetics of vancomycin during SLEDD. The first included 11 patients in the intensive care unit (ICU) with acute renal failure [9]. Patients were dosed with 15 mg/kg of vancomycin, based on actual body weight. Patients underwent SLEDD using F4 and F5 hemodialyzers (Fresenius 2008H dialysis machine; Fresenius Medical Care) at a mean blood flow rate of 200 mL/min and a dialysate flow rate of 100 mL/min. The pharmacokinetics of vancomycin during SLEDD were as follows: apparent volume of distribution ($V_d$), 0.84 L/kg (range, 0.58–1.24 L/kg); half-life, 43.1 h (range, 18.8–96 h); and clearance, 24.3 mL/min (range, 16.3–42 mL/
Patients received maintenance doses to maintain trough levels of 10–20 mg/L at dosing intervals ranging from every 24 h to every 72 h. Because of the wide variability of the vancomycin half-life in their critically ill patients undergoing SLEDD, the authors recommended an initial dose of 15 mg/kg followed by a 24-h postinfusion vancomycin level to determine the replacement dose.

The second study of vancomycin during SLEDD evaluated 10 ICU patients with acute renal failure [10]. A 1-g dose of vancomycin was infused 12 h before dialysis. The Genius batch system with high-flux polysulfone dialyzer (F60S; surface area, 1.3 m²), and a mean blood and dialysate flow rate of 160 mL/min for 8 h was used for SLEDD. Drug concentrations were measured in the dialysate to determine the amount of total drug removed by the system. The clearances of vancomycin were 2.1 L/h and 3.8 L/h, depending on the analysis method, and the half-life was 11.2 h (range, 7.6–19.5 h) during dialysis, whereas the clearance was 1.58 L/h (range, 0.37–2.38 L/h) and the half-life was 37.3 h (range, 14.6–65.9 h) when dialysis was not being administered. The fraction of vancomycin removed by dialysis was estimated to be ~25%. There was a 10% rebound in vancomycin concentrations after SLEDD. These authors recommended an initial dose of 20–25 mg/kg.

Gentamicin
A single-dose study of gentamicin was performed involving 8 non-hospitalized patients with end-stage renal disease undergoing long-term hemodialysis [11]. Gentamicin (dose, 0.6 mg/kg, based on actual body weight) was given immediately after 8 h of SLEDD. The dialyzer used a high-flux polysulfone F50 filter (surface area, 0.5 m²) with a blood flow rate of 200 mL/min and a dialysate flow rate of 300 mL/min. The mean half-life of gentamicin during and after SLEDD was 3.7 ± 0.8 h and 20.4 ± 4.7 h, respectively. Gentamicin clearance during SLEDD was 75.9 ± 38.4 mL/min/1.73 m², with 70.5% ± 19.3% removal of the dose over the 8-h dialysis period. The mean Vd was 0.28 L/kg, which is similar to the Vd range of 0.2–0.3 L/kg observed in healthy subjects. In this study, <4% rebound of drug was seen, compared with the 28% observed in a study of patients undergoing hemodialysis [12]. The authors attributed the differences in drug rebound to the slower blood and dialysate flow rates and to the smaller dialyzer used with SLED, which results in a slower rate of gentamicin removal, thus allowing for more time for redistribution of drug. This finding is important in considering dosing adjustments based on measured gentamicin plasma concentrations. Because ~30% of gentamicin remains after SLEDD and little rebound occurs, the authors recommend that replacement doses of 2.0–2.5 mg/kg should be given after dialysis to maintain therapeutic levels (7.5 mg/L peak at 1 h after dose and a trough of 0.7 mg/L after SLEDD).

Fluoroquinolones: Moxifloxacin and Levofloxacin
Moxifloxacin and levofloxacin were studied in SLEDD using the Genius batch system with high-flux polysulfone dialyzer (F60S; surface area, 1.3 m²), and a mean blood and dialysate flow rate of 160 mL/min for 8 h [13]. In 1 arm of the study, 10 adult ICU patients, 6 with a Child-Pugh score of class C, received 400-mg doses of moxifloxacin 8 h before dialysis. Clearance of moxifloxacin when not undergoing dialysis was 15.7 L/h (range, 8.1–49.3 L/h), with a half-life of 12.3 h (range, 3.7–34.0 h). The clearance was estimated to be 2.0–3.1 L/h, with a half-life of 6.0 h (range, 3.9–11.0 h). The estimates of the fraction of moxifloxacin removed ranged from 8% to 35%, depending on the method used. In this study, the pharmacokinetics of moxifloxacin in patients undergoing SLEDD were comparable to those in healthy subjects and in patients without renal impairment. Severe hepatic impairment had no significant effect on pharmacokinetics. Thus, the authors recommend that, regardless of liver impairment, patients with acute renal failure undergoing SLEDD should be given a standard 400-mg dose of intravenous moxifloxacin once daily after dialysis.

In the other study arm, 5 adult ICU patients, 1 with a Child-Pugh score of class C, received 250 or 500 mg intravenous doses of levofloxacin at 12 h before dialysis. Clearance of levofloxacin when not undergoing dialysis was 3.07 L/h (range, 2.96–3.17 L/h), with a half-life of 34.5 h (range, 21.2–47.7 h). The clearance was estimated to be 2.93–3.12 L/h, with a half-life of 10.3 h (range, 10.0–10.6 h). The fraction removed by dialysis was estimated to be 17%–27%, depending on the method. The total drug recovered from the dialysate was 91 mg (range, 12–170 mg), which corresponds to the estimations of dialysis clearances. The percentage of levofloxacin removed by SLEDD was similar to that removed by standard intermittent hemodialysis, but with SLEDD, the estimated half-life was shorter. The authors suggested that dose adjustments of levofloxacin are needed for patients undergoing SLEDD, and the dose should be administered after dialysis.

Carbapenems
Meropenem. Meropenem was studied in 10 ICU patients undergoing SLEDD using a Genius batch dialyzer with a 1.3-m² polysulfone membrane, blood and dialysate flow rates of 160 mL/min, and duration of 8 h [10]. A dialysate clearance of 5 L/h and fractional excretion of 51% were estimated by the Fick equation; dialysate clearance of 2 L/h and fractional excretion of 18% were derived from recovery of drug in the dialysate. This discrepancy is most likely because of adsorption of the drug to the dialyzer. The Vd was 0.72 L/h, which is 3-fold greater than that in stable patients undergoing hemodialysis. Their data suggest that elimination of meropenem by SLEDD is similar...
to that by CVVH, and they recommend dosing of 0.5–1 g every 8 h.

Ertapenem. A single-dose study of ertapenem disposition was performed involving 6 septic patients with anuric acute renal failure [14]. SLEDD was performed using a Genius batch dialyzer with a 1.3-m² polysulfone membrane with blood and dialysate flow rates of 160 mL/min. Clearance with SLEDD was 48 mL/min, which was comparable to that seen for ICU control subjects and healthy control subjects with normal renal function. Free concentrations were 1.3 ± 1.0 mg/L at 24 h after a single intravenous administration of 1 g, which is greater than the minimum inhibitory concentration at which 90% of isolates are susceptible (MIC₉₀) (<1 mg/L) for most common aerobic and anaerobic pathogens. The authors recommend dosing of 1 g every 24 h for ICU patients receiving SLEDD and not halving the dose as suggested by the manufacturer.

Daptomycin

Daptomycin was examined for a single ICU patient with aortic valve endocarditis and septic shock [15]. A dose of 660 mg of daptomycin was given to a 110-kg white man (ie, a dose of 6 mg/kg). The blood flow rate was 200 mL/min, the dialysate flow rate was 100 mL/min, and the duration of treatment was 12 h. The half-life during SLEDD was 9 h, comparable to that for patients with normal renal function, and the clearance was 3-fold greater than that for patients undergoing intermittent hemodialysis. The total amount of daptomycin in the dialysate was 346 mg, which was half the given dose. The low serum albumin level of 2.1 mg/dL probably facilitated clearance in this individual. The authors suggested that the daptomycin dosing interval of 48 h, recommended for hemodialysis, may be inadequate for SLEDD.

There were many limitations to this study. It was a single-dose, non–steady state study involving a single patient. Pharmacokinetic studies of daptomycin in an in vitro model of CVVHd and CVVH indicated that the extent of daptomycin transmembrane clearance was dependent on hemofilter type, dialysate rates, and ultrafiltration rates [16]. These parameters, especially dialysate rates, are also likely to affect clearance with SLEDD and possibly may lead to substantial variability in daptomycin clearance. We thus recommend dosing of daptomycin every 24 h for patients undergoing SLEDD, until additional data are available.

Linezolid

The pharmacokinetics of linezolid during SLEDD were examined in a single-dose, non–steady state study involving 5 ICU patients with acute renal failure [17]. The patients received a single 600-mg infusion before SLEDD, which was performed with a low-flux polysulfone filter for 8–9 h with a blood flow rate of 200 mL/min and a dialysate flow rate of 100 mL/min.

The mean serum concentrations were 13.65 mg/L at the peak, 9.73 mg/L at the start of SLEDD, and 2.76 mg/L after 8 h. A mean of 205 mg, ~33.9% of the dose, was removed by SLEDD. The calculated pharmacokinetics of linezolid during SLEDD were as follows: $V_d = 30.19 \text{ L}$; $V_j$ per kg, 0.414 L/kg; $\beta$ half-life, 5.88 h; and clearance, 33.3 mL/min. After undergoing SLEDD, 3 of 5 study patients had linezolid levels that were <4 mg/L, and all patients had levels <4 mg/L at the end of the 12-h dosing interval. The authors recommended that linezolid be given at the end of SLEDD to maintain adequate serum concentrations, especially when targeting Staphylococcus species with MIC₀ of 4 mg/L.

DISCUSSION

Antimicrobial dosing in renal failure has become increasingly complex because of the use of multiple dialysis modalities and confusing terminology. Further compounding the complexity is the lack of uniformity in dialysis flow rates and membranes. The pharmacokinetic studies reviewed here provide only very limited guidance, because most were non–steady state studies and included small numbers of patients. Additional, larger studies are needed with a wider array of antimicrobial agents. Fortunately, for most antibiotic agents, there is considerable latitude in dosing. For example, in the case of time-dependent agents, such as $\beta$-lactams, the free level of drug needs to be above the MIC for only 40%–50% of the dosing interval to achieve a good outcome [18, 19]. For concentration-dependent agents, such as aminoglycosides and quinolones, it is the dose itself that is related to efficacy, rather than the dosing frequency.

The pharmacokinetic studies are generally consistent with theoretic predictions based on the blood and dialysate flow rates and the guidelines for CVVH and intermittent hemodialysis. For the most part, daily clearances for SLEDD are in the range for CVVH, except that they are achieved over a shorter time period; clearances are similar to those for an intermittent hemodialysis session but are achieved over a longer time period. Thus, SLEDD dosing can be conveniently estimated from tables such as those in The Sanford Guide to Antimicrobial Therapy [2], based on data for continuous renal replacement therapy. We recommend, however, that in the case of SLEDD, for a dose given every 24 h, it should be given at the end of SLEDD, and for a dose given every 12 h, it should be given at the end of SLEDD and again 12 h later. Although there will be differences in clearances for different dialysate and/or blood flow rates, even if SLEDD achieves a clearance greater than normal, antibiotic levels are unlikely to be subtherapeutic for more than one-half of the SLEDD session (ie, 3–6 h). In the worst-case scenario, as long as a post-SLEDD dose is given, levels will be less than the MIC for not more than 25% of the dosing interval, well within the standard of 40%–50% as stated above.

Remember that, if SLEDD is performed around the clock,
then antibiotic dosing will have to be proportionately increased to avoid underdosing. Another logistical problem occurs when an antibiotic is ordered to be given "post-SLEDD" but SLEDD is held; in this case, no additional doses will be given, creating a potentially dangerous situation.

Until there are better data, we recommend the following:

1. Infectious diseases and critical care specialists should communicate directly with nephrologists regarding the type of dialysis being administered to the patient each day.
2. Nonnephrologists should be aware of the terminology and essential differences between the various dialysis modalities.
3. Physicians writing antimicrobial orders for these patients should speak directly to nursing staff to ensure that post-SLEDD doses are administered.
4. As a general rule of thumb, for patients undergoing SLEDD for 6–12 h per day, renally cleared antimicrobial agents should be adjusted as they would be for continuous renal replacement therapy—namely, a creatinine clearance of 10–50 mL/min (per the current recommendations for continuous renal replacement therapy in The Sanford Guide to Antimicrobial Therapy).
5. For antimicrobial agents normally administered every 24 h that experience significant removal during dialysis, consideration should be given to administration of a supplemental dose immediately after SLEDD or simply to administration of the daily dose after SLEDD each day.
6. For antimicrobial agents normally administered every 12 h that experience significant removal during dialysis, the dose should be given after SLEDD and 12 h later.
7. Serum trough levels of antibiotics (eg, vancomycin and gentamicin) should be measured immediately after SLEDD, to determine the need for a post-SLEDD supplemental dose.

Acknowledgments

We thank Dr. Tom Folden, Senior Director Patent Technical and Research Specialist at Fresenius Medical Care NA, for providing us with in-house clearance data for the Fresenius AV600 polysulfone hemodialyzer. He had no role in deciding how to present the data or in the writing of the manuscript.

Potential conflicts of interest. All authors: no conflicts.

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