

Drug Dosing Considerations in Alternative Hemodialysis

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The provision of renal replacement therapy for patients with chronic kidney disease has been reasonably standardized for decades, with thrice-weekly hemodialysis being the standard. Short-daily and nocturnal hemodialysis are 2 new hemodialysis techniques, each are administered 6 to 7 days a week but differ primarily in the duration of the treatment and blood-flow rate. The emergence of these hemodialysis regimens has shown promise in attenuating some of the complications associated with chronic kidney disease. The benefits of these daily regimens are postulated to be a result of enhanced solute clearance and improved extracellular volume management. The improved solute clearance associated with daily hemodialysis is likely to lead to altered dialytic clearance of drugs given to patients receiving these therapies. The purpose of this paper is to review the concepts pertinent to drug removal by hemodialysis and discuss the issues related to these new dialysis techniques and how they may have an impact on drug removal and the design of dosing regimens.

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Key Words: Daily hemodialysis; pharmacokinetics; pharmacodynamics; mathematical modeling; computer simulation; drug dosing

The provision of renal replacement therapy for patients with chronic kidney disease (CKD) has been relatively standardized for decades. Debates over hemodialysis membrane type and amount of delivered Kt/V_{urea} have occurred, but thrice-weekly hemodialysis has been used as the standard for as long as most nephrologists have practiced. Despite improvements in dialysis machine and filter technology and refinements in providing an adequate "dose" of hemodialysis, patients receiving thrice-weekly hemodialysis have an alarming 20% annual mortality.¹ Concurrent with this high mortality, patients with CKD stage V also endure poorer qualities of life and medical complications such as anemia, infection, accelerated cardiovascular disease, and bone disease.²

Pharmacotherapy to prevent and treat some of these comorbidities has always presented a challenge for the clinician. This challenge is caused not only by recalcitrance of these disease states to treatment but also by the altered pharmacokinetics encountered in CKD patients and the specific aspects of the hemodialysis process related to drug removal. Specifically, these attributes include the type of hemodialysis filter, flow rates, and frequency and duration of hemodialysis. Even with the issues described, drug dosing in dialysis-dependent CKD patients is relatively well understood, and many papers and books have been written that describe pharmaco-

netics and dialytic removal by a variety of different dialyzer types.³⁻⁵ However, with the introduction of alternative hemodialysis regimens, dosing of drugs will require additional study.

Alternative Hemodialysis Modalities

Short-daily and nocturnal hemodialysis are two alternative hemodialysis techniques. Both modalities are administered 6 to 7 days a week but differ primarily in the duration of the treatment and blood-flow rate. Short-daily hemodialysis is typically for 2 hours per session; nocturnal hemodialysis occurs overnight for 6 to 8 hours but at lower blood and dialysate flow rates.⁶⁻¹¹ The emergence of these quotidian or daily hemodialysis regimens has shown promise in attenuating a subset of the medical complications associated with CKD,

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as well as in improving the hemodialysis patient's quality of life.⁶⁻¹¹ Specifically, short-daily hemodialysis regimens have led to improvements in anemia, with reductions in erythropoietin doses.^{9,10} In addition, daily hemodialysis has improved blood pressure control; a majority of the patients in one study were able to discontinue all antihypertensive medications, possibly because of better fluid management.^{9,10} Hyperphosphatemia is more manageable in patients who receive a daily hemodialysis regimen.^{12,13} In one study of patients receiving nocturnal hemodialysis, all of the patients were able to stop their phosphorus binders, and some actually required intradialytic phosphorus supplementation.^{12,13} The medical benefits of daily regimens are believed to be secondary to enhanced solute clearance and improved extracellular volume management. However, as it applies to the dosing of drugs, improved solute clearance from increased frequency and duration of the daily regimens may lead to altered dialytic clearance of drugs. These issues will be addressed in the remainder of the paper.

Dialyzer Membrane Composition and Solute Clearance

Over the decades, as hemodialysis has evolved as an effective therapy for both acute kidney injury and CKD, significant changes have occurred in the composition of the hemodialysis filters used. The changes in hemodialysis filters have conferred vastly different properties in solute removal. The early nonsubstituted cellulosic filters, such as cuprophane, provided low-flux removal of solutes, with substantial complement activation as an adverse effect. The subsequent development of cellulose diacetate and cellulose triacetate membranes resulted in increased water permeability and the removal of larger solutes.¹⁴ More recently, synthetic membranes such as polyacrylonitrile, polymethylmethacrylate (PMMA), and polysulfone have been designed to confer both low-flux and high-flux properties. The high-flux versions of these synthetic membranes have resulted in greater middle-molecule clearance with less complement activation. In addition, the greater hydrophobicity of some of these synthetic membranes (eg, PMMA) results in greater adsorptive clear-

ance of solutes. Currently, high-flux membranes have gained the most prominence for use in both intermittent and daily hemodialysis regimens.

Solute and Drug Clearance

Solute clearance and drug clearance during both intermittent and daily hemodialysis can occur by 3 different processes: adsorption, diffusion, and convection.² Adsorption is non-specific, representing a relatively minor means of removing solutes, and varies with the composition of the hemodialyzer hollow fibers. The type of hemodialysis and filter composition determines which of the other 2 processes predominates. Diffusive solute removal occurs across the semipermeable dialysis membrane. In this process, solutes diffuse down a concentration gradient from either the blood or dialysate compartment during hemodialysis to achieve equilibrium.² For drugs, this process occurs from blood to dialysate. Diffusive transport is rapid for small solutes but slows with increasing molecular size. Other important diffusive solute transport factors include the membrane thickness, porosity, and the steric hindrance between the membrane pores and solute. Convection occurs when blood has a positive pressure relative to the other side of the hemofilter membrane. Plasma that contains dissolved solutes cross the membrane and is termed ultrafiltrate.²

Drug and solute removal by dialysis, regardless of the type, is dependent on the characteristics of the drug (or solute) molecule, characteristics of the dialysis membrane, blood-flow rate, dialysate-flow rate, composition of dialysate, duration of dialysis treatment, and ultrafiltration rate.^{3,4} The first facet of drug removal to consider is the physiochemical characteristics of the drug being used. Regardless of the dialysis modality or filter type, the characteristics of the drug(s) or solutes under consideration are the same. That is, the molecular weight and pharmacokinetic properties of the drug remain the same and may allow some predictions relative to drug removal. Factors that affect drug dialyzability have been re-

viewed in numerous other papers and will not be discussed further.^{3,4}

To our knowledge, at the time of the writing of this paper, only 1 paper that evaluated drug pharmacokinetics and removal during slow-daily hemodialysis in CKD patients has been published.¹⁵ The authors used the terminology, “slow-daily” hemodialysis, which would be consistent with a nocturnal hemodialysis schedule. Manley and colleagues¹⁵ investigated the removal of gentamicin during slow-daily hemodialysis. Eight subjects with CKD stage V were administered 0.6 mg/kg gentamicin immediately after hemodialysis. Interdialytic pharmacokinetics and removal during the next hemodialysis session were determined. The study was conducted in an 8-hour hemodialysis session, with a high-flux polysulfone F50 dialysis filter with blood-flow and dialysate-flow rates of 200 and 300 mL/min, respectively. At these conditions, the authors observed an average gentamicin clearance of 75.9 ± 37.6 (range: 37.6 to 141) mL/min. As evidenced by these data, the variability in clearance was high and not significantly explained by either Kt/V_{urea} or urea-reduction ratio. The gentamicin-clearance values reported in this study are similar to previous data for various types of dialyzers used in conventional hemodialysis sessions, but utilizing higher blood and dialysate flow rates. However, because of the longer dialysis time and similar dialytic clearance values, considerably more drug was removed. Consistent with enhanced removal, the authors recommended dosing changes. The authors recommended that full-dose (2 to 2.5 mg/kg) gentamicin should be administered daily after dialysis, although they expressed caution that further studies should be conducted before applying these recommendations clinically. Given the enhanced removal by this technique, further study is required to explore alternative aminoglycoside regimens, such as extended-interval dosing strategies.¹⁶⁻¹⁸ Some of these additional studies, with appropriate data, can be conducted either by use of computer simulations (*in silico* studies) or by combining *in vitro* hemodialysis data with *in vivo* pharmacokinetic data. Numerous investigations have used this approach with solute kinetics.¹⁹⁻²¹

The results of Manley’s pharmacokinetic paper highlight the potentially important issues associated with drug dosing in long-duration, low blood-flow hemodialysis. Small molecules such as urea, creatinine, and most drugs exhibit flow-dependent clearance, whereas larger molecules exhibit time-dependent clearance.²² Drugs (and solutes) in the middle molecular-weight range (about 500 to 5,000 Daltons) may exhibit differences in removal during longer, lower-flow hemodialysis, as opposed to short, high-flow hemodialysis. Examples of such drugs are gentamicin, vancomycin, and daptomycin, with molecular weights in this range or close to this range.

Hemodialyzers are considered to have discrete pores or channels that allow the passage of drugs (and other solutes) from the blood into the dialysate or vice versa. The molecular size of a drug in relation to the hemodialyzer pore size is one factor that has an impact on drug clearance. A drug must be able to pass through these pores or adsorb to the membrane to be cleared during renal replacement therapy. However, diffusion is affected more than convection by pore size. The water solubility of a drug also has an impact on its ability to be removed by hemodialysis. Drugs that are water soluble tend to cross into the aqueous-based dialysate much more effectively than lipid-soluble drugs. Lipid-soluble drugs are not effectively removed, as they are unable to partition into the water-based dialysate. More importantly, lipophilic drugs are less likely to be in the plasma and available for removal by hemodialysis. They also tend to have larger volumes of distribution and lower access to the dialyzer, as they partition into tissues more avidly than do water-soluble drugs. The extent of protein binding of a drug or solute is another key determinant of its removal by hemodialysis. Just as only unbound drugs are able to cross the physiologic membrane at the glomerulus, only an unbound drug is able to cross hemodialyzer membranes. Thus, drugs with low plasma-protein binding are more effectively removed than drugs with high plasma-protein binding.

Pharmacokinetics related to CKD and hemodialysis are illustrated in Figure 1, which mathematically shows how drug movement in the body can be modeled. Like urea

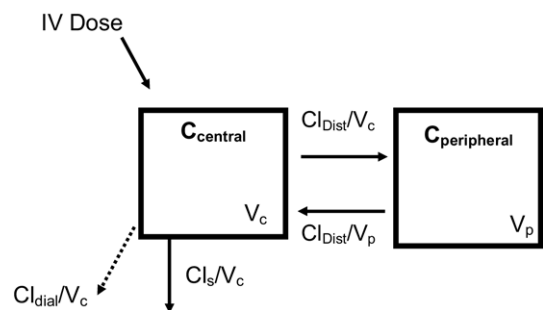


Figure 1. Schematic representation of a 2-compartment open-pharmacokinetic model in concert with drug removal by hemodialysis. Drugs are assumed to be removed from the central compartment either by hemodialysis or through endogenous means. Abbreviations: C_c , concentration of drug in the central compartment; C_p , concentration of drug in the peripheral compartment; V_c , volume of distribution of drug in the central compartment; V_p , volume of distribution of drug in the peripheral compartment; Cl_s , systemic clearance (sum of all endogenous clearances, such as renal and nonrenal clearance); Cl_{Dist} , distribution clearance or intercompartmental clearance; Cl_{dial} , dialytic clearance. During hemodialysis, the hatched line is “turned on” with an indicator variable, in the absence of hemodialysis the hatched line is turned off.

kinetics, most drugs exhibit multicompartmental behavior. In Figure 1, this behavior is shown as 2 compartments. More complicated approaches with more than 2 compartments can be used if necessary. The central compartment is commonly referred to as the plasma compartment (this compartment is where blood samples are obtained during pharmacokinetic studies). The other compartments represent “deeper” compartments, which may represent tissue sites in the body. Which anatomic body tissue (if any) corresponds to a particular compartment in human *in vivo* pharmacokinetic models is very difficult to state.

Typically, in pharmacokinetic literature, distribution is quantified by the term, apparent volume of distribution. This parameter is an important determinant of drug removal by hemodialysis. Drug distribution describes the process by which drugs leave the systemic circulation and are transported to the extravascular spaces of the body.³ Volume of distribution is an apparent term that relates the amount of drug in the body to the concen-

tration of drug in the plasma or blood. Volume of distribution is an apparent volume and not a true physical volume. The rate and extent of drug distribution throughout the body is determined by blood flow, tissue permeability, plasma-protein binding, and tissue binding. The determinants of the steady-state volume of distribution of a drug are the plasma-protein binding, tissue-protein binding, plasma or blood volume, and tissue volume. Drugs with large volumes of distribution are typically highly bound to tissue sites and, thus, inaccessible to the hemodialyzer. Digoxin is an example of a drug with low plasma-protein binding that is cleared by hemodialysis but not effectively removed, because most of the total-body content of digoxin is not in plasma, but in tissue and, thus, not exposed to the dialyzer. In contrast, aminoglycoside antibiotics have relatively small volumes of distribution and are not highly protein or tissue bound. Their volume of distribution is highly dependent on blood or plasma volume, and as a result, aminoglycosides are more likely to be removed by hemodialysis, as they are more accessible to the dialyzer.²³

Another observation in the paper by Manley and colleagues¹⁵ dealt with the rebound of gentamicin concentrations after the completion of hemodialysis. In that study, the post-dialysis rebound of gentamicin concentrations were much smaller than observed in conventional hemodialysis studies. This outcome was most likely caused by the lower blood-flow rates used in slow-daily hemodialysis. In low-flow hemodialysis, the transfer of drug from the “deeper” or peripheral compartments is faster than the removal of drug by the dialyzer. In contrast, in high-flow thrice-weekly or daily hemodialysis, the drug is rapidly removed from the central compartment (if the drug has appropriate characteristics), and the rate-limiting step for further removal is the transfer of drug back into the central compartment from the peripheral compartment. In other words, unbound drug is “stripped” from the central compartment. The extent of further removal will be related to the size of the peripheral compartment(s) and the rate at which the drug can reach equilibrium between the central and deep compartments. Unfortunately, several issues complicate the ability to determine these compartmental volumes and

transfer rates. First, in an *in vivo* human pharmacokinetic study, acquiring samples from these deep compartments is difficult or impossible. Second, the pharmacokinetic parameters that describe these volumes and transfer rates will vary among patients, as will any pharmacokinetic parameter. Third, each drug will likely have a different set of volumes and transfer rates related to the pharmacokinetics of the drug. In the study by Manley and colleagues,¹⁵ the slower gentamicin dialytic clearance, relative to the transfer of gentamicin from peripheral compartments into the central compartment, and longer treatment duration allow for equilibration to occur between the peripheral and central compartments. Thus, minimal rebound from the deep compartments back into plasma after dialysis ends is observed.²³ Clinicians must recognize that this concept is different than the observations in high-flow hemodialysis. The concept of stripping of drug is unlikely to occur with smaller-molecular-weight substances that have relatively small volumes of distribution, but instead will occur with higher-molecular-weight substances that have larger volumes of distribution.

Simulation of Drug Pharmacokinetics During Daily Hemodialysis

To illustrate examples of what may occur when short-daily hemodialysis regimens are used, we conducted computer simulations. We simulated plasma drug concentrations during conventional hemodialysis (4 hours, thrice weekly) and daily hemodialysis (2 hours, 6 times weekly). Dialytic clearance and pharmacokinetic data for 3 drugs, vancomycin, gentamicin and levofloxacin, were available from our previous conventional hemodialysis studies.²⁴⁻²⁶ In this com-

puter simulation experiment, we chose to utilize the data available for these 3 drugs for several reasons. First, they span the small to middle molecular-weight range, levofloxacin (370 Da), gentamicin (477 Da), and vancomycin (1,448 Da). Second, these 3 compounds are distinctly different from a pharmacokinetic standpoint. The volume of distribution of these compounds spans from small (gentamicin: about 0.2 to 0.3 L/kg) to large (levofloxacin: about 1 L/kg); Third, the protein binding of each of the drugs is low,^{3,25} so that their dialytic clearance will not be limited by protein binding. Fourth, they are all commonly used drugs in hemodialysis patients and, thus, are important clinically.

The pharmacokinetic model used in this simulation has been used previously in our laboratory in these and other studies.²⁴⁻²⁸ A similar mathematical model has been used^{20,21} previously to investigate the effect of alternative hemodialysis regimens on small-molecule and middle-molecule removal. Drug pharmacokinetics were simulated by a two-compartment open pharmacokinetic model parameterized as shown by Figure 1. The pharmacokinetic parameters utilized in this simulation for the 3 drugs are shown in Table 1. The values were obtained experimentally in the previously described studies. Differential equations describing the two-compartment open-pharmacokinetic model were used to generate concentration-time data by use of the pharmacokinetic parameters in Table 1. As shown in Figure 1, C_c is the concentration of drug in the central compartment, C_p is the concentration of drug in the peripheral compartment, V_c is apparent volume of distribution in the central compartment, V_p is apparent volume of distribution in the peripheral compartment, Cl_d is distribution clearance between the central

Table 1. Pharmacokinetic Parameters Used In The Monte Carlo Simulations Of The Three Drugs And Nine Dosing Regimens

	V_c (L)	V_p (L)	Cl_{dist} (mL/min)	Cl_s (mL/min)	Cl_{dial} (mL/min)
Levofloxacin	19.3	85.4	877	37	84.4
Gentamicin	8.1	5.27	182	3.89	104
Vancomycin	7.1	27.6	215	7.95	57.5

Abbreviations: Cl_{dial} , dialytic clearance; Cl_{Dist} , distribution clearance or intercompartmental clearance; Cl_s , systemic clearance; V_c , volume of distribution of drug in the central compartment; V_p , volume of distribution of drug in the peripheral compartment.
Data obtained from²⁴⁻²⁶.

and peripheral compartments, Cl_s is systemic clearance, and R is an indicator variable that has the value of 0 during the interdialytic period and a value of 1 during dialysis. Cl_{dial} is the dialytic clearance. The interdialytic and intradialytic periods were simulated simultaneously. Volumes of distribution and clearances were assumed to be constant during the entire study period, as we have assumed in past studies. In addition, the dialysis clearance in all simulations for each drug was assumed to be the same in both the conventional dialysis regimen and the alternative hemodialysis regimens.

Three dosing regimens were simulated for each drug, 1 for conventional thrice-weekly hemodialysis and 2 for a 6 times weekly hemodialysis regimen. The first regimen (regimen A) employs the thrice-weekly conventional hemodialysis treatment schedule and typical drug-dosing regimens that are utilized clinically in patients who receive conventional hemodialysis (ie, administers replacement doses after each hemodialysis session). The second regimen (regimen B) employs a daily 2-hour hemodialysis treatment and applies typical conventional hemodialysis drug dosing (ie, administers replacement doses after each hemodialysis session). Finally, the third regimen (regimen C) employs a daily 2-hour hemodialysis treatment and applies empiric dosing adjustments (extension of the dosing interval to accommodate the reduced clearance per each dialysis session) for daily hemodialysis. These regimens are shown in detail in Table 2.

The conditions for the 2 hemodialysis modalities utilized in these simulations were (1) conventional hemodialysis, a 4-hour treatment 3 times a week; and (2) alternative hemodialysis, a 2-hour treatment 6 times a week. Thus, the weekly time on hemodialysis was the same for the conventional and alternative hemodialysis therapies. The blood and dialysate flow rates utilized in these simulations were 400 and 600 mL/min respectively, the median flow rates utilized in our previous studies. The dialyzer used in these studies was a non-reused cellulose acetate (CAHP-210) hemodialyzer (Baxter Healthcare Co., McGaw Park, IL), with a surface area of 2.1 m² and ultrafiltration coefficient of 13.2 mL/h/mm Hg. Using these dialysis conditions and dia-

Table 2. Dosing Regimens of Levofloxacin, Gentamicin and Vancomycin Used in Monte Carlo Simulations

Regimen	HD Regimen	Levofloxacin	Gentamicin	Vancomycin
A	Conventional	LD: 500 mg (0 hours) MD: 250 mg every other day (48, 96, and 144 hours)	LD: 2 mg/kg (0 hours) MD: 1.25 mg/kg every HD session (48 and 96 hours)	LD: 15 mg/kg (0 hours) MD: 7.5 mg/kg every HD session (48 and 96 hours)
B	Daily	LD: 500 mg (0 hours) MD: 250 mg every day (24, 48, 72, 96, 120, and 144 hours)	LD: 2 mg/kg (0 hours) MD: 1.25 mg/kg every HD session (24, 48, 72, 96, 120, and 144 hours)	LD: 15 mg/kg (0 hours) MD: 7.5 mg/kg every HD session (24, 48, 72, 96, 120, and 144 hours)
C	Daily	LD: 500 mg (0 hours) MD: 250 mg every other day (48, 96, and 144 hours)	LD: 2 mg/kg (0 hours) MD: 1.25 mg/kg every other HD session (48, 96, and 144 hours)	LD: 15 mg/kg (0 hours) MD: 7.5 mg/kg every other HD session (48, 96, and 144 hours)

Abbreviations: HD: hemodialysis; LD, loading dose; MD, maintenance dose.

All drugs were infused immediately after hemodialysis, according to manufacturer's recommendations. Levofloxacin and vancomycin were administered as an intravenous infusion over 1 hour; gentamicin was administered as an intravenous infusion over 30 minutes.

Conventional dialysis: regimen A, hemodialysis administered 3 times weekly at 44 to 48, 92 to 96, and 164 to 168 hours.

Daily hemodialysis: regimens B and C hemodialysis administered 6 times weekly at 22 to 24, 46 to 48, 70 to 72, 94 to 96, 118 to 120, and 142 to 144 hours.

lyzer, the median equilibrated Kt/V_{urea} for the conventional hemodialysis measured 1.41. This result was calculated by means of an equilibrated single-pool model that used a predialysis and 30-minute postdialysis blood urea nitrogen value according to the method of Daugirdas as previously described. The simulated patients were assumed to have a weight of 75 kg, the average weight of the patients in our previous studies. Five-hundred simulated patient data sets were generated by use of the SIM module in the Adapt II.²⁹ computer software package (Biomedical Simulations Resource, University of Southern California, Los Angeles, CA). Similar approaches have been used previously with ceftazolin and levofloxacin.^{25,27}

The results of the simulations are shown in Figure 2. The average central compartment (assumed to be plasma) concentration-time profiles for levofloxacin (panel A), gentamicin (panel B), and vancomycin (panel C) are shown. These panels illustrate the concentrations of the 3 drugs over a 1-week treatment time, during both the interdialytic and the intradialytic periods. What should be quite apparent from these 3 concentration-time curves is that decisions about drug removal will need to be drug specific and dependent on drug characteristics. Employing conventional hemodialysis dosing-replacement schedules (that is, replacement after each dialysis session at conventional doses) will result high plasma concentrations when applied to alternative dialysis regimens. This outcome is shown for each of the 3 drugs in regimen B. It occurs because weekly dialytic clearance is the same in the 2 dialysis regimens, but more drug has been administered. Adjustments to the way supplementation is approached will be necessary for many drugs. This case is illustrated in regimen C, in which the drugs are replaced after every other hemodialysis session, rather than after every dialysis session. This approach may be intuitively obvious to nephrologists who are intimately involved in the design of these alternative hemodialysis regimens but may not be for others involved in the development of drug-dosing schedules.

The most important piece for developing dosing regimens for these 3 drugs, or for any other drug, is to maximize therapeutic outcomes while minimizing adverse effects. The

dosing intervals provided here simply provide potential plasma concentration-time profiles for these 3 commonly used drugs. We do not suggest that these doses are the optimal doses for use in patients who receive these therapies. The inclusion of appropriate pharmacodynamic endpoints into therapeutic regimens is the next step in determining the most appropriate regimens.^{30,31} Because these concepts are essential to the development of appropriate dosing, we will now discuss some basic concepts related to the pharmacodynamics of gentamicin, vancomycin, and levofloxacin. To maximize therapeutic outcomes, aminoglycosides should be dosed to maximize peak-to-MIC ratios. In conventional hemodialysis, aminoglycosides are typically given after hemodialysis at low doses to replace the amount removed during the hemodialysis session. This dosing approach does not maximize pharmacodynamics. Recent data¹⁶⁻¹⁸ suggest that extended interval aminoglycosides (higher doses given less often) may be used in hemodialysis patients by administering the drug before hemodialysis (perhaps 2 to 6 hours before). During the next dialysis session, dialysis will remove a substantial portion of the drug. This technique allows these patients to be exposed to high peaks but not to excessively high "trough" or residual concentrations. This dosing concept may be more easily applied to daily hemodialysis, in which removal of drug occurs each day and may maximize pharmacodynamic endpoints. Before this approach is used clinically, studies will need to be conducted to investigate this potential dosing regimen.

Levofloxacin is similar to aminoglycosides from a pharmacodynamic standpoint in that it exhibits concentration-dependent killing.³⁰ Thus, maximizing peak-to-MIC ratios is the most important predictor of efficacy. Levofloxacin is different than gentamicin, however, in that it is removed to a lesser extent, most likely because of a considerably larger volume of distribution. In addition, it exhibits very little rebound, mainly because of a very high intercompartmental clearance in relation to the dialytic clearance.

For vancomycin (and β -lactams, although not simulated in this study), the peak concentration is not the primary determinant of phar-

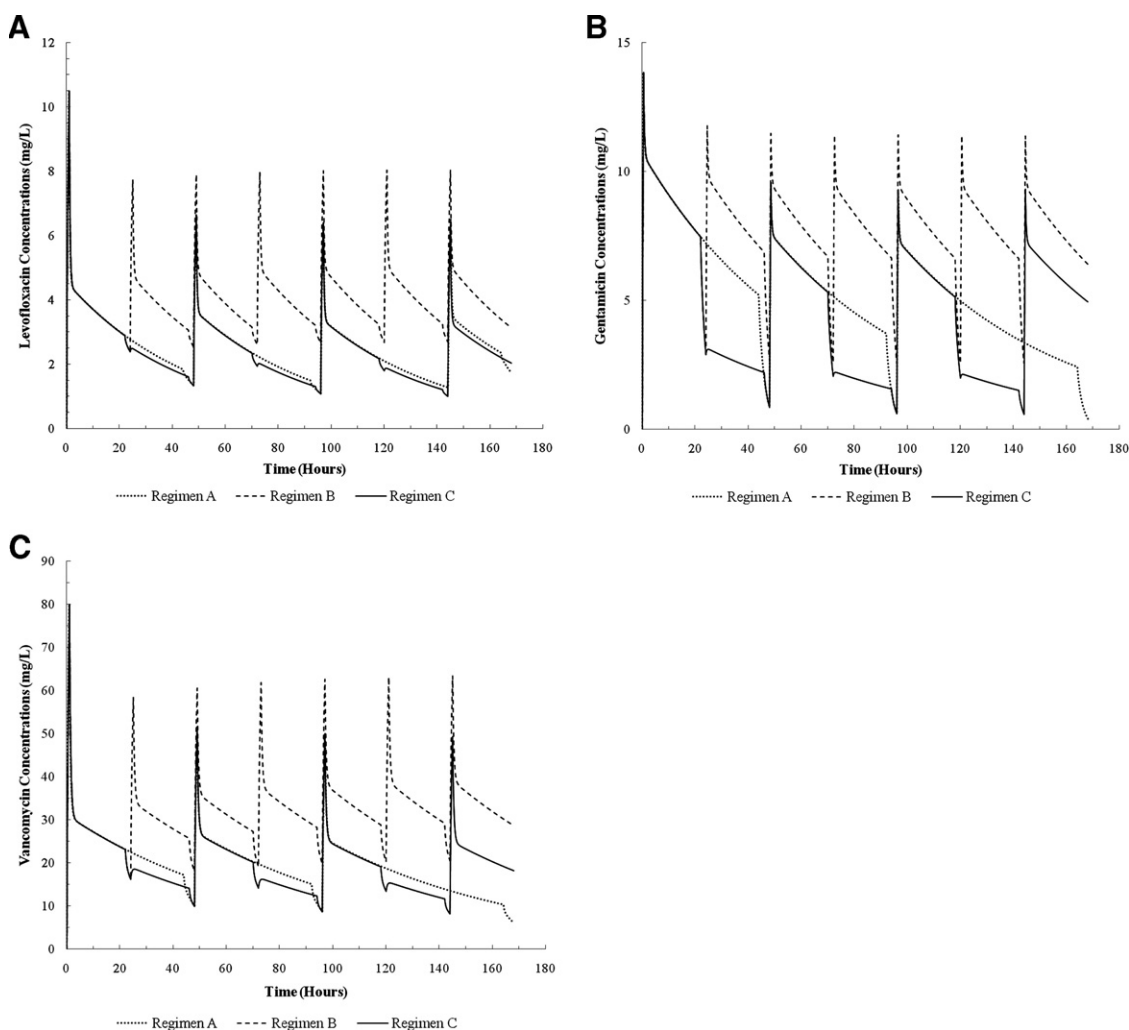


Figure 2. Levofloxacin (A), gentamicin (B), and vancomycin (C) concentration-time profiles for the central (plasma) compartment in regimens A, B, and C (see Table 2 for dosing regimens). The profiles are shown for the intradialytic and interdialytic periods for 1 week after the administration of the first drug dose. Regimen A is conventional hemodialysis administered 3 times weekly for 4 hours each session. The times for the dialysis session were 44 to 48, 92 to 96, and 164 to 168 hours. Regimens B and C were daily hemodialysis administered 6 times weekly for 2 hours each session. The times for the dialysis session were 22 to 24, 46 to 48, 70 to 72, 94 to 96, 118 to 120, and 142 to 144 hours. Abbreviations: V_c , volume of distribution of drug in the central compartment; V_p , volume of distribution of drug in the peripheral compartment; Cl_s , systemic clearance; Cl_{Dist} , distribution clearance or intercompartmental clearance; Cl_{dial} , dialytic clearance.²⁴⁻²⁶ All drugs were infused immediately after hemodialysis, according to manufacturer's recommendations. Levofloxacin and vancomycin were administered as an intravenous infusion over 1 hour; gentamicin was administered as an intravenous infusion over 30 minutes. Abbreviations: LD, loading dose; MD, maintenance dose; HD, hemodialysis Conventional dialysis: regimen A, hemodialysis administered 3 times weekly at 44 to 48, 92 to 96, and 164 to 168 hours. Daily hemodialysis: regimens B and C, hemodialysis administered 6 times weekly at 22 to 24, 46 to 48, 70 to 72, 94 to 96, 118 to 120, and 142 to 144 hours.

macodynamic response, rather the time spent above the MIC of the organism is important. Giving frequent replacement doses, but less than what would be administered during conventional hemodialysis (since less drug will be

removed), may be more optimal. Each of these compounds is an antibiotic, with relatively well-defined pharmacodynamic endpoints and are easily incorporated into pharmacokinetic-pharmacodynamic studies. Many other drugs do not

have such information as it relates to prediction of clinical response. However, clinicians have general ideas about how standard drugs will work in most patients. Examples include vasopressors and blood pressure response, β -blockers and heart rate response, and statins and cholesterol response. Future studies must incorporate these response measures into standard pharmacokinetic studies during dialysis.

Many of the decisions regarding drug dosing in alternative hemodialysis modalities must be extrapolated from principles gained with conventional hemodialysis. For the majority of drugs, no studies are available or will ever be conducted to investigate removal by alternative hemodialysis. Additionally, because the way therapies are delivered will likely have many variations, dosing guidelines for individual patients will be difficult to develop. Strategies for the development of appropriate regimens on the basis of both pharmacokinetic and pharmacodynamic principles will be required to assure the administration of safe and effective drug regimens in patients who receive alternative hemodialysis schedules. More research in this area is required to develop these strategies.

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