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Higher Renal Replacement Therapy Dose Delivery Influences on Drug Therapy

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Abstract: Higher doses of renal replacement therapy have profound effects on pharmacotherapy, yet little research has been conducted in this area. High-volume renal replacement therapies influence both the pharmacokinetic and the pharmacodynamic profiles of all drugs administered to these critically ill patients. Intermittent high-dose "hybrid" hemodialysis therapies remove drugs to a much different degree than standard thrice-weekly hemodialysis, yet pharmacokinetic studies have not been performed in patients receiving these therapies. High-volume continuous renal replacement therapies offer dosing challenges not seen with standard low-dose therapies. This article describes the pharmacokinetic and pharmacodynamic issues presented by high-volume renal replacement therapies. Given the importance that pharmacotherapy has on optimal patient outcomes, a better understanding of the influence that high-volume renal replacement therapy has on drugs is essential if these high volume therapies are to be used successfully in the intensive care unit. **Key Words:** Pharmacokinetics—Pharmacodynamics—Renal replacement therapy—Hemodialysis.

Drug-dosing recommendations for patients with acute renal failure (ARF) receiving renal replacement therapy (RRT) have not kept pace with the advances in RRT technology. Published dosing recommendations for intermittent hemodialysis (IHD) typically are based on studies conducted in otherwise healthy patients with chronic kidney disease (CKD) treated with older low-permeability hemodialyzer membranes thrice weekly. Drugs, such as vancomycin, that were not appreciably removed by these conventional dialysis membranes, are removed by newer high-permeability dialyzer membranes (1,2). Nonetheless, recently published dosing guidelines do not reflect these changes in vancomycin dialytic removal (3,4). CRRT dosing guidelines are finally becoming available (4,5), but the dosing guidelines are based on low ultrafiltrate and dialysate flows with older hemodiafilters, often conducted in the arteriovenous mode. The growth of higher delivered RRT doses in critically ill patients with ARF has rendered these dosing guidelines ineffectual and, potentially, dangerous.

Discussions about the merits and faults of higher delivered RRT doses often include discussions of sepsis and mediator removal (6,7), but not of antibiotic removal to treat the causative infection. Indeed, drug dosing in high-dose renal replacement therapy (HRRT) was excluded from discussion in the first consensus conference on CRRT (8). Patient outcomes with higher delivered therapy has resulted in mixed results (9–11), but consideration of the effect that these therapies have on the removal of life-saving drugs is understated. Costs of increased RRT have begun to be quantified (12,13), but costs related to pharmacotherapy (drug cost, administration costs, additional lab costs, etc.) have not been included in these analyses. The purpose of this article is to discuss pharmacokinetic and pharmacodynamic issues of higher delivered RRT doses and to stimulate awareness of this aspect of treating the critically ill patient requiring of higher delivered doses of RRT.

Most clinicians are familiar with a drug's pharmacokinetics, or how the body handles a drug once it is administered. Fewer are familiar with the concept of pharmacodynamics. Pharmacodynamics is the study of the biochemical and physiological effects of drugs

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and their mechanisms of action, or, in other words, how the drug affects the body. Clinically, we are more interested in the pharmacodynamics of a drug, because it is these drug effects that determine a cure or amelioration of symptoms. RRT can influence both pharmacokinetics and pharmacodynamics.

Pharmacokinetics

The influence of older, lower volume CRRT regimens and thrice-weekly IHD regimens on drug and solute removal are fairly well understood. The low-flow CRRT regimens can be thought of as an artificially functioning kidney providing continual first-order drug clearance. Solute dialytic clearance data from patients with CKD were extrapolated to thrice-weekly IHD regimens in critically ill ARF patients. However, these generalized approaches are not entirely correct. For example, dialytic drug clearance during hemodialysis in ARF patients likely differs from that of an otherwise healthy CKD patient. In the unstable ARF patient, blood flow (Qb) often cannot be maintained at rates that can be maintained in the CKD patient. Other pharmacokinetic differences exist between patients with ARF and CKD. Unlike stable CKD patients, ARF patients often are massively fluid overloaded, which may result in a larger volume of distribution for water-soluble drugs with relatively small apparent volumes of distribution (e.g., aminoglycosides). CRRTs are able to effectively remove this fluid, which yields a patient with a rapidly changing apparent drug volume of distribution. A smaller apparent volume of distribution yields a higher relative Kt/V_{urea} at the same dialysate rate (Qd) or ultrafiltration rate (Quf), and consequently it yields a higher Kt/V_{drug} as well. Continuous therapies do not always yield stable drug removal, as Qb and Quf are quite variable in CAVH therapies, for example.

Figure 1 illustrates a pharmacokinetic model that demonstrates many important pharmacokinetic challenges of HRRT. Nephrologists dose dialysis based on urea clearance, and in the course of monitoring BUN, have noted that urea exhibits characteristics suggestive of a two-pool or two-compartment model. The best evidence of this is the fact that urea serum concentrations rebound soon after hemodialysis ends. Most drugs will exhibit a similar "rebound" (2,14,15), and pharmacokinetic experiments have found that many drugs exhibit two and three compartment characteristics. One often refers to the first (central) compartment as the plasma space, whereas the other compartments are "deeper" compartments representative of various tissues in the body. In truth, it is difficult to state exactly which anatomical

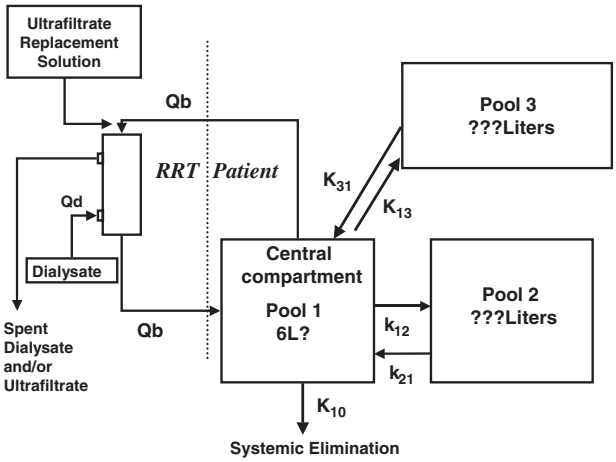

FIG. 1. Depiction of a pharmacokinetic view of drug removal by RRT. The patient is to the right of the vertical dotted line and the RRT is on the left. Most solutes exhibit multicompartment characteristics in patients, consisting of central and peripheral compartments. Solutes are removed from the central compartment either by RRT or through nonextracorporeal means. In HRRT, drugs are rapidly cleared from the first compartment, possibly even faster than the drugs can equilibrate from other deeper compartments. In this scenario, the rate-limiting step for drug removal becomes how fast the drug can transfer to the central compartment from these deeper compartments.

space(s) corresponds to each modeled compartment. Much of drug distribution depends on factors such as the drug's lipophilicity, and the degree of protein and tissue binding. The rate of transfer between these compartments is typically determined mathematically as opposed to simultaneously sampling plasma and other anatomical spaces in order to determine drug concentration. Much of this concern over pharmacokinetic modeling would be an academic pharmacokinetic discussion were it not for the advent of HRRT.

In standard low-dose CRRT, the rate-limiting step of solute clearance (including drugs) has been Qd and/or Quf because Qb greatly exceeds Qd or Quf. The rate of drug removal by low-dose CRRT from the first compartment is probably slower than the rate of transfer of the drug from the deep compartment(s) to the first compartment (K21, K31). Consequently, no appreciable rebound occurs after low-dose CRRT stops because drugs transfer to the first compartment at least as fast as the drug is being removed by the CRRT. With high-volume CRRT, a process more like what is seen in IHD occurs. With HRRT, the drug is rapidly removed from the first (plasma) compartment if the drug has the appropriate characteristics. At HRRT initiation, the first compartment becomes rapidly stripped of unbound drug. The rate-limiting step of any further drug removal

becomes the rate at which drug can transfer from the deeper compartments into the first compartment for removal by HRRT. Similarly, the size of the compartments (apparent volumes of distribution) of each drug also influences actual drug removal. Just like identification of where anatomically the deeper compartments exist is difficult without being able to sample from these spaces, actual transfer rates between compartments are very difficult to rigorously determine. Further complicating this picture is the likelihood that every drug has a different set of transfer rates and distribution volumes and that these differ for each patient (just like any other pharmacokinetic parameter). However, clinicians should recognize that HRRT drug removal might change from when HRRT is initiated to later in therapy when the first (plasma) compartment has been stripped of drug. Serum concentration monitoring and thoughtful interpretation of those results in HRRT are essential.

Drug and urea clearances via low-volume continuous hemodialysis (CVVHD) and hemofiltration (CVVH) have been considered to be equivalent. Large molecular weight substances may have been more readily cleared with convection than diffusion, but these differences are thought to be negligible. Indeed, at low flows, drug-dosing recommendations for low-volume CRRT have not differentiated between the diffusive and convective clearance. In a purely convective therapy, such as CVVH, the appropriate measure of a solute's ability to cross the membrane is the sieving coefficient (SC). SC is calculated as the ratio of ultrafiltrate solute concentration divided by the simultaneous arterial solute concentration. SC is generally thought to be unchanged despite changes in Quf, although this has not been thoroughly investigated. In contrast, the calculation of dialytic clearance requires the use of the saturation coefficient (SA). At a fixed set of blood and dialysate flow rates, the SA equals the ratio of spent dialysate solute concentration divided by the simultaneous arterial solute concentration. Early low-volume-based CRRT dosing guidelines suggested that SA = SC (16,17). This assumption is appropriate with low-volume CRRT because Qd is slow enough to allow almost complete equilibrium of solute concentration between the dialysate and blood sides of the dialysis membrane. However, this assumption is almost certainly incorrect with high-dose CRRT.

Few studies have been conducted on the issue of SA and SC differences in high-dose CRRT, but early reports suggest a marked difference between the two. The difference likely will be more pronounced with larger molecular weight substances than smaller substances because diffusivity is inversely related to molecular size. As molecular size increases, the difference between SA and SC should grow, although this difference will likely be dependent on hemofilter characteristics. Clinically, this separation of SA and SC ought to be seen with solutes of larger molecular weight.

The SA of urea and vancomycin (molecular weight 65 and ~1,450 Daltons, respectively) were determined in an in vivo trial conducted in CKD patients receiving experimental CVVHD at varying dialysate flow rates (5). At relatively low Qd (8.3 ml/min), the SA for urea and vancomycin were between 0.71 and 0.88, and 0.63 and 0.9, respectively. The variation of SA was found to be hemodiafilter dependent. However, as Qd increased from 8.3 ml/min up to 33.3 ml/min, the SA of each solute changed from a 9% increase to a 30% decline. The largest decline (30% decline in vancomycin SA and 8% decline in urea SA) was seen with AN69 hemodiafilters, a commonly used hemofilter in HRRT. Using this same AN69 hemodiafilter (Multiflow 60, Hospal, Lyon, France), Brunet found that increasing dialysate flow rates above 1,000 ml/hr did not enhance β-2 microglobulin clearance (molecular weight 11,600 Daltons) (18). In contrast, smaller drugs such as ceftazidime tend to have increased dialytic clearance as dialysate flow is increased (19). These data indicate that doubling dialysate flow rates from standard low-volume flows (1,000 ml/hr) to higher dialysate flows (2,000 ml/hr) may result in substantially less than a doubling of solute dialytic clearance, particularly for larger solutes. Increasing dialysate flow rates (≥2,000 ml/hr) should result in decreasing SA, but the rate of SA decline is filter dependent (5).

Many centers utilizing HRRT use a combination of diffusion and convection, hemodiafiltration. These combination therapies provide the most difficulty in determining rational drug dosing because all of the concerns of purely diffusive (differences between SA for solutes of differing molecular weight at higher flows, assumption that SA = SC, etc.) and convective therapies (predilution of replacement solutions affecting convective solute clearance, hemoconcentration throughout the length of the filter resulting in premature clotting, inability to achieve desired UF rate at high-UF flow rates, etc.) become critical issues in high-volume hemodiafiltration. The combination of diffusive and convective therapies results in additional solute removal confounders. Brunet determined the small solute (urea, creatinine, urates, and phosphorus) and β-2 microglobulin clearances in purely dialytic and purely convective RRT operated

at varying rates (18). These clearances were added together and compared to clearances achieved by a hemodiafiltrative therapy using the same dialysate and ultrafiltration rates given simultaneously. When convection and diffusion occurred simultaneously, as in hemodiafiltration, the clearance of large solutes such as β-2 microglobulin was less than what was attained by adding the expected clearances of the convective and diffusive if they were delivered independently (18). The mathematics behind the interaction of convection and diffusion are complex (20). However, it is likely that the hemodiafiltrative clearance of large drugs such as vancomycin, daptomycin, teicoplanin, and the aminoglycosides will differ from that attained by purely convective or diffusive therapies. Concurrent diffusion and convection will result in lower drug clearances than what is achievable by these therapies given individually, but so few data exist on this issue that determining appropriate drug-dosing regimens in patients receiving high-volume continuous hemodiafiltration is exceedingly difficult.

Pharmacodynamics

Our understanding of antibiotic therapy has matured over the past years as pharmacodynamic research has influenced how we dose drugs in infected patients. For example, the expanded use of dosing regimens like "once-daily aminoglycosides" in patients with normal renal function have come into being because data suggest that aminoglycosides have a long postantibiotic effect against many Gram's stain-negative bacteria. In most hospitals, this method of aminoglycoside dosing has replaced conventional dosing (lower doses given more often) due to equal or better cure rates with lower toxicity rates (21). Other antibiotics have different bactericidal and bacteriostatic pharmacodynamic characteristics that have recently come to light. Consequently, dosing regimens, based on these pharmacodynamic characteristics, have been developed to capitalize on a drug's pharmacodynamic properties. By virtue of their ability to affect drug pharmacokinetics, HRRT is also likely to influence pharmacodynamics. Thus, conventional drug-dosing schemes may need adjustment due to the pharmacokinetic and pharmacodynamic influences of HRRT.

There are many examples of where HRRT may have profound clinical effects on antibiotic pharmacodynamics. The pharmacodynamics of aminoglycosides are well described. Aminoglycosides work most effectively when high maximal serum concentration (C_{max}) in relation to the organism's minimal inhibitory concentration (MIC) is achieved. Once-daily dosing can be used due to the prolonged postantibiotic effect, and microbiologic cure without high toxicity can be attained provided the high C_{max}/MIC ratio is reached (22,23). Once-daily aminoglycoside regimens are contraindicated in patients with kidney disease. Consequently, conventional dosing is most often used in patients with acute renal failure. It is possible the enhanced drug clearance of HRRT may allow for the use of once-daily aminoglycoside dosing in these critically ill infected patients.

In contrast to aminoglycosides, other antibiotics require a different pharmacodynamic profile to be maximally effective. Beta lactam antibiotics require the maintenance of serum concentrations above the MIC of the infecting organism at the infection site. In the case of beta lactams, it is likely that those that are not highly protein bound are rapidly removed by HRRT and that much more frequent dosing is required to meet this pharmacodynamic requirement. Indeed, some have suggested continuous beta lactam antibiotic infusions to treat infections in patients without acute renal failure (24). It is possible that continuous beta lactam infusions might also be effective in infected ARF patients treated with HRRT.

Like beta lactams, vancomycin is most effective when serum concentrations remain above critical MIC values. Positive patient outcomes with vancomycin have been associated with the maintenance of trough serum concentrations above 10 mg/L (25). HRRT, particularly convective therapies using high-flux membranes, should efficiently clear vancomycin (5,26). Consequently, more frequent dosing and serum concentration monitoring will be essential to maximize therapeutic outcomes and minimize toxicity.

Similar to aminoglycosides, the pharmacodynamic profile of fluoroquinolones is known to require prolonged serum concentrations (as measured by the area under the serum concentration time curve for 24 hr, AUC_{0-24}) above the MIC. Maintenance of the AUC_{0-24}/MIC and C_{max}/MIC ratios above critical values has been shown to correlate with clinical and bacteriologic outcomes for this antibiotic class (23,27).

In addition, a suboptimal AUC_{0-24}/MIC ratio has been shown to be strongly associated with the selection of antimicrobial resistance during therapy (28). As HRRT will affect fluoroquinolone pharmacokinetics, consequently fluoroquinolone pharmacodynamics will be compromised as well. As HRRT removes higher amounts of the fluoroquinolone, the serum concentrations fall, resulting in lower ratios. Antibiotic dosing recommendations that are mindful of the pharmacokinetic and pharmacodynamic

influences of HRRT must be developed for HRRT to become a fully mature therapy.

Pharmacodynamic influences of HRRT go beyond simply affecting antibiotic pharmacokinetics. For example, HRRT is often suggested as a treatment option for septic shock. Clearly sepsis mediators are removed by HRRT (6,7,29,30), and removal of these mediators may provide a salutary effect, but thus far the evidence for this benefit in humans is scant (6–8). In addition to the removal of the "bad" mediators by HRRT, it is possible that beneficial cytokines are removed as well (31). These cytokines may augment the action of antibiotics, and their removal by HRRT may influence the pharmacodynamics of administered antibiotics. The clinical aspects of this antibiotic and beneficial cytokine removal have yet to be determined.

Previously published dosing guidelines

Many recommendations for determining the appropriate drug dosing for RRT have been published. Intermittent dialysis dosing recommendations appear in most drug package inserts and in textbooks (4). However, the hemodiafilters, flows, and treatment times from which these recommendations are based are considerably different than what are used in HRRT. Recommendations based on standard IHD have almost no applicability to HRRT involving dialysis. Very few studies have been published for the high-volume hybrid dialysis therapies such as SLED, but they do indicate large differences in drug removal between low-volume and hybrid HRRT (32).

Dosing guidelines for continuous therapies typically are not presented in a drug's package insert. Perhaps it is time for this to be required for those drugs commonly used in patients with ARF. Published CRRT dosing texts typically are based on low-volume therapies (3,4). Recommended doses likely would require large changes to be used in patients receiving HRRT.

Actual pharmacokinetic studies conducted in patients receiving HRRT are rare, though a few have been published recently. Most of these reports focus on antibiotics that are used in critically ill patients with acute renal failure (33–36). These are typically case reports or small case series. Care must be made when attempting to extrapolate the author's recommendations to patient care, as there are great differences between filter types and flow rates. Pharmacodynamic goals of drug therapy must be considered before determining a dosing regimen, and they are not always assessed in these reports.

Nonetheless, many dosing algorithms have been developed for continuous therapies that can be modified for the individual flow rates used in continuous HRRT. These approaches can be grouped into two types. Method 1 begins with the drug's dosing regimen in normal renal function and adjusts it downward to the ultrafiltrate/dialysate flow rates (20,37). Method 2 begins with the dosing regimen used in chronic kidney disease and applies a dosing multiplication factor to account for extracorporeal clearance (16,17,38,39). Table 1 provides some comparisons of the calculated daily maintenance drug requirements using these two methods with CRRT at varying dialysate/ultrafiltration rates.

A review of Table 1 reveals that these published dosing methods do not perform well with HRRT. Indeed, in many cases, clinical judgment precludes the use of some of these recommendations (shaded areas of Table 1) even at the lower dialysate/ultrafiltration rates. Indeed, it is interesting how much of a difference in calculated gentamicin and vancomycin doses there is even at dialysate/ultrafiltrate rates of 1,000 ml/hr. Clinical experience indicates that method 1 appears to perform better than method 2, particularly for drugs with higher sieving coefficients. Due to the equations used, method 2 consistently overestimates the daily dosing needs for drugs with low nonrenal clearance rates in anuria. For drugs with lower sieving coefficients, method 1 tends to result in higher doses than method 2. These two dosing methods produce similar results at all flow rates for only two of the five drugs (ciprofloxacin and phenobarbital) in Table 1.

Both dosing methods have inherent flaws, and the authors of methods 1 and 2 acknowledge the limitations of these proposed dosing algorithms (16,17,38,39). Whether one starts with the doses for patients with normal renal function or patients with CKD, it is evident that there are fundamental pharmacokinetic differences between these patients and critically ill patients with ARF treated with HRRT. Differences between normals and patients with CKD or ARF with respect to volume status, drug protein binding, and nonrenal drug clearance are well described. Pharmacokinetic studies conducted with imipenem (33,40) and vancomycin (41) have shown that application of pharmacokinetic drug properties such as nonrenal drug clearance derived in patients with CKD would result in serious dosing errors. With both of these drugs, the nonrenal clearance in ARF is substantially higher than that seen in CKD patients. Doses assuming the nonrenal clearance of CKD will result in severe underdosing of these antibiotics.

Both dosing methods assume that SA and SC remain constant at any combination of ultrafiltrate

TABLE 1. *Comparison of calculated daily maintenance drug requirements (mg/day) for 70 kg anuric patient with ARF using two published dosing methods*

(Not meant to be dosing recommendations to be used in patients.)

Drug Dose for normal RF†/ Dose for CKD†	Assumed SA/SC	Dialysate/Ultrafiltrate Production Rates					
		1 L/hr		3 L/hr		6 L/hr	
		Method 1	Method 2	Method 1	Method 2	Method 1	Method 2
Gentamicin 120 mg Q8 120 mg Q72	0.9	69 mg/day	190 mg/day	193 mg/day	500 mg/day	378 mg/day	800 mg/day
Vancomycin 1000 mg Q12 1000 mg Q120 hr	0.8	400 mg/day	1,587 mg/day	1,100 mg/day	4,167 mg/day	2,137 mg/day	6,667 mg/day
Ciprofloxacin 400 mg Q12 400 mg Q24	0.7	417 mg/day	412 mg/day	448 mg/day	444 mg/day	502 mg/day	488 mg/day
Phenobarbital 50 mg Q8 50 mg Q12	0.5	254 mg/day	238 mg/day	552 mg/day	515 mg/day	998 mg/day	926 mg/day
Phenytoin 300 mg Q24 300 mg Q24	0.25	351 mg/day	318 mg/day	453 mg/day	357 mg/day	606 mg/day	416 mg/day

† Doses taken from (4).

Shaded boxes are not doses recommended by the authors; they are simply results of calculations using published dosing algorithms. All dosing should be guided by serum concentration monitoring when possible.

Method 1: Begin with dose for patients with normal renal function and adjust (20,37).

Method 2: Begin with dose for patients with chronic kidney disease and adjust (16,17).

and dialysate flow rates. This assumption is most certainly incorrect, but in the absence of SA/SC data at high flows and combinations of flows, it may be the best available guess. Finally, all of these approaches are based on inferences made from adult patients. High-volume therapies are being used increasingly in children. Drug-dosing challenges in pediatric patients receiving HRRT are vast, and it is unlikely that the solution to them will be found in these algorithms.

Higher drug doses tend to be used in HRRT, and simple changes in patient management can lead to disastrous results. When HRRT systems are stopped due to filter clotting, access problems, patient transportation, or procedures, drug-dosing regimens must be altered immediately to prevent acute overdoses and toxicity. Conversely, HRRT initiation requires rapid changes in drug dosing to compensate for the extracorporeal drug clearance. Titration of vasopressor, paralytics, anticoagulants, and pain medications may be necessary as HRRT parameters change.

Conclusion

The growth of HRRT in ICUs around the world presents great challenges to the delivery of appropriate pharmacotherapy. Pharmacotherapy in HRRT is a rich area for research, as currently published guidelines were not designed for these RRT and do not work well when they are used in HRRT. These high-volume therapies may prove to be superior to low-volume therapies in selected patients, but they will not be found to be so until we have a better understanding of pharmacotherapy management in HRRT.

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