CHAPTER 147

Principles of Pharmacodynamics and Pharmacokinetics of Drugs Used in Extracorporeal Therapies

Federico Pea

OBJECTIVES

This chapter will:

1. Identify the major factors affecting drug removal during renal replacement therapy (RRT).
2. Define the principles for appropriate dosage adjustments during RRT.
3. Describe the potential relevance of RRT in modifying the pharmacodynamic behavior of antimicrobial agents during RRT.

When a drug is administered for therapeutic purposes, its pharmacodynamic effect is the result of the achievement and maintenance of therapeutically effective free concentrations at the site of action. This result depends on several complex pharmacokinetic processes occurring after drug administration according to the drug's peculiar physicochemical properties. As a consequence, a wide interindividual variability in plasma protein binding, distribution with tissue accumulation, metabolism (mainly by the liver), and/or elimination (mainly by the kidney) of drugs may exist, and appropriate dosing regimens must be defined to guarantee the therapeutic effect.

When clinicians start drug treatment, the first dose, namely the loading dose, has the intent of rapidly achieving therapeutically effective concentrations, and its amount depends on volume of distribution (Vd).[1] The subsequent doses, namely the maintenance doses, are administered with the intent of maintaining over time these effective levels. Accordingly, their amount depends mainly on the amount that is eliminated from the body by drug clearance (K) during the dosing interval.[1]

In the presence of acute renal failure, the application of renal replacement therapies (RRTs) may consistently alter drug clearance, especially for those compounds that are cleared normally by the kidney.[2] Consistently, the maintenance dose, but not the loading dose, of a given drug may require significant adjustments during the application of RRT to avoid either therapeutic failure related to underexposure or toxicity risks related to overexposure, especially whenever using drugs with low therapeutic index.

The amount of drug removal may vary greatly according to several factors related to the functioning processes of RRT, the peculiar physicochemical and pharmacokinetic properties of the drug, and the properties of the device.

FACTORS AFFECTING DRUG CLEARANCE DURING RENAL REPLACEMENT THERAPY

Principles of Drug Removal

RRT may employ two different physicochemical processes, diffusion and convection, to replace renal function in the elimination of several solutes from blood through semipermeable membranes, and these processes may influence greatly drug removal by RRT (Table 147.1).[2]

Diffusion is the typical working principle of hemodialysis; it occurs passively through a semipermeable membrane, according to the concentration gradient and in countercurrent respect to blood flow, and generally needs time to reach equilibrium. Diffusive clearance is correlated inversely to the molecular weight (MW) of the solutes, being especially efficient for small molecules (MW < 500 Da).[2]

Conversely, convection represents the typical working principle of hemofiltration; it is an active process, similarly to glomerular filtration, and occurs rapidly and efficiently thanks to a pump-driven pressure gradient. Drug removal is independent of the MW, considering that almost all drug molecules are smaller than the very high hemofilter cutoffs, which are targeted expressly to allow filtration of large solutes (e.g., inflammatory cytokines).[3,4] Similarly to the glomerular filtration process in the kidney, hemofiltration produces an ultrafiltrate, so that a replacement fluid must be administered to preserve adequate circulatory volume.

The most frequently applied RRTs in patients with acute renal failure are intermittent hemodialysis (IHD), continuous venovenous hemofiltration (CVVH), and continuous venovenous hemodiafiltration (CVVHDF). Whereas IHD is essentially a diffusive technique, CVVH is a convective technique, and CVVHDF is a combination of both.[3]

Drug Properties

The drug characteristics that affect clearance during RRT are shown in Table 147.2.

Molecular Weight

Drug removal is expected to be dependent on MW only if the filter membrane cutoff is lower than the size of the considered drug. This aspect is absolutely irrelevant for hemofiltration techniques such as CVVH or CVVHDF, because almost all of the therapeutic drugs have MW < 2000 Da, which is a value significantly lower than the hemofilter cutoffs, which are optimized to be impermeable

TABLE 147.1

Comparison of Characteristics of Drug Removal During Renal Replacement Therapy

DIFFUSION	CONVECTION
Typical of dialysis	Typical of hemofiltration
Passive process	Active process
Movement results from concentration gradient and is countercurrent to blood flow	Movement results from pump-driven pressure gradient
Dependent on drug molecular weight	Independent of drug molecular weight
Long time to equilibrium	Rapid equilibrium
No need for replacement fluid	Need for replacement fluid to reconstitute blood volume (predilution or postdilution mode)

TABLE 147.2

Factors Potentially Affecting Drug Clearance During Renal Replacement Therapy

DRUG PROPERTIES	DEVICE PROPERTIES
Molecular weight	Composition
Plasma protein binding	Surface area
Volume of distribution	Pore size
Proportion of renal clearance	Adsorption

to plasma proteins (about 30,000 to 50,000 Da). On the other hand, MW becomes relevant in IHD because the filters are optimized for small solutes, often with a cutoff value of less than 800 to 1000 Da.[2] Accordingly, almost all drugs are expected to be removed at least partially by CVVH and CVVHDF, whereas most, but not all drugs, may be removed by IHD.[2] For example, the glycopeptide antibiotics vancomycin and teicoplanin are not removed during classic IHD because they have an MW higher than 1500 Da.[2]

Plasma Protein Binding

The second relevant factor conditioning drug clearance during RRT is the amount of plasma protein binding. Only the unbound moiety of a drug is available for elimination by RRT so that higher plasma protein binding means lower drug clearance.[5]

Volume of Distribution

The volume of distribution (Vd) reflects where a given drug is compartmentalized in the body, and it can vary greatly according to the drug's physicochemical properties, namely hydrophilicity or lipophilicity. Hydrophilic compounds, because of their inability to passively cross the plasmatic membrane of the eukaryotic cell, present a distribution limited to the plasma and to the extracellular space; therefore they are removed promptly and efficiently by RRT. This is typically the case with most antibacterials belonging to β-lactam, glycopeptide, lipoglycopeptide, and aminoglycoside classes, for which supplemental dosing (in comparison with the regimen used in patients with complete renal failure) is often mandatory during RRT.[2,6,7] On the other hand, most of the available therapeutic drugs are lipophilic compounds, which, thanks to their ability to freely cross the plasmatic membrane of the eukaryotic cells according to the concentration gradient, may accumulate significantly in the intracellular compartment. The larger the Vd, the less likely it is that the drug will be removed by RRT. For most lipophilic drugs with wide Vd, only a small fraction of the total drug amount present in the body can be removed, even with 100% extraction across the RRT filter, so supplemental dosing during RRT is unnecessary.[2]

Proportion of Renal Clearance

Drug clearance from the body is the result of elimination by renal excretion and by extrarenal pathways (nonrenal clearance), usually hepatic metabolism. Because RRT replaces renal function, it is clear that drug clearance during RRT is clinically relevant only with those drugs for which renal clearance is normally dominant (i.e., ≥30% of the total body clearance). This is usually the case with most hydrophilic and/or moderately lipophilic antibiotics, for which supplemental doses (beyond the regimen used in patients with complete renal failure) usually are needed during RRT. Conversely, drugs exhibiting mainly nonrenal clearance are expected to be only minimally cleared by RRT so that no major dosing modification (compared with the full dosing regimen in patients with normal renal function) usually is needed.

Estimation of Drug Clearance During Hemofiltration

Although estimation of drug removal during IHD may be difficult, it is more easily calculable during continuous treatments.

The sieving coefficient (S) identifies the drug fraction cleared during continuous hemofiltration and may be defined by the following equation:

$$S = C_{UF}/C_P$$

where C_{UF} is the drug concentration in the ultrafiltrate and C_P is the drug concentration in plasma.

The efficiency of drug clearance during CVVH depends on the administration mode of the replacement fluid. If the replacement fluid used to reconstitute blood volume is added in the postdilution mode (i.e., hemofiltration), drug clearance by the hemofilter (K_{HF}) is equal to the ultrafiltration rate (Q_{UF}) so that:

$$\text{Postdilution } K_{HF} = Q_{UF} \times S$$

Conversely, in the predilution mode, drug clearance will be lower, because plasma entering the filter is diluted by the substitution fluid, so that a dilution factor (DF) must be taken into account:

$$D_F = Q_{BF}/(Q_{BF} + Q_{RF})$$

where Q_{BF} is the blood flow rate and Q_{RF} is the replacement flow rate. Drug clearance in these circumstances is defined by the following formula:

$$\text{Predilution } K_{HF} = Q_{UF} \times S \times Q_{BF}/(Q_{BF} + Q_{RF})$$

Accordingly, it may be postulated that during CVVH drug removal will increase in a manner directly proportional to the applied ultrafiltration rate and generally will be higher in the postdilution mode.[2,8]

Considering that the hemofilter cutoffs are typically greater than the MW of almost all drugs, S in most cases should be equal to the unbound moiety of the drug, and, theoretically, K_{HF} should be estimated easily. However, several authors have demonstrated that predicted and

TABLE 147.3

Factors Potentially Increasing Drug Clearance During Renal Replacement Therapy

RRT OPERATING CONDITIONS	PATIENT'S PATHOPHYSIOLOGY
Hemodiafiltration	Hypoalbuminemia
High-volume ultrafiltration	Residual renal function

RRT, Renal replacement therapy.

observed S frequently do not overlap. If drug removal is higher than expected, the explanation may lie in the influence of several factors related to the properties and operating conditions of the device and to the patient's pathophysiologic status.

Device Properties

Devices present different characteristics in terms of composition, surface area, and ultrafiltration coefficient (see Table 148.2), and these factors may be correlated directly to diffusive and convective transport. In addition, drug removal may be increased because of drug adsorption to the hemofilter.[9] This adsorption rate may vary significantly over time because it is expected to reach maximum immediately after starting RRT and then to decrease progressively until filter exhaustion.

Operating Conditions

The efficiency of drug removal for a specific compound is expected to be greater for continuous than for intermittent RRT, and, generally speaking, the order is CVVHDF > CVVH > IHD.[2] However, the total removed amount can vary greatly, even according to the ultrafiltration flow rate (Table 147.3). The application of high-volume ultrafiltration rates (>35 mL/kg/hr), which is a technique rather frequently applied for removing cytokines during septic shock[4,10] and for improving survival in acute renal failure,[3,11] may increase significantly the extracorporeal clearance of hydrophilic antimicrobials with low Vd and low protein binding so that more aggressive dosing regimens must be advocated under these circumstances.[12,13]

Patient's Pathophysiology

In severely critically ill patients, there are often some peculiar pathophysiologic conditions that may work together in altering drug clearance during CRRT (see Table 147.3). First of all, the unbound fraction of a drug that is usually moderately to highly bound may vary in critically ill patients who have hypoalbuminemia; in some cases, drug clearance may be expected to increase under this circumstance.[5] It was shown recently that this effect may be clinically relevant for some highly protein-bound antimicrobial agents, namely ceftriaxone, daptomycin, ertapenem, and teicoplanin.[5]

In addition, the existence of residual renal function eventually must be taken into account, considering that it may increase significantly the total clearance of drugs that are highly removable by RRT, such as most hydrophilic antibiotics.[2,13]

Finally, for drugs with limited extracellular distribution, the presence of an extra volume in the interstitial compartment of critically ill patients may enlarge their Vd greatly. For example, this may occur because of capillary leakage resulting from sepsis or polytrauma.[1] In these situations, when starting therapy with hydrophilic antimicrobials, an increased loading dose should be administered, with the intent of promptly achieving therapeutic concentrations.[1]

PRINCIPLES FOR DOSAGE ADJUSTMENTS DURING CONTINUOUS RENAL REPLACEMENT THERAPY

In critically ill patients with acute renal failure, different approaches for drug dosage adjustments should be pursued according to the relative importance of the extracorporeal clearance (K_{CRRT}) compared with the total body clearance (K_T).

One of the most investigated field concerns the use of antibacterial agents. The clinical relevance of CRRT during antimicrobial treatment is related mainly to the need to prevent underdosing by administering substitutional or increased doses, with the double intent of avoiding the risk of therapeutic failure and containing the spread of breakthrough bacterial resistance.[6,14]

Unfortunately, definite guidelines on antibiotic dosing during CRRT are still lacking.[15,16] However, as a general rule, clinicians may take into account four different situations for appropriate dosing (Table 147.4). First, when using drugs with low Vd and normally at high renal clearance, for which K_{CRRT} represents a significant percentage of K_T, patients usually require additional doses (in comparison with those used for anephric patients).[2,13] It is clear that the relative importance of CRRT in drug removal is maximal for hydrophilic compounds with low plasma protein binding (Box 147.1), this being the typical profile of several hydrophilic antimicrobial agents, such as most β-lactams, aminoglycosides, and daptomycin.

Second, when using drugs with moderately high Vd and normally at high renal clearance, for which K_{CRRT} represents a significant percentage of K_T (e.g., levofloxacin), additional doses frequently are required in comparison with anephric patients.

Third, when using drugs with high Vd for which renal clearance normally varies because of the presence of other compensatory mechanisms, K_{CRRT} may represent a moderate and variable percentage of K_T (e.g., ciprofloxacin) so that doses similar to those used in patients with moderately impaired or even normal renal function may be required.

Fourth, when using drugs normally at low renal clearance, K_{CRRT} is expected to represent only a poor percentage of K_T so that doses similar to those used in patients with normal renal function frequently are required.

From all of the aforementioned considerations, it appears that, when hydrophilic antibacterial agents highly cleared by extracorporeal RRTs are used during CVVH or CVVHDF, significant dosage increases (versus anephric patients) sometimes may be necessary in critically ill patients with acute renal failure, especially in the presence of high-volume ultrafiltration rates.[2]

PHARMACODYNAMICS AND DOSAGE ADJUSTMENTS OF ANTIMICROBIAL AGENTS DURING RENAL REPLACEMENT THERAPY

Considering that dosage increase may be performed in two different ways, by enlarging the amount of each single dose

TABLE 147.4

Handling of Some Antimicrobial Agents During Continuous Renal Replacement Therapy (CVVH and/or CVVHDF)[a]

CHARACTERISTICS OF ANTIMICROBIAL AGENT	DOSAGE ADJUSTMENT	EXAMPLE DRUGS
1. Low Vd + normally high renal clearance: K_{CRRT} is a significant part of KT	Require additional doses, compared with anephric patients	Aminoglycosides: Amikacin Gentamicin Netilmicin Tobramycin Penicillin: Amoxicillin or amoxicillin-clavulanate Ampicillin or ampicillin-sulbactam Piperacillin or piperacillin-tazobactam Cephalosporins: Cefepime Cefotaxime Ceftazidime Carbapenems: Doripenem Ertapenem[b] Imipenem-cilastatin Meropenem Monobactams: Aztreonam Glycopeptides: Vancomycin Teicoplanin[b] Lipopeptides: Daptomycin[b] Other agents: Colistin Fosfomycin
2. High Vd + normally high renal clearance: K_{CRRT} is a significant part of K_T	Require additional doses, compared with anephric patients	Fluoroquinolones: Levofloxacin
3. High Vd + normally variable renal clearance: K_{CRRT} is a variable part of K_T	May require doses similar to those for patients with moderately impaired renal function	Fluoroquinolones: Ciprofloxacin
4. Normally low renal clearance: K_{CRRT} is a poor part of K_T (≤ 30%)	Require doses similar to those for patients with normal renal function	β-Lactams: Ceftriaxone[b] Oxacillin Fluoroquinolones: Moxifloxacin Others: Clindamycin Linezolid Quinupristin/dalfopristin Tigecycline

CVVH, Continuous venovenous hemofiltration; *CVVHDF,* continuous venovenous hemodiafiltration; K_{CCRT}, extracorporeal clearance; K_T, total body clearance; *Vd,* volume of distribution.
[a]For theoretical dosages, see Pea et al.[12] and Vossen et al.[17]
[b]Higher doses may be necessary in the presence of hypoalbuminemia.

BOX 147.1

Drug Properties Conditioning the Highest Potential Clearance During Renal Replacement Therapy

Low molecular weight*
Low plasma protein binding
Low volume of distribution
High renal clearance

*Relevant only for intermittent hemodialysis.

or by shortening the dosing interval, the approach chosen should be based on the pharmacodynamic behavior of the specific drug.

Antiinfective agents may exhibit time-dependent or concentration-dependent antimicrobial activity. For time-dependent antimicrobial agents, namely β-lactams, macrolides, glycopeptides, oxazolidinones, clindamycin, and azole antifungals, the time (t) during which concentrations are maintained above the minimum inhibitory concentration (MIC) of the etiologic agent (t > MIC) is considered the most relevant pharmacodynamic parameter.[18] For these agents, exposure may be optimized by maintaining trough plasma levels (C_{min}) greater than the MIC (C_{min} > MIC).[18] Accordingly, for those time-dependent agents that are significantly removed by CRRT, the most suitable approach for dosage increase to preserve efficacy would be to intensify the frequency of drug administration by shortening the dosing interval.

For concentration-dependent antimicrobials, namely aminoglycosides, fluoroquinolones, and daptomycin, the most important pharmacodynamic parameter, to ensure efficacy and to prevent the spread of bacterial resistance, is the ratio between the peak plasma level (C_{max}) and the MIC (C_{max}/MIC), which in most cases should be at least 10.[18] In addition, the total daily drug exposure, in terms of the area under the curve of plasma concentration versus

time (AUC), must be many tensfold higher than the MIC; the thresholds for optimal pharmacodynamic exposure is different AUC/MIC ratio according to the type of the concentration-dependent antibacterial agent.[18] Accordingly, for those concentration-dependent agents that are highly removable by CRRT (i.e., daptomycin), to improve efficacy during extracorporeal therapy, it may be more helpful to increase the amount of each single dose while extending the dosing interval.[19]

CONCLUSION

Drug removal during RRT is a complex process that may vary greatly even in a brief period of time as a consequence of frequent variations in CRRT characteristics and in operating conditions or in the patients' pathophysiologic status.

Several authors suggested different approaches with the intent of estimating drug clearance during CVVH or CVVHDF to calculate the appropriate dose, and useful dosage recommendations during CRRT, specifically for antimicrobial agents, have been published recently.[6,7,14,16,20,21] Although these may be helpful in starting therapy, several pharmacokinetic studies carried out in critically ill patients during extracorporeal therapies have documented very large interindividual and intraindividual pharmacokinetic variability.[8] Higher than currently recommended dosages may be needed, especially for some hydrophilic compounds during the application of high-volume ultrafiltration rates or in the presence of residual renal function.[8,12]

Tailored therapy with hydrophilic antimicrobials by means of therapeutic drug monitoring should be considered in critically ill patients undergoing CRRT because this is probably the only way to optimize exposure in each individual patient.[22] This could be especially relevant whenever clinicians are dealing with infections resulting from multi-drug–resistant (MDR) gram-negative bacteria. In fact, pharmacokinetic-pharmacodynamic optimization of drug exposure based on therapeutic drug monitoring is considered a helpful tool to overcome in vitro resistance.[23–25]

Key Points

1. The drugs that are most efficiently removed by renal replacement therapies are those with low volume of distribution, low protein binding, and high renal clearance; this is the case for most hydrophilic antibiotics belonging to the classes of β-lactams and aminoglycosides.
2. Continuous venovenous hemodiafiltration (CVVHDF) is generally the most efficient technique in drug removal.
3. High-volume ultrafiltration rates may significantly increase drug removal.
4. The underlying presence of hypoalbuminemia and/or sepsis may cause underdosing.
5. Therapeutic drug monitoring of plasma concentrations should be applied to optimize drug exposure, especially when using hydrophilic antimicrobials for treating infections caused by MDR bacteria.

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A complete reference list can be found online at ExpertConsult.com.

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