

# Pharmacokinetics and drug dosing adjustments during continuous venovenous hemofiltration or hemodiafiltration in critically ill patients

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Continuous renal replacement therapy (CRRT) in critically ill patients with renal failure may significantly increase drug clearance, requiring drug dosing adjustments. Drugs significantly eliminated by the kidney often undergo substantial removal during CRRT, and a supplemental dose corresponding to the amount of drug removed by CRRT should be administered. Clearance by CRRT can either be measured or estimated. The high-flux membranes used in CRRT make no filtration barrier to most drugs, and the filtrate concentration can be estimated by the unbound fraction of the drug in plasma. When adding dialysis to filtration, this approach overestimates drug clearance, and a correcting factor should be used. A method for estimating drug clearance as a function of creatinine clearance is also sug-

gested, but it has the same limitations in overestimating drug clearance when dialysis is combined with filtration. For non-toxic drugs, doses can safely be increased 30% above actual estimates to ensure adequate dosing. For drugs with a narrow therapeutical margin, monitoring plasma concentrations are mandatory. When appropriate, the use of a readily available reference for drug dosing is recommended.

**Key words:** Acute renal failure; continuous renal replacement therapy; drug dosing; hemofiltration; hemodiafiltration; pharmacokinetics.

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**I**N THE INTENSIVE care unit (ICU) both intermittent and continuous renal replacement therapies (CRRTs) are used for treatment of acute renal failure (ARF). During the last two decades there has been an evolution of continuous therapies from the initial arteriovenous hemofiltration (CAVH) driven by the patient's arteriovenous pressure difference, to the more sophisticated pumpdriven devices performing continuous venovenous hemofiltration (CVVH), hemodialysis (CVVHD) or hemodiafiltration (CVVHDF). In critically ill patients, CRRT is superior to intermittent hemodialysis (IHD) in maintaining hemodynamic stability (1). Together with better volume, electrolyte, and acid-base control, this is probably the main reason for it becoming the therapy of choice for ARF in the ICU (2).

Critically ill patients with ARF often have multi-organ dysfunction, sepsis, or other conditions that require complex drug therapy, and which may influence drug concentrations through changes in absorption, distribution, metabolism, and elimination. The addition of CRRT may further complicate drug therapy, and the purpose of this review is to outline the general principles determining whether a dose adjustment is required to compensate for drug elimination during

CRRT, and to provide some practical guidance for drug prescription in this setting.

## Drug properties

Total body clearance of a drug is the sum of clearances from different sites in the body which may include hepatic, renal, and other metabolic pathways. It is the contribution of renal clearance to total body clearance that is the major determinant of making drug dosing adjustments in renal failure. If the renal clearance of a drug is normally less than 25–30% of total body clearance, impaired renal function is unlikely to have clinically significant influence on drug removal (3). Similarly, drug removal by CRRT will have little influence on total body clearance and dosing adjustments do not have to be considered. If patients develop hepatic failure, the extent to which CRRT contributes to total body clearance may increase, and dose adjustments may become necessary. Drugs significantly eliminated by the kidney often undergo substantial removal during CRRT, and dosing adjustments are frequently required.

However, there are other drug properties affecting clearance by CRRT, including protein binding, vol-

ume of distribution (Vd), molecular weight, and drug charge. Only the unbound fraction of a drug is available for filtration, and drugs with a high protein binding are poorly cleared by CRRT. Many factors may alter the fraction of unbound drug such as systemic pH, heparin therapy, hyperbilirubinemia, concentration of free fatty acids, relative concentration of drug and protein, as well as presence of uremic products and other drugs that may act as competitive displacers (4–6). Most of our knowledge about alterations in protein binding and pharmacokinetics is derived from studies on chronic renal insufficiency. The influence of ARF on protein binding is not well described. Critically ill patients often have low albumin values which may increase the unbound fraction of many drugs with possible deleterious effects, as documented for phenytoin (7). These patients also often have increased levels of acid  $\alpha_1$ -glycoprotein, which may increase protein binding of some drugs. Thus, the reported unbound fraction in healthy volunteers and in patients with chronic renal insufficiency may differ substantially from the unbound fraction of drugs in critically ill patients receiving CRRT.

Drug charge affects clearance by the Gibbs-Donnan effect: Retained proteins on the blood side of the membrane make the membrane negatively charged and the filtered fraction of cationic drugs will be a little less than expected from the unbound fraction, whereas the opposite is true for anionic drugs.

A large Vd reflects a drug that is highly tissue bound, and consequently only a small proportion actually resides in the vascular compartment available for clearance by endogenous or extracorporeal routes. The Vd is a mathematical reflection of the volume in which a drug would need to be dissolved to obtain the observed blood concentration, assuming homogeneous mixing in the body. For intravenously administered drugs, the Vd determines the dose (D) needed to achieve the desired plasma concentration (C):

$$D = C \cdot Vd \cdot \text{Body weight}$$

In critically ill patients the actual Vd may differ from values obtained from pharmacological tables, and it shows great inter- and intraindividual variations (8). This may increase the error when using Vd in estimating drug dosing. The Vd of aminoglycosides increases approximately 25% in the critically ill, whereas vancomycin, metronidazole, and most  $\beta$ -lactam antibiotics show near normal values, but with individual variations (8). A drug with a small Vd ( $\leq 1 \text{ l} \cdot \text{kg}^{-1}$ ) is more likely to be cleared by extracorporeal therapies than a drug with a large Vd ( $\geq 2 \text{ l} \cdot \text{kg}^{-1}$ ). However, there is a significant difference between

IHD and CRRT. A drug with a large Vd and high clearance during high-flux IHD will rapidly be removed from plasma, but only a small amount of the body's drug content is removed during one dialysis session, and plasma concentration will be restored between therapies. CRRT by its continuous and slower action has much less influence on plasma concentrations of drugs with large Vds, because there is time for continuous redistribution of the drug from the tissues to the blood. Although drug elimination during CRRT is much slower for drugs with large Vds than for drugs with small, the same is true for endogenous (hepatic) elimination which has to clear the same Vd. As a consequence, drug dosing adjustments to be made during CRRT are much more dependent on the relative contribution of CRRT to total body clearance of the drug than on the drug's Vd (9).

Most drugs have a molecular weight  $\leq 500$  Da, and very few are greater than 1500 Da (vancomycin at 1448 Da). Conventional dialysis membranes favor diffusive clearance of low molecular weight solutes below 500 Da, whereas the typical high-flux membranes used for CRRT have larger pores (20 000–30 000 Da), making no significant filtration barrier to unbound drugs.

## Methods of drug removal

Essential to rational drug prescribing in patients undergoing CRRT is an understanding of the different methods of solute removal that occur with the various types of treatments. Diffusion, convection, and adsorption are the three mechanisms for solute removal during CRRT. The process of moving a solute through a membrane from an area of high concentration to an area of lower concentration is called diffusion, and it is the primary method of solute removal during dialysis. Diffusive clearances varies between filter membranes and are greater for polyacrylonitrile (PAN, AN-69) than for polyamide membranes (10). In a study by Morabito et al. (10), diffusive equilibrium between dialysate and plasma for urea could only be obtained with the AN-69 filter at a dialysate flow rate of  $1.5 \text{ l} \cdot \text{h}^{-1}$  during CAVHDF. Similarly, the diffusive clearances of drugs will vary depending on the filter used.

Convection is the removal of solutes along with the solvent in which they are present, and the rate of ultrafiltration determines the convective clearance of a solute during CRRT. It is not influenced by the concentration gradients across the membrane and is only dependent on membrane pore size.

The diffusion of a solute is inversely proportional

to its molecular weight, and the relative importance of convection increases with increasing molecular weight. Diffusion favors clearance of small solutes whereas middle- and large-sized molecules mainly are removed by convection. As an example: for the 1448 Da molecule, vancomycin, convection is quantitatively more important than diffusion for its removal during CRRT (11).

Adsorption to filter membranes leads to increased removal from plasma (12) and the various filters have different absorptive capacity. Some filter membranes, such as the commonly used polyacrylonitrile, may adsorb a substantial amount of drug to its surface (13, 14). However, adsorption is a saturant process, and the influence on drug removal will depend on the frequency of filter changes. In general, with filters lasting approximately 18–24 h, adsorption probably has minor influence on drug removal, but at present, information about the various filters' adsorptive capacity for most drugs is lacking. Filter adsorption is not accounted for in drug dosing guidelines (9, 15). CRRT is mainly performed as CVVH or CVVHDF. In CVVH, solutes are removed only by convection, and drug removal is limited by the ultrafiltration rate. By adding dialysis to filtration, as in CVVHDF, solutes are removed by both convection and diffusion, increasing the removal of small molecules more than middle-sized and large molecules. It also gives the possibility for the two processes to interact in such a manner that solute removal is significantly less than what is expected if the individual components are simply added together. In a study by Brunet et al. (16), the clearance during CVVHDF of small molecules, such as urea and creatinine, was approximately the sum of the two clearances obtained when CVVHD and CVVH were performed separately. Even with the highest flow rates of 2.5 and  $2.0 \text{ l} \cdot \text{h}^{-1}$  of dialysate and ultrafiltration, respectively, the differences between actual and predicted clearances from addition of the two procedures differed by less than 10%, indicating minimal interaction between diffusion and convection. For  $\beta_2$ -microglobulin, however, combining diffusion and convection did not increase clearance compared to convection alone, indicating that this small protein was only removed by convection. This means that the diffusive clearance of a drug during CVVHDF is difficult to predict and will depend on its molecular weight, blood and dialysate flow rates, and the membrane used.

In CVVH and CVVHDF, the method by which replacement fluids are administered influences solute removal efficiency. In post-dilution procedures the re-

placement fluid is administered distal to the filter, and mass removal per unit volume of effluent fluid is relatively high. For small solutes the effluent concentration may be the same as in plasma water. However, the ultrafiltration rate is limited by the operating characteristics of the system, mainly the hematocrit and the blood flow rate. The upper limit of ultrafiltration rate is approximately 25–30% of plasma flow rate (17). In pre-dilution procedures, the replacement fluid is administered proximal to the filter, diluting the concentration of solutes in the blood, and thus reducing solute clearances approximately 15–20% (16). This modest decrease in efficiency can be overcome by increasing the ultrafiltration rate which in this setting is not restricted by hematocrit and blood flow (18).

## Drug dosing adjustments

The critically ill patient with renal failure is at risk for drug accumulation and overdose, but also for underdosing that may be life threatening, such as in the case of insufficient antibiotic treatment. Drug dosing adjustments can be performed by reducing the dose in proportion to the reduction in total body drug clearance. For the anuric patient this makes:

$$D = D_N \cdot Cl_{ANUR} / Cl_N$$

where  $D_N$  is the normal dose,  $Cl_{ANUR}$  is drug clearance in anuric patients, and  $Cl_N$  is normal drug clearance.  $Cl_{ANUR}$  and  $Cl_N$  are retrieved from pharmacological tables. If CRRT contributes significantly to the total body clearance of a drug ( $\geq 25$ –30% of total body clearance), a supplemental dose, corresponding to the amount of drug removed by CRRT, should be administered, making:

$$D = D_N (Cl_{ANUR} + Cl_{CRRT}) / Cl_N$$

where  $Cl_{CRRT}$  is the CRRT drug clearance. Clearance by CRRT can be measured and is:

$$Cl_{CRRT} = Q_E \cdot C_E / C_P$$

where,  $C_E$  and  $C_P$  are drug concentrations in effluent fluid and plasma, respectively.  $Q_E$  is the effluent flow rate which is the sum of ultrafiltration flow rate ( $Q_{UF}$ ) and dialysate flow rate ( $Q_D$ ). Substitution into the above equation makes:

$$D = D_N (Cl_{ANUR} + Q_E \cdot C_E / C_P) / Cl_N$$

For most drugs, measurements are not available, and CRRT clearances have to be estimated. The sieving coefficient ( $S$ ) of a drug is the concentration in ultrafil-

trate ( $C_{UF}$ ) divided by the concentration in plasma, making:

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

The exact formula for the sieving coefficient is  $S = 2 C_{UF} / (C_{Pin} + C_{Pout})$ , but the differences between  $C_{Pin}$  and  $C_{Pout}$  are negligible, making the above equation almost correct. For readily filtrable molecules  $C_{UF}$  approximates the concentration of unbound drug in plasma, and  $S$  can be estimated by the unbound fraction ( $f_u$ ) of the drug, making:

$$Cl_{CRRT} = f_u \cdot Q_{UF} \text{ or } Cl_{CRRT} = f_u \cdot (Q_{UF} + Q_D)$$

during CVVH or CVVHDF, respectively. The value of  $f_u$  is retrieved from pharmacological tables, but as outlined above, the unbound fraction in the critically ill may differ from these values. However, with some exceptions and individual variations, Golper and Marx found that for most of the 60 drugs measured, the filtered fraction during CRRT correlated well with the unbound fraction known from studies on healthy subjects (19). If CRRT is performed in a predilution mode,  $f_u$  has to be corrected by the dilution factor = plasma flow rate / (plasma flow rate + replacement fluid flow rate). The dialysate flow rate during CVVHDF is low ( $750\text{--}2500 \text{ ml} \cdot \text{h}^{-1}$ ), allowing almost diffusive equilibrium to occur between dialysate and plasma concentrations for small molecules, making  $f_u \cdot Q_D$  an acceptable estimate of diffusive clearance. However, it will always be overestimated, and increasingly overestimated with increasing molecular weight and dialysate flow rate. Vos and Vincent (20, 21) found a close exponential correlation of a drug's diffusive mass transfer coefficient through membranes in CAVHDF:

$$Kd_{rel} = Kd / Kd_c = (MW / 113)^{-0.42}$$

where  $Kd$  and  $Kd_c$  are the diffusive mass transfer coefficients for the drug and creatinine, respectively, and  $MW$  is the drug's molecular weight (113 is the molecular weight of creatinine). The limiting factor of diffusive clearance can be approximated by  $Kd_{rel}$  (22), giving:

$$Cl_{CRRT} = f_u \cdot (Q_{UF} + Q_D \cdot Kd_{rel})$$

Dose estimates ( $D_E$ ) will be as follows:

$$D_E = D_N \cdot [P_X + f_u \cdot (Q_{UF} + Q_D \cdot Kd_{rel}) / Cl_N]$$

where  $P_X$  is the extrarenal clearance fraction of the drug ( $= Cl_{ANUR} / Cl_N$ ). Using this approach for antimicrobiological agents during CVVH ( $Q_D = 0$ ), Joos et al. (23) found that CCVH clearance deviated less than 15% from estimated, whereas total body clearance

was underestimated in the range of 30%. This means that the actual non-CRRT clearance was greater than estimated from  $P_X$ . Kroh et al. (22) found very good correlations between doses calculated from measured kinetic data and doses estimated by the above equation during CVVH, but they did not tell how  $P_X$  was estimated. For CVVHDF data are lacking, but when using the  $Kd_{rel}$  on CAVHDF clearances reported in the literature, Kroh et al. (22) found very good correlations between observed and estimated clearances ( $y = 0.004 + 0.96x$ ).

For non-toxic drugs, doses can safely be increased beyond actual estimates and a 30% increase is recommended to ensure adequate dosing (8).

Making these estimates is time consuming, requiring a careful search for basic pharmacokinetic data, and they are based on totally non-functioning kidneys. Today there is a tendency to start CRRT earlier in the course of illness, and residual renal function may contribute to drug clearance. According to Dettli's equation as quoted by Keller and Czock (24), actual total body clearance ( $Cl_{ACTUAL}$ ) of a drug is a linear function of creatinine clearance ( $Cl_{CR}$ ):

$$Cl_{ACTUAL} = Cl_{ANUR} + a \cdot Cl_{CR}$$

where  $a = (Cl_N - Cl_{ANUR}) / Cl_{CRn}$ .  $Cl_{CRn}$  is normal creatinine clearance. To simplify and individualize drug dosing estimation, Keller et al. (25) suggested to apply this equation during CRRT by introducing the total  $Cl_{CR}$  concept ( $Cl_{CRtot}$ ) as the sum of renal  $Cl_{CR}$  ( $Cl_{CRren}$ ) and extracorporeal  $Cl_{CR}$  ( $Cl_{CRfilt}$ ):

$$Cl_{CRtot} = Cl_{CRren} + Cl_{CRfilt}$$

$Cl_{CRtot}$  can easily be calculated from creatinine measurements in urine, effluent fluid and blood. These calculations can then be substituted into dosing adjustment equations. Using the same approach as above, and setting  $P_X = Cl_{ANUR} / Cl_N$ , the estimated dose will be:

$$D_E = D_N \cdot [P_X + (1 - P_X) \cdot Cl_{CRtot} / Cl_{CRn}]$$

This equation uses an individual's actual creatinine clearance to estimate drug clearance and drug dosing, and dose estimates will automatically be adjusted as changes occur in the patient's renal function. However, extracorporeal creatinine clearance may overestimate extracorporeal drug clearance, especially diffusive clearance of high molecular drugs during CVVHDF.  $P_X$  is not measured, and patients with severe ARF have a residual clearance that is sometimes remarkable (22), leading to underestimating of drug dosing. The applicability of this approach to drug dosing has not been clinically evaluated yet, and it

remains to be seen whether it represents any improvement in making drug dosing adjustments during CRRT.

Another and strongly suggested approach to drug dosing during CRRT is to utilize a readily available reference. In a publication by Kroh (8), there is a table of normal kinetic data of many actual drugs, and suggested dosing adjustment factors for different ultrafiltrate rates during CVVH. If using references that utilize glomerular filtration rate (GFR) in its specific recommendations, such as the Bennett tables (26), it is useful to regard CRRT as a GFR of 10–50 ml · min<sup>-1</sup> depending on dialysate and hemofiltration flow rates. However, these tables (26) are based on measurements from patients with chronic renal insufficiency and do not take into account the pharmacokinetic changes induced by acute critical illness as discussed above.

All predictions have shortcomings, and for toxic drugs and for drugs with a narrow therapeutic range such as aminoglycosides, drug monitoring with measurements of plasma concentrations is mandatory for safe drug dosing. This method addresses the actual total body clearance in which CRRT is only one part, and adjustments can be made as total body clearance is changed by the clinical condition and/or by CRRT adjustments. The following dosing formula is often used to achieve the desired peak concentration ( $C_{\text{PEAK}}$ ) from the actual trough (or any concentration) ( $C_{\text{ACTUAL}}$ ):

$$D = (C_{\text{PEAK}} - C_{\text{ACTUAL}}) \cdot V_d \cdot \text{Body weight}$$

The estimated  $V_d$  in this equation may differ from the actual  $V_d$ , but with repeated measurements this error is self-correcting. As outlined above, the  $V_d$  of aminoglycosides is increased in critically ill patients, indicating higher doses to achieve the desired  $C_{\text{PEAK}}$  and longer intervals than expected from actual renal and CRRT clearances to reach acceptable trough concentrations. There has been a discussion lately about aminoglycoside dosing and dosing intervals, and it seems that giving the total daily dose as one single bolus is at least as effective and less toxic than divided doses in patients with normal renal function (27). The consequences for adjusting aminoglycoside dosing during CRRT are not clear, but probably one should be more concerned about avoiding high trough than high peak values.

In conclusion, drug dosing adjustments during CRRT can be guided by measuring or estimating CRRT drug clearance, by using available references, or by monitoring drug plasma concentrations. For non-toxic drugs, doses 30% above actual estimates are

recommended to ensure adequate dosing. For drugs with a narrow therapeutic margin, drug monitoring is mandatory.

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