Minireview

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Continuous Renal Replacement Therapy Does Not Have a Clear Role in the Treatment of Poisoning

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Introduction

Management of poisoned patients often requires extracorporeal techniques to remove toxins. Whether extracorporeal removal therapies are effective depends on the characteristics of the toxin and the modality of removal. The modalities we address here include hemodialysis, charcoal hemoperfusion, and continuous renal replacement therapies (CRRT) such as continuous venovenous hemofiltration (CVVH). The term CRRT is commonly used to describe all continuous modalities of hemofiltration in which the blood passes through large-pore hollow fiber membranes, allowing the convective removal of molecules with molecular weights (MWs) up to 40 kDa. CVVH is the most commonly used of the CRRT modalities. In continuous venovenous hemodiafiltration (CVVHDF), diffusive transport of molecules is combined with convective removal in order to improve the solute clearance.

The role of CRRT for the removal of xenobiotics (a term used to include drugs and toxins) is not well defined. In this review, we express a skeptical view of the indications for using CRRT instead of hemodialysis. Peritoneal dialysis is too ineffective to be recommended except when other modalities are not available or perhaps in the treatment of infants.

Our recent analysis of the use of different extracorporeal removal techniques for removal of toxins in a na-
tional database showed increasing use of hemodialysis with a decreasing use of charcoal hemoperfusion [1]. Unfortunately, this database does not currently track the use of CRRT. However, case reports describing the use of CRRT for the treatment of intoxications appear frequently, often not justifying the use of CRRT instead of hemodialysis. Given the infrequency of cases where utilization of these modalities is appropriate, randomized controlled trials comparing different modalities for treatment of poisoning have not been performed and are not likely to appear in the future.

**Clearance of Xenobiotics**

There are many determinants of the rate of solute removal from a patient by extracorporeal modalities. Variables include rates of flow of blood and dialysate (if used) and the properties of the membrane which include pore size, surface area, and membrane thickness. The variables regarding the solute to be removed include MW, proportion bound to plasma proteins and its volume of distribution (VD). Table 1 summarizes some of these properties for solutes discussed later in this review. ‘Clearance’ refers to the virtual volume of blood from which a solute is completely removed during a period of time. The extraction ratio (ER) is the percentage of the molecule removed from the plasma as it passes through the membrane and is expressed as:

$$ER = \frac{[\text{plasma}]_{\text{in}} - [\text{plasma}]_{\text{out}}}{[\text{plasma}]_{\text{in}}}$$

Clearance can be calculated using an estimate of the plasma flow rate and ER: clearance = ER × plasma flow rate. A low MW substance with a low apparent VD so that it is primarily within the extracellular space and has no significant protein binding may be easily removed by an extracorporeal modality. Conversely, a large molecule with lipophilic properties or a high degree of protein binding will have a larger VD and will not be cleared well by these dialytic modalities. A solute with a VD much larger than the total body water or approximately 60% of total body weight (i.e. 0.6 liter/kg of body weight) has its distribution outside of the extracellular fluid where it will not be removable by dialytic therapies.

Rebound refers to the increase in plasma solute levels following the cessation of extracorporeal therapy. A solute may be effectively removed from the extracellular space and then, depending on VD, there may be solute within the intracellular space including fat stores or bound to plasma or tissue proteins. The intracellular space functions as a second compartment, a reservoir of drug. Over time, there will be movement of the substance from these other compartments to the bloodstream as the drug redistributes from the intracellular space to the extracellular space. The rate of redistribution varies considerably for different substances and may influence the utility of a technique such as CRRT.

While ultrafiltration (convective clearance) and dialysis (diffusive clearance) are the primary mechanisms for solute clearance in CRRT, adsorption of molecules to the membrane may also be significant [2]. The synthetic membranes can bind some proteins, cytokines, and drugs, and the amount of a substance adsorbed depends on the characteristics of the drug, membrane composition, and serum pH [3]. Most of the data on drug adsorption are based on studies of antibiotic dosing or inflammatory mediators and markers. An illustrative example comes from a study of single doses of levofloxacin in CVVH [4]. The investigators found that 19–40 mg of a single 100-mg intravenous dose of levofloxacin could bind to a CVVH membrane, depending on membrane composition. While similar studies of most poisons have not been done, these data suggest that adsorption could play a significant role in xenobiotic clearance.

**Advantages and Disadvantages of CRRT**

The main advantage of CRRT is its applicability in hemodynamically unstable patients, even in the presence of shock. It can be easily set up and run by regular intensive care unit staff, thereby avoiding the need for specially
trained dialysis nurses and technicians. The membranes used in CRRT are typically more permeable compared to standard intermittent hemodialysis membranes. Most high-flux hemodialysis membranes allow for the clearance of molecules up to 1,000 Da. CRRT membranes allow for the clearance of molecules as large as 20,000–40,000 Da [5]. Substances such as heparin, myoglobin, vancomycin, and other xenobiotics are therefore cleared by CRRT. The major disadvantage of CRRT is its relatively lower clearance rate when compared to standard intermittent hemodialysis. This large comparative advantage to hemodialysis has made the technique the gold standard for extracorporeal removal of xenobiotics. While a lower clearance rate may be adequate when applying the technique for days in support of a patient with acute kidney injury in intensive care, a patient with acute poisoning and manifestations of cellular toxicity usually requires more rapid and immediately effective therapy. Especially because sicker patients are successfully hemodialyzed today with biocompatible membranes, bicarbonate-based dialysate and ultrafiltration control, a patient would have to have a truly life-threatening degree of hemodynamic compromise before one concluded that a slower course of CRRT was likely to be more effective than an attempt at performing hemodialysis.

Another putative advantage touted for CRRT is the ability to avoid rebound of compounds removed from the blood compartment which then reequilibrate from intracellular space to plasma. Slower clearance rates by CRRT lead to less dramatic decreases in plasma drug levels and are not associated with marked increases in plasma levels following a course of therapy. We remain uncertain whether such rebound is worth avoiding as it represents the movement of the solute from the intracellular compartment, where it is likely having its toxic effect, to the extracellular space, where it is susceptible to removal by hemodialysis. In essence, the lack of rebound with CRRT is testimony to the relatively low clearance that could be associated with less benefit than a faster, rebound-associated hemodialysis.

There are other disadvantages of CRRT. It usually requires more intensive anticoagulation which can place a patient at risk for bleeding and electrolyte disturbances. In addition, patients must remain immobile for long periods of time to ensure proper machine function. Finally, CRRT is not available at many smaller hospitals, possibly due to high equipment, training, and staffing costs and relatively infrequent utilization.

### Specific Xenobiotics

Selected xenobiotics for which extracorporeal therapy might be important are discussed below. Table 2 summarizes therapy options for some agents, including a few examples for which extracorporeal treatments such as CVVH and hemodialysis are considered inappropriate.
Lithium

Lithium has an MW of 6.94 Da, a VD of 0.6–0.9 liter/kg and no protein binding. Standard intermittent hemodialysis can achieve clearances of 70–170 ml/min when blood flow is 250 ml/min, which is significantly higher than the renal clearance of 10–40 ml/min seen in subjects with normal kidney function [6]. It is also significantly higher than the clearances achieved with CRRT, described below.

Leblanc et al. [7] published a series of 7 patients with lithium poisoning – 4 acute intoxications and 3 chronic poisonings. Five patients were treated with continuous arteriovenous hemodiafiltration (CAVHDF) and 2 were treated with continuous veno-venous hemodiafiltration (CVVHDF). The continuous CAVHDF used dialysate flows of 4 liters/h, resulting in a mean lithium clearance of 41 ml/min (range 28–56 ml/min). The CVVHDF used dialysate flows of 1–3 liters/h and ultrafiltration rates of 2 liters/h, generating clearances of 48 and 62 ml/min. The authors concluded that these modalities provide excellent lithium clearance, prevent rebound, and may be particularly useful in cases of chronic poisoning due to high intracellular drug accumulation. However none of the 7 patients were reported to be hypotensive, which would be an unusual and late manifestation of lithium toxicity. In none of the cases was conventional hemodialysis attempted. Therefore, a basis for choosing CRRT over hemodialysis is not offered, unless logistical issues such as availability of staff or equipment are taken into consideration.

Lithium is often associated with rebound of plasma levels following hemodialysis. Most cases of lithium intoxication treated with hemodialysis require at least a second session of hemodialysis following rebound [8]. As described above, the use of CRRT can avoid this rebound though the clinical importance of avoiding rebound remains unproven [9, 10]. Another way to utilize CRRT is to institute it following a hemodialysis session. This avoids the need for a second hemodialysis session, allows the hemodialysis staff to give way to the intensive care unit staff, and may be useful for these logistical problems. If only medical issues are considered, we recommend performance of hemodialysis with a second session to follow the first by 6–12 h.

Toxic Alcohols

Methanol and ethylene glycol are toxic alcohols found primarily in windshield washer fluid and antifreeze, respectively. Methanol has MW of 32.0 Da and the VD is 0.6–0.7 liter/kg. Ethylene glycol has MW of 62 Da and a VD of 0.6 liter/kg [11]. Methanol is metabolized by alcohol dehydrogenase and aldehyde dehydrogenase to form-aldehyde and formate, respectively, while ethylene glycol is metabolized by the same enzymes to glycoaldehyde and glycolate, then to glyoxylate and oxalate. All of these metabolites are toxic and associated with elevated anion gap metabolic acidosis. The small size, low VD, and low protein binding for these alcohols make them readily dialyzable, making standard hemodialysis the first-line therapy for extracorporeal elimination. Hemodialysis can achieve clearances of 200–250 ml/min for ethylene glycol, 200 ml/min for methanol [11], 170 ml/min for glycolate [12], and 223 ml/min for formate [13]. These rates easily exceed those achieved using CRRT. In a case series of 3 patients, CVVHD effectively removed methanol and normalized bicarbonate but at clearance rates significantly lower than conventional hemodialysis: clearances of 45 and 48 ml/min in the 2 patients treated with CVVHDF compared to 237 ml/min for the patient initially treated with hemodialysis, respectively [16]. Given the lack of evidence, CRRT cannot be routinely recommended, except in cases where hemodialysis is not available or in the setting of significant hypotension when hemodialysis is unsuccessful.

However, the indications for performing hemodialysis or CRRT for toxic alcohol intoxication are changing. The efficacy of fomepizole, an inhibitor of alcohol dehydrogenase, may make extracorporeal removal superfluous. Recent guidelines suggest that particularly if treated with fomepizole early, before toxic metabolites are formed and profound metabolic acidosis is present, repeated doses of fomepizole may preclude the necessity for any extracorporeal modality [14, 15]. We believe that conventional hemodialysis is the preferred modality of extracorporeal removal for toxic alcohol intoxication if fomepizole is not available or the drug is given after significant metabolism to toxic metabolites has already occurred.

Salicylates

Acetylsalicylic acid has an MW of 138 Da, a VD of 0.17 liter/kg, with 90% protein bound at therapeutic levels [17]. The fraction of unbound drug increases as the serum con-
concentration rises. Hemodialysis is the preferred method of treating severe salicylate toxicity, serving to both remove the drug and correct the acidosis. There is a small case series detailing the use of CVVHDF for 3 patients with severe salicylate toxicity and hemodynamic instability [18]. The indications for renal replacement therapy, the CRRT prescription, and the duration of treatment all varied. In addition, 1 patient was treated with 2 h of conventional hemodialysis prior to CVVHDF. All 3 patients survived without sequelae, but it is impossible to determine whether the CRRT affected outcome. Therefore, hemodialysis remains the preferred modality of extracorporeal detoxification for severe salicylate overdose and there is insufficient evidence to support the use of CRRT.

Carbamazepine

Carbamazepine is an anticonvulsant with an MW of 236 Da, a VD of 0.8–1.8 liters/kg and it is 75–78% protein bound in plasma [19]. Its therapeutic serum concentration is 4–12 mg/l. Its active metabolite, carbamazepine-10,11-epoxide, is approximately 50% protein bound. Because of the protein binding, the treatment of carbamazepine toxicity has traditionally involved orally administered activated charcoal or multidose oral activated charcoal as first-line therapy, and if indicated and available, charcoal hemoperfusion because of significant binding of the drug to plasma proteins. High-efficiency hemodialysis may reduce serum carbamazepine levels to a similar degree [20].

In one case report, an experimental technique, albumin-enhanced CVVHDF, was successfully used to remove carbamazepine and presumably had greater efficacy than conventional CVVHDF. The procedure requires adding 25% albumin to the dialysate to achieve a concentration of 4.5 g/dl. Albumin adsorbs drug in the plasma and serves as a sink to maintain a low dialysate concentration and a high concentration gradient [21]. The estimated half-life for carbamazepine was reduced from 15 h before treatment to 4.5 h during therapy. Conventional CVVHDF would not be expected to offer similarly effective clearance rates.

Valproic Acid

Valproic acid is an anticonvulsant with an MW of 144.2 Da, VD of 0.1–0.2 liter/kg and is more than 90% protein bound in the plasma. It is metabolized by the liver. As levels rise, the proportion of the drug that is protein bound decreases and free serum levels rise, making it more amenable to removable by dialysis modalities. Success with intermittent hemodialysis, especially high-flux hemodialysis, has been consistently reported in the literature [22]. One report of CRRT in an unstable patient with valproic acid overdose did not demonstrate a significant impact of CRRT on drug removal nor did it prevent a rebound in plasma levels [23]. The paucity of literature on CRRT for the treatment of valproic acid overdose precludes any recommendations regarding its use. Conventional hemodialysis remains the preferred first-line methodology of extracorporeal drug removal for valproic acid.

Metformin

Metformin has an MW of 165.6 Da, no protein binding, and a VD of about 0.5 liter/kg. An oral load is excreted by the kidneys in 24 h [24]. Extracorporeal removal is indicated only with associated lactic acidosis which occurs rarely in patients with acute or chronic kidney disease. The low MW, negligible plasma protein binding, and rapid transport of drug from cells to serum allow for drug removal by hemodialysis despite a relatively large VD. Barrueto et al. [25] used CVVHDF to treat a patient with both metformin and diltiazem overdose. Using a dialysate flow rate of 2.5 liters/h and a blood flow rate of 180 ml/min, metformin clearance was 50.4 ml/min. Hemodialysis clearance can be 170 ml/min while endogenous clearance with normal kidney function can reach 450 ml/min. Although this case report illustrates that CRRT can remove metformin, hemodialysis will more rapidly correct the acidosis and constitutes the preferred modality of therapy with lactic acidosis.

Conclusion

The efficacy and effectiveness of CRRT in the treatment of the poisoned patient remain unproven. There is a lack of good evidence from numerous case reports and small case series in the medical literature with varying techniques and outcomes to guide therapy. At the present time, there is insufficient evidence to support its routine use for the treatment of poisoning except in hemodynamically unstable patients who truly are not candidates for conventional hemodialysis.
Kim and Goldfarb review the evidence in favour and against continuous renal replacement therapy (CRRT), mainly continuous venous-venous hemofiltration (CVVH), in the management of poisoning and conclude that haemodialysis rather than CRRT should be the treatment of choice for those suffering from severe poisoning. Their conclusion is based on insufficient evidence to support CRRT and the fact that clearance of poisons is more effectively undertaken by the diffusive (haemodialysis) compared to convective (ultrafiltration) clearance. They also draw attention to the additional potential of dialysis/ CVVH membranes to adsorb some of the poisons. The authors carefully examine issues related to rebound of cleared poisons/toxins and side effects, cost as well as availability of CVVH. However, the fact remains that most patients suffering from severe poisoning are often hemodynamically unstable and treated in intensive care units where CVVH may be the treatment of choice. This issue, like many others in nephrology, is unlikely to be settled by randomized clinical trials; instead management of such critically ill patients will have to depend on local knowledge, skills and expertise.