═══ BLOOD PURIFICATION IN POISONING ═══

Principles and Operational Parameters to Optimize Poison Removal with Extracorporeal Treatments

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ABSTRACT

A role for nephrologists in the management of a poisoned patient involves evaluating the indications for, and methods of, enhancing the elimination of a poison. Nephrologists are familiar with the various extracorporeal treatments (ECTRs) used in the management of impaired kidney function, and their respective advantages and disadvantages. However, these same skills and knowledge may not always be considered, or applicable, when prescribing ECTR for the treatment of a poisoned patient. Maximizing solute elimination is a key aim of such treatments, perhaps more so than in the treatment of uremia, because ECTR has the potential to reverse clinical toxicity and shorten the duration of poisoning. This manuscript reviews the various principles that govern poison elimination by ECTR (diffusion, convection, adsorption, and centrifugation) and how components of the ECTR can be adjusted to maximize clearance. Data supporting these recommendations will be presented, whenever available.

Principles of Poison Removal

The various methods available for poison removal by ECTR are diffusion, convection, adsorption, and centrifugation. This manuscript reviews the principles and parameters that may influence poison clearance. A detailed understanding of these principles is useful for the nephrologist because they guide how adjustments to the ECTR prescription can optimize solute clearance. These principles can be used to individualize ECTR in the context of its indication.

Diffusion

Thomas Graham first suggested the concept of dialysis in 1861, based on the process of diffusion.

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During diffusion, the movement of particles (solutes) is driven by a concentration gradient from one compartment to another through a semi-permeable membrane. In the case of hemodialysis, the two compartments are the blood and dialysate and mainly small molecules (defined as a molecular weight (MW) less than 500–1000 Da), and some middle molecules, readily cross the filter membrane.

Operational characteristics influencing diffusive clearance include the magnitude of the concentration gradient (blood and dialysate flow rates), duration of therapy, and the filter composition. These factors will be discussed here and are also summarized in Table 1.

Maximization of Blood and Countercurrent Dialysate Flow Rates

Principles. Both blood (Q_B) and dialysate (Q_D) flows influence solute clearance. In general, the maximum possible clearance corresponds to the slower of the two flows, which will be the rate-limiting step. In intermittent hemodialysis (IHD), Q_B is usually slower than Q_D, whereas the opposite is true in continuous venovenous hemodialysis (CVVHD).

TABLE 1. Summary of the most important parameters for optimizing clearance with the different extracorporeal therapies

	Operational parameters to optimize clearance		
	For small molecules (MW <500–1000 Da)	For middle-sized molecules	For protein-bound molecules (>80%)
Diffusion (e.g. IHD)	High Q_B (up to 400 ml/minute)[a] Ratio Q_D: $Q_B \geq 2.5$ High-efficiency filter Adding a second filter?	Convection preferred over diffusion[a] High-flux filter[a] with a large surface area[a] High Q_B Adding a second filter?	High Q_D Filter with a large surface area Adding a second filter?
Convection (Intermittent hemofiltration)	High Q_B[a] High Q_{UF}[a] Maximize postdilution then add predilution	High Q_B High Q_{UF}[a], maximize postdilution then add predilution High-flux filter[a]	High-flux filter Predilution?
Convection &/or diffusion (in CRRT)	High $Q_{effluent}$ ($Q_D > Q_{UF}$)[a] High Q_B Maximize postdilution then add predilution High-efficiency filter Filter changed <48 hours Adding a second filter?	High $Q_{effluent}$ ($Q_{UF} > Q_D$)[a] Maximize convection: CVVH > CVVHDF (because replacement fluid is greater) High Q_B High-flux filter[a] Filter changed <48 hours Adding a second filter?	
Adsorption (e.g. IHP)	Charcoal vs. resin column (depending on poison)* High Q_B (max 350 mL/min) Filter change <4 hours		
Centrifugation (e.g. therapeutic plasma exchange)	Centrifugation or filtration ≥2 plasma volumes exchanged* Central catheter High Q_B (100–200 ml/min for filtration and 100 ml/min for centrifugation) Replacement fluid tailored to the poison Heparin vs. citrate anticoagulation		
For all processes	Right jugular catheter ≥ femoral. For a femoral site, use catheter >20 cm long. Subclavian site probably equivalent to jugular but avoid in patients at risk for end-stage renal disease. Both subclavian and jugular sites may require X-ray confirmation of placement. Longer treatment time		

CRRT, continuous renal replacement therapy; CVVH, continuous venovenous hemofiltration; CVVHDF, continuous venovenous hemodiafiltration; MARS, molecular adsorbent recirculating system; SPAD, single pass albumin dialysis; Q_B, blood flow rate; Q_D, dialysate flow rate; Q_{UF}, ultrafiltration rate.
[a]Most important.

Therefore, when adjusting the dialysis prescription to maximize solute clearance, the greatest impact will follow an increase in Q_B in IHD, compared with an increase in Q_D in CVVHD.

Because the mobility of the solute between the compartments influences clearance, the clearance of small water-soluble solutes will exceed that of larger particles.

Peritoneal dialysis (PD) has been used for the treatment of acute poisoning and clearance is also influenced by Q_D. However, PD is not usually recommended in the treatment of poisoning because clearance is universally less than that achieved with other ECTRs.

Supporting Data. In IHD, an increase of 100–200 ml/minute in Q_B will significantly enhance the clearance of small solutes like urea (1–8). A similar effect is, therefore, expected for small poisons like lithium and alcohols.

In IHD, some authors suggest targeting a Q_D/Q_B ratio >2.5:1 to ensure that clearance of small molecules is not restricted by dialysate flow (9). Therefore, if a Q_B of 400 ml/minute is achievable, Q_D should opti-mally be 1000 ml/minute, although any increment over 600 ml/minute only modestly improves performance (10). A mechanism by which Q_D increases clearance is via better distribution of flow between the filter bundles, thereby increasing the effective surface of the filter. In addition, countercurrent direction of dialysate flow provides 20–30% better clearances for small molecules than a concurrent direction of flow (11).

In CVVHD, an increase in Q_D will improve small solute clearance with a near-linear relationship (Fig. 1) (12–17).

Although there are some limitations, these principles also apply to protein-bound toxins and medicines such as phenol, p-cresol, hippurate, carbamazepine, and valproic acid (15,18–20), particularly when protein binding is saturated (21).

There are data supporting the application of these principles in the treatment of poisoned patients. For example, increasing Q_B from 200 to 300 ml/minute in IHD increases the clearance of valproic acid from 43 to 80 ml/minute (22). Increasing Q_B also increases the clearance of middle molecules like vancomycin when a high-flux filter is used (23). Similar results were shown in poisonings to phenobarbi-
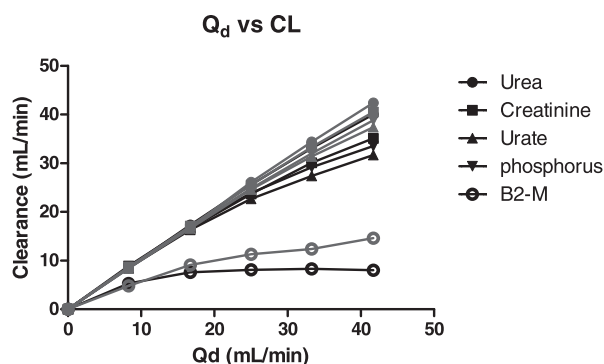
Q_d vs CL

FIG. 1. Influence of Q_D and molecular weight on mean solute clearance at Q_B 150 ml/minute. Color indicates the type of filter, where black-colored has a surface area of 0.6 m^2 and gray-colored has a surface area of 0.9 m^2 (graphs redrawn from data in Brunet et al (13)., with permission from Elsevier)

tal, lithium, and phenytoin, where clearance plateaued when Q_B exceeded approximately 300 ml/minute in the context of Q_D 500 ml/minute (24,25).

Peritoneal dialysis (PD) also uses the principle of passive diffusion, although fluid and solute exchange occurs in the peritoneal cavity across the peritoneal membrane. The use of PD in poisoning has almost disappeared due to its limited clearance capacity compared with IHD (26–29). In PD, increasing the dialysate flow rate (Q_D) maximizes clearance. Increasing Q_D is possible by increasing the frequency and volume of the exchanges (28,30–32). Extremely high dialysate flows, provided by continuous-flow PD over a short period of time, may allow good clearance of solutes that readily diffuse through the peritoneal membrane. For example, a urea clearance of 35 ml/minute was achieved when dialysate flow was 6–9 l/hour (33,34), and 48 ml/minute when using a double-lumen catheter (35). In another study, methanol clearance was 70 ml/minute with a dialysate flow of 6 l/hour (36), a significant result but still minor compared with that obtained by IHD (37). Small MW clearance may be enhanced when PD is performed in the supine position (38). Tidal PD does not appear to improve clearance over intermittent PD (39).

Limitations. Increases in Q_B and Q_D are associated with a lesser increase in clearance of middle-sized molecules by diffusion, such as vitamin B$_{12}$ (40) (MW 1355 Da) and β_2-microglobulin (1,9,10) (MW 11,000 Da) (Fig. 1), and no significant change for larger molecules like dextran (41).

Q_B is usually limited to <400 ml/minute when using an intravascular catheter due to blood turbulence and resistance in the tubing. However, advances in catheter design may allow for greater Q_B (42–44). Notably, however, increasing levels of blood recirculation (compromising clearance) occur when Q_B exceeds 400 ml/minute in femoral vein catheters.

In IHD, increasing the $Q_D:Q_B$ ratio does not proportionally increase solute clearance. For example, for a Q_B of 300 ml/minute, augmenting Q_D from 300 to 500 ml/minute will increase clearance by a greater proportion than an increase from 500 to 800 ml/minute, regardless of the filter used (1,2,4,9,45). Augmenting Q_D increases clearance by approximately 10–20% for small MW molecules (1–3,10,13,20,46), but does not affect the clearance of larger molecules (13,14,47). A dialysate flow over 800 ml/minute may exceed the operational capacity of some machines and/or increase the cost of the treatment due to the larger volume of dialysate solutions.

In CVVHD, because Q_B is already approximately three times higher than Q_D, there is no benefit from further increases in Q_B, at least with a Q_D up to 4 l/hour (12,15).

Use of a High-Efficiency Filter, Particularly for Smaller Solutes

Principles. Efficiency and flux are two characteristics of filters that relate to solute clearance, reflecting filter surface area and composition.

Efficiency refers to the capacity to clear urea, which is a surrogate measure of low MW solutes, and is quantified by the product of its *mass transfer area coefficient* (*Ko*) and surface area (*A*), *KoA*. The higher the *KoA* of a filter, the higher will be the clearance of small solutes. The actual clearance achieved by a particular filter depends on the MW of the solute and other specifics of the dialysis prescription, in particular the Q_B and Q_D, as well as ultrafiltration. Therefore, some aspects relating to convection are also discussed here.

In contrast, *flux* refers to the permeability of the filter to middle-sized MW solutes; it is most often assessed using β_2-microglobulin (MW 11,000 daltons). The ultrafiltration capacity of the filter, quantified according to the ultrafiltration coefficient (K_{UF}), typically correlates with this (48).

The simultaneous use of two filters or machines will further increase clearance.

Supporting Data. Extracorporeal membranes can be characterized by their surface area, material, morphology, fiber length and thickness, permeability to water, and hydrophilicity (Table 2). Newer synthetic filters differ dramatically from conventional filters used prior to the 1990s in their clearance capacity and biocompatibility (49).

The *KoA* estimates the maximum clearance of urea by the filter when Q_B and Q_D are infinite (1,2,6). High-efficiency membranes are defined as having a K_OA >600 ml/minute (50) and much of the gain in *KoA* relates to an increase in surface area. The clearance of middle molecules such as B$_{12}$ (40), teicoplanin (47), and β_2-microglobulin (1) can also slightly increase with the use of a large surface area filter. Clearance of protein-bound solutes can also increase (18–20), although not consistently (51).

With high-flux membranes, there is improved clearance of larger MW solutes relative to small MW solutes (41,49). This concept reflects the greater solute permeability of high-flux membranes.

TABLE 2. Dialyzer classification

	Surface area (m^2)	K_{UF} (ml/h/mmHg)	ß$_2$-microglobulin clearance (ml/minute)	Albumin loss	Application
Conventional	<1.5 m^2	0–10	<20	0	HD
High-flux	Variable	20–40	>40	+	HD, HF, HDF
High-efficiency	>1.5 m^2	0–10	<20	+	HD
Protein leaking		>40	>80	+++	HD

HD, hemodialysis; HF, hemofiltration; HDF, hemodiafiltration.

The simultaneous use of more than one filter, or even two distinct circuits, can increase clearance. Using two filters in parallel circuits has the effect of increasing the surface area for filtration and improves clearance of small molecules; it may be of particular benefit in larger sized patients (52). This set-up can also increase the clearance of other small and middle MW compounds (40), like iohexol (52). In contrast, adding a second filter in series may improve the overall clearance of small (19,53), middle molecules (40), and also protein-bound solutes (19). This has also been applied to poisoning cases, when two circuits were used to facilitate elimination enhancement of metformin (54,55).

Limitations. Clearance of middle MW solutes varies among types/brands of high-flux filters, which limits generalizability. For example, the clearance of β_2-microglobulin clearance differed almost two-fold between filters with similar surface area (56), which may be due to other processes such as molecule trapping and adsorption.

There are limited data about the cost–benefit ratio of simultaneously using two filters/machines in poisoned patients. Although either is anticipated to increase clearance, more research is required to confirm its effect and role in clinical management. Current evidence suggests that the benefit of either configuration (series or parallel) provides an incremental clearance gain of approximately 5–7% (52,53); however, a potential downside in the use of two filters is cost and that it may delay the start of the procedure.

High-flux filters are capable of removing molecules as large as myoglobin (MW 17,200 Da) by diffusion, although significantly less than by convection for this range of MW (57).

Addition of Albumin to Dialysate

The underlying principle of albumin dialysis is that addition of albumin to the dialysate may facilitate clearance of highly protein-bound toxins because the unbound fraction diffuses into the dialysate side where it binds to albumin and is trapped. This creates a protein-binding disequilibrium on the blood side and more drug would become unbound and cross the membrane to be cleared. These techniques have been used in the treatment of intoxications with varying degrees of success and supporting clinical data are scarce (58,59).

Q_B and Q_D influence solute clearance in albumin dialysis (60). For example, in an in vitro model of CVVHD with albumin-supplemented dialysate (2.5% g/l), an increase in Q_D will greatly influence the clearance of bound solutes, while increments in Q_B had an almost null effect (15). A favorable impact of larger albumin concentration on clearance of protein-bound toxins has been reported for diazepam (61), as well as for valproic acid and carbamazepine (15), but not for phenytoin (15). Also, higher surface area filters increase clearance by albumin dialysis compared with lower ones (15). Other factors impacting clearance of extracorporeal liver assist devices (ELADs) are pore size, placement of filters, membrane material, amount and active surface of adsorbers, as well as free fraction of albumin-bound substances and time on therapy (62).

Convection

During convection, the patient's blood passes through a circuit and makes contact with a semipermeable filter. A positive transmembrane pressure forces water to cross the filter and solutes follow the bulk movement of the solvent (water; known as solvent drag). Convection allows middle molecules to be cleared much more efficiently than with diffusion. The only ECTR that utilizes convection exclusively for clearance of uremic toxins is hemofiltration (HF). Large volumes of replacement fluid are required and can be infused before (predilution), after (postdilution), or before and after (mixed dilution) the hemofilter in continuous and intermittent HF/HDF. The replacement fluid can also be infused with a special filter design called mid-dilution in intermittent hemofiltration. Operational characteristics influencing solute clearance during convection include Q_B, ultrafiltration rate (Q_{UF}), the site of fluid replacement, and the type of hemofilter (Tables 1 and 3).

Although convection is often used in intermittent dialysis to remove excess fluid in ESRD, its impact on solute clearance is likely negligible because ultrafiltration during IHD rarely surpasses 25 ml/minute.

Maximization of the Blood and Ultrafiltration Rates

Principles. Clearance increases when either Q_B and/or Q_{UF} are increased, analogous to the principles previously discussed for diffusion. In continuous venovenous HF (CVVH) and postdilution intermittent HF, Q_B exceeds Q_{UF}, so Q_{UF} is the rate-limiting step; Q_B may be the rate-limiting step

TABLE 3. Relative comparison of the influence of the different parameters on the clearance of small and middle molecules in intermittent hemodiafiltration

|	Increasing surface area from 1.4 to 2.2 m^2	Increasing Q_B from 300 to 500 ml/minute	Addition of convection
Urea	6%	40%	18%
β_2-microglobulin	22%	16%	75%

Data adapted from Wizemann, 2001 (45).

FIG. 2. Influence of Q_{UF} and molecular weight on mean solute clearance at a blood flow of 150 ml/minute. Color indicates the type of filter, where black-colored has a surface area of 0.6 m^2 and gray-colored has a surface area of 0.9 m^2 (graphs redrawn from data in Brunet et al (13)., with permission from Elsevier).

in intermittent HF with the predilution mode, as Q_{UF} can be similar or exceed Q_B.

Clearance by postdilution HF is superior to predilution HF when all other factors are equal. However, the maximum possible Q_{UF} with postdilution is less than that which can be achieved with predilution. To maximize clearance by convection, administration of the highest tolerable postdilution HF should be combined with some predilution.

Supporting Data. The effect of convection on the clearance of middle molecules is exemplified for β_2-microglobulin; its clearance by IHD when using a high-flux membrane is 20–40 ml/minute under usual IHD operational conditions, but when the same membrane is used with HF, clearance is 100–150 ml/minute (45,63). This is further supported by studies with ß2-microglobulin and complement factor D (24,000 Da), although the achieved clearance is highly dependent on Q_{UF}(45,64–71). The difference in clearances between convection and diffusion increases as the solute's MW increases. For example, vancomycin removal (MW 1448 Da) is about 20% greater during convection compared with diffusion. Daptomycin (MW 1620 Da) clearance is >25% higher by HF than HD at standard CRRT effluent rates (72).

The clearance of small and middle molecules proportionately increases with higher Q_{UF} (13,14, 65,66,71) whether using intermittent HF, CVVH (Fig. 2), or continuous venovenous hemodiafiltration (CVVHDF)(73). In postdilution HF, the clearance of small molecules is approximately equal to Q_{UF}. Increasing Q_{UF} to exceed 4–6 l/hour is associated with a smaller proportional increase in overall clearance. Increasing Q_B allows a higher postdilution Q_{UF} without compromising the filtration fraction (74). Once Q_{UF} exceeds 4–6 l/hour, Q_B should be maximized to 350 or even 450 ml/minute if tolerated (75).

Although postdilution HF provides higher convective clearances than predilution at the same Q_{UF}, greater replacement volumes can be administered in predilution HF so the maximum possible clearance could exceed that achieved by postdilution HF. With predilution HF alone, there is a decrease in the concentration of the solute, so each incremental increase in Q_{UF} has a more modest impact on small nonprotein-bound molecule removal (45,75), although the effect remains significant, even for ß2-microglobulin
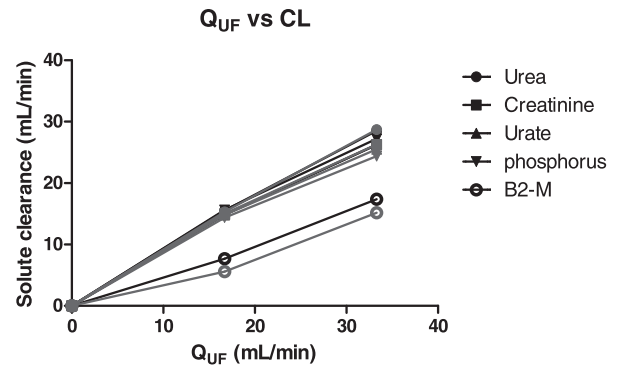
(45,75). In predilution HF, the Q_{UF} can be theoretically as high as 400 ml/minute during intermittent HF (76,77). With CRRT, the total effluent can reach 8–10 l/hour with current machines.

Clearance is also proportional to Q_B (75), as higher Q_B reduces the extent to which the predilution replacement fluid dilutes the solute concentration. For example, at a Q_{UF} of 2 l/hour, tripling Q_B from 150 ml/minute to 450 ml/minute increases urea clearances by approximately 15%; at a Q_{UF} of 6 l/hour, tripling Q_B rates from 150 to 450 ml/minute increases urea clearances by approximately 35% (45,75). Increases in Q_B have a more limited effect on the removal of larger molecules such as ß2-microglobulin compared with smaller molecules (45).

The usual Q_B in intermittent HF is 300 ml/minute, compared with 150–250 ml/minute in CRRT, although higher flows are possible depending on the vascular access.

Limitations. Although postdilution hemofiltration can be associated with enhanced clearance compared with a similar Q_{UF} administered predilution, it has been argued that for small, middle, and protein-bound molecules this advantage is of minor clinical significance (13,65). However, in other studies, a 40% increase in clearance occurred as Q_{UF} increased (45,66).

In postdilution HF, the maximum Q_{UF} depends, in part, on Q_B and the relationship can be described by the filtration fraction, which is calculated as Q_{UF} divided by Q_B. The filtration fraction should be less than 30% to avoid hemoconcentration and high filter transmembrane pressures (TMP), which impair filter performance (74,77,78).

Postdilution HF is associated with an increased risk of clotting of the filter and requires anticoagulation, which is not essential in predilution (77).

Use of a Large High-Flux Filter, Particularly for Middle-Sized Solutes

Principles. The clearance of middle MW solutes depends, in part, on solvent drag due to ultrafiltration.

Therefore, the preferred ECTR for middle molecules is hemofiltration using large high-flux membranes.

Supporting Data. Most existing high-flux membranes have a ß2-microglobulin clearance of at least 20 ml/minute and a K_{UF} >20 ml/hour/mmHg (79); this K_{UF} value represents the current recommendation for filters used in intermittent haemodiafiltration (78).

When convection is performed in isolation, high-efficiency and conventional dialysis filters have a minor effect compared with lower efficiency filters on the clearance of small (<500–1000 Da) (45,66,80) and larger molecules (1,13,40,41,45,56,81). However, clearances of middle-sized solutes up to 10,000 Da are clearly higher with a high-flux membrane and become negligible with a MW >20,000 Da (63,82). Another advantage of a larger filter surface area (for example, 2.2 m^2 compared to 1.4 m^2) is that it can withstand greater transmembrane pressures for a longer period of time (13), allowing higher Q_B and convective fluxes across the membrane (45,74).

Newer dialyzer membranes have been developed for certain clinical scenarios. Protein-leaking membranes, also named high cut-off (HCO) or "super-flux" membranes, are highly permeable membranes with improved removal of protein-bound solutes and larger sized unbound solutes (63). For example, compared with high-flux filters, protein-leaking membranes increase ß2-microglobulin removal, although this is at the expense of a heavier albumin loss (83). These filters have a more complex effect than the simple leakage of albumin and its bound constituents across their membrane (63). Current applications include the removal of light chains in multiple myeloma (84). Very high capacity filters are also used during therapeutic plasma exchange using a filtration technique. Protein-leaking membranes have potential applications in toxicology for poisons that are highly protein-bound, especially considering that albumin loss likely has negligible clinical significance when these filters are used for a limited number of sessions (63).

Limitations. The material used for the filter membrane can influence clearance. For example, solute clearances with AN69 seem lower than with other membranes (72,85–88). In convection, solutes may be adsorbed to the filter. The effect is more pronounced for middle and large MW molecules and is maximal within the first hours after a filter change (89–93). However, the impact of adsorption cannot be easily predicted by analyzing the filter and the MW of the poison (68). Therefore, it should not be assumed that all high-flux hemofilters provide comparable clearance simply based on their characteristics (66,69,74). Filter efficacy also decreases with time, especially after 48 hours (94,95). Recommendations from the manufacturers include filter change every 48–72 hours to preserve the filter clearance capacity, regardless of the adsorptive process (91).

It is unclear whether protein-leaking membranes offer benefits beyond those obtained with conventional high-flux membranes, because data are limited (63).

Use of Convection and Diffusion

Diffusion and convection have a comparable effect on the clearance of smaller MW molecules (<500–1000 Da), while convection provides much higher clearances for middle MW molecules (1000–10,000 Da) compared with diffusion. Therefore, clearance of small MW molecules can be enhanced by adding convection to diffusion, thereby increasing total effluent rate (96), although the opposite is not true for middle MW molecules. As previously mentioned, for each modality, the actual clearance achieved will depend on the Q_B, Q_{UF}, or Q_D used. Examples from the poisoning literature are limited, but lithium clearance in one report was similar with CVVH and CVVHD at similar effluent rates (96).

Although the two clearances are not additive, there seems to be only a minimal interaction between them in CVVHDF (13). However, in HDF, ultrafiltration and predilution may have a negative impact on transmembrane concentration gradients (77,78). Nevertheless, the addition of convection may improve clearance of some solutes, like phosphorus (97). With newer machines, the maximal effluent flow in CRRT is 8–10 l/hour, while Q_{UF} can reach 24 l/hour in predilution HDF, assuming a Q_B of 350–400 ml/minute.

Adsorption

Adsorption is a process by which particles located in the blood compartment bind reversibly or irreversibly to the surface of a column (or sorbent). This process is central to hemoperfusion and is covered in detail in the dedicated article on hemoperfusion presented in this issue.

Although adsorption may occur during diffusive and especially convective techniques, its contribution to total clearance is variable, and cannot be easily predicted by considering the type of filter and/or the MW of the poison (68). Adsorption is usually considered to have a minor effect on clearance compared with convection and diffusion, is more pronounced for middle and large MW molecules, and largely occurs within the first hour after a filter change (89–93).

Centrifugation

Centrifugation and convection are the major processes implicated in plasmapheresis techniques. Centrifugation separates the whole blood into various components according to their specific gravity, and is usually used to remove pathogenic proteins such as antibodies. Centrifugation may also be useful to remove large or protein-bound solutes located in the plasma.

Centrifugation can be performed intermittently or continuously (98). With intermittent centrifugation, blood is drawn in successive batches through flow separators to remove a target volume of plasma. With continuous-flow equipment, blood flows continuously into a rotating device in which red cells, leukocytes, platelets, and plasma separate into layers according to their respective specific gravity. Any of these layer(s) can be removed, and the remainder is returned to the patient along with a replacement fluid. Continuous-flow centrifugation is fully automated and is faster than intermittent centrifugation (98).

Maximization of the Volume of Plasma Exchanged

The major factor influencing clearance with centrifugation is the total volume of plasma exchanged per session (99). In therapeutic plasma exchange (TPE), a single exchange of one plasma volume (defined as a patient's entire plasma volume and corresponds to 3 l for a 70 kg patient) removes 63% of all solutes in plasma. An exchange of 2 plasma volumes removes 86% of solutes, while a third would decrease initial solute concentration by 95% (100,101).

In the treatment of a poisoned patient, the American Society for Apheresis (ASFA) guidelines recommend an exchange volume of one to two total plasma volumes per day until clinical symptoms have decreased and the release of toxin from tissues is no longer significant (102). However, as acknowledged, this recommendation was based on limited data.

Choice of Replacement Fluid

The choice of the replacement volume may be guided by the affinity of the poison to its main binding protein. For example, the ASFA guidelines suggest that fresh frozen plasma may be the most appropriate choice in poisoning from drugs like quinidine, imipramine, and propranolol, as these drugs have a great affinity for alpha-1-acid glycoprotein (102). However, this is debatable because of their large V_D, which limits total body removal, and the relatively small concentration of alpha-1-acid glycoprotein in plasma (21). Finally, in TPE with filtration, the surface area of the filter does not seem to significantly influence clearances, which is different than for dialysis or convection (99).

Clearance Parameters Applicable to All Processes

Treatment Time

Assuming that a poison is removable by ECTR and there is no filter saturation, the concentration of poison in the blood would decrease steadily and progressively, usually according to first-order kinetics. For some molecules, the treatment time is the most important factor determining poison removal (81), so the "routine" 4-hour treatment reserved for patients with end-stage renal disease (ESRD) should be challenged in the treatment of a poisoned patient. Classical examples include prolonged IHD for poisoning from lithium or aspirin (103).

Location, Length, and Size of the Intravascular Catheter

The maximum achievable Q_B depends on the location of the intravascular catheter, its lumen size, and length. A recent large randomized trial from the Cathedia study group showed that catheters placed in the right jugular or the femoral vein are associated with less dysfunction than those placed in the left jugular vein (104); the subclavian site is not favored in patients at risk for ESRD (105), although its recirculation rate is similar to that in the jugular vein (106). If a femoral catheter is used, its length should be longer than 20 cm, ideally 25 cm, to minimize recirculation (104,106–108).

These considerations should be weighed against the experience of the operator, complication rate, and the time required to install the catheter, as well as the delay to perform a X-ray confirming the position of the subclavian or jugular catheter. While these data are derived from diffusion-based techniques, they are likely valid for convection as well. For TPE by centrifugation and filtration, a central catheter also allows optimizing blood flow rate and clearance (109,110). However, as the Q_B is much lower in TPE than with other techniques, the catheter location, size, and length are not as important as with other techniques. As an example, the Q_B is usually 100 ml/minute for TPE with centrifugation (104,105) and 100–200 ml/minute for TPE with filtration (99).

Administration of Anticoagulation According to Usual Procedure

Anticoagulation is usually required for ECTR to ensure continuing efficacy of the procedure. Clotting reduces filter/column performance and may reduce the overall effect of ECTR if the circuit needs to be changed. During diffusion-based procedures, heparin-free chronic IHD does not appear to significantly reduce solute clearance if there is no clotting of the circuit (111). Studies in acute settings are required to validate this observation.

Clinical experience suggests that predilution intermittent HDF can be performed without anticoagulation, while postdilution intermittent HDF usually requires anticoagulation because of increased viscosity of blood in the hemofilter. In CRRT, filter life is independent of heparin dose (including 700 U/hour) (112). However, filter life is significantly shorter when postdilution is used instead of predilution (113,114). Anticoagulation is required for TPE, whereby citrate is most frequently used during cen-

trifugation, while heparin is used for filtration (98). The influence of anticoagulation on the elimination of poison needs to be further studied in TPE.

Conclusion

The use of an ECTR for enhanced elimination in poisoned patients can be effective for a limited number of poisons. Optimizing extracorporeal clearance can benefit patients by reducing toxicity, but it may also reduce the utilization of health resources by shortening the duration of treatment and overall hospital length of stay.

In this manuscript, we aimed to review the various components of ECTR and highlight the modalities and parameters that are most likely to enhance clearance. However, data supporting some of these recommendations are limited, particularly in the context of poisoning. Therefore, clinical decisions should be made on a case-by-case basis by specifically considering the actual poison, clinical circumstances, patient characteristics, and available techniques.

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