Use of extracorporeal treatments in the management of poisonings

Marc Ghannoum[1], Robert S. Hoffman[2,3], Sophie Gosselin[4], Thomas D. Nolin[5], Valery Lavergne[6] and Darren M. Roberts[7,8]

[1]Verdun Hospital, University of Montreal, Montreal, Canada; [2]New York University School of Medicine, New York, New York, USA; [3]New York City Poison Control Center, New York, New York, USA; [4]Centre antipoison du Québec, Québec, Canada; [5]University of Pittsburgh Schools of Pharmacy and Medicine, Pittsburgh, Pennsylvania, USA; [6]Sacré-Coeur Hospital, University of Montreal, Montreal, Canada; [7]New South Wales Poisons Information Centre, Sydney, NSW, Australia; and [8]St Vincent's Hospital, Sydney, NSW, Australia

Historically, the clinical application of extracorporeal treatments (ECTRs), such as hemodialysis or hemoperfusion, was first intended for poisoned patients. With time, ECTRs were used almost indiscriminately to facilitate the elimination of many poisons, albeit with uncertain clinical benefit. To determine the precise role of ECTRs in poisoning situations, multiple variables need to be considered including a careful risk assessment, the poison's characteristics including toxicokinetics, alternative treatments, the patient's clinical status, and intricacies of available ECTRs, all of which are reviewed in this article. Recently, evidence-based and expert opinion-based recommendations from the EXTRIP workgroup were also published to help minimize the knowledge gap in this area.

Kidney International (2018) **94,** 682–688; https://doi.org/10.1016/j.kint.2018.03.026

KEYWORDS: continuous renal replacement therapy; hemodialysis; hemofiltration; pharmacokinetics; plasmapheresis

Correspondence: *Marc Ghannoum, Specialized Medicine, Verdun Hospital, 4000 Lasalle Blvd., Verdun, Quebec H4G2A3, Canada. E-mail: marcghannoum@gmail.com*

Received 13 February 2018; revised 16 March 2018; accepted 22 March 2018; published online 27 June 2018

The use of hemodialysis for enhancing the elimination of exogenous poisons predates its use for end-stage kidney disease (ESKD) by many decades (Here, the general term *poison* refers to any medicine, drug, natural toxin, or other potentially toxic substance that may induce illness following poisoning regardless of the intention.).

In fact, the first successful *in vivo* experiment with hemodialysis was carried out in 1913 and demonstrated removal of salicylates from poisoned animals.[1] Yet, more than 100 years later, the application of extracorporeal treatment (ECTR) in the management of poisoned patients remains a topic of controversy, uncertainty, and debate. Recently, a multidisciplinary and multinational collaborative known as EXTRIP (EXtracorporeal TReatment In Poisoning) aimed to clarify the role of ECTRs in clinical practice through the development of evidence- and expert opinion–based recommendations.[2] This article will review both the theoretical rationale of ECTRs and their practical application in the management of the poisoned patient.

Approach for the consideration of ECTR

Clinical toxicity results from a complex interplay of factors that include a poison's intrinsic properties, dose, formulation, route of administration, and the presence of co-ingestants, as well as the underlying health of the patient. Despite the ubiquity of poisons, the vast majority of poisoned patients who present to a modern health care facility are successfully treated and recover without sequelae, having only received supportive care.[3]

ECTR is typically reserved for the small subset of patients who either are likely to suffer life-threatening toxicity (e.g., salicylate overdose), prolonged admission in the intensive care unit with coma and mechanical ventilation (e.g., barbiturate overdose), a high likelihood of permanent disability (e.g., methanol overdose) or develop toxicity despite standard supportive measures. The following discussion provides an approach to assess the potential usefulness of ECTR in a poisoned patient. This approach (Figure 1) should be used when evidence-based decision support (such as those developed by EXTRIP[4]) are lacking.

Risk assessment and alternate therapies

The risk assessment attempts to estimate the likelihood of significant sequelae after a specific exposure. If the identified

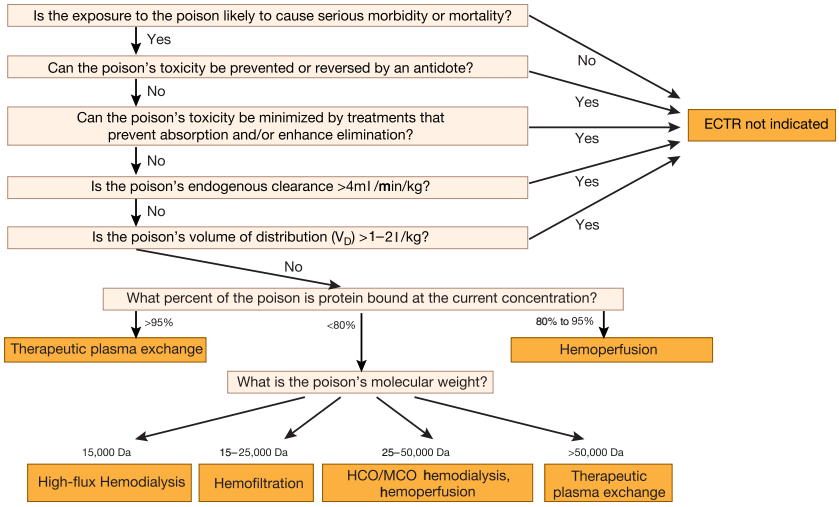

Figure 1 | An overall clinical approach for the consideration of an extracorporeal treatment for the management of a generic poison. HCO, high-cutoff membrane; MCO, middle-cutoff membrane.

poison has limited intrinsic toxicity and if the estimated threshold dose (in mg/kg) or plasma concentration is not associated with toxicity, ECTR is usually not indicated. When the actual poison concentration cannot be readily measured, the maximum possible concentration can be approximated from the following equation:

$$\text{Concentration} = \text{bioavailable dose}/(\text{volume of distribution} \times \text{body weight in kg})$$

The applicability of this estimation is limited by many toxicokinetic factors such as unpredictable bioavailability in overdose and a changing volume of distribution at high concentration (e.g., salicylates).

The next step is to evaluate whether alternative modalities to prevent, limit, or reverse toxicity are available, such as antidotes. For example, sulfonylureas can cause lethal hypoglycemia, but the use of ECTR is unnecessary given the relative efficacy, ease, safety, and cost-effectiveness of dextrose and octreotide administration. A similar argument can be constructed regarding the use of naloxone in opioid overdoses. Likewise, for most patients with acetaminophen (paracetamol) poisonings, acetylcysteine is highly cost-effective at preventing or mitigating toxicity, making ECTR unnecessary, except in rare cases of massive ingestions with acidemia due to mitochondrial toxicity when the efficacy of acetylcysteine is reduced.[5]

In addition to antidotes, several therapies may either prevent absorption (gastric emptying, activated charcoal, or whole bowel irrigation) or enhance elimination (multiple dose activated charcoal or urinary alkalinization). When used appropriately, these techniques slow the progression of toxicity thereby negating requirements for ECTR. Further discussion regarding techniques for decontamination and enhanced elimination are beyond the scope of this work, so the reader is referred to standard reviews.[6,7]

When the patient has either developed life-threatening manifestations of poisoning or appears likely to do so, and alternative treatments are either not available or unlikely to be sufficient, timely consideration for ECTR is indicated if the poison is considered dialyzable (Figure 1).

Characteristics of poisons amenable to ECTR

The physicochemical and toxicokinetic properties of a poison predict whether it is "dialyzable", or able to be cleared from the plasma by an extracorporeal device. Perhaps more importantly, these properties predict the extent to which ECTR enhances total body clearance, thereby lowering the total body load faster than without the treatment. The primary determinants of poison removal by ECTR are the molecular weight (MW), volume of distribution (V_D), hydro- and lipophilicity, protein and tissue binding, and endogenous clearance.

The lower the MW the more likely that a poison is dialyzable. Contemporary high-efficiency high-flux dialyzers with diffusive modalities are capable of clearing poisons in the middle MW range ($< \cong$ 15,000 Da). Convective modalities such as hemofiltration and hemodiafiltration can permit clearance of solutes approaching 25,000 Da. New high-cutoff and middle-cutoff membranes may remove poisons up to 50,000 Da, although data are limited and the membranes' availability restricted.[8,9]

Perhaps the most important determinant of effective removal by ECTR is the poison's V_D. The V_D relates the amount of poison in the body to the concentration in plasma or blood. Because ECTR only clears poisons from the intravascular compartment, poisons exhibiting a smaller V_D (<1 L/kg) are more amenable to removal by ECTR.[10] The larger the V_D, the greater the fraction of poison located in extravascular tissues and thus not exposed to the extracorporeal filter.[11] Importantly, even if the poison could be cleared from the plasma by an extracorporeal device, if the poison exhibits