Blood Purification in Toxicology: Nephrology's Ugly Duckling

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Contrary to popular opinion, application of extracorporeal therapies for poisonings predates their use for ESRD. Despite this observation, the science of blood purification in toxicology remains desperately stagnant today. In fact, much of our current knowledge is derived from George Schreiner's 1958 review. Original publications are almost exclusively composed of case reports and case series, from which good inference is impossible. Until randomized controlled trials become available, the medical community would be well served by a group mandated to systematically review available literature, extract relevant information, provide recommendations based on current evidence, and propose research initiatives. The EXtracorporeal TReatments In Poisoning workgroup, formed by several international experts in different medical fields and represented by over 20 societies, now has this mission.

Key Words: Hemodialysis, Extracorporeal therapy, Hemoperfusion, Overdose, Intoxication, Poisoning

Any internal medicine resident can state the accepted indications for acute hemodialysis. Emergency physicians regularly deal with hyperkalemia and fluid overload in their units and are well-acquainted with situations necessitating urgent dialysis. Although most physicians are aware of the potential benefits of extracorporeal treatments (ECTRs) in the treatment of selected poisonings (eg, lithium, methanol), its precise application, indications, contraindications, and judicious timing largely remain a mystery to the medical community.

Most clinicians forget that the use of ECTR for acute poisonings was already thriving in the 1960s, while it was still contraindicated for ESRD. It is therefore remarkable that these indications have suffered such different fates: its use in ESRD has flourished and benefited from a remarkable input of research, investment, and dynamism; several national and international guidelines have been published on a wide variety of topics ranging from bone metabolism to vascular access.[1,2] Conversely, although medical toxicology benefited indirectly from the technical advancements in equipment (ie, dialysis machines, filters) and improved procedures (ie, water purification, anticoagulation), there has been a paucity of good science in that area, apart from scattered individual efforts and sporadic panels.[3] This cannot be explained by sheer numbers; in 2008, there were more than 350,000 prevalent patients with ESRD receiving chronic hemodialysis in the United States,[4] whereas the American Association of Poison Control Centers documented 150,000 poisonings considered to be at least "moderate" in severity.[5]

For the sake of uniformity and simplicity, we have preferentially used the terms "poisons" and "poisoning" in the text: a poison includes xenobiotics (exogenous chemicals, including therapeutic drugs) and endogenously found chemicals (eg, iron, copper, vitamins) resulting from exogenous exposure. Poisoning, although usually implying intent, will be defined as exposure to a chemical causing or capable of causing toxicity. It includes intoxication, toxicity, and overdose.

Historical Perspective

Although Thomas Graham developed the principles of dialysis in the 1800s and is generally considered the father of modern nephrology, the construction of the first artificial kidney is attributed to Abel and colleagues in 1913.[6] Interestingly, the aim of the technique was primarily to remove salicylate from the blood of a living animal, instead of treatment of kidney failure. This experiment was successful, and opened the door for renal replacement therapies.

Haas and colleagues performed the first successful dialysis in human beings in 1924, but it was not until 1943 that Kolff built a rotation drum kidney that could be used practically for acute kidney failure.[7] In 1948, Bywaters and Joekes first reported the use of dialysis in a human case of salicylate poisoning, similar to that carried out by Abel in animals 34 years earlier.[8] Several other physicians followed suit, among whom Paul Doolan, Laurence Kyle, and George Schreiner were the most prominent pioneers. By the end of the 1950s, several poisons had been shown to be dialyzable, including barbiturates, salicylates, and hypnotics. Schreiner even published his first

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series in 1958, thereby solidifying the promise of hemodialysis as a therapeutic option for poisoning and popularizing its use.[9] By 1970, most poisonings were considered amenable to treatment by dialysis.[10] The 1980s saw a new skepticism toward extracorporeal therapies, helped by better understanding of toxicokinetic principles as well as improved supportive care for poisoned patients. The last 10 years have yet again seen another pendulum swing, as the introduction of better dialysis membranes has permitted new possibilities, especially for poisons not traditionally considered "dialyzable."

Although hemodialysis undoubtedly remains the most popular ECTR for kidney failure and poisoning, it is worthwhile to observe how other techniques have come to light. In 1958, Schreiner essentially invented hemoperfusion, by using an anion exchange column to help remove pentobarbitone from blood,[9] a technique later refined by Rosenbaum and Chang,[9a] among others. Later, in 1964, Yatzidis used charcoal-based hemoperfusion for treatment of uremia and poisoning,[11] although its use for the former indication was later abandoned.

Exchange transfusion became popular for hemolytic disease of the newborn in 1925 but only appeared in toxicology circles in 1950, when Axtrup used it for 2 poisoned children.[12] Abel described *plasmapheresis* as a technique to separate plasma from blood elements,[13] although its indication for uremia was soon abandoned. Rubinstein and colleagues performed plasmapheresis in 1959 for a patient with thrombotic thrombocytopenic purpura,[14] whereas Kuzmin and Vedenskii used this technique for an atropine overdose case in 1967.[15]

Hemofiltration was unintentionally discovered in 1977 by Kramer and colleagues, with the realization that arterial flow could provide a pressure gradient for filtration, after which fluids lost with solutes could be substituted by an appropriate replacement solution.[16] Its potential in poisoning management was soon recognized.[17]

Although peritoneal dialysis is not, per se, an ECTR (because poison removal does not occur outside the body), it too became a popular treatment for poisoning. Ganter pioneered its use in 1923,[18] but survival by a patient with acute kidney failure was only reported by Frank and colleagues in 1946.[19] Not more than a year later, Baggenstoss described the first case of poisoning treated by peritoneal dialysis.[20]

Why the Confusion?

The confusion reigning over the role of ECTR in poisonings can be better illustrated by a survey conducted by us among 30 Canadian nephrologists (and discussed later in text). The following 3 clinical situations were presented and all participants were asked in which case they would consider ECTR:

1. A 24-year-old man presenting 7 hours after ingesting 80 gm of aspirin with severe symptomatic salicylate toxicity, including metabolic acidosis and seizures. All nephrologists (100%) surveyed indicated that they would perform dialysis.
2. A 45-year-old man presenting 12 hours after an acute lithium ingestion, completely asymptomatic, with a serum lithium concentration of 4.4 mEq/L. In this situation, 80% of nephrologists surveyed indicated that they would perform dialysis without delay. When asked why, the majority explained this choice as based on "current evidence."
3. An 18-year-old woman presenting with severe tricyclic antidepressant poisoning. Only 30% of nephrologists surveyed indicated that they would perform dialysis or hemoperfusion without delay. Another 33% considered dialysis or hemoperfusion to be useless in this setting.

CLINICAL SUMMARY

- Hemodialysis remains a valuable therapeutic option for severe poisonings today.
- Yet, indications of extracorporeal therapy are often based on erroneous toxicokinetic and/or clinical assumptions.
- Recommendations by a mandated group would help gather current evidence and standardize current practice.

Problems Interpreting Data

The use of extracorporeal therapy for poisonings was historically guided by intuitive, although debatable, assumptions: the higher the body burden of a poison, the higher its toxicity. Conversely, the more this poison can be removed, the lesser the toxicity. From these premises, ECTR can show clinical efficacy only if: (1) ECTR can remove poison, and (2) removal of poison by ECTR enhances survival.

Can ECTR Remove the Poison?

How does one assess removal of poisons by ECTR? This concept is understood and applied in pharmacokinetic studies evaluating extracorporeal clearance of therapeutic drugs in chronic dialysis patients; drug dosage, in this case, is simply modified to account for the quantity cleared by dialysis. In medical toxicology, ideally, removal of poison from the target organ, instead of plasma, would be assessed (ie, central nervous system for lithium, heart muscle for digoxin, lung parenchyma for paraquat). Despite the existence of numerous pharmacokinetic parameters that can be easily measured or calculated, such as total systemic clearance, percent body burden eliminated, percent ingested dose removed, half-life, extraction ratio, and others, none of them correlates with poison concentration at the target organ.