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Developments in extracorporeal therapy for the poisoned patient☆,☆☆

Nikunjkumar Patel, George P. Bayliss *

Division of Kidney Diseases and Hypertension, Rhode Island and the Miriam Hospitals, Providence, RI, USA
Alpert Medical School, Brown University, Providence, RI, USA

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ABSTRACT

The modern use of extracorporeal therapies to treat poisoning and drug overdoses dates back to the early 20th century and has evolved along with their use as treatment for acute kidney injury or as maintenance therapy in advanced kidney disease. As our understanding of drug pharmacokinetics and membrane materials has increased, the technologies of extracorporeal therapy and their applications have become more sophisticated. Despite that, there is little robust evidence to guide clinicians on the optimal use of extracorporeal therapy in treating poisoning beyond case reports and series. New efforts are underway to remedy that: the Extracorporeal Treatments in Poisoning Workgroup (EXTRIP) is an international effort on the part of nephrologists, pharmacists and toxicologists to review the available data and formulate evidence-based guidelines on how to use extracorporeal techniques to treat poisoning and improve patient outcomes. Meanwhile, new techniques and membranes are under development. This review will summarize those key scientific and technologic developments, the efforts to optimize their use and new directions in research.

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1. Introduction

The modern use of extracorporeal therapy as a way to treat intentional and accidental ingestion of harmful compounds or overdoses of therapeutic compounds (poisoning) had its start in the early 20th century. As understanding of the principles of extracorporeal therapy grew, the technology and its uses as renal replacement therapy continued to evolve. At the same time, our understanding of drug pharmacokinetics has advanced. Even so, evidence for the optimal use

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* Corresponding author at: Division of Kidney Diseases and Hypertension, APC 9, Rhode Island Hospital, 593 Eddy St., Providence, RI 02903, USA. Tel.: +1 401 444 5445; fax: +1 401 444 8453.
E-mail address: gbayliss@lifespan.org (G.P. Bayliss).

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of these therapies as treatments in poisoning remains largely anecdotal, and experts in pharmacology, toxicology and nephrology have begun joint efforts to review existing data and develop evidenced-based guidelines or make expert recommendations in the absence of robust data.

This review will examine key developments in technologies and their uses for treating poisoning, the evolution of therapies and the efforts to develop guidelines. For purposes of discussion, we will define the extracorporeal therapies as hemodialysis and related slow continuous therapies, hemoperfusion, plasmapheresis, and continuous renal replacement therapies. While not technically extracorporeal, peritoneal dialysis will also be considered since it involves extra-renal removal of substances through diffusion down a concentration gradient into dialysate that is then removed from the peritoneal cavity and discarded as waste. Gastrointestinal dialysis with multi-dose activated charcoal will be discussed briefly along with efforts to develop extracorporeal therapy for liver disease. The terms poison and poisoning will be used broadly to include compounds with recognized therapeutic uses that are intentionally or unintentionally ingested in ways that make their effects toxic as well as substances without recognized therapeutic value and known toxic effects at any concentration. The paper will not discuss removal of urea and uremic toxins since this goes to the crux of extracorporeal therapy in end-stage renal disease. Use of extracorporeal therapies to remove ammonia is well established and will be discussed in brief. While ammonia, like uremic compounds, is an endogenous substance, its toxicity at high concentrations makes it similar to drugs that have therapeutic value but are toxic at high concentrations.

2. Development of membranes, technology and early experience

The principles behind dialysis stretch back to ancient Greece and the development of the concept of the atom as a theory of matter into the 19th century understanding of atoms as the building blocks of elements (Table 1). Thomas Graham used animal membranes and later cotton treated with albumin to conduct experiments on osmotic pressure as driving force to separate crystalloids (salts) from colloids (albumin). German and French chemists are credited with developing collodion, which was known as guncotton because of its tendency to explode at high temperature, from nitrocellulose dissolved in ether and ethyl alcohol [1]. Adolph Fick published his work on the passive movement of solute across membranes as a result of differences in concentration soon after Graham [2]. Fig. 1 summarizes some of the key events and people in the development of extracorporeal therapy in treating poisoning.

2.1. Vividiffusion

The first uses of dialysis to remove substances from the body were reported by Abel and colleagues in 1913 [3]. They proposed their technique for "toxic states in which the eliminating organs, especially the kidneys, are incapable of removing at an adequate rate either the autochthonous or foreign substances whose presence in excessive amount is detrimental to life process." They performed their first experiments with "vividiffusion" on a rabbit in 1912. Their initial "vividiffusion apparatus" consisted of sixteen 8 mm by 20 cm "celloidin" (collodion) tubes in parallel, enclosed in a glass casing The membranes were made from a concentrated mixture of pyroxylin, produced by exposing cotton (cellulose tetranitrate) to nitric acid and sulfuric acid, and were about 0.05 mm to 0.1 mm thickness.

Abel and colleagues touched on two of the basic principles still in use today in deciding to dialyze for poisoning: for extracorporeal therapy to be useful it must occur at a faster rate than native clearance; and a larger membrane surface area provides greater clearance. After an infusion of sodium salicylate, they found that they were able to remove 19.1% of the salicylate by dialysis compared to renal removal of 17.5%. But they noted that the removal by dialysis of salicylate was depressed relative to renal clearance because of the smaller dialyzing surface area of their apparatus (each gram of celloidin made about 430 cm^2 of diffusing surface by their calculations). In a subsequent paper they argued that increasing the surface area of the dialyzer would lead to a proportional increase in nitrogen diffusing across the dialyzer [4].

Haas preformed the first dialysis treatment on humans in 1924, using collodion tubes in a U shape, surrounded by dialysate in a glass tube; he later introduced the use of heparin [5]. The total length of the

Table 1
Membranes.

Membrane	
Collodion (gun cotton)	Developed in the 1830s, thickness 17–80 μm, depending on % alcohol in composition; poor size dependent on % alcohol in composition; fragile and difficult to manufacture; Abel, Haas and others use in early experiments
Cellophane	Thickness around 99 μm, pore radius nm; developed as sausage casing; Kolff used in his kidney
Cupraphane	35 μm; Kiil among the first to use; pore radius 4 nm; low flux only non-biologically compatible
Cellulose acetate	Ultrathin capillary membranes, thickness 5 μm, 200 μm capillary diameter, ultrafiltration coefficient 12.8 ml/h/mmHg
AN69	Developed by Rhone–Poulenc, copolymer of acrylonitrile and methallylsulfonate pore size twice that of cellophane membranes, hydrophilic, high specificity for medium sized proteins
Polysulfone	High flux membranes in widespread use; wall thickness 35 nm, inner capillary diameter 185 nm; ultrafiltration coefficient 40 ml/h/mmHg
Peritoneum	1 m^2 membrane surface area, 2 m^2 capillary surface area; blood flow 100–150 ml/min; large pores >20 nm; small pores 4–6 nm; ultrapores or aquaporins <0.8 nm; limited data on acute use as membrane to clear poisons
Renal assist device	Ultrafiltrate from conventional dialysis membrane delivered to semipermeable hollow fibers covered with porcine, then human renal epithelial cells, while blood delivered to extracapillary space; studied in patients with acute kidney injury, discontinued due to thrombocytopenia, problems, and difficulty manufacturing; no data on use in poisoning
Bioartificial kidney/high cut-off membrane	Polyethersulfone/polyvinylpyrrolidone membrane with immortalized human proximal tubular epithelial cells, collagen IV coating; research to investigate renal drug handling, drug toxicity; initial application envisioned for AKI, sepsis with multisystem organ failure. Benefits include removal of higher weighted molecules; in acute kidney injury, may be able to remove inflammatory cytokines such as IL-8, IL-6 and TNF-alpha. Risk of albumin loss. Studied in myeloma and used in 500 patients around the world with renal recovery rate of 63%. Studied in rhabdomyolysis, shown to increase myoglobin removal compared to conventional dialysis filters. Need more randomized controlled trials.
Hemoperfusion	Indicated for removal of protein-bound molecules; cellulose coated activated charcoal granules, or resins; side effects include thrombocytopenia, emboli, and hemolysis; use has dropped in the US; limited data, but US Food and Drug Administration accepted less stringent regulatory controls on the technology in cases of poisoning
Potential future membranes[1, 2]	Human nephron filter — two membranes, the G and T membranes working in concert to attain clearance and ultrafiltration. Theoretically to be made using a commercial polycarbonate membrane. Goal to have customized pore sizes for different functions. Modeling studies; awaiting animal trials. Silicone nanopore membrane — theoretical membrane-less dialysis.

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