Have Advances in Extracorporeal Removal Techniques Changed the Indications for Their Use in Poisonings?

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During the past 25 years, numerous changes have taken place in the use of hemodialysis as a therapeutic modality. Advances in technologies and a progression in our collective understanding of the pharmacokinetics of certain xenobiotics have resulted in alterations in the indications, effectiveness, and safety of hemodialysis. However, these changes have not necessarily been reflected in the current published data regarding treatment of intoxications. Reported clearance rates often reflect what was achievable in the 1970s and 1980s, and more recent reports are frequently lacking. Our goal in this review is to summarize the changes in hemodialysis and in other extracorporeal removal technologies and highlight the effects of these changes on the current indications for hemodialysis of the poisoned patient. Changes in dialysis performance that are reviewed in this article include the use of high-efficiency and high-flux dialysis membranes, improved hemodynamic stability because of ultrafiltration control, and the use of bicarbonate as a source of base. We review the indications for hemodialysis for removal of specific toxins, including vancomycin, methotrexate, carbamazepine, and valproic acid.

Published by Elsevier Inc. on behalf of the National Kidney Foundation, Inc.

Key Words: Carbamazepine, Hemoperfusion/trends, Methotrexate, Overdose, Poisons, Poisoning/therapy, Sorption detoxification/methods, Valproic acid

The use of extracorporeal removal (ECR) techniques to enhance the elimination of certain toxins has been used for decades in the treatment of the severely poisoned patient. Between 1985 and 2005, a total of 19,351 poisoning cases in which an ECR technique was used were reported to the American Association of Poison Control Centers. The number that received hemodialysis increased significantly in this period, from 231 per million calls in 1985 to 707 per million calls in 2005.[1,2] During the past 25 years, numerous changes have taken place in the use of hemodialysis as a therapeutic modality.[3] Advances in technologies and a progression in our collective understanding of the pharmacokinetics of certain xenobiotics have resulted in alterations in the indications, effectiveness, and safety of hemodialysis. However, these changes have not necessarily been reflected in the current published data regarding treatment of intoxications. Reported clearance rates often reflect what was achievable in the 1970s and 1980s,[4] and more recent reports are frequently lacking. In essence, the literature is old. Our goal in this review is to summarize the changes in hemodialysis and other ECR technologies, and highlight the effects of these changes on the current indications for hemodialysis of the poisoned patient.

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Published by Elsevier Inc. on behalf of the National Kidney Foundation, Inc.
1548-5595/$36.00
doi:10.1053/j.ackd.2011.01.009

Advances in ECR Techniques

Although many changes in the technical aspects of hemodialysis have occurred in the last decades, we will highlight only those we consider relevant to treatment of poisonings in this review, and not those related only to treatment of end-stage kidney disease. When we write about "conventional hemodialysis," we are referring to the generic form of dialysis which was routinely used 3 times a week in the treatment of patients with chronic kidney failure before the more widespread use recently of larger and more porous membranes.

High-Efficiency Hemodialysis Membranes

"High-efficiency" is a term used to describe hemodialysis membranes that achieve higher clearances of the traditional low-molecular-weight marker of dialysis adequacy, urea. The definition of high-efficiency hemodialysis is usually considered urea clearance greater than 210 mL/min.[5] Higher flow rates of blood and dialysate are required to achieve these clearance rates. With the impetus in end-stage kidney disease, both in the United States and worldwide, to deliver higher urea clearances, the requirements of high-efficiency hemodialysis became standard of care and are likely to be used in the treatment by a nephrologist of any life-threatening intoxication. To some extent, however, blood flow rates may be limited by hypotension and low-molecular-weight clearance thereby impaired.

High-Flux Membranes

Traditionally, hemodialysis has been considered to be effective only for low-molecular-weight xenobiotics with molecular weight (MW) <500 Daltons (Da). In the 1990s, the desire to remove amyloidogenic β_2-microglobulin and other "middle molecules" in the setting of end-stage kidney disease led to the development and popularization

of "high-flux" dialysis membranes.[5] As opposed to the older, conventional, usually cellulose-derived membranes, the high-flux membranes are composed of various synthetic polymers, such as polysulfone, polyamide, polyacrylonitrile, and other proprietary compounds.[6] Advances in techniques of mass production contribute to significant reductions in price, which has also led to their wide availability. Their larger pore size allows for the clearance of larger molecules. As compared with conventional "low-flux" dialysis, dialysis with high-flux membranes demonstrates improved efficacy in the removal of middle molecules ranging in size from 1000 to >15,000 Da.[7] The clearance of β_2-microglobulin (MW, 11,800 Da) is often used to express the high-flux dialysance of a membrane. High-flux membranes are those that achieve >20 mL/min of β_2-microglobulin clearance.[5] The widespread availability of such membranes has made the consideration of clearance of more high MW xenobiotics possible.

Ultrafiltration Control

Ultrafiltration (also called hemofiltration) is the movement of fluid across a membrane in response to hydrostatic pressure gradients. Dialysis membranes used for treatment of end-stage kidney disease have had progressively higher ultrafiltration coefficients, a measure of the amount of fluid moved across a membrane in response to a pressure gradient per unit time. High-flux membranes have high ultrafiltration coefficients. In the past, frequent hypotensive episodes complicated dialysis therapy, due in large part to the need for repeated calculations and manipulations of the ultrafiltration rate. The development of computerized hemodialysis machines that register small variations in the inflow and outflow of dialysate allows fine control of ultrafiltration rates and the ability to limit extracellular fluid volume losses despite the membrane's high ultrafiltration coefficient. Ultrafiltration control has become more important with the use of high-flux membranes, as their higher water permeability requires more precise volume control.

CLINICAL SUMMARY

- High flux dialysis membranes now allow dialysis of larger molecules, though efficacy remains limited to molecules with relatively low volumes of distribution and low protein binding.
- Despite advances in membrane technology, the number of poisonings for which hemodialysis is indicated has expanded relatively little with scant evidence of clinical significance.
- Instead of focusing on the technology of dialysis membranes, attention should be focused on improving access to dialysis in a timely manner in cases in which it will have the most clinical impact.

Improved Hemodynamic Stability

In addition to ultrafiltration control, other changes in hemodialysis technology have allowed patients to experience less hemodynamic instability than that in the past. One such change is in the source of base in the dialysate. The use of sodium acetate caused vasodilation, hypotension, metabolic acidosis, and decreased cardiac output, and has now been entirely replaced by sodium bicarbonate.[8] Older literature, before the late 1980s, reporting on hemodialysis as a treatment of poisoning may be limited by hemodynamic instability caused by acetate. The use of sodium modeling, a technique by which the sodium concentration of the dialysate can be programmed to vary during the course of the procedure, may also act to promote hemodynamic stability. Although bicarbonate-based hemodialysis is now the standard of care, sodium modeling as a useful technique in hemodynamic stabilization during ECR of xenobiotics has not been explored.

Higher Blood Flow Rates

Historically, blood flow rates during hemodialysis ranged from 250 to 400 mL/min. Now, higher blood flow rates, of a maximum of 400 to 500 mL/min, are routinely achieved and are considered as the standard of care in the treatment of end-stage kidney disease, in which higher urea clearance rates have been emphasized in recent years. These higher blood flows are achievable because of the improved hemodynamic parameters that arise from bicarbonate-based dialysate, ultrafiltration control, and the use of larger dual-lumen catheters. The direct result of these innovations is the capacity for improved clearance of toxins, which may have significant clinical effect in certain settings. Higher dialysate flow rates to values beyond those usually used currently might maintain concentration gradients and somewhat increase clearance of protein-bound solutes.[9]

Hemodiafiltration

Hemodiafiltration is hemodialysis and ultrafiltration performed together, as with conventional hemodialysis, but with the difference that the rate of removal of extracellular fluid volume vastly exceeds that needed to remove excess sodium and water.[10] This technique is now widely used in Europe, but not in the United States, for management of end-stage kidney disease. Augmentation of ultrafiltration leads to significant enhancement of solute clearance by the addition of convective removal of plasma to add to the diffusive clearance offered by hemodialysis. The removal of large volumes of plasma necessitates infusions with large volumes of manufactured replacement fluid. Clearance is then determined by the total volume of both the dialysate and replacement solution. Because data suggest higher