Sorbent Augmented Hemodialysis Systems: Are We There Yet?

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ABSTRACT

Recent publications have reintroduced the concept of using sorbent systems to augment the efficiency of the dialysis process, either by making stationary or compact wearable devices to regenerate dialysis fluid or to target larger molecules for removal by direct blood or plasma contact with sorbent particles. Many of the inherent problems associated with older sorbents have been overcome by designing sorbents with improved biocompatibility and potential for removing molecules beyond the limits of conventional dialysis membranes. One system is approved for use in acute renal failure in the United States, but other devices are not approved for use in humans and continue to be tested in animals and humans. A prototype wearable sorbent device under investigation is not yet able to meet acceptable small molecular weight solute removal, and the other sorbent devices that possess the ability to remove unconventional uremic toxins have not been studied sufficiently in dialysis patients to define their role as augmentation devices. That there is a renewal of interest in sorbents in augmentation of dialysis points to the dissatisfaction with current dialysis technology.


Recent studies suggested that sorbent systems contribute to the long-awaited goal of a wearable artificial kidney for chronic kidney disease (CKD-HD). We examine here a number of issues related to the deployment and evaluation of sorbent systems in the treatment of uremia. Compared with 20th-century dialysis, modern conventional dialysis has improved dialysis prescription and delivery but with little incremental survival benefit for long-term dialysis patients. Survival benefit has improved neither by increasing dialysis dosage for conventional small water-soluble uremic toxins (urea, creatinine) nor by high-flux membranes, suggesting that other toxins may be involved in uremic pathophysiology.

The discovery of other uremic toxins has led to alternatives to standard or high-flux hemodialysis to remove these molecules. These methods include hemodiafiltration with1,8 or without sorbent/enzyme dialysate regeneration,9,10 addition of carbon to dialysate,11 and hemoperfusion using adsorbents such as charcoal/carbon12 and resins.13 There are two equally important goals for those investigating sorbents in clinical dialysis: (1) To develop stationary or compact and wearable devices that achieve solute removal/ultrafiltration equal to that of modern dialysis and (2) to develop devices that remove an additional spectrum of molecules in an attempt to improve on the dialysis technique. The former can be achieved with sorbents used in dialysate/ultrafiltrate regeneration, but the latter cannot be achieved unless the sorbent is exposed to whole blood or plasma.

There is great interest in the malnutrition inflammation atherosclerosis syndrome in CKD-HD as a result of finding high plasma concentrations of inflammatory mediators (IL-6, C-reactive protein, TNF, and other cytokines), advanced glycosylation end products, advanced lipoxidation compounds, or carbonyl and oxidative stress proteins in patients with CKD-HD. Many of the substances observed in increased concentration in CKD predict cardiovascular mortality in nondialysis patients. Most of the putative toxic proteins exceed the molecular weight pore size limits of conventional high-flux dialysis membranes. High-efficiency hemodiafiltration, especially with ultrapure water-derived replacement fluid and dialysate, may reduce some of these proteins, but the molecular species of interest have led many to believe that sorbents will be required to augment the dialysis procedure.

Adsorption is separation of a solute from its solvent by a solid agent in a process equivalent to size-selective chromatography. The pore structure in artificial sorbents can be set in the manufacturing process by polymerization of resins or controlled pyrolysis of synthetic materials, which form novel carbons that...
augment pore structure compared with naturally formed carbons. Sorbents exist in granules, spheres, cylindrical pellets, flakes, powder, and nano-carbons. The most common are solid particles with a single particle diameter between 50 nm and 1.2 cm. Surface area to volume ratio is extremely high, varying from 300 to 1200 m²/g. Pores are defined as macro-porous (>500 Å [50 nm]), mesoporous (20 to 500 Å), and microporous (<20 Å); at the lower end of the mesopore size, creatinine, urate (but not urea), and some drugs are adsorbed, whereas, at the upper range, low molecular weight proteins are adsorbed, usually in pores that are approximately three times the random coil diameter of the protein.

In the pilot study of the prototype wearable artificial kidney, the sorbents used were activated carbon (for adsorption of creatinine, urate, Cu, Hg, Pb, and particulates), urease to convert urea to ammonium carbonate, zirconium oxide (phosphate, fluoride, and chloride adsorption in exchange for acetate, bicarbonate, and sodium), and zirconium phosphate (ammonium, Ca, Mg, and K adsorption in exchange for Na and H). These sorbents are similar to those used in the Allient system (Renal Solutions, Warrendale, PA), reengineered from the original REDY system (Organon Teknika, Oss, The Netherlands). Treatment time was between 4 and 8 h, and average solute clearance for urea was 10.3 mmol (range 5.7 to 18) and for creatinine was 7.7 mmol (range 3.6 to 15.2), and Kt/Vurea was 18) and for creatinine was 7.7 mmol (range 5.7 to 15.2). Similarly, a styrene polymer with an enhanced proportion of mesopores in the range of 2 to 20 nm was shown in a pilot study of humans to remove β2–microglobulin (β2M; 11.8 kD), angiotenin (17 kD), leptin (16 kD), retinol binding protein (21.2 kD), and IL-18 (18 kD).

Another device available for addition to hemodialysis is the Lixelle cartridge (Kaneka Corp., Osaka, Japan). This device is a column that contains a porous cellulosic bead that covalently binds β2M on ligands. Use of the device along with hemodialysis for periods of 25 to 62 wk resulted in symptomatic improvement and partial radiographic improvement in dialysis-related amyloidosis.19 Removal of circulating cytokines from blood is also achieved by coupled plasma filtration adsorption.20 The use of a resin similar to that in coupled plasma filtration adsorption showed that substances contributing to a malignant process (e.g., etoxin, ILs, macrophage inhibitory proteins) can be removed in vitro from blood of patients with various malignancies.21

Although gradual improvements (including improved hemoglobin and bone disease) in the dialysis process have taken place in the past 10 to 20 yr, it has become clear that the process does not result in the dramatic reversal of symptoms and additional years of life achieved with transplantation. Solute removal is the main goal of dialysis, and improvements may be achieved by daily and nocturnal dialysis, but the basic limitation is the dialysis membrane. Although sorbent devices remain in their infancy, they do hold great promise for improving the solute spectrum removed.

DISCLOSURES
J.F.W. is consultant to MedaSorb Technologies, Inc.

REFERENCES