Activated Carbon and the Artificial Kidney II

R. A. Van Wagenen and J. D. Andrade

Institute for Biomedical Engineering, University of Utah, Salt Lake City, Utah 84112

Research on charcoal hemoperfusion was initiated at the University of Utah in the summer of 1970. At that time the goal of the research was to eliminate the problems which had prevented the hemoperfusion concept from being widely accepted. The major problems were: (1) decreased platelet and white cell levels after hemoperfusion, (2) charcoal caking, packing and blood clotting which resulted in blood channeling and significantly reduced adsorption efficiency, (3) loss of blood in the column after hemoperfusion, (4) excessively high heparin dosage levels, (5) possible occurrence of pyrogenic reactions, and (6) the microparticle "emboli" problem. It was felt that if these problems could be solved, the simplicity, low cost and efficiency of charcoal hemoperfusion could benefit a large number of dialysis patients who now rely on two or three hemodialysis treatments each week.

Our approach to these problems was to coat the granular activated carbon with a material that was blood compatible. Acrylic hydrogels with high water content were chosen as coating materials on the basis of previously reported results,[15] and the belief that by minimizing the interfacial energy between a gel-like surface and an aqueous liquid (blood), the interactions across the interface (protein absorption, platelet adhesion, etc.) would be minimized.[16, 17] The acrylic hydrogel chosen for coating was poly (hydroxyethyl methacrylate) (polyHEMA), also called Hydron-S. Much of the emphasis during our early research was oriented toward evaluation of various hydrogel coatings and circuit designs.[16] The evaluations were primarily in vitro stirred batch adsorption studies using radiolabeled creatinine and uric acid and in vivo perfusions utilizing sheep and dogs.[16, 18] We found that a combination of proper heparin doses and polyHEMA coatings prevented fibrin buildup, platelet sticking, and subsequent clot formation.[16, 18] This in turn prevented carbon packing and resultant blood channeling during hemoperfusion. The decrease in blood channeling exposed the blood to more activated carbon surface, resulting in an optimal adsorption capacity for the total amount of carbon in the circuit.

The direction of our research changed during the second year when we realized that the major problem remaining was the possibility of microemboli generation during hemoperfusion. Initial in vitro evaluations showed that some carbons were cleaner and more resistant to fragmentation than others and also that various brands of carbon could be washed cleaner than other brands.[18] In vivo animal experiments were continued and substantiated the in vitro stirred batch adsorption studies with creatinine, uric acid and salicylate. We found that a properly and thoroughly washed carbon which is then encapsulated and contained in a single compartment cartridge will not produce readily detectable carbon emboli. This confirms Chang's histopathological findings for thoroughly washed albumin-colloidion activated carbon.[12]

During the last two years the research emphasis in this laboratory has been directed toward selection of the optimum grade of carbon and coating material which will give the best hemoperfusion results for the solutes of interest (creatinine, uric acid, salicylates, barbiturates, etc.). Evaluations of most commercially available activated carbons as well as some specialty grades of carbon have been con-

*Part I was published in this Journal. Parts I and II of this paper supported in part by U.S.P.H.S. Contract PH-43-68-1027, National Institute of Arthritis and Metabolic Diseases and by the University of Utah Artificial Organs Development Fund.

ducted for initial carbon cleanliness (presence of microparticles which could become emboli during hemoperfusion), carbon washability, and resistance to fragmentation.[19] In vitro adsorption evaluations for endogenous and exogenous toxins are conducted on activated carbons which show promising cleanliness and also as an evaluation test for various kinds of polyHEMA coatings.

An ingenious method of encapsulating activated carbon particles is being developed by a research group at Southern Research Institute. They are producing polymer fibers loaded with activated carbon particles. The fibers are then wound on a spool and packed in a cartridge for blood perfusion.[24]

The results of clinical hemoperfusion experience reported by Chang et al[11-14] and the optimization of carbon selection, washing, hydrogel coating, and in vitro/in vivo evaluations carried out in our laboratories and elsewhere are promising. Hemoperfusion over thoroughly characterized, washed and coated activated carbon deserves serious consideration as a possible adjunct to chronic hemodialysis and as a method for the extracorporeal treatment of acute poisoning episodes.

DIALYSATE REGENERATION

One of the limitations to miniaturization of the membrane-type artificial kidney is the extremely large volume of dialysate fluid required to maintain a high concentration difference across the membrane for waste metabolites. Kolobow and Dedrick have described a new kind of hemodialyzer with a high dialysance at a low dialysate flow rate.[20] The presence of finely powdered activated carbon in the dialysate served as a "sink" for many waste metabolites. The adsorption of these metabolites on the carbon kept the concentration in the dialysate low, maintaining a high concentration gradient. Blaney, Lindan and Sparks applied the concept of a low dialysate volume containing activated carbon to a "wearable" artificial kidney design.[21] They found that creatinine and uric acid are strongly and irreversibly bound to activated carbon but the capacity for urea is low and it binds somewhat reversibly. Blaney et al. [21] envisioned a small cartridge containing adsorbent for creatinine, uric acid and urea. Since carbon can only remove a relatively small amount of urea, another method would be required for urea removal. The adsorbent plus a low volume of dialysate would be coupled with a small wearable dialyzer and pump to recirculate the dialysate. Periodically dialysate would be replaced and the adsorbent regenerated or replaced. Recently, Dharnidharka et al. devised an artificial kidney utilizing isotonic ultrafiltrate as the dialysate. The ultrafiltrate was generated by a partial vacuum around the fibers of a hollow-fiber artificial kidney.[22] Water and salt homeostasis can be maintained by removal of the desired amounts of ultrafiltrate and an adsorbent such as charcoal can be used in the dialyzing fluid to remove waste metabolites. Dharnidharka et al., concluded that utilization of present hardware and oral doses of anticoagulant make it feasible to develop an artificial kidney based on ultrafiltrate as the dialysate. This eliminates the problems inherent in the use of large volumes of dialysate. Since a blood pump is not required, the weight reduction enhances the feasibility of a wearable artificial kidney. Small quantities of charcoal are sufficient for the removal of creatinine and uric acid but for adequate urea removal by adsorption, 20 to 40 times as much activated carbon would be required.[22] This begins to bring weight limitations of a wearable artificial kidney back into the picture.

A commercial approach to dialysate regeneration is the REDY (Recirculating Dialysate) system.[23] The objective of this system is to utilize an appropriate combination of adsorbents to regenerate a small volume of dialysate which is then recirculated through the artificial kidney. A combination of activated carbon,

zirconium phosphate, zirconium oxide and urease all contained in a single disposable cartridge effect the removal of waste metabolites from the blood. The sorbent system operates on the principles of ion exchange and physical adsorption. Dialysate from the artificial kidney enters the sorbent pack and urea is converted to ammonium ion and bicarbonate. The ammonium, calcium, magnesium and potassium ions are exchanged for sodium and hydrogen ions on the zirconium phosphate. As the dialysate passes through zirconium oxide, phosphate ion is removed. Organic waste metabolites (creatinine, uric acid, guanidine, etc.) are removed by adsorption on activated carbon. Magnesium and calcium ions are infused to the dialysate before it is returned to the dialyzer. The REDY system offers a significant reduction in weight and volume compared to previous designs. It is portable and requires no special electrical or plumbing hook-ups. However, it is not wearable.

Ideally, a wearable artificial kidney would need to be small, light in weight and simple to operate and power.

SUMMARY

Activated carbon has a large capacity for adsorption of nitrogenous waste products from blood or dialysate by virtue of its high porosity and resulting large surface area. Many of the problems associated with early clinical hemoperfusion attempts have been overcome by proper washing and by coating the granular activated carbon with polymeric materials to improve blood tolerability. The added mechanical strength due to the polymeric coatings also helps prevent the fragmentation and embolization reported in early in vivo animal experiments. A number of successful clinical trials have been reported. Activated carbon also finds application in dialysate regeneration schemes. In the future it may serve as a valuable sorbent for removal of waste metabolites in miniaturized wearable artificial kidneys. It is also of great usefulness for the removal of many poisons and drugs in acute poisoning episodes.

REFERENCES

1. *Basic Concepts of Adsorption on Activated Carbon,* a brochure provided by Pittsburgh Activated Carbon Division of Calgon Corporation, subsidiary of Merck & Co., Inc. Calgon Center, Box 1346, Pittsburgh, Pennsylvania 15230.

2. Andrade, J. D., Kopp, K., Van Wagenen, R., Chen, C., and Kolff, W. J., "Activated Carbon and Blood Perfusion: A Critical Review," *Proc. Europ. Dial. Transplant Assn.* 9:290 (1972).

3. Yatzidis, H., "A Convenient Haemoperfusion Micro-Apparatus over Charcoal for the Treatment of Endogenous and Exogenous Intoxications," *Proc. Europ. Dial. Transplant Assn.* 1:83 (1964).

4. Dunea, G. and Kolff, W. J., "Clinical Experience with the Yatzidis Charcoal Artificial Kidney," *Trans. Amer. Soc. Artif. Int. Organs* 11:178 (1965).

5. Yatzidis, H., "The Charcoal Artificial Kidney in Clinical Practice," Papers presented at the Cleveland Clinic, Cleveland, Ohio, October 18, 1966.

6. DeMyttenaere, M. H., Maher, J. F. and Schreiner, G. E., "Hemoperfusion Through a Charcoal Column for Glutethimide Poisoning," *Trans. Amer. Soc. Artif. Int. Organs* 13:190 (1967).

7. Rosenbaum, J. L., Ronquillo, E. and Argyres, S. N., "Column Hemoperfusion and Hemodialysis Techniques to Treat Barbiturate Intoxication in Dogs," *J. Albert Einstein Med. Center* 16:67 (1968).

8. Chang, T. M. S., "Semipermeable Aqueous Microcapsules ('Artificial Cells') with Emphasis on Experiments in an Extracorporeal Shunt System," *Trans. Amer. Soc. Artif. Int. Organs* 12:13 (1966).

9. Chang, T. M. S., Pont, A., Johnson, L. J. and Malave, N., "Response to Intermittent Extracorporeal Perfusion Through Shunts Containing Semipermeable Microcapsules," *Trans. Amer. Soc. Artif. Int. Organs* 14:163 (1968).

10. Chang, T. M. S., *Artificial Cells,* Charles C. Thomas, Publisher, 1972.

11. Chang, T .M. S., Gonda, A., Dirks, J. H., and Malave, N., "Clinical Evaluation of Chronic, Intermittent, and Short-Term Hemoperfusions in Patients with Chronic Renal Failure Using Semipermeable Microcapsules (Artificial Cells) Formed with Membrane-Coated Activated Charcoal," *Trans. Amer. Soc. Artif. Int. Organs* 16:246 (1971).

12. Chang, T. M. S. and Malave, N., "The Development and First Clinical Use of Semipermeable Microcapsules (Artificial Cells) as a Compact Artificial Kidney," *Trans. Amer. Soc. Artif. Int. Organs* 16:141 (1970).

13. Chang, T. M. S., Gonda, A., Dirks, J. H., Coffey, J. F. and Burns, T. L., "ACAC Microcapsule Artificial Kidney for the Long Term and Short Term Management of Eleven Patients with Chronic Renal Failure," *Trans. Amer. Soc. Artif. Int. Organs* 18:465 (1972).

14. Chang, T. M. S., Coffey, J. F., Lister, C., Taroy, E., and Stark, A., "Methaqualone, Methyprylon, and Glutethimide Clearance by the ACAC Microcapsule Artificial Kidney: In Vitro and In Patients with Acute Intoxication," *Trans. Amer. Soc. Artif. Int. Organs* 19:87 (1973).

15. Levowitz, B. S., et al. "Biologic Compatibility and Applications of Hydron," *Trans. Amer. Soc. Artif. Int. Organs* 14:82 (1968).

16. Andrade, J. D., Kunitomo, K., Van Wagenen, R., Kastigar, B., Gough, D., and Kolff, W. J., "Coated Adsorbents for Direct Blood Perfusion: Hema/Activated Carbon," *Trans. Amer. Soc. Artif. Int. Organs* 17:222 (1971).

17. Andrade, J. D., "Interfacial Phenomena and Biomaterials," *Med. Inst.* 7:2 (1973).

18. Andrade, J. D., Van Wagenen, R., Chen, C., Ghavamian, M., Volder, J., Kirkham, R., and Kolff, W. J., "Coated Adsorbents for Direct Blood Perfusion II," *Trans. Amer. Soc. Artif. Int. Organs* 18:473 (1972).

19. Van Wagenen, R., Lentz, D. and Andrade, J. D., Manuscript in preparation.

20. Kolobow, T. and Dedrick, R. L., "Dialysate Capacity Augmentation at Ultra-Low Flow Rates with Activated Carbon Slurry," *Trans. Amer. Soc. Artif. Int. Organs* 12:1 (1966).

21. Blaney, T. L., Lindan, O. and Sparks, R. E., "Adsorption: A Step Toward a Wearable Artificial Kidney," *Trans. Amer. Soc. Artif. Int. Organs* 12:7 (1966).

22. Dharnidharka, S. G., Kirkham, R. and Kolff, W. J., "Toward a Wearable Artificial Kidney Using Ultrafiltrate as Dialysate," *Trans. Amer. Soc. Artif. Int. Organs* 19:92 (1973).

23. Greenbaum, M. A. and Gordon, A., "A Regenerative Dialysis Supply System," *Dialysis and Transplantation,* 1:19 April/May 1972.

24. Davis, T., Cowsar, D., Proc. Artificial Kidney Program Contractors' Meeting, N.I. A.M.D., Bethesda, Md., February, 1973.