ACTIVATED CARBONS IN EXTRACORPOREAL METHODS OF MEDICAL TREATMENT - TIME TO REACTIVATE THE IDEA?

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INTRODUCTION

The term "extracorporeal therapy" means a medical treatment utilising an extracorporeal circuit. Blood, plasma or another body fluid is passed through the extracorporeal purification device, where the toxic substances are separated and the purified fluid returns to the body. A range of extracorporeal therapies are available at present, based on physical (dialysis or filtration) or physicochemical (adsorption) mechanisms (Table 1).

Table 1. Physical and physico-chemical principles of extracorporeal therapy.

Method	Principle
Haemodialysis (HD)	Diffusion and convective transport through a semipermeable membrane, osmosis
Haemofiltration (HF)	Ultrafiltration and convective transport of solutes across a semipermeable membrane or filter
Combined HD/HF, or haemodiafiltration	Diffusion, ultrafiltration and convective transport
Apheresis and plasmapheresis	Membrane or centrifuge separation of blood into cells and plasma and further plasma fractionation using various methods
Haemoadsorption, or haemoperfusion (HP)	Physical adsorption, ion exchange or chemisorption

The concept of extracorporeal therapy (dialysis) can be traced back as early as 1913 [1], and the use of activated carbons in medicine for detoxification has been known since ancient Egypt and Greece [2], but real progress in the development and clinical applications of extracorporeal methods was made in 1960s-1980s. During these three decades commercial devices for extracorporeal treatment became available. Although extracorporeal adsorption was introduced along with dialysis and filtration, currently its use is limited to acute poisoning with low molecular drugs, whereas dialysis and filtration are widely used for the treatment of acute poisoning, acute and chronic organ failure and in various life support systems [3-6]. It is shown in this paper that recent progress in carbon science makes adsorption over activated carbons competitive to other extracorporeal methods. Current status, problems and prospects of extracorporeal adsorption therapy are discussed.

BIOCOMPATIBILITY OF ACTIVATED CARBONS

The first clinical use of charcoal in a HP device was reported by Yatsidis [7]. Haemoperfusion was carried out on a column of 200 g charcoal at a flow rate of 150-300 ml/min for 30-90 min. The results of the treatment of patients with terminal chronic renal failure were encouraging, and the charcoal column efficiently removed creatinine, uric acid and other uraemic metabolites. It was estimated that a 60-min HP was as efficient as a 4 to 6-hr HD. Blood perfusion over activated carbon was also successfully used for treatment of acute poisoning. However, this procedure induced hypotension, reduction in glucose, calcium and potassium concentration and damaged blood cells [8,9]. The most severe problem was the release of fine particles from the carbon granules causing microemboli. Despite thorough washing, microparticles of 5-35 μm size were persistently detected in the blood samples and washing solutions at the outlet of the carbon column. Use of plasma perfusion followed by its filtration to remove fine particles, instead of blood perfusion was suggested [10].

The problem of fine particle release from activated carbon granules was solved by coating them with a semipermeable membrane [9,11]. The most common commercially available activated

carbon haemoperfusion column 'Adsorba' is manufactured by Gambro, Sweden/Germany. In the 'Adsorba' column, Norit RXS extruded peat charcoal is coated with a 3-5 μm thick cellulose membrane. Coating carbon granules makes them more biocompatible but it also dramatically affects performance of a haemoperfusion column reducing the rate of diffusion to the carbon surface and efficiency of haemoperfusion. Adsorption of high molecular weight solutes is particularly affected. A thick membrane virtually cuts off HMW molecules and significantly reduces adsorption of "middle molecules" with molecular mass between 300 and 15,000 [12]. Removal of 'middle molecules' is essential as they play an important role in the development of many pathological conditions.

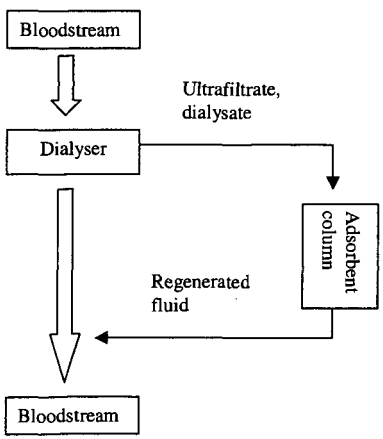
Use of coated adsorbents instead of uncoated dramatically reduces efficiency of haemoperfusion both in terms of adsorption capacity and rate of adsorption. Not surprisingly, information about the ability of coated activated carbons to remove even low molecular uraemic toxins is controversial [13]. As a result, HP has been limited in use to only acute poisoning with certain low molecular toxins [14].

UNCOATED ACTIVATED CARBONS FOR EXTRACORPOREAL THERAPY

The growing economic pressure on medical care provides a strong incentive for further development of adsorption therapy [15]. Patients in need of chronic extracorporeal treatment are usually of advanced age, and their number is rapidly increasing. For example, by the middle of this century the number of 75+ aged people will have doubled and the population over age 90 will have more than tripled in the U.K. [16]. This will result in a heavy burden on NHS. A similar situation is happening in other developed countries. Current expenditures on the treatment of chronic renal, liver and multiorgan failure – life threatening conditions in which HD and HF are widely used, far exceed the health care funding of all but a few nations [15]. Unless a cost-effective solution is found, this situation can only worsen.

An adsorption column could be used in-line with HD or HF to reduce the cost of treatment and achieve higher efficiency. Current dialysis membranes remove about 10-40% of middle molecular weight toxins. It has been found that up to 100% of this amount is removed by adsorption to the membrane surface which is about 1-2 m^2 g^{-1} [17]. The surface area of an activated carbon is much higher. Thus, the capacity for removal of middle molecular weight toxins by adsorption far exceeds that of dialysis.

Use of dialysis or filtration technique inevitably results in a loss of large volume of water along with dissolved useful metabolites and nutrients. To compensate for such a loss, an isotonic and sterile replacement fluid is provided. In the treatment of intensive care patients who develop acute renal failure more than 50% of the total cost of HD or HF is associated with the purchase of replacement fluid [18]. In-line adsorption would increase efficiency of the extracorporeal procedure and reduce the loss of liquid by its recycling (Scheme).



Scheme.

In-line use of adsorbent column with HD or HF.

In this circuit the adsorbent does not come into contact with blood directly and the biocompatibility problem is reduced significantly.

A recently developed "BioLogic-DT" system combines haemodialysis and adsorption in one unit, utilising a carbon powder suspension to accelerate removal of toxins from blood [19]. In this system blood passes through a dialysis cellulose membrane package surrounded by a

suspension of fine particles of an activated carbon and a cation exchanger. The adsorbent and the blood are separated by a membrane. Removal of LMW toxins is accelerated by the adsorption mechanism that increases the concentration gradient across the dialysis membrane.

A similar approach has been suggested in a **M**icrospheres **B**ased **D**etoxification system (MDS) [20]. In this case blood is separated from plasma in the first circuit, and an adsorbent suspension is used in the secondary circuit for plasma purification. Although cellulose microbeads were used in the first instance, the system allows for the use of any other microparticles including activated carbon.

A specific problem with in-line carbon adsorption is related to its low adsorption capacity towards urea. Urea is one of the substances-markers of renal failure and it is efficiently removed from blood by dialysis. To tackle this problem, the ultrafiltrate regenerated by adsorption is infused into the additional diffusive dialyser that removes urea and then it is returned to the bloodstream. [21].

UNCOATED ACTIVATED CARBONS FOR DIRECT HAEMOPERFUSION

A much more challenging problem is synthesis of uncoated activated carbons that are as haemo-compatible as coated adsorbents. Neither the exact nature of bio/haemocompatibility, nor the mechanism of 'blood-foreign surface' interactions are fully understood [22]. Despite this uncertainty, there is a general agreement that a haemocompatible material should meet the following criteria: (i) absence of thrombogenic, toxic, allergic or inflammatory reactions; (ii) no damage of blood cells or adjacent tissue; (iii) no undesirable changes in the blood composition; (iv) no immunological reaction; (v) no carcinogenic effect [23].

Carbon surface is considered to be rather biocompatible and some artificial organs are made from carbon materials. Such materials, however, have low surface area. The problem could be solved using activated carbons produced from synthetic polymers [24,25].

Using synthetic polymers as the precursor material eliminates any uncontrolled impurities. Coated activated carbons used for HP are made from natural raw materials. They have never been designed specifically for medical applications. In fact, they were technical grade carbons taken 'off the shelf' and used after a very simple pretreatment with hydrochloric acid and/or deionised water. Further pre-treatment such as electrolyte balancing is necessary to adjust the ionic composition of the carbon surface to the mineral composition of the blood. The fact that carbon surface contains a variety of functional groups having ion exchange properties, has been frequently ignored resulting in significant changes of pH and ion composition of the blood brought in contact with activated carbon.

It has been shown that two conflicting properties - large surface area and high mechanical strength – could be combined in polymer pyrolysed activated carbons. Thus a simple washing procedure removes microparticles from carbon granules eliminating the major concern about carbon biocompatibility.

Pore size distribution of activated carbons can be controlled by using porous polymeric precursors. In addition to micropores, polymer pyrolysed activated carbons have a unique mesoporous structure within 10-100 nm range which is predetermined by the pore size of the precursor.

It has been shown that mesoporous carbons possess high adsorption capacity towards middle and large protein molecules [26]. This is of particular importance for treatment of autoimmune diseases when removal of HMW immune complexes is necessary.
Activated carbons are considered to be non-specific adsorbents. Whilst high adsorption selectivity is desirable, nonspecific adsorption is also an advantage especially in the treatment of disorders with unknown etiology.

Despite chemically inertness of carbon, generation of chemically reactive functional groups such as -COOH, $-NH_2$ on its surface allows the use of carbon matrix for covalent binding of bioligands [27]. Carbon surface has been activated by oxidation and molecular bioligands have been attached covalently to the carboxylic functional groups via water soluble carbodiimide technique.

Carbon based bioselective adsorbents such as immunoadsorbents could potentially combine the selectivity of a bioligand action and the nonspecific adsorptive capacity of the carbon matrix.
The use of bioselective adsorbents for direct hemoperfusion would eliminate an expensive plasma separation stage.

CONCLUSIONS

The use of adsorbents for regeneration and recycling of dialysate or ultrafiltrate would decrease the volume of extracorporeal devices and relacement fluid, thus significantly reducing operational costs. Direct haemoperfusion over uncoated haemocompatible activated carbon offers more efficient, rapid and cost-effective means of medical treatment as in comparison with other extracorporeal techniques. Research in this area, almost abandoned in the 1980s, is becoming active again and very intensive development of adsorption methods should be expected.

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