

EXTRACORPOREAL APPLICATIONS OF ACTIVE CARBONS

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Introduction

Hemoadsorption, or hemoperfusion (HP) was introduced by H. Yatzidis in early 1960s [1]. It is an extracorporeal technique that cleanses blood by passing it through an adsorbent column. Active carbon (AC) was the first choice due to its undisputable superiority as an adsorbent over other materials. Although the initial results were very successful, this procedure induced a series of complications, the most severe being the release of fine particles from the carbon granules causing blockage of blood microvessels [2]. The solution was found in coating of adsorbent granules with a haemocompatible semi-permeable membrane [3]. Required biocompatibility thus was achieved, but at the cost of the adsorbent performance. Adsorption of high molecular weight solutes is particularly affected. A 3-5 μ thick membrane virtually cuts off HMW molecules and significantly reduces adsorption of "middle molecules" with MW between 300 and 15,000 [4]. Initially this was not recognized as the major drawback as the main application of HP remained in the treatment of acute poisoning, usually with low MW substances. Commercial haemoperfusion columns contain charcoal produced from peat or pitch and coated with cellulose (Adsorba 300 C and Adsorba 150C, Gambro), poly-HEMA (Hemosorba, Asahi Medical and Nextron Medical Technologies), or heparin hydrogel (Clark R&D) [5-7]. As many small molecules are strongly protein-bound in the blood, usually with serum albumin, MW 67 kDa, they cannot cross the coating membrane; hence, haemoperfusion over coated adsorbents would be efficient in removing only protein-free solutes of low MW.

Alternative extracorporeal methods based on dialysis and filtration proved to be more versatile than haemoperfusion over coated adsorbents and gradually took over, although in 1960s - 1970s all three groups of methods seemed to have similar opportunities for clinical use [8].

Since 1990s, however, interest in the use of adsorbents in extracorporeal medical devices has been rising again at least for three reasons: (i) inefficiency of other methods in treatment of some autoimmune diseases, severe sepsis and multi-organ failure, resulting in high mortality or morbidity [9]; (ii) shift of the priorities in the desirable outcome of treatment towards providing good quality of life for patients who require regular treatment, such as patients with chronic renal failure. Use of dialysis dramatically increased life expectancy of these patients, but the quality of life remains unsatisfactory [10]; (iii) the extracorporeal methods based on dialysis and filtration are expensive; they have already become a significant economic burden on health care services, which is projected to increase further due to the problem of ageing population

in the developed world [11]. In this paper some recent developments in synthesis and applications of medical adsorbents and future trends are discussed.

Adsorption vs other Physicochemical Methods in Extracorporeal Techniques

Adsorption as a method of blood cleansing has a series of advantages over other physicochemical methods (Table 1). Provided they have sufficiently large pores, uncoated adsorbents could remove solutes of any molecular size. Unlike dialysis and filtration, not to mention drug-based therapy, adsorption can potentially remove toxic substances without introducing anything else instead [12]. If no fluid removal from the body is necessary, adsorption is more cost effective than dialysis or filtration, as significant volume of expensive replacement solutions is required in the latter. It also appears that even in the cases when dialysis or filtration remove middle and high MW solutes, such as inflammatory cytokines and endotoxin, the mechanism of this action is based on adsorption and retention by the filter or hollow fibre surface rather than convection or diffusion through the membrane [13, 14].

Table 1. Extracorporeal techniques - mechanisms and efficiency of blood cleansing

Substance removed	Haemodialysis (HD)	Haemofiltration (HF)	Haemoperfusion (HP)
Fluid/Water	Ultrafiltration	Ultrafiltration	None
Solute	Diffusion	Convection	Adsorption
Small molecules	High	Moderate to high	Variable
“Middle molecules”	Low	Variable	Potentially high
Large molecules	Low to none	Low to none	Variable
Selectivity of action	Non-selective	Non-selective	Non-selective

Neither of the extracorporeal techniques is selective, which means that useful blood components such as nutrients and normal metabolites are removed along with the target solutes causing pathological response. In dialysis and filtration this problem is resolved by using expensive replacement fluids containing essential blood components. In HP replacement fluid is either not required or used in substantially lower quantity than in HD or HF. This aspect of HP always attracts a good deal of criticism as apparently adsorption depletes the organism from essential substances. Interestingly, there are no reported cases of such an adverse effect of HP in the vast medical literature on this subject, except for the earliest publications in 1960s. Sometimes non-selective adsorption may be advantageous, for example in the treatment of patients poisoned with a substance of unknown origin. Introduction of highly biocompatible uncoated active carbons produced by pyrolysis of synthetic polymers significantly broadened the scope of HP applications.

Adsorbents with high selectivity of action can be produced using the same principles as in manufacturing of adsorbents for affinity chromatography, namely, by physical adsorption or covalent attachment of a bioligand with specific affinity towards a particular target molecule. The most selective adsorbents have immobilized antibodies against target antigens or vice versa. Being selective, such adsorbents are also very expensive and this approach is seldom used in HP. It is more feasible to use biospecific adsorbents which selectively act with a group of substances rather than one substance. This method can be applied to active carbons and biospecific carbon adsorbents have been synthesized by covalent immobilization of biomolecules to the carbon surface via its functional groups [15]. The major problems with clinical use of an adsorbent with immobilized bioligand are as follows: storage; sterilization; high cost and regeneration (to reduce the cost). Alternatively, selectivity of adsorption can be increased using a single or a combination of several approaches, such as regulation of pore size, chemical modification of the surface hydrophilicity/hydrophobicity, introduction of ionogenic groups and surface charge alteration. In principle, a carbon adsorbent made from a porous polymer precursor can be 'tailor made' for specific interaction with the toxic solute. Although its selectivity will hardly ever be higher than that of a bioselective adsorbent, it will have much lower cost and problems related to storage and sterilization will be avoidable and regeneration not required.

Results recently obtained by our group prove that active carbons can efficiently remove such 'difficult' substances as lipopolysaccharide (LPS, or endotoxin) responsible for sepsis, pro-inflammatory cytokines such as $\text{TNF}\alpha$ and $\text{IL-1}\beta$ and protein-bound drugs such as ibuprofen [16, 17].

Why carbon?

In addition to its superior adsorption features, activated carbon has a series of other advantages over other adsorbents in this respect. Firstly, it is a rigid material, which does not swell in water or other solvents unlike polymers and does not require special pre-treatment in such a solvent. It is also easier to maintain stable flow characteristics of a biological fluid through a column packed with carbon granules rather than a column with soft polymer granules. Secondly, AC is chemically inert compared with polymers, as it does not contain any plasticizer, catalyst or monomer that can leak from the material into the bloodstream. Chemical inertness of carbon is a direct consequence of the physical conditions, in which it is synthesized. Physical activation, or development of the pore structure occurs by treating the carbonized material at 800 - 1000° C with carbon dioxide or steam [18]. Under these conditions no organic matter can exist being converted either into carbon or gaseous products. (A common and persistent belief that carbon is carcinogenic has its origin in the fact that some volatile products of incomplete combustion of coal are carcinogenic, but this process has nothing to do with the production of activated carbon!) [19]. This comment, obvious to the participants of a Carbon conference, is made here to show how little is understood about active carbon by general public including medical specialists. It is often forgotten that AC like other carbon materials has good biocompatibility. As much as a few hundred grams of activated carbon could be consumed orally by a person who suffers from acute

poisoning without any negative consequences confirming very low toxicity and chemical inertness of this substance [20]. Pyrolytic carbon is used in artificial organs such as mechanical heart valves and it shows excellent biocompatibility [21, 22]. Chemically pyrolytic and activated carbons are the same substance, making it a good reason to expect good biocompatibility of AC.

Potential for commercialization

It is simply enormous. To support this statement, it is sufficient to give a few figures about sepsis treatment. Sepsis contributes to the high mortality (approximately 80%) reported for patients in the late post-traumatic period and consequent lengthened periods of stay on ITU of up to 21 days. It costs the health care provider a basic £1500 per day plus additional drug costs. It is clear therefore, that sepsis is a major burden in terms of both financial and human cost. A new HP device that can achieve a significant reduction in the systemic levels of circulating endotoxins and pro-inflammatory cytokines will have a major impact on the prognosis for septic patients with systemic inflammatory response and multi-organ failure (MOF). It can be estimated that a reduction in the length of stay of patients successfully treated for MOF would save the health care provider associated costs well in excess of £30,000 per patient. With approximately 30,000 patients a year being treated for sepsis in the UK only, the potential cost savings are considerable.

And this is just one example of the potential benefits of HP over active carbon. There have already been reports about successful use of this procedure in the treatment of autoimmune diseases, which suggests that we are still in the beginning of realizing high clinical potential of hemoperfusion over active carbon.

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