BIOCOMPATIBILITY ISSUES IN HAEMODIALYSIS

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Chronic haemodialysis is directly responsible for the maintenance of life in more than 150,000 patients throughout the world. Despite this impressive fact, the mortality rate of dialysis patients is approximately 10 to 15 per cent per year [1], which is substantially higher than age-adjusted figures for the general population. Morbidity of the dialysis procedure is also substantial; the frequency of haemodialysis treatment with adverse symptoms such as hypotension, cramps, headaches, nausea and vomiting is conservatively estimated to be 20 per cent of all treatments. Even when the dialysis procedure is accompanied by no adverse effects, patients often leave the dialysis unit unable to perform routine activities. In a recent study in the United States, only 50 per cent of patients on haemodialysis were able to fulfill levels of activity commensurate with their previous functional status, and only 30 per cent of patients could maintain gainful employment while they were on haemodialysis [2].

In the discussion that follows, it is important to keep in mind that the complications of haemodialysis result not only from the dialysis process, but from the complex interaction that occurs between process and patient. It is well known for example that the incidence and severity of complications and their sequelae is clearly related to the age of the patient, associated medical conditions such as heart disease and diabetes, and the presence of intercurrent illnesses or conditions such as pulmonary oedema or sepsis. But beyond these general concepts, we must examine more specifically the extent to which the biocompatibility of haemodialysis contributes to the morbidity of dialysis patients.

Biocompatibility can be defined as the sum of specific and non-specific interactions that occur between the patient and the dialysis procedure. Although the broad definition of biocompatibility includes issues of biocompatibility of dialysate, (sodium concentration, acetate versus bicarbonate), the biocompatibility of the dialysis procedure (simultaneous or sequential dialysis/ultrafiltration, haemofiltration), my major emphasis will be on the biocompatibility of dialysis membranes.
Biocompatibility of dialysis membranes

When blood comes in contact with dialysis membranes, several pathways are activated. These pathways include the activation of the complement cascade, the activation of the coagulation pathway as well as activation of the kallikrein-kinin system. In addition to these protein mediated pathways, which do not directly involve participation of blood cells, increasing evidence suggests that cellular pathways are activated also during dialysis. Recent work has documented the activation of platelets, leading to the release of thromboxane products [3], neutrophils leading to the production of leucotrienes, and possibly mononuclear cells leading to the production of the interleukin-products. In many instances these pathways are interrelated, and the participation of one leads to the participation of the other.

Complement pathway

The recent introduction of radioimmunoassay techniques has allowed the study of the activation of the complement pathway in a detailed manner. It has become clear that the degree of complement activation depends on the type of membrane used and whether that membrane is new or reused [4,5]. These and other studies have also confirmed the evidence that complement activation during dialysis can be used as an index of biocompatibility of dialysis membranes.

Detection of products of complement activation of the common pathway, without evidence of pronounced activation of the classical pathway (e.g. C4a) have suggested that complement activation during dialysis occurs via the alternate pathway. This pathway is phylogenetically older, and responds to surface structures that have hydroxyl derivatives, but lack sialic acid residues [6]. Cellulose based membranes fulfil these criteria.

Detection of complement products in plasma during dialysis occurs maximally at 15 minutes (Figure 1). However, it is likely that complement activation occurs most vigorously as soon as blood comes in contact with the membrane. The peak at 15 minutes reflects the balance between the activation within the extracorporeal circuit and clearance of the products of complement via a large pool of cellular receptors in the blood. As dialysis proceeds, the rate of complement activation decreases, as suggested by the difference between the simultaneously drawn efferent and afferent samples across the dialyser. The mechanism of passivation of these surfaces after initiation of dialysis and with reuse have not been well defined, but probably include specific deposition of complement fragments such as C3b or kallikrein on the activating sites as well as non-specific deposition of fibrin on the dialyser membrane surface [4,5].

Several questions remain about the role of complement activation in the morbidity associated with dialysis. First, if complement activation depends on the type of membrane, why is it that some patients have more adverse symptoms than others in their reaction to a new cuprophan membrane? We have shown that first-use syndrome patients activate complement earlier and to a greater degree than patients who do not have first-use syndrome [7].
These patients also have a propensity for more vigorous complement activation in vitro in response to zymosan, a well known activator of the alternate pathway of complement. The basis for this hyperactivity is not clear at present although preliminary evidence suggests that one of the major control proteins of the alternative pathway, C₃b INH, may be defective or reduced in these patients. The molecular or genetic basis of this defect has not been investigated.

Another question related to complement activation is the extent to which complement products are direct mediators of some of the adverse haemodynamic responses that occur during dialysis with cellulosic membranes. Products of complement activation such as C₃a and C₅a are potent, biologically active, anaphylatoxic agents: However, in vivo, these products are quickly inactivated by the carboxypeptidase enzyme which cleaves the arginine residue of these...
proteins and transforms them into \( C_{3\Delta} \text{desArg} \) and \( C_{5\Delta} \text{desArg} \) respectively [8]. The former has negligible biological activity and the latter has attenuated biological activity. At present, there are no simple assays to differentiate between the parent and the derivative (des Arginine) compounds. Although it is possible that some patients can inactivate these compounds at different rates, measurement of the serum carboxypeptidase enzyme in first-use and non-first-use patients however does not reveal a significant difference in activity.

**Cellular pathways**

*Platelets* Complement products may not be the only effector agents in the adverse symptoms associated with cellulose membrane dialysis. Animal (sheep) experiments have clearly shown that contact of blood with dialysis membrane leads to events similar (but perhaps more pronounced) to events occurring in humans with first-use syndrome. These same experiments have shown that pre-treatment of the sheep with indomethacin, a substance known to inhibit platelet activation and release reaction, causes a significant blunting of the haemodynamic response to contact with cuprophan dialyser membranes, suggesting that platelets play a role in the haemodynamic response of these animals [9]. We have shown that with new cuprophan membranes, significant platelet activation, as evidenced by thromboxane \( \beta_2 \) release and aggregation as evidenced by transient decrease in platelet count, occurs during clinical dialysis [3]. These data have been supported by recent work suggesting that human platelets can express complement receptors similar to those seen in neutrophils [10].

*Neutrophils* There is also preliminary evidence that neutrophils participate in the haemodynamic response associated with dialysis with cuprophan membranes. We have shown that during dialysis, and under the influence of activated complement products, specifically \( C_{5\Delta} \), there is an increased expression of \( C_{3\Delta} \) receptors which is associated with the enhancement of phagocytosis of \( C_{3\beta} \) bearing particles [11] and \( \text{Mol} \) receptors, a ligand associated with neutrophil adhesion [12]. However once the receptors are expressed and neutrophils sequestered in the lung parenchyma, they continue their metabolic activity, releasing the constituents of their cytoplasmic granules such as lysosomal hydrolases, lactoferrin and toxic superoxide molecules [13]. In addition, activated neutrophils release significant quantities of leucotrienes \( B_4 \).

Leucotrienes are biologically active derivatives of arachidonate and are defined as autacoids: substances which exert their effect in the local micro-environment of the tissue where they are generated and have to be synthesized de novo in cells, in response to a specific stimulus [15]. At least two pathways of metabolism have been demonstrated for arachidonates: the cyclooxygenase pathway leading to the production of prostaglandins and thromboxanes and the lipoxygenase pathway leading to the formation of leucotrienes. These pathways are not exclusive although one or the other may predominate in a given cell type, e.g. cyclooxygenase pathway in platelets and 5-lipoxygenase pathway in bone marrow derived cells involved in the inflammatory process: neutrophils, mast
cells and macrophages [16]. We have obtained, in collaboration with Dr K Frank Austen’s laboratory, preliminary evidence that leucotriene B₄ is released during haemodialysis within the first few minutes of initiating dialysis with cellulose membranes.

Other pathways

A pathway worthy of greater attention in the area of blood–membrane interaction is the kallikrein-kinin pathway. Factor XII (Hageman factor), pre-kallikrein and high molecular weight kininogen participate in the initiation of blood coagulation and fibrinolysis. This contact pathway leads to the generation not only of activated Factor XIIa, but the generation of kallikrein and kinins as well as the generation of plasma which can activate C₃ directly. Bradykinins have been implicated in the development of hypotension, increased vascular permeability and bronchoconstriction in animal preparations [17].

Release of interleukin-1 by monocytes has been considered as an agent that may account for several events that generally occur late in the dialysis session, such as development of fever, or hypotension. Monocytes can be activated by C₅α and release interleukin-1 after three to four hours, coinciding with the development of fever and late hypotension. However, studies which have documented the presence of interleukin-1 during dialysis have not been published to date.

Interactions between pathways

The activities of the above pathways have been documented frequently in isolated in vitro systems. Studies of interactions and modulations of different pathways by each other as occurs during haemodialysis have been few, but in each instance in which such studies were attempted, interrelationships in the activation of different pathways, additive or synergistic effects of the products of each pathway’s activation on the target organ has been shown. For example, synergism in the oedema formation in guinea pig lung strips has been shown between C₅α, the product of complement activation, PGE₂, a product of platelet activation and LTB₄, a product of neutrophil activation [18]. In addition, one cell type may use intermediate metabolites manufactured by other cells in its own metabolic pathway to synthesize new products which may have important biological properties [16]. Finally, the pathological effect of some of these agents may be considerably increased under different environmental conditions. For example the ability of C₅α to produce pulmonary injury is greatly enhanced in the presence of mild hypoxia, a situation similar to that existing during dialysis with new cuprophan membranes and acetate dialysate [19] (Figure 2).

Clinical effects

Do these blood–membrane interactions have an effect on patient well-being? For many dialysis patients, the use of one membrane or the other does not
appear to have any important acute sequelae. But it must be remembered that in dialysis, these interactions are repetitive; thus even mild interactions may, on a chronic basis, lead to adverse long-term clinical sequelae. A recent study has shown a significant difference in morbidity of a large number of dialysis patients dialysed with two types of membranes: patients dialysed with cuprophan membranes (complement-activating surface) had twice the frequency of hypotension and three times the hospitalization days of patients dialysed with a non-complement-activating surface (PAN) [20]. Similarly, morbidity of patients who practice reuse is significantly less than those who do not, presumably a reflection of improved biocompatibility achieved with reuse [21]. Finally, as pointed out earlier, hypersensitivity reaction, a potentially fatal complication, as well as first-use syndrome which causes significant patient morbidity in
approximately five per cent of patients on dialysis, have been well described in patients using complement activating surfaces, but not in those who are dialysed with a non-complement activating surface or a reused dialyser [7]. Bearing these concepts in mind and the information derived from clinical studies we would like to conclude that the study of biocompatibility of dialysis membranes is not only of scientific interest but has important implications as far as the well-being of the more than 150,000 worldwide dialysis patients.

**Biocompatibility of dialysate**

Several studies have documented the improved tolerance to dialysis due to high sodium (e.g. 140–145mEq/L) dialysate solutions. More controversial have been the studies on the effects of acetate or bicarbonate as the dialysate base, particularly in the chronic dialysis patient. This controversy is perhaps due to the small number of patients in many of these studies. Studies with larger patient populations have allowed the differentiation of dialysis patients into those who are not affected by the choice of base, and those who may benefit from the use of bicarbonate. Whereas young patients with no myocardial disease show only modest improvement in their tolerance to dialysis with bicarbonate dialysate, older patients and those with myocardial disease manifest markedly improved tolerance to dialysis with substitution of bicarbonate [22].

**Biocompatibility of the dialysis procedure**

The dialysis procedure is an additional issue of biocompatibility. Several studies have shown an improvement in tolerance to removal of solutes by haemofiltration techniques that allow equivalent removal of small molecules, but a greater removal of large molecules. Technological problems, particularly with the preparation of large amounts of sterile and non-pyrogenic fluids in the preparation of dialysate has hampered efforts to extend this modality of treatment [23].

**Conclusion**

Haemodialysis can substitute adequately for the major functions of the kidneys, including volume regulation, electrolyte and acid base balance and the excretion of uraemic products, and accomplishes this in approximately 10 per cent of the time that the native kidneys take. Because of this efficiency, it is important to optimize all factors involved in dialysis. Improvement in the biocompatibility of dialysis membranes, the choice of dialysate and the dialysis procedure should be directed toward decreasing the potential and inherent complications of haemodialysis and thus improving the quality of life for those who are dependent upon it for their survival.
References

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