Acute haemodialysis membrane-associated reactions

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Introduction

Acute reactions to the haemodialysis membrane have been reported as early as 1975 [1]. Because their severity is usually mild, their frequency is probably widely underestimated. However, these reactions may occasionally be life-threatening [2]. The aetiological mechanisms of these reactions are multiple, the best characterized being allergy to ethylene oxide and combined exposure to the polyacrylonitrile AN69 (AN69) membrane and angiotensin-converting enzyme (ACE) inhibitors.

Mechanisms, clinical manifestations, and treatment of hypersensitivity reactions to foreign material

Two categories of acute reactions to foreign material can be distinguished on the basis of their pathophysiology [3]. One is the acute hypersensitivity reaction and involves specific IgE which binds to high affinity receptors at the surface of mast cells and basophils. Subsequent binding of the corresponding antigen to these IgE results in degranulation of preformed mediators of the inflammatory reaction (e.g. histamine, proteoglycans, serine protease, aryl sulphatase) and de novo synthesis of other mediators that are secreted later on (cytokines, lipid-derived mediators) [2–4]. The acute hypersensitivity reaction to a foreign substance constitutes an acquired phenomenon and requires the previous exposure of a susceptible subject to the triggering substance, followed by the generation of specific IgE antibodies. Such reactions can be induced by exposure to a number of proteins and substances acting as haptons, either by the oral, percutaneous or parenteral route [3]. The prototype in the setting of haemodialysis is allergy to ethylene oxide. The second type of acute reaction to foreign material is the anaphylactoid reaction; it refers to a reaction that cannot be clinically distinguished from an acute hypersensitivity reaction, which occurs also in a susceptible individual, but that is not IgE-mediated and does not require a preliminary sensitization to the offending agent [3]. The mechanisms of these anaphylactoid reactions are unknown in most cases. In the setting of haemodialysis, the prototype of anaphylactoid reactions is represented by reactions due to the concomitant exposure to AN69 and ACE inhibitors.

Anaphylactoid and acute hypersensitivity reactions generally occur during the first 30 min (and most often during the first 10 min) of haemodialysis; however, acute hypersensitivity due to ethylene oxide allergy may start later on and even after the end of the haemodialysis session [5]. Symptoms are multisystemic and may involve the skin (pruritus, erythema, urticaria, angioedema), the mucosae (eye, mouth, and respiratory tract mucosae: pruritus and oedema), the central nervous system (dizziness, syncope, alteration of consciousness, seizures), bronchospasm and hypermotility of the gastrointestinal tract (vomiting, diarrhoea, abdominal cramps), hypotension, cardiovascular collapse, and shock [3]. The severity is highly variable and occasionally leads to the patient’s death. A non-exhaustive list of suspected mediators includes histamine, prostaglandins, leukotrienes, platelet activating factor, bradykinin and substance P, all of which can induce vasodilatation and hypotension, and smooth muscle contraction [5]. In the setting of haemodialysis, acute reactions have been mostly observed with new dialysers, so that they have often been referred to as ‘first-use syndromes’ [6].

A better understanding of the causes and mechanisms of these acute reactions during haemodialysis should allow their prevention. When an acute hypersensitivity or anaphylactoid reaction develops, treatment is based on resuscitation measures to maintain vital functions, and adrenaline that both antagonizes the effects and limits further liberation of the mediators of anaphylaxis [7]. Histamine antagonists may be helpful to limit vasodilatation [3]. Corticoids can be useful to limit protracted reactions, namely bronchospasm [8].

Allergy to ethylene oxide

Allergy to ethylene oxide constitutes the historically most important cause of acute hypersensitivity reaction.
in haemodialysis [1], the epidemiology of which has been extensively reviewed elsewhere [5]. The prevalence of acute hypersensitivity due to ethylene oxide has been reported to be about 4 per 100,000 haemodialysis sessions with hollow-fibre dialysers [9]. This figure did probably underestimates the actual prevalence of these reactions because it was based on a spontaneous declaration by nephrologists, and most of these reactions are rather benign.

Patients allergic to ethylene oxide can be identified by the fact that they have hypereosinophilia [10], elevated IgE, and by a specific radioallergosorbent assay (RAST) to the ethylene oxide–albumin complex [11]. Acute hypersensitivity reaction due to allergy to ethylene oxide can now be prevented by the use of dialysers and blood lines sterilized either with steam or γ-rays. Besides, if such a material is not available, acute hypersensitivity in sensitized patients can be limited by prolonged degassing and abundant rinsing of the extracorporeal circuit to get rid of residual ethylene oxide [1].

**Anaphylactoid reactions to the AN69 membrane**

Since our first description in 1990 [12], many groups have reported the occurrence of anaphylactoid reactions early in the course of haemodialysis with the AN69 membrane in patients treated concomitantly with an ACE inhibitor [13–20]. The recurrence of these reactions can be prevented either by avoiding exposure to AN69 or by discontinuing the administration of ACE inhibitors [12]. The epidemiology of these reactions has been detailed elsewhere [5]. They are not observed in patients treated with ACE inhibitors and dialysed either on cellulotic or other high flux membranes [17] (with the possible exception of reused polysulfone) [21]. Allergy to ethylene oxide could be clearly excluded in many cases [12].

The hypothetic mechanism we have proposed to explain these reactions supposes the accumulation of bradykinin [12]. Indeed, we have speculated that contact of plasma with the negatively charged AN69 membrane would initiate the contact phase of coagulation leading successively to the activation of the Hageman factor (HF), the conversion of prekallikrein to kallikrein, which in turn would cleave bradykinin from the high molecular weight kininogen. Normally, this bradykinin would be almost completely cleared during its first passage through the lung circulation by the kininases. This would of course not occur in patients under ACE inhibitors (ACE is identical to kininase 2) allowing bradykinin accumulation and the development of anaphylaxis.

Results involving proteins and peptides of the contact phase of coagulation were published recently that support the bradykinin hypothesis. Schulman et al. [22] showed that both cuprophane and AN69 activate the contact phase of coagulation of normal plasma in vitro, but this activation is much greater and occurs much more quickly (within 5 min) with PAN. After 10 min of contact with AN69 bradykinin is no longer detectable because it is adsorbed onto the membrane. Moreover, Lemke et al. found the plasma bradykinin generated by AN69 in vitro to be greater in presence of ACE inhibitors, in a dose-dependent manner [23]. During experimental haemodialysis in sheep, Krieter et al. [24] found markedly increased bradykinin in the efferent blood line (maximal at 5 min) with AN69 but not with SPAN (a modified polyacrylonitrile membrane); also, animals pretreated with captopril had still greater bradykinin concentrations and four of the six sheep developed overt symptoms of shock. During clinical haemodialysis, Akizawa et al. [25] demonstrated bradykinin generation within the dialyser during the first 5 min of dialysis with AN69 but not with polysulfone. Finally, Verresen et al. [26] found increased bradykinin in historical samples that had been harvested from the afferent blood line of several patients during anaphylactoid reaction due to combined use of AN69 and ACE inhibitors. Most interestingly, the same authors made the same observation during anaphylactoid reaction in two patients dialysed on AN69 but who were not on ACE inhibitors [26].

Thus, we may speculate that large quantities of bradykinin are generated within the dialyser during the first minutes of AN69 dialysis. In most patients, this bradykinin will be quickly inactivated resulting in no symptoms. However, because of individual variation in the activity of the kininases, occasional patients would accumulate bradykinin and develop anaphylactoid reaction, even in the absence of ACE inhibition. The latter of course greatly increases the risk for developing anaphylaxis by interfering with bradykinin catalysis. Even among patients treated with both AN69 and ACE inhibitors, the risk for developing anaphylaxis varies widely (from 0 to 100%) [15,18,27]. This ‘centre’ effect suggests that additional factors are implicated in the pathogenesis of the anaphylactoid reaction. Again, factors such as individual ability to generate or degrade kinins [28] or the timing of the ACE inhibitor intake in relationship to the start of haemodialysis might modulate the risk of developing an anaphylactoid reaction. Finally, it must be reminded that other mediators of anaphylaxis, such as substance P, prostaglandins and leukotrienes—the metabolism of which is also ACE dependent—might be involved concomitantly.

**Other causes of acute reactions to haemodialysis material**

Even when allergy to ethylene oxide and anaphylactoid reactions to AN69 are excluded, acute reactions to dialysis material still occur. In a prospective ongoing survey we found their prevalence to be about 1 per
2000 haemodialysis sessions. Acute reactions have been reported with any type of membrane [5] but the mechanisms are largely unknown. A role has been tentatively ascribed to the anaphylatoxins C3a and C5a in certain acute reactions [29] but this point remains controversial [30]. A subgroup of acute hypersensitivity reaction has been called 'type B first-use reaction' and is characterized by chest and lumbar pain [6]. This syndrome occurs during the very first minutes of haemodialysis on cellulose membranes and can be prevented by dialysers reuse [31]. It is considered benign and non-specific and its incidence lies between 0.6% and 5% [5]. Some other acute reactions have been occasionally attributed to the acetate buffer in the dialysate, to allergy to phtalates (present in the polyvinylchloride bags and blood lines) and isocyanates, or to residues of formaldehyde in reused dialysers. Several groups have also speculated on the role of bacterial contamination of the dialysate in the pathogenesis of acute hypersensitivity, but this hypothesis lacks scientific background [5].

Finally, we have recently reported that 47% of our patients developed hypereosinophilia during the first 6 months on haemodialysis, despite the absence of allergy to ethylene oxide [32]. This hypereosinophilia is associated with an increased incidence of allergic events (itching, asthma) that can be induced during the haemodialysis sessions. This hypereosinophilia is significantly associated with the use of cellulose-based membranes (cuprophane, hemophane, cellulose di- and triacetate), rather than the synthetic membranes.

Conclusion

Although uncommon, acute reaction to the membrane remains a worrying problem in the setting of haemodialysis. Except for allergy to ethylene oxide and bradykinin generation by contact of blood with the AN69 membrane, the mechanisms of these reactions are generally unknown. A better knowledge of the epidemiology and understanding of the complex mechanisms of these reactions appear as the mandatory steps to identify patients at risk and for the efficient prevention of these sometimes life-threatening side effects of haemodialysis.

References

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