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Hypersensitivity reactions to synthetic haemodialysis membranes — an emerging issue?

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INTRODUCTION

Anaphylactic and anaphylactoid reactions that occur during haemodialysis (HD) have been known since 1975[1]. Since then, many articles on these types of reactions have been published, although most of them deal with few cases, with different membranes, sterilising agents, medication administered during dialysis and water purity level, etc. There are no well-designed prospective epidemiological studies that inform us about the exact incidence and the effect of these types of reactions. In a study carried out in 1985, Daugirdas reported 21 severe reactions, with one fatal case, in 260,000 HD sessions[2]. In 1987, the prevalence of "first use" hypersensitivity reactions was studied in the United Kingdom. Results showed that 1 in every 20 to 50 patients were likely to experience an anaphylactoid reaction with a new dialyser, which indicates the magnitude of the problem[3]. These reactions were not related to a specific membrane, type of dialyser or dialysis technique. Years later, another study analysed the incidence of reactions in 1536 patients from 30 dialysis centres (122,694 sessions), observing a yearly incidence rate of 0.17 per 1000 sessions with cellulose membranes and 4.2 per 1000 sessions with synthetic membranes[4]. Thus, these reactions are not extremely common; however they occur from time to time in all dialysis units and they are more frequently associated with the use of synthetic membranes.

TYPES OF REACTION

The reactions that occur during HD are the result of an immunoallergic response by the patient after exposure to foreign substances present in the extracorporeal circuit and/or a response induced by the interaction of blood with the dialysis membrane[5]. There are two types[6].

Type A or hypersensitivity reactions

This type normally occurs in the first minutes of the dialysis, although they can occur up to 30 minutes after dialysis begins. Symptoms are urticaria, coughing, rhinorrhoea, lacrimation, abdominal cramps, pruritus, a burning sensation, angioedema, dyspnoea and even circulatory collapse and death. These are severe reactions and require the immediate discontinuation of dialysis, and it is recommended that the blood from the extracorporeal circuit not be returned. Type A reactions can, in turn, be anaphylactic when they are mediated by IgE or anaphylactoid if they are not mediated by IgE.

The most characteristic reactions have been reported in relation to ethylene oxide (EO), the reuse of dialysers, and the combination of polyacrylonitrile membranes (PAN AN69) and angiotensin-converting-enzyme (ACE) inhibitors.

The classic reaction to EO only occurred during the first use of a dialyser sterilised with EO that had not been primed properly. Most cases found IgE against EO in the plasma of the patients who suffered these types of reactions[1,7]. Nowadays this sterilising agent is no longer used in dialysers and has been replaced with gamma radiation or steam. In any case, in the event of a reaction in dialysis, we must be aware that EO is still used as a sterilising agent for some needles, syringes and dialysis lines. Anaphylactoid reactions have also taken place when polysulfone and cellulose acetate dialysers are reused[8]. There was also an increase in the risk of hypersensitivity reactions when sodium hypochlorite or hydrogen peroxide were used to clean the dialysers' blood compartments[9].

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In the nineties, the occurrence of anaphylactoid reactions was reported in patients on dialysis with the AN69 (PAN) membrane who were receiving ACE inhibitors at the same time[4,8,10,11]. These were type A reactions, given the time they appeared (in the first minutes of dialysis) and the symptoms developed in patients. Bradykinin is the mediator in these reactions. The AN69 membrane surface has a highly negative electric charge capable of activating the contact system and inducing production of the Hageman factor. This converts prekallikrein to kallikrein, which acts on kininogen to release bradykinin. ACE inhibitors, which inhibit bradykinin degradation, make the latter accumulate in blood until it reaches a level that is 20 or 30 times more than normal, thereby facilitating the onset of anaphylaxis symptoms[12,13]. The coating of the AN69 membrane surface with a biocompatible polymer (SPAN, AN69 ST) provides a partial neutralisation of the electro-negativity and reduces the production of bradykinin. This modification in the membrane allowed patients who were treated with ACE inhibitors and had a history of anaphylactoid reactions during HD with AN69 to be dialysed with AN69 ST, without there being any problems[14].

Finally, other compounds used in dialysis units such as formaldehyde[15], latex[16], heparin[17,18] and intravenous iron[19] can cause hypersensitivity reactions. Thus, finding the agent causing type A reactions during HD is often difficult.

Type B or unspecified

These reactions are more common and less severe than type A reactions. Symptoms are chest pain, dyspnoea, nausea, vomiting and hypotension. These reactions take longer to appear, about 15-30 minutes after the beginning of dialysis, although they can also occur later. These symptoms generally resolve during the session, without the need to disconnect the patient. They are due to a pulmonary leukostasis secondary to activation of the complement by the dialysis membrane, which generates C3a and C5a. The free hydroxyl groups of the dialysis membrane activate the alternative complement pathway, generating C3a and C5a anaphylatoxins. The latter binds to the receptors of the leukocyte membrane, causing activation, aggregation and adhesion of the leukocyte to the endothelium of the pulmonary capillary, thus producing the aforementioned pulmonary leukostasis, leucopoenia and hypoxaemia[20-23]. The leucopoenia nadir occurs 15 minutes into the session. Subsequently, the number of leukocytes in blood increases with pre-dialysis values being recovered approximately one hour later. Patients with these symptoms have a higher activation of the complement, and C3a values are higher than in patients who do not have symptoms[21]. The lower the biocompatibility of dialysis membranes, the higher the activation of the complement, and as such these reactions are more common with cellulosic membranes than with synthetic membranes. AN69 induces a minimum activation of the complement whilst polisulfone does activate it. However, anaphylatoxins are absorbed by the membrane and the systemic effect is minimal.

Other reactions

In 2001, there was an unexpected increase in fatalities in patients in HD, over a specific period of time, in Croatia, Spain and the United States. This was associated with the use of dialysers of the Althane (Baxter) series. Death occurred during the HD session or shortly after and it did not precisely meet the criteria that defines a hypersensitivity reaction. It was called perfluorocarbon syndrome. Subsequent research showed that the PF-5070 fluid that was used as a test to detect capillary leaks during the dialyser manufacturing process was the cause of this epidemic. It was concluded that PF-5070 is a highly toxic compound when it is administered intravenously given its emulsifier properties. Its use or that of any liquid fluorocarbon compound must be avoided in medical devices in contact with blood and particularly in the manufacturing of dialysers[24].

HYPERSENSITIVITY TO SYNTHETIC MEMBRANES

This journal issue has published a series of clinical cases in hospitals in Madrid, in which hypersensitivity reactions to synthetic dialysis membranes occurred in seven patients. With this editorial comment we will attempt to clarify the type of reaction into which they may fall, what all the cases have in common and if it is a new emerging problem or if it is a mere coincidence of specific cases, bearing in mind the high number of prevalent patients in our HD units and the high proportion of synthetic membranes that are used today. Sánchez-Villanueva et al.[25] reported 6 cases: the first patient suffered a reaction to the polyamide dialyser, which combines polymers of polyamide, polyarylethersulfone and polyvinylpyrrolidone (PVP), and to another polynephron dialyser (state-of-the-art polyethersulfone). The second patient reacted to polynephron and helixone (polysulfone). The other four patients reacted to the helixone dialyser. Martín-Navarro et al.[26] reported one case in which the patient had hypersensitivity reactions to different synthetic membranes: polyamide, helixone and PMMA. The patient suffered urticaria and eosinophilia with the PAN (AN69) dialyser, and there was only haemodynamic instability with plate PAN (AN69) without PVP. All reactions disappeared when the dialyser was changed to a cellulose triacetate dialyser.

What types of reactions do these patients suffer?

Most cases meet some criteria for a type A reaction and others for a type B reaction. The times of the occurrence of

the reaction are very variable, ranging from 5 minutes after initiating dialysis[26] to one hour before finishing the session[25]. Most patients do not develop angioedema symptoms; breathing symptoms, however, are prevalent (dyspnoea and decreased oxygen saturation), as well as low blood pressure. In addition, in some cases patients did not need to be disconnected, as their clinical profile tended to improve as the HD session progressed, although, in general, the symptoms were severe.

What do these cases have in common?

They all occur with synthetic membranes and do not occur when a substituted cellulosic membrane is used (cellulose triacetate). It seems that patients are sensitive to synthetic membranes of different compositions, although in most cases, one of the membranes used is a polysulfone and almost all contain PVP, which is used to hydrolyse the polysulfone membrane and other synthetic membranes. Other causes of hypersensitivity reactions in HD such as intravenous iron, heparin or latex allergies were ruled out in all the cases. In addition, ultrapure water is used in both units, and as such, we can rule out the reaction to pyrogens which occurs at the beginning of dialysis due to backfiltration, through the membrane, of a contaminated dialysate to the blood compartment[27]. With regard to the sterilisation method of the dialysers, EO was not used in any of the cases. Instead, gamma radiation and steam were used. Although it has been published that the sterilising agent can affect the biocompatibility of the membrane[28], neither gamma radiation nor steam have been reported as causes of hypersensitivity reactions.

The replacement of the synthetic membrane with another cellulosic membrane stopped allergic reactions from occurring in all patients. In principle, any cellulose membrane may cause a type B reaction due to its capacity to produce anaphylatoxins. However, substituted cellulose is more biocompatible than other celluloses. In particular, triacetate acts as a high permeability dialyser but has a lower capacity of activating the complement and a high level of biocompatibility. It has been reported that polysulfone, in comparison to cellulose triacetate, causes a higher activation of the GPIIb/IIIa[29] platelet membrane receptors. This glycoprotein is the receptor for the fibrinogen that mediates the aggregation and adhesion of the platelets, and could be a biocompatibility marker. In addition, in a recent study it has been demonstrated by proteomics that both membranes allow the adsorption of different plasma proteins. Furthermore, cellulose triacetate is capable of adsorbing a high amount of albumin and apolipoproteins, which would increase biocompatibility and reduce platelet aggregation. Polysulfone adsorbs more proteins than participate in the blood-membrane interaction, such as ficolin-2, fibrinogen fragments and proteins from red blood cells (such as carbonic anhydrase and haemoglobin), which could be a sign of shear stress of the red blood cells and partial haemolysis[30]. Ficolin-2, which participates in the lectin-dependent complement pathway has also been found to be adsorbed in the polisulfone membrane by other authors[31,32], which suggests that this membrane may activate the complement in some specific cases, and, in theory, lead to a type B reaction. However, its high capacity to adsorb fractions of the complement makes a reaction due to anaphylatoxins uncommon. Finally, PVP which is included in most polysulfone membranes (but not that of cellulose triacetate) may also play a role. PVP is a well-known allergen used to hydrolyse the membrane and inhibit its interaction with plasma proteins and platelets. Its release into the bloodstream during HD may cause severe anaphylactic reactions. Recently, a case of type A reactions with extremely high IgE levels were reported in a patient who was treated with polisufone dialysers and PVP from different manufacturers who used different sterilising methods. Symptoms disappeared when the dialyser was changed to a cellulose diacetate dialyser[33]. The Martín-Navarro et al. patient suffered urticaria and eosinophilia with the AN69 dialyser with PVP. Symptoms disappeared when the dialyser was changed to a plate AN69 dialyser without PVP.

Is this an "epidemic" or a mere coincidence of cases?

In the study by Simon et al, the relative risk of a hypersensitivity reaction was 10 to 20 times higher with synthetic membranes than with cellulose membranes. The prevalence of a severe reaction was 0.25% in the total population on dialysis, 0.5% in patients treated with synthetic membranes, 1.1% in patients with AN69 and 4.9% in patients treated with AN69 membranes and ACE inhibitors[4]. This means that reactions to synthetic membranes are not rare. The fact that one hospital in Madrid experienced the highest number of cases in two years may be a coincidence as it did not report more cases in that time and the Spanish Agency of Medicines did not receive other notifications, as its authors indicated. Cases of severe reactions to polysulfone were reported with and without PVP[33,34], both of high and medium permeability[35,36], with very high permeability polyetherulfone filters (PUREMA®)[37] and with one polisufone dialyser from a manufacturer and the other not[38]. Cross reactions between polysulfone, PMMA and polycarbonate[39] also occurred in one patient.

In spite of substantial improvements in the biocompatibility of membranes, filters and sterilising methods, etc., the repeated exposure of blood to foreign substances may cause

a sensitisation in predisposed patients and favour the onset of hypersensitivity reactions.

In summary, we have reported the occurrence of non-specific hypersensitivity reactions with synthetic membranes, which are more common with polysulfone (which are also used the most), over a specific period of time, grouped into some hospitals, whose aetiology has not been clearly defined, and which is yet to be classified.

Conflicts of interest

The authors declare the following conflicts of interest.

Alejandro Martín-Malo has received fees from Abbie, Amgen, Bellco, Fresenius Medical Care, Gambro and Shire, and Mª Antonia Álvarez de Lara has received fees from Abbie, Amgen, Bellco, Fresenius Medical.

KEY CONCEPTS

1. Adverse reactions in dialysis are the result of an interaction between blood and the different materials that comprise the dialyser and the other components of the extracorporeal circuit. They can be type A or hypersensitivity reactions (anaphylactic or anaphylactoid) and type B or non-specific reactions (generally mediated by the activation of the complement).
2. There may be reactions both with cellulose and synthetic membranes, although synthetic membranes, at present, cause more allergic reactions.
3. It is possible that the use of PVP, which is a highly allergenic substance used to hydrophilise some membranes, may increase the probability of suffering a hypersensitivity reaction.
4. Other causes of allergic reactions such as latex, intravenous iron, heparin and formaldehyde must be ruled out in patients who suffer hypersensitivity reactions in dialysis.

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