Fatal acute systemic hypersensitivity reaction during haemodialysis

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Introduction

Haemodialysis (HD)-associated anaphylactic and anaphylactoid reactions are found to be a complex problem, and though they have been well-documented in literature, a number of unexplored aspects remain.

Anaphylaxis is a severe, life-threatening, generalized or systemic form of hypersensitivity. The clinical diagnosis is based on case history and physical examination, and includes symptoms of airway obstruction, generalized skin reactions—particularly flushing, itching and urticaria—angio-oedema, cardiovascular symptoms including hypotension and gastrointestinal manifestations. These symptoms result from the action of mast cell and basophil mediators, especially histamine, leukotrienes and platelet-activating factor (PAF) upon shock tissues: blood vessels, mucosal glands, smooth muscles and nerve endings. Mediator release can be triggered by both immunoglobulin E (IgE) and non-IgE factors. As a result, anaphylaxis may be considered to comprise anaphylactic (IgE mediated) or anaphylactoid reactions (non-IgE mediated) [1].

The majority of reported cases have been due to sensitization to ethylene oxide (ETO) [2]. However, a considerable number of publications have focused on other HD substances and materials such as heparins, different dialyser membranes, iron, erythropoietin, polyacrylonitrile AN69® high flux membranes (accumulation of bradykinin) with or without angiotensin-converting enzyme inhibitors (ACEIs), latex, anti-septic or formaldehyde [3]. Many different underlying mechanisms have been postulated.

This case report describes a severe clinical syndrome of anaphylaxis during HD, and demonstrates both the complex nature of hypersensitivity reaction to HD and the life-threatening severity of such a reaction.

Case report

A 45-year-old male with renal failure due to chronic glomerulonephritis started peritoneal dialysis in 1982. In 1986 he received a cadaver renal transplant, and in 1988, suffered chronic rejection. He did not have asthma, nor any drug or food allergy. The patient showed persistent high eosinophil counts from the start of HD (mean eosinophil count 788.5 ± 441.0/mm³).

Reaction in April 1988

During the first HD with an ETO-sterilized cuprammonium membrane, the patient developed pruritus, facial erythema, urticaria, breathing difficulty and laryngeal oedema. After stopping the dialysis and the administration of 40 mg of urbason i.v., the patient recovered. Hypersensitivity towards cellulose membranes was suspected. At this point no attempt was made to further establish the potential cause of the reaction.

Reaction in May 1996

In the first 5 min during an HD session, in which the habitual filter was replaced by an NT1975 membrane (an ETO-sterilized cellulose membrane, 1.8 m², of low permeability), the patient suffered pruritus, erythema, breathing difficulty and laryngeal oedema. After stopping the dialysis and the administration of 40 mg of urbason i.v., the patient recovered. Hypersensitivity towards cellulose membranes was suspected. At this point no attempt was made to further establish the potential cause of the reaction.

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For 5 years the patient has undergone HD with several different dialysers involving synthetic membranes sterilized with ETO, such as F8 polysulphone (synthetic polymer, 1.8 m², of low permeability) and PMMA (polymethylmethacrylate, 1.8 m², of high permeability), without complications.

From 2002, he received the same HD prescription. He was dialysed during 4:15 h, 3 days a week via an arteriovenous fistula, using a F10HPS polysulphone dialyser (synthetic polymer, 2.4 m², of medium permeability and steam-sterilized, i.e. not using ETO) and without changes in the materials or manufacturers (γ radiation-sterilized tubes and ETO-sterilized needles). Treatment was provided in the form of 4000 units of Epoetin α i.v. after HD. No i.v. iron was provided. A bicarbonate dialysate was used. One litre of saline solution was used with 1 ml of 5% heparin sodium in the dialyser purge, and anticoagulation was provided with low-molecular weight heparin at the start of HD.

**Reaction in September 2005**

The patient developed sudden pruritus, urticaria, dyspnoea and severe hypotension (blood pressure 60/30 mmHg) immediately after initiating HD. The latter was stopped immediately, without returning the blood to the patient. He was then treated with fluids, 5 mg of polaramine i.v., 40 mg of methylprednisolone i.v., 100 mg of actocortin i.v. and 0.5 mg of epinephrine via the subcutaneous route. In view of the lack of response and impaired patient consciousness (Glasgow score 3), a total of 200 mg of actocortin was administered, together with 3 mg of epinephrine, 1 mg of atropine, an inhaled B2-agonist, and oxygen—followed by symptom resolution within ~30 min. The blood tests revealed a leucocyte count of 4700/mm³, with 39.6% neutrophils, 31.7% lymphocytes, 14.8% monocytes, 13.1% eosinophils, haemoglobin 13.3 g/dl, haematocrit 40.5%, mean corpuscular volume (MCV) 96, platelet count 185 000/mm³, glucose 95 mg/dl, urea 126 mg/dl, sodium 142 mEq/l, potassium 6.0 mEq/l, calcium 9.5 mg/dl, phosphorus 3.6 mg/dl, total proteins 8.0 g/dl, bilirubin 0.34 mg/dl, normal aminotransferases and C-reactive protein 0.1 mg/dl. LDH, CKand troponins were normal.

On the day after this reaction, we received the following results corresponding to the first reaction: total IgE 221, positive IgE antibodies against ETO (22 KU/l) and negative against formaldehyde and latex (<0.35 KU/l). Tryptase (88.3 μg/l, normal range: 0–13.5), histamine (0.40 μg/dl, normal range: 0–0.1) and eosinophil count (6157/mm³) were elevated.

We investigated all the materials in contact with the patient’s blood during HD, and found that the HD needles had been sterilized with ETO. It was postulated that residual ETO in the needle might have triggered this last attack. Following confirmation of ETO hypersensitivity, the next HD session incorporated needles sterilized with γ irradiation, not ETO.

**Reaction in October 2005**

Despite the preventive measures adopted, a second hypersensitivity reaction developed. Five minutes after the start of dialysis the patient developed generalized pruritus, breathing difficulty, angio-oedema and bronchospasm. Blood pressure dropped from 120/70 to 80/50 mmHg. No heparin had been administered. Dialysis was interrupted and 0.5 mg of subcutaneous epinephrine was administered, along with 200 mg of actocortin and 80 mg of urbason, oxygen therapy and Ventolin aerosol—followed by symptom resolution within ~30 min. The blood tests revealed a leucocyte count of 4700/mm³, with 39.6% neutrophils, 31.7% lymphocytes, 14.8% monocytes, 13.1% eosinophils, haemoglobin 13.3 g/dl, haematocrit 40.5%, mean corpuscular volume (MCV) 96, platelet count 185 000/mm³, glucose 95 mg/dl, urea 126 mg/dl, sodium 142 mEq/l, potassium 6.0 mEq/l, calcium 9.5 mg/dl, phosphorus 3.6 mg/dl, total proteins 8.0 g/dl, bilirubin 0.34 mg/dl, normal aminotransferases and C-reactive protein 0.1 mg/dl. LDH, CK and troponins were normal.

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*Reaction in November 2005*

Once again, after 23 uneventful HD sessions without ETO-sterilized material in the HD circuit (i.e. using γ-sterilized needles, dialysers and tubes), the patient experienced another reaction similar to the previous reactions, but of increased severity (pruritus, urticaria, flushing, severe hypotension, severe bronchospasm leading to syncope and vomiting, just after the start of dialysis). The eosinophil count was 1050/mm³, with platelets 196 000/mm³. Blood glucose was 97 mg/dl, sodium 143 mEq/l, potassium 6.8 mEq/l, calcium 10.3 mg/l, phosphorus 4.5 mg/dl, total proteins 8.2 g/dl, bilirubin 0.35 mg/dl, normal aminotransferases, ferritin 612, C-reactive protein 0.2 mg/dl. Lactic dehydrogenase (LDH), creatinine kinase (CK) and troponins were normal. The HD dialysate culture showed <10 CFUs/ml and <0.125 U/ml of endotoxins. No other patients in the HD unit showed similar symptoms.

Preventively, we rinsed the dialyser and tubes (both sterilized with γ irradiation) with 31 of saline without heparin. The β-blockers were changed to α-blockers, and pre-medication was started with antihistamines and 20 mg of urbason i.v. route at the start of the session.
stopped immediately without returning the blood to the patient. Despite intensive care with antihistamines, steroids, epinephrine, inhaled B2-agonist, vasopressors, oxygen and intubation, the patient died.

Discussion

Hypersensitivity reactions have been estimated to occur in ~4/100000 dialysis treatments. A postal survey of all HD centres in the UK suggested that 1/20 to 1/50 patients may be susceptible to anaphylactoid reaction to a new haemodialyser at some time in between, while the risk of reaction occurring with any single HD session is ~1/1000 to 1/5000. Although it is likely that many reactions are unrecognized or unreported, the scale of the problem is larger than many nephrologists have suspected [4], and a considerable number of articles describing severe and potentially life-threatening immediate hypersensitivity reactions, including cardiac arrests, have been published.

The clinical picture of our patient was suggestive of anaphylaxis [1]. All the reactions started in the first few minutes of HD with pruritus and urticaria, followed by hypotension and dyspnoea and tryptase and histamine levels were elevated. Quantification of total serum tryptase can yield important information on the mechanism underlying these hypersensitivity reactions. An increase in total tryptase can be measured in serum 30 min after the first allergic manifestations, reaching the peak 1 h after initiation of the anaphylactic reaction, and the remaining elevated for ~6 h [1]. However, it must be taken into account that the elevated levels of total tryptase in patients with chronic renal failure have been reported, and that mature tryptase might be a more specific marker of effector cell degranulation [5]. Plasma histamine levels become elevated within 5–10 min after mast cell activation, but return to baseline after 30–60 min.

Systemic mastocytosis could not be excluded in this patient, because baseline tryptase data were not available, though our patient presented no skin lesions or symptoms outside the aforementioned episodes.

Other clinical conditions that may give rise to sudden hypotension and dyspnoea in HD such as cardiac arrhythmias, ischaemic heart disease or gaseous emboli, were reasonably discarded. Repeated hypersensitivity-like reactions have been observed during the first few minutes of dialysis in a small number of patients treated with high-flux membranes, postulating backfiltration of pyrogens through the membrane into the blood compartment. This situation is associated with a fall in blood pressure, though hypotension is delayed in endotoxaemia, and is commonly associated with fever. In contrast, hypotension accompanying anaphylaxis is virtually immediate, and is not associated with a rise in body temperature [6]. This patient was treated with medium-flux dialysers (polysulphone and CTA), and no contaminated dialysate fluid was detected.

It has been reported that HD-related eosinophilia occurs in 13–25% of the HD population. Its aetiology, however, remains unclear. Eosinophilia may have been induced by an allergic reaction to HD-related materials, and constitutes a clinically useful marker of exaggerated HD-associated cytokine production. Cellular cytokine production in response to HD is not uniform. Cytokine production depends on individual responsiveness and is probably related to atopia [7]. Our patient showed persistent high eosinophil counts from the start of HD.

We did not witness the reactions before 2005. The information was retrieved from the case history, and it seems that no attempt was made to further establish the potential cause of this reaction. Only suspected diagnoses were cited. In fact, the case was focused towards possible cuprophan-type membrane allergy, since the first two reactions (1988 and 1996) occurred with membranes of this type and subsided upon changing to a polycrylontirile filter. However, at that time, all the materials used were ETO-sterilized, but the reactions disappeared after changing the membrane, and not the method of sterilization.

Identification of the offending materials and potential cross-reactive compounds is an absolute requisite for effective management. Depending on the mechanism involved, diagnostic methods for this identification comprise skin tests, the quantification of specific IgE, lymphocyte transformation and basophil activation assays and, eventually, in vivo challenge tests. Except for ETO, latex, formaldehyde and chlorhexidine, immunoassays for quantifying serum-specific IgE antibodies are not readily available [3]. Although the determination of IgE antibodies was carried out before 4–6 weeks, in our case we determined only IgE antibodies directed against ETO, because they have been responsible for most hypersensitivity reactions during HD. IgE antibodies directed against ETO were present, but not those directed against latex or formaldehyde could be detected. Antibody targeting to chlorhexidine was not assessed because the antiseptic used in this patient was povidone–iodine (betadine®). Generally, the diagnostic work-up of such reactions should not be carried out earlier than 4–6 weeks after the acute event, because of IgE and/or basophil or mast cell mediator depletion, or possible influences upon the test results by the medication used to treat the events [3]. Moreover, the short interval among reactions permitted no further studies in our patient.

Anaphylactoid reactions towards recombinant erythropoietin and darbepoetin remain anecdotal and might result from sensitization to excipient, such as polysorbate [3]. Heparins used for anticoagulation in patients undergoing HD also can precipitate anaphylactoid reactions [4]. In our case, all the reactions developed prior to the administration of heparin and erythropoietin, as a result of which the latter substances were unlikely to be the causal agents.
Antiseptics constitute another potential source of HD-associated hypersensitivity. Delayed-type hypersensitivity reactions occur regularly and rare, well-documented events can be found in the literature. Conversely, immediate hypersensitivity, presenting as acute urticaria that can result in anaphylactic shock, is rarer, but sometimes these life-threatening manifestations can even occur from simple skin application [3] and could constitute another possibility in our patient.

Subcutaneous challenge with heparins or antiseptics is accepted as the most reliable method for identifying these reactions. For safety reasons, for identification of the offending drug, in vitro testing such as lymphocyte transformation and basophil activation and/or appropriate skin tests should precede subcutaneous challenge tests [3,8].

However, there is still a significant number of materials for which diagnostic testing has not yet been developed and cannot be excluded. Severe anaphylactoid shock may be caused by biocompatible dialyser membranes (PMMA, polysulfone and poly-carbonate) [9], and the reactions of patients to each polysulfone membrane may differ among polysulfone membranes made by different manufacturers [10].

ETO has been widely used for gas sterilization of biomedical devices, and has been responsible for most hypersensitivity reactions during HD. It is extremely irritant, and even at low concentrations, can alter native protein and potentially create neoantigens. The true question is whether ETO-sterilized materials should be banned entirely from HD units. At present, although dialysis material sterilized with ETO has decreased considerably in HD units, particularly regarding dialysers and tubing—replacing ETO with alternative modalities of sterilization such as γ-radiation or steam—the same has not applied to the sterilization of dialysis needles. Furthermore, most syringes, needles or infusion systems used in hospitals are sterilized with ETO. These materials, while not part of the dialysis circuit, could interact with the latter and pose a serious threat for patients who are sensitized to ETO. The only way to avert further reactions is not using ETO. In those few patients who suffered repeated reactions, increasing the volume of saline in the initial rinse of the haemodialysers is not sufficient to prevent further problems and these reactions can persist despite double-rinsing of the dialysers, the use of several different dialysers, and a variety of sterilization methods. Dialysis-induced cytokine release by different sterilization methods, such as steam, has been described. Contrary to claims of better biocompatibility, steam sterilization does not result in a reduced production of pro-inflammatory IL-1[b] [11].

Between 1996 and 2002, the patient was dialysed with ETO-sterilized materials without apparent problems. Between 2002 and 2005 he was dialysed on steam-sterilized membranes and suddenly a new anaphylactic reaction occurred. The only potential ETO source at that moment seemed to be the needles but after elimination of these, another reaction occurred. The possibility of double sensitization to other HD materials cannot be eliminated.

The patient was pre-treated in all HD sessions after the September 2005 reaction, up to October 2005. Pre-medication does not guarantee a safe outcome and cannot be considered as an appropriate alternative for prevention. We withdrew pre-medication when we withdrew the ETO-needles after the October 2005 reaction, because we assumed that the causal factor had been eliminated.

Our patient was dialysed during 12 and 23 HD sessions after anaphylactic episodes without symptoms. The clinical outcome (the intensity of the reaction) is not only influenced by the degree of sensitization, but also by other concomitant factors: sometimes individuals only develop anaphylaxis after simultaneous exposure to the allergen and infection, physical exercise, psychological stress or concomitant medication (e.g. β-blockers). In our patient, β-blockers were eliminated after the first hypersensitivity reaction and apparently there was no evidence for intercurrent infections. Another possibility that could justify the uneventful HD sessions is refractoriness. It is frequently observed that patients who have experienced an anaphylactic/anaphylactoid episode tolerate re-administration (or re-exposure) to the culprit antigen shortly after the acute event. This tolerance, however, can be transient due to refractoriness of the system or the administered drugs. Early onset reactions tend to be more severe, and patients with a history of severe immediate hypersensitivity are at increased risk for anaphylaxis in the future. In this context, exposure to high doses of antigen via a route ensuring rapid absorption (e.g. intravenously) will increase the risk of repeat anaphylaxis.

Patients who have experienced anaphylaxis should be evaluated by an allergy specialist. Continuous exposure to substances in HD can produce IgE-mediated sensitization, leading to potentially fatal hypersensitivity reactions. However, a significant number of dialysis patients continue to suffer such reactions, in which the underlying mechanism remains to be identified.

Conflict of interest statement. None declared.

References


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