ANAPHYLACTOID REACTIONS DURING HAEMODIALYSIS ARE DUE TO ETHYLENE OXIDE HYPERSENSITIVITY

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Summary

Anaphylactoid reactions during haemodialysis are unusual, but increasingly recognised. It has recently been reported that there is a significant association between such reactions and the presence of IgE to albumin exposed to ethylene oxide (ETO). Review of the clinical features and epidemiology of dialysis anaphylaxis in the light of this new data suggests that these reactions are due to ETO hypersensitivity.

Introduction

In 1982 we reported a series of patients who had experienced severe reactions resembling anaphylaxis during haemodialysis, or more rarely, during haemofiltration and membrane plasma separation [1]. The same adverse reactions have also been widely reported from various centres in the United States [2], and in abstract form from several other European dialysis units (Cledes J. Abstracts EDTA–ERA 1983: 58; Perez-Garcia R. Abstracts EDTA–ERA 1983: 134; Zirovannis P. Abstracts EDTNA 1983: 21).

Recently published laboratory data on our patients suggested an association between these reactions and IgE specific to albumin exposed to ETO (ETO-HSA) [3]. The purpose of this communication is to review the clinical features of these anaphylactoid reactions to dialysis (the ‘first-use syndrome’ [2]) in the light of this new information, and to propose that the reactions are due to ETO hypersensitivity.

Clinical features of anaphylactoid reactions to dialysis

These attacks occurred in 16 long-term haemodialysis patients. Most frequently a single brand of flat-plate dialyser or another manufacturer’s hollow-fibre dialyser was involved, but identical and extremely serious anaphylaxis occurred on one occasion with a haemofilter and a membrane plasma separator. Seven
patients had an isolated reaction, six had two or three reactions, often with different dialysers; while three patients had repeated stereotyped attacks on every use of a new dialyser, which could be avoided only by treating a new dialyser with formalin before its first use. These last three patients had persistent blood eosinophilia. It is normal practice for our patients to rinse dialysers and sterilise them with formalin, but we have never had a reaction reported with a formalin sterilised dialyser.

The attacks all began within a minute or two of blood returning from a new ETO sterilised extracorporeal device to the patient, and were witnessed by a doctor or dialysis nurse in the majority of cases. The commonest symptom (in over two thirds of cases) was wheezing, while 50 per cent had urticaria and nearly 40 per cent chest pain. Less commonly cardiovascular collapse, sneezing, a runny nose, flushing, diarrhoea, vomiting and watery eyes were present. Most patients suffered several simultaneous anaphylactoid symptoms, and all remarked that the onset coincided with the initial flow of blood from the dialyser. There were no deaths; recovery from severe attacks occurred rapidly and spontaneously when haemodialysis was stopped, while milder attacks resolved spontaneously within two hours if dialysis was continued.

Possible causes

We have argued elsewhere [1] that these reactions are clearly distinguishable from other adverse reactions to haemodialysis, including dialysis-triggered asthma [4], pulmonary leucostasis with hypoxaemia [5], and febrile rigors related to endotoxin [6]. The illness bore all the hallmarks of generalised histamine release [7] and could thus have been due either to direct mast cell degranulation, or to an IgE mediated response to a foreign antigen. Ethylene oxide, used in the sterilisation of these devices, seemed a likely culprit as antigen (or hapten) in view of the fact that it had been incriminated in anaphylaxis before [8], can be readily eluted by blood from ETO-sterilised products [9], and was the only agent common to all the reactions observed.

In vitro studies

Laboratory investigations to investigate a possible association between these reactions and ETO hypersensitivity have been published elsewhere [3]. In brief, we obtained serum from seven patients who had suffered reactions (cases 4, 5, 9, 10, 11, 12 and 15 from the series reported previously [1]), and from age and sex matched controls who had been on regular haemodialysis with identical devices, for a similar length of time. Serum was also obtained from three non-atopic non-dialysed controls with no known exposure to ETO. The following measurements were made: total IgE, total antibody binding to ETO-HSA, and IgE against ETO-HSA.

It was found that six of seven reactors had detectable amounts of IgE to ETO-HSA compared with only one of six non reactors (p<0.05) and that the geometric mean value of IgE to ETO-HSA was 2.0ng ETO-HSA bound by IgE per ml of serum in reactors compared with 0.2ng/ml in non reactors (p<0.05).
No significant differences in total IgE or total antibody binding to ETO-HSA were found.

Discussion

We felt that these reactions were unlikely to be due to the dialysis membrane or type of extracorporeal device as they occurred with four different devices utilising membranes made of cuprammonium cellulose ('cuprophan', Enka AG), cellulose acetate, and anisotropic polysulphone. Furthermore, as they only occurred during first use, blood lines, heparin or saline could not be incriminated. Our suspicions therefore, fell upon ethylene oxide as the likely partial antigen triggering immediate-type hypersensitivity.

The above results are consistent with this hypothesis, the very close association between the presence of IgE to ETO-HSA and a history of dialysis anaphylaxis being in favour of a causal link. We suggest that repeated exposure to trace amounts of ETO in new dialysers can sensitise susceptible individuals, who may then exhibit an anaphylactoid reaction on subsequent exposure. It is not clear however, why these reactions affected patients in such an apparently sporadic and haphazard fashion, with only three patients suffering repeated reactions.

The one reactor with undetectable IgE to ETO-HSA had only a very mild reaction to dialysis (sneezing and runny nose) which might not have been a true anaphylactoid reaction; and she only had reactions with a hollow-fibre dialyser whereas all the other six patients reported here had reactions to a flat-plate dialyser of different manufacturer. It is also possible that the antigen in this patient was ETO linked to a serum protein other than HSA.

It is interesting to note that one control patient had a moderate amount of IgE to ETO-HSA but denied reactions. This could be due to various causes; dialysers containing little ETO; poor releasability of patient’s mast cells; or perhaps protection by the rather elevated amount of total antibody binding to ETO found in that patient.

Although we believe that dialysis anaphylaxis is mediated through IgE to ETO-HSA, measurement of total antibody binding indicates exposure to hapen-conjugated proteins. As yet there are too few patients to be certain if there is a significant link between total antibody binding and first use reactions.

It has been suggested that the incidence of anaphylactoid reactions to the first use of a dialyser is 0.0035 per cent [2]. However, lack of awareness of the syndrome has probably led to many reactions being unreported, unrecognised, or attributed to other causes such as disequilibrium, hypotension and cardiac ischaemia.

These first use reactions can certainly result in significant morbidity and even mortality [2], so understanding the mechanism and predicting patients at risk is desirable. If it can be confirmed that these are due to ETO hypersensitivity, additional measures may be necessary in rinsing new dialysers before use to ensure the absence of even trace amounts of ETO.

Finally, if exposure to ETO can evoke specific IgE antibodies, this might account for the commonly observed and hitherto unexplained phenomenon.
of eosinophilia in haemodialysis patients [10] which was present in some of our patients.

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References


Open Discussion

BONADONNA (Padua) Have you any information on the pH of the dialysate? In our experience of three cases of anaphylactoid reaction we found that the pH of the dialysate was very low.

NICHOLLS No, I'm afraid I haven't.

WALKER (London, Ontario) There has been reports in the literature of people who have had apparent ethylene oxide sensitivity and when they were changed from cuprophan hollow fibre dialysers to cellulose acetate hollow fibre dialysers, sterilised with ETO, they did not have any further allergic symptoms. In addition Hakim* in Boston has looked at patients who have had the first use syndrome and/or the hypersensitivity phenomenon and found that the degree of complement activation is significantly higher in people who have hypersensitivity reactions than in people who do not have hypersensitivity reactions. I just wonder whether what we are seeing here is in fact just a person who has a very responsive immunological system and this may just be a marker rather than an aetiological agent.

NICHOLLS To deal with your first point, I think this is extremely important, if you recall what Dr Leonard was saying about leachability of potential noxious agents from dialysers† I think we can incriminate ethylene oxide to account for differences between dialysers on different occasions. It may be that either the

*Hakim RM, Breillatt J, Lazarus JM, Port FK. N Engl J Med 1984; 331: 878
membrane or the potting compounds release ethylene oxide at different rates. I’m suggesting that ethylene oxide is an agent and it may require certain potting or certain membranes to produce this reaction. So far as your other point is concerned all I can say is that it is an interesting hypothesis but I have no particular data.

GOTCH (Chairman) Can I ask what technical steps such as changes in dialyser processing were required to terminate your incredible epidemic?

NICHOLLS We changed to priming dialysers with two litres of saline and ensuring all patients ran the dialysate for half an hour before starting dialysis. It was very interesting that the reactions occurred at the time when our unit was being rebuilt and we had to go over to single use. On many of these occasions, owing to pressure on staff, dialysate had only been run for as little as 10 minutes through the dialysate side and the priming had been done with possibly slightly less than one litre. In addition the throughput of disposable dialysers in our unit was extremely fast and so the dialysers were not lying on the shelves as they previously had been.

KOCH (Chairman) Did you ever use non ETO sterilised disposables in your reactors?

NICHOLLS No. The difficulty we had in studying patients who had repeated reactions was that one of them could not tolerate the reactions any longer and opted to switch to CAPD and refused to be studied on dialysis, the other two patients were home dialysis patients who spontaneously started formalising their dialysers, even when they were new, and they also refused to be studied in hospital. I also feel that it would have been unethical to study these patients in hospital in view of the deaths that have been recorded in the States.