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CUTANEOUS HYPERSENSITIVITY REACTIONS TO DIALYSER EXTRACT AND ETHYLENE OXIDE IN HAEMODIALYSIS PATIENTS

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Summary

Hypersensitivity reactions in haemodialysis patients may result from various factors: cellulose membrane derivatives, additives from the manufacturing process and ethylene oxide (ETO). Potential hypersensitivity was sought by skin testing with ETO and hollow fibre rinsing solution extract in 37 patients currently treated on cuprophan hollow fibre dialysers. Positive skin reactions were found in eight patients (22%) for both ETO and dialyser extract, and in 10 patients (27%) for dialyser extract only. There was no correlation between skin tests and serum IgE, specific IgE to ETO antibody, or clinical features. Long-term exposure to cuprophan hollow fibre dialysers seems to enhance delayed cutaneous hypersensitivity against cellulose derivatives and/or additives from the manufacturing process and/or ETO.

Introduction

Most authors correlate dialysis hypersensitivity reactions and ethylene oxide (ETO) sensitivity [1] and describe the appearance of specific IgE to ETO antibodies in reactive patients [2]. The frequency of such manifestations seems to be more specific for hollow fibre as compared to plate dialysers [3]. Butcher [4] suggested that the implication of ETO may not be exclusive. Since skin tests are known to be more sensitive for detecting sensitized patients, we evaluated the prevalence of cutaneous reactions to specific skin tests with ETO and cuprophan hollow fibre dialyser extract and their relations with specific IgE to ETO antibodies and clinical symptoms.

Patients and methods

Thirty-seven patients (15 females, 22 males), treated by chronic haemodialysis for more than six months (6–192) with material sterilized by ETO, were studied.

All were dialysed with cuprophan hollow fibre dialysers for at least six months (6–60), three times weekly. Rinsing was always performed with one litre of 0.9% NaCl.

During the test period the patients were orally questioned by a physician regarding the appearance of haemodialysis related clinical symptoms, such as face or hand flushing, itching, pruritus, urticaria, dyspnoea or chest tightness. Headaches, nausea, and vomiting were not considered.

Specific IgE to ETO antibodies were tested and quantified by RAST preparation using human serum albumin exposed to ETO [5], and IgE concentrations were determined by EIA; normal levels were respectively 50 PRU and 0.24mg/L.

Skin tests were performed with reagents prepared with 0.9% NaCl saline solution containing 2ppm diluted ETO for one, and from one litre of rinsing solution of a cuprophan hollow fibre dialyser for the other. Control was with isotonic saline solution. Intradermal injections of 0.1ml of these solutions were made at one time on the same forearm, by one physician, before a dialysis session. Results were noted 10 minutes and 48 hours after the injections.

Results

No early skin reaction was observed. Late positive skin reactions were found in 18 patients (40%) for the dialyser extract test. Eight of these reactive patients had a positive ETO test, but none had an isolated positive ETO test. Ten patients reacted for only the dialyser extract test. Control tests were negative in all patients (Table I).

TABLE I. Results of skin tests performed with isotonic saline, ethylene oxide and dialyser extract

Skin test	Number of patients	
	Positive	Negative
Isotonic saline	0	37
Ethylene oxide	8	29
Dialyser extract	18	19

TABLE II. Number of patients with adverse reactions out of 37 patients studied

Adverse reactions	Number of patients
Flushing of the skin	3
Itching	3
Urticaria	1
Bronchospasm	2
Anaphylaxis	1

Ten patients (27%) experienced some dialysis related clinical manifestations (Table II). Flushes and pruritus were most frequent. Reactions were more severe in two cases of bronchospasm and dramatic in a patient who suffered an acute allergic reaction when he was treated with a cuprophan membrane. Exposure to material sterilized by ETO was continued in all patients.

Twelve of 18 patients with positive skin reactions had never shown clinical symptoms. Four of them had both positive ETO and dialyser extract skin tests, and eight were only dialyser extract positive.

Six of the 10 symptomatic patients had positive skin tests: four of them had both ETO and dialyser extract positive skin tests, and two were only dialyser extract positive (Figure 1).

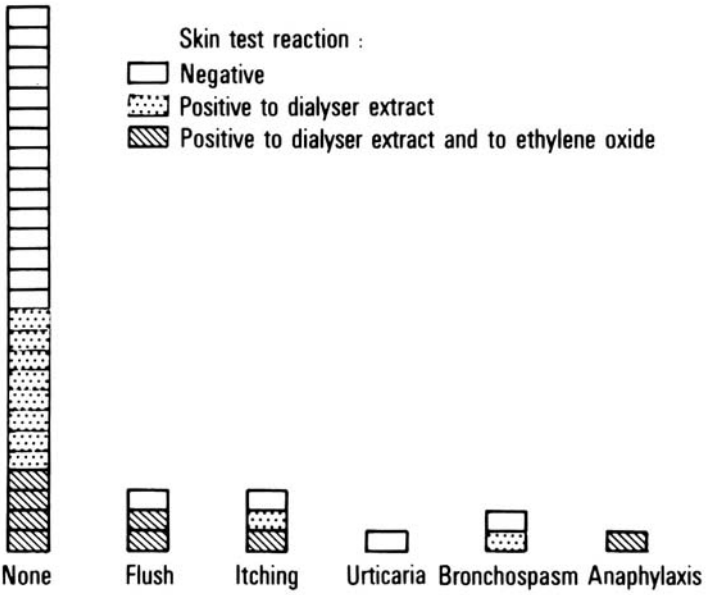

Figure 1. Number of patients having clinical symptoms with various skin test reactions

Twenty-two patients had IgE antibodies above the upper limit of normal: eight of them had positive dialyser extract tests and only one was both ETO and dialyser extract positive. Six patients had an increased level of antibodies specific to ETO: only one was dialyser extract and ETO positive and three had positive skin tests to dialyser extract (Figure 2).

Discussion

Skin tests with ETO induced no early reactions, and late manifestations did not correlate with clinical symptoms. Marshall found no clinical correlation in the nine per cent of patients reactive at 10 minutes to skin tests performed by the

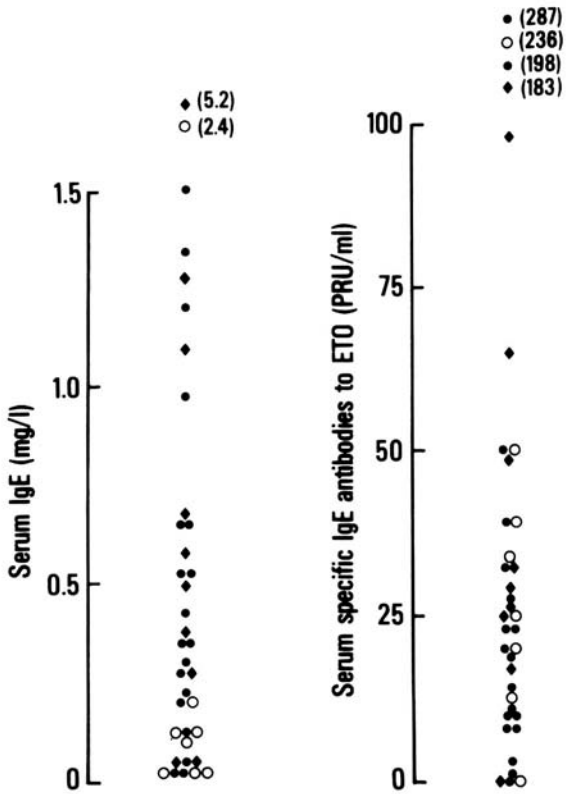

Figure 2. Serum concentration of IgE and specific IgE to ethylene oxide antibodies in 37 patients with various skin reactions. •=negative skin test; ♦=positive skin test to dialyser extract; ○=positive skin test to dialyser extract and to ethylene oxide

prick method with human serum albumin coated ETO [6]. Stability of ETO in isotonic saline solution might explain this discrepancy. However, we observed about 50 per cent positive delayed reactions, nearly half of which were with ETO.

ETO concentration was 2ppm defined, and dialyser extract dilution was related to rinsing volume: different concentrations of dialyser extract and ETO by lower rinsing volume might enhance test reactions and detect sensitive patients to give a better correlation. That positive ETO patients were positive on the dialyser extract test is consistent with residual ETO in the rinsing solution, and population responsive to both tests might be different with another concentration of ETO alone and in dialyser extract. However, we have not tested delayed hypersensitivity to ETO and dialyser extract in normal controls.

The lack of early skin test reactions made it impossible to seek a correlation between cutaneous tests and IgE.

Clinical features reported in this study were observed in 27 per cent of the patients, whereas Marshall noted similar findings in 50 per cent of a dialysis

population. Our study, however, excluded such symptoms as headaches and nausea because of possible confusion with manifestations of dialysis discomfort. We did not find any correlation between clinical symptoms and IgE specific ETO levels. Clinico-biological comparison did not permit the classification of the patients in Marshall's series: only 10 per cent of the patients had specific IgE. However, a close correlation with the clinical pattern in sensitive patients was found by Nicholls [7] and Lemke [5].

It was not possible to correlate clinical reactions and sensitivity to ETO or dialyser residual components, even if these two factors may be implicated [4,8]. Sensitive patients might be detected using, for example, a more concentrated test solution, in relation to other tests (e.g. phytohaemagglutinin) to determine the delayed immunity level in these patients. Patient sensitization might be the result of inadequate rinsing procedure. Therefore, it is suggested that modification of rinsing procedure should prevent hypersensitivity reactions in patients treated with cuprophan hollow fibre dialyser sterilized by ETO.

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