
Severe hypersensitivity reaction during hemodialysis

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Background: Hemodialysis-associated hypersensitivity reactions are well documented in the literature. Ethylene oxide sensitization and activation of complement are important factors involved during such reactions. The majority of severe hypersensitivity reactions in dialysis patients, however, is due to sensitization to ethylene oxide.

Methods: We report a patient admitted to the hospital with worsening of his renal function. He subsequently required three hemodialysis treatments, all of which resulted in severe hypersensitivity reactions requiring endotracheal intubation. The initial hypersensitivity episode was thought to be due to complement activation to the cupramonium-rayon membrane dialyzer. Despite changing to a polyacrylonitrile membrane, which does not activate complement, a second hypersensitivity reaction developed. Suspecting ethylene oxide hypersensitivity, the third hemodialysis session incorporated a biocompatible dialyzer that was sterilized with gamma irradiation, not ethylene oxide. Yet again, an anaphylactoid reaction resulted. It was postulated that residual ethylene oxide in the tubing might have triggered this last attack.

Results: Despite a negative RAST (radioallergosorbent test) to ethylene oxide, the strong history surrounding each of the hypersensitivity episodes and high index of suspicion pointed to ethylene oxide hypersensitivity as the etiologic factor. To this end, the patient fared much better when peritoneal dialysis was initiated. The patient subsequently died from other complications of his illness.

Conclusions: This case report demonstrates both the complex nature involving a hypersensitivity reaction to hemodialysis and the life-threatening severity of such a reaction. Replacing ethylene oxide with steam or gamma radiation to sterilize dialyzers and thoroughly rinsing new dialyzers and tubing with normal saline may help circumvent this problem.

Ann Allergy Asthma Immunol 1997;78:217-20.

INTRODUCTION

Sensitization to ethylene oxide accounts for the majority of severe hypersensitivity reactions in dialysis patients. Antibodies (IgE) directed against ethylene oxide and complement activation from the dialysis membrane are considered factors for hypersensitivity reactions during hemodialysis. Prevention involves rinsing saline through blood lines and dialyzer and proper selection of di-

alyzer membrane. In some cases, after reaction, it is necessary to avoid the use of new ethylene oxide sterilized dialyzers.

MATERIALS AND METHODS

Case History

A 66-year-old Hispanic American man with a history of hypertension and renal insufficiency was admitted to the hospital with worsening of his renal function and a decrease in exercise tolerance with progressive dyspnea at rest. During the past 11 months in the Renal Clinic, his serum creatinine had risen exponentially from 1.7 to 7.8 mg/dL. The following studies had been negative or within normal limits: anti-streptolysin O antibody titer, antinu-

clear antibody, rheumatoid factor, hepatitis B surface antigen, hepatitis C antibody and antigen, urine and serum electrophoresis for monoclonal antibodies. Renal ultrasound examination had shown nonspecific abnormalities and a magnetic resonance imaging scan 2 months earlier had suggested the possibility of right renal artery stenosis. The patient stated that he had been on foscarnet 10 mg, enalapril 10 mg, furosemide 40 mg, diltiazem 120 mg, and metolazone 2.5 mg each day. The past medical history included smoking, herniorrhaphy and glaucoma treated with levobunolol 0.5%. Physical examination on admission disclosed weight 133 pounds, oral temperature 97 °F, blood pressure, and 110 to 100/70 to 60 mm Hg. Physical findings included left conjunctivitis, coarse rales in both upper lobes, and a trace of pretibial edema. Laboratory studies on the day of admission included white blood cell count, 5,000/mm³ with 11% lymphocytes, 15% monocytes, 68% neutrophils, 3% eosinophils, 3% basophils, 214,000 platelets/mm³; hemoglobin, 12.8 g/dL; hematocrit, 33.7%; serum sodium, 136 mEq/L; potassium, 4.3 mEq/L; chloride, 102 mEq/L; bicarbonate, 19 mEq/L; calcium, 7.1 mg/dL; inorganic phosphorus, 8.77 mg/dL; magnesium, 2.3 mg/dL; total protein, 6.0 g/L; albumin, 3.7 g/dL; alkaline phosphatase, 70 U/L; alanine aminotransferase, 10 U/L; and aspartate aminotransferase, 11 U/L (all normal). Arterial blood gas studies disclosed Po₂ 90 mm Hg, PCO₂ 39 mm Hg, pH 7.29, HCO₃ 16.7 mmol/L; and % O₂ saturation, 95.5.

The patient was not continued on angiotensin converting enzyme inhibitor and did not receive this class of drug after admission. Diltiazem and furosemide were continued. Daily

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Received for publication February 5, 1996.

Accepted for publication in revised form August 22, 1996.

weight declined, blood pressure remained at 110/70, and serum creatinine and blood urea nitrogen rose further to 8.0 and 92 mg/dL. On the second hospital day eosinophils were 4% of white blood cell count 5,000/mm³. On the third day eosinophils were 5% of white blood cell count 5,400/mm³. Retrospectively, it was noted that the day of the second exposure to the dialyzer, there were 8% eosinophils of white blood cell count 6,000/mm³ and after the third exposure there were 8% of white blood cell count 5,600/mm³. The eosinophils were low after the fourth exposure resulted in anaphylaxis, when either continuous or pulse corticosteroid therapy was given. In a careful retrospective review, during the first dialysis, it was noted that the patient did complain of shortness of breath and was treated with a bronchodilator and nasal oxygen during the second dialysis. He again complained of shortness of breath during the third dialysis. His serum creatinine on admission was 7.8 mg/dL (1.7 mg/dL 11 months earlier). The patient received three hemodialysis treatments using a new ethylene oxide sterilized cuprammonium-rayon membrane dialyzer of 1.2 m² surface area without major incident. On the 12th hospital day while undergoing the fourth hemodialysis treatment with an identical dialyzer, the patient developed severe bronchospasm, hypotension, and bradycardia. This required intubation and mechanical ventilation. Cuprammonium-rayon membrane dialyzer complement activation hypersensitivity was suspected; however, serum complement component fractions C3a and C5a levels were not obtained.

On day 14, a 1.2-m² dialyzer with polyacrylonitrile (AN69) membrane, which does not produce acute leukopenia or complement activation, was sterilized with ethylene oxide was utilized for hemodialysis. The dialyzer and blood lines were pre-rinsed with 3 L of sterile saline. Despite these precautions, at 15 minutes into the treatment, the patient developed severe dyspnea and hypoxemia. Dialysis was discontinued, the blood in the circuit

was not returned and the patient was given intravenous epinephrine, diphenhydramine, and methylprednisolone but again required endotracheal intubation. Ethylene oxide anaphylactoid reaction was suspected.

For the next hemodialysis treatment on day 19, a biocompatible 1.2-m² surface area dialyzer with polymethylmethacrylate (PMMA) membrane sterilized by gamma irradiation was used. The only blood lines available, however, were ethylene oxide sterilized. The lines were therefore rinsed with 5 L of sterile saline (compartment volume approximately 200 mL) and the dialysate compartment was rinsed at 500 mL/min for 60 minutes. The patient also received intravenous methylprednisolone, 100 mg, and diphenhydramine, 50 mg, one hour prior to initiating dialysis. Despite these precautions, severe respiratory distress occurred at five minutes (O₂ saturation fell from 100% to 70%), dialysis was discontinued, the blood in the circuit was not returned. Epinephrine, diphenhydramine and methylprednisolone were again administered intravenously. Orotracheal intubation was again required. Residual ethylene oxide in the tubing connecting the dialyzer to the patient was postulated to have elicited this last attack. Total serum C3 and C4 complement levels on this day were within normal limits. These determinations are not sensitive markers of indirect activation of complement.

Peritoneal dialysis was initiated due to the failure of hemodialysis secondary to these hypersensitivity reactions. This procedure was well tolerated, however the patient continued to have minor reactions during peritoneal dialysis perhaps due to the fact that the solution bags, entire tubing set, and even the peritoneal dialysis catheter were sterilized with ethylene oxide. During the subsequent hospital course, the patient developed atrial flutter, right bundle branch block, and a right lower lobe pneumonia. On hospital day 46, the patient developed complete heart block requiring a temporary transvenous pacemaker. The patient

died the next day after going into asystole and failing to respond to resuscitation.

DISCUSSION

Hemodialysis is a safe procedure with a very low risk of death due to human error or technical failure. Hypersensitivity reactions during hemodialysis, however, have been well documented.¹⁻⁴ In this patient ethylene oxide as the cause of hypersensitivity was suspected when the reactions persisted despite switching to a more biocompatible, polyacrylonitrile (AN69) dialyzer membrane.

Cellulosic membrane bioincompatibility and ethylene oxide allergy are the two main causes of hypersensitivity reactions associated with hemodialysis.^{5,6} The data suggest that sensitization to ethylene oxide is responsible for the majority of hemodialysis hypersensitivity reactions.⁷

In the United States, most dialyzers have Cuprophane, cuprammonium rayon, cellulose acetate or triacetate, polysulfone or polyacrylonitrile membranes. Dialyzers may also be classified into hollow-fiber (eg, cuprammonium cellulose), parallel-plate (flat-plate), or coil dialyzers. Cuprammonium cellulose is the most common dialysis membrane in use.

Hypersensitivity reactions during hemodialysis in the US patient population from 1982 through 1984 were calculated to be 0.3 reactions per year per 1,000 patients exposed to flat-plate dialyzers and 3.3 reactions per year per 1,000 patients exposed to hollow-fiber dialyzers.⁶

Compared with Caucasian patients, blacks and other minorities had nearly three times as many hypersensitivity reactions. The largest number of reactions were seen in those under 29 years of age with the 30- to 49-year-old age group having half as many reactions. Patients more than 50 years of age had roughly half as many reactions as those in the 30- to 49-year-old range.⁶

Major and minor criteria have been defined by Daugirdas and Ing⁸ to describe two types of reactions that occur at the onset of hemodialysis. Major

criteria include onset within 20 minutes of starting dialysis, dyspnea, angioedema, and burning/heat sensation at the access site or throughout the body. The minor criteria are urticaria, rhinorrhea and lacrimation, itching, and abdominal cramps. Villarroel and Ciarkowski⁶ have graded the severity of hypersensitivity reactions as follows: grade 1 - not life threatening, mild, able to complete dialysis without medication; grade 2 - medications given, severe, and/or dialysis discontinued; and grade 3 - death.

Dialyzer reactions have also been classified as type A or B.³ A type A reaction is characterized by three major criteria or by two major and one minor criterion. A type B reaction includes chest and back pain, hypotension, nausea, vomiting, cramps, and shortness of breath. When a type B reaction is associated with the first time use of dialyzers, usually to new cellulosic membranes but not to the same reused membranes, this is referred to as the "first use syndrome." This is not reported to occur after thorough rinsing of the new dialyzer with saline.⁹ This syndrome occurs in roughly 3% to 5% of the dialysis population which is far more frequent than overt dialysis anaphylaxis.⁹

It has been reported⁶ that a history of allergic reactions exists in about 40% of patients with hemodialysis-associated hypersensitivity reactions. With regards to IgE levels, it has been shown¹⁰ that nearly 70% of dialysis patients with symptoms had an elevated IgE, whereas only 10% of asymptomatic patients demonstrated elevated IgE levels. In as many as 20% to 30% of patients undergoing dialysis, elevated eosinophil counts have been reported which appear to be associated with dialyzer-associated allergic reactions.¹¹

Ethylene oxide hypersensitivity, which was first described in 1975,¹² is responsible for the majority of hemodialysis-associated hypersensitivity reactions.⁷ The gas is often used to sterilize medical equipment and residual amounts of it may remain in exposed materials for a long period of time after

the process and act as a potential source of sensitization. Different brands of dialyzers may leach ethylene oxide at different rates after sterilization. Dialyzers contain a potting compound in which the membrane fibers are embedded. It is the potting compound which is the main reservoir for ethylene oxide in dialyzers. High antibody titers against ethylene oxide have been demonstrated during dialysis in patients having severe anaphylactoid reactions.⁴ Such reactions are rare with non-cuprammonium cellulose dialyzers, the majority of which are also sterilized with ethylene oxide. The reason for this is unknown. It has been suggested that ethylene oxide may act as a hapten with increased allergenicity after contact with cuprammonium cellulose dialyzers.³ Ethylene oxide exposure only occurs with the first use of a new dialyzer.

The activation of complement has been shown to peak at 15 minutes of dialysis when blood has come into contact with cellulosic membranes and the activation process invariably results in the generation of C3a and C5a, potent anaphylatoxins.¹³ These levels have been noted to be markedly elevated with anaphylactoid reactions. Complement activation that occurs in the dialyzer is via the alternative pathway. It has been demonstrated that only slight activation of complement occurred when non-cellulosic membranes were used such as polymethylmethacrylate or polyacrylonitril.¹⁴ Complement activation is much less when the dialyzers are reused regardless of dialyzer type. First-use syndrome patients have an earlier and more marked activation of complement than asymptomatic patients.¹³

Aside from a good history and clinical evaluation, which is important in eliciting the diagnosis of hemodialysis-associated hypersensitivity reactions, laboratory testing may be of importance as well. Since ethylene oxide is a gas, skin-prick testing may be carried out with ethylene oxide conjugated with human serum albumin, histamine (positive control), and normal serum albumin serving as the negative control.¹⁵ Ra-

dioallergosorbent testing (RAST) measuring IgE antibodies to ethylene oxide-albumin is another option, albeit less sensitive than skin testing, that may be employed.⁴ Specific IgE against ethylene oxide-albumin has been detected in one patient with reaction to ethylene oxide-sterilized tubing.¹² Due to the unavailability of the skin test reagent, RAST was performed by the Johns Hopkins University Reference Laboratory for Dermatology, Allergy and Clinical Immunology. The ethylene oxide IgE antibody level was negative in this subject. Reasons for a negative test might be limited sensitivity of the test and/or serum collecting during a quiescent period in the clinical course with a lower level of antibody. More sensitive than either RAST assays or skin testing is the measurement of histamine release from basophils in response to ethylene oxide-albumin.¹⁵

If a systemic reaction does occur during dialysis, the procedure should be discontinued immediately and the blood not returned to the patient. Depending on the severity of the reaction, cardiovascular support, epinephrine, bronchodilators, corticosteroids, and antihistamines may be required. In addition, blood in the extracorporeal circuit should be discarded. After the patient has been stable for one hour, dialysis may be resumed only with a biocompatible membrane, preferably not sterilized with ethylene oxide.

In Japan, steam or gamma radiation has essentially replaced ethylene oxide for the sterilization of dialyzers. This has led to a virtual disappearance of adverse reactions to ethylene oxide.¹⁶ Since hypersensitivity reactions have not been described with reused dialyzers¹⁷ and the risk of exposure to ethylene oxide occurs only with the first use of a dialyzer, the frequent reuse of compatible membranes would appear to be both cheaper and safer.

Inadequate rinsing of new dialyzers has been implicated as a predisposing factor in hypersensitivity reactions. To this end, it has been recommended³ that the blood compartment of a cuprammonium cellulose dialyzer as well as all lines be rinsed with 2 L of sterile

saline and that the dialysate compartment also be rinsed with 10 L of dialysate shortly before initiating dialysis. This case report demonstrates the severity and complexity of the problem of hypersensitivity reaction to hemodialysis.

REFERENCES

1. Bhat K, Lee SMK, Lozano J. Anaphylactic reaction on subsequent exposure to Cuprophane-Hollow Fiber Dialyzer: a case report. *Ann Allergy* 1984;52:282-4.
2. Daugirdas JT, Ing TS, Rixe DM, et al. Severe anaphylactoid reactions to cuprammonium cellulose hemodialyzers. *Arch Intern Med* 1985;145:489-94.
3. Dolovich J, Marshall CP, Smith EKM, et al. Allergy to ethylene oxide in chronic hemodialysis patients. *Artif Organs* 1984;8:334-7.
4. Rault R, Silver MR. Severe reactions during hemodialysis. *Am J Kidney Dis* 1985;5(2):128-31.
5. Bommer J, Ritz E. Ethylene oxide (ETO) as a major cause of anaphylactoid reactions in dialysis (a review). *Artif Organs* 1987;11:111-7.
6. Villarreal F, Ciarkowski AA. A survey on hypersensitivity reactions in hemodialysis. *Artif Organs* 1985;9(3):231-8.
7. Lemke HD, Heidland A, Schaefer RM. Hypersensitivity reactions during hemodialysis: role of complement fragments and ethylene oxide antibodies. *Nephrol Dial Transplant* 1990;5:264-9.
8. Daugirdas JT, Ing TS. First-use reactions during hemodialysis: a definition of subtypes. *Kidney Int Suppl* 1988;24:S37-43.
9. Henderson LW, Cheung AK, Chenoweth DE. Choosing a membrane. *Am J Kidney Dis* 1983;3:5-20.
10. Röckel A, Klink B, Hertel J, et al. Allergy to dialysis materials. *Nephrol Dial Transplant* 1989;4:646-52.
11. Scheuermann EH, Fassbinder W, Frei U, et al. Eosinophilia in hemodialysis. *Contrib Nephrol* 1983;36:133-8.
12. Poothullil J, Shimizu A, Day RP, Dolovich J. Anaphylaxis from the product(s) of ethylene oxide gas. *Ann Intern Med* 1975;82:58-60.
13. Hakim RM, Breillatt J, Lazarus JM, Port FK. Complement activation and hypersensitivity reactions to dialysis membranes. *N Engl J Med* 1984;311:878-82.
14. Suzuki Y, Uchida J, Tsuji H, et al. Acute changes in C3a and C5a in an anaphylactoid reaction in hemodialysis patients. *Tohoku J Exp Med* 1987;152:35-45.
15. Leitman SF, Boltansky H, Alter HJ, et al. Allergic reactions in healthy plateletpheresis donors caused by sensitization to ethylene oxide gas. *N Engl J Med* 1986;315:1192-6.
16. Takahashi S, Ohsima H, Watanabe H, Hirasawa Y. Eosinophilia observed in regular hemodialysis patients. *Nippon Jinzo Gakkai Shi* 1979;21:959-74.
17. Villarreal F. Incidence of hypersensitivity in hemodialysis. *Artif Organs* 1984;8:278-80.

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