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An Anaphylactic Reaction to Protamine in a Patient Allergic to Fish

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Protamine sulfate, a low molecular weight protein found in the sperm of certain fish, is widely used as a heparin antagonist. Although hypotension can occur with rapid administration of high doses, slow rates of infusion have little effect on blood pressure.¹ Severe anaphylactic reactions to protamine sulfate have been reported, although these are rare.^{2,3} We describe a patient who was allergic to fish and developed a severe anaphylactic reaction after receiving protamine sulfate.

REPORT OF A CASE

A 55-year-old man had suffered from angina pectoris and was scheduled for coronary artery bypass surgery. He smoked 15-20 cigarettes per day. For the past 30 years he had symptoms of chronic bronchitis. Preoperative questioning elicited no history of allergy. There was no apparent relationship between the bronchitis and his occupation; he worked in a fish processing factory. An intracutaneous screening test with different allergens showed a slightly positive reaction only to human dandruff. Differential white cell count was normal. A preoperative chest roentgenogram was normal. On physical examination the patient was wheezing and slightly dyspneic. Pulmonary function tests showed a vital capacity (VC) of 3.65 l and a forced expiratory volume in one second (FEV₁) of 1.81 l. Inhalation of salbutamol, a selective beta-2 receptor agonist, increased the VC to 5.1 l and the FEV₁ to 2.05 l. He was treated with physiotherapy, prednisone, 10 mg/day and aminophylline. Five days later, his VC was 4.6 l and his FEV₁ was 1.9 l.

Premedication consisted of 5 mg lorazepam, with 250 mg aminophylline, and 20 mg prednisone, orally. Anesthesia was induced with 15 mg etomidate, 2 mg fentanyl and 8 mg pancuronium, iv, and maintained with etomidate, 0.02 mg·kg⁻¹·min⁻¹. He was ventilated with a 40 per cent oxygen-air mixture. The clinical condition before and during extracorporeal circulation remained satisfactory. Grafts were placed on the left anterior

descending and left circumflex coronary artery. Extracorporeal circulation was discontinued without problems after 62 min; arterial blood pressure was 130/80 torr; left atrial pressure 16 torr; and the electrocardiogram showed sinus rhythm with a rate of 96/min.

Protamine sulfate, 50 mg, was given intravenously. Within 1 min the peak airway pressure rose to 52 torr. The lungs were severely distended and not moving. A suction catheter was easily passed through the endotracheal tube. Arterial blood pressure dropped rapidly to 45/20 torr, and the left atrial pressure to 3 torr. Ischemic changes were visible on the electrocardiogram. There was no visible blood loss. Cyanosis developed with a bradycardia of 40 beats/min with ventricular ectopic beats. Controlled ventilation with an inspired concentration of 100 per cent oxygen was attempted, but effective ventilation was impossible. An intravenous bolus injection of 250 mg aminophylline resulted in an immediate improvement in ventilation. Packed erythrocytes and fresh frozen plasma were infused rapidly to maintain adequate filling pressures. A second dose of aminophylline, 250 mg, methylprednisolone, 30 mg/kg, and calcium gluconate, 1 g, were given intravenously. Infusions of epinephrine, 0.2 µg·kg⁻¹·h⁻¹, and aminophylline, 0.9 mg·kg⁻¹·h⁻¹ were started. Within seven minutes, the arterial blood pressure was 60/25 torr, left atrial pressure 17 torr, and the electrocardiogram showed a sinus tachycardia of 120/min without ischemic changes. Peak airway pressure was now 38 torr. Controlled ventilation with an inspired concentration of 100 per cent oxygen and a minute volume of 7.5 l resulted in a Pa_{O₂} of 420 torr, Pa_{CO₂} 53 torr and pH_a 7.26. The patient continued to improve slowly and surgery was completed within 80 min. No additional protamine was given. Although blood loss was not excessive, a total of 3 l of packed erythrocytes, plasma and crystalloids was needed to maintain a left atrial pressure of 18 torr.

On transfer to the intensive care unit, the arterial blood pressure was 70/40 torr, and left atrial pressure 15 torr with a sinus tachycardia of 110 beats/min. Peak airway pressure was 21 torr. Fourteen hours postoperatively, the trachea was extubated.

On the second postoperative day, the patient stated that each time he ate fish he felt puffy and experienced dyspnea, palpitations, sweating and often fainted. These experiences were not related to the type of fish, since this reaction occurred when codfish, herring, or mackerel were eaten. Prior to working in a fish processing factory 30 years ago, he had had no symptoms of bronchitis. He had not had a vasectomy. More detailed laboratory investigations were carried out on the fourth postoperative day. Leukocyte count was 6400/mm³ with 18 per cent eosinophils. The results of protein electrophoresis were within normal limits. Total serum IgE level was 1145 IU/ml (normal value: 130 IU/ml). A radio allergosorbent test for estimating IgE against specific antigens was negative with milk and egg antigens, weakly positive with mussel antigens and positive with codfish antigens. With a modified enzyme-linked immunosorbent assay technique,⁴ IgA specifically directed against our protamine sulfate could not be demonstrated. However, high

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titers of IgG (1:2048), IgM (1:256), and IgE (1:1024) were found. In control sera no immunoglobulin subclasses against the protamine sulfate could be demonstrated. Intracutaneous testing with protamine sulfate in a dilution of 0.1 mg/ml was positive.

DISCUSSION

This patient probably developed an anaphylactic reaction to protamine sulfate. This conclusion is supported by an elevated serum IgE level and the presence of high titers immunoglobulin subclasses IgG, IgM, and IgE specifically against protamine sulfate and the positive skin test.

IgA against protamine was not found in the serum. This is not surprising, however, since IgA antibodies are mainly produced by plasma cells in exocrine glands and are involved with local immunity. Thus, IgA will be found in lymphoid tissue associated with the site of entry of the allergen.⁵ We were unable to ascertain why this patient became sensitized against protamine. However, Moorthy *et al.*² described a diabetic patient using protamine zinc insulin who developed an anaphylactic reaction to a protamine dose administered intravenously. Our patient had not previously received any form of protamine.

Protamine is produced from sperm or mature testis of salmon or related species belonging to the family salmonidae or clupeidae. Earlier attempts to demonstrate the antigenicity of protamines were unsuccessful.^{6,7} Recently, in a Letter to the Editor, Caplan and Berkman described four patients who experienced an allergic reaction to protamine. Two of these patients were allergic to fish. They speculate that these allergic reactions represent hypersensitivity to highly antigenic salmon determinants.⁷ Perhaps the previous ingestion of fish or the handling of fish in his occupation could have played an important role in sensitizing our patient. The extent to which his bronchitis was influenced by this possible allergy remains unknown.

Samuel⁸ suggested that such allergic reactions may be the result of an immune response to protamines themselves. In infertile or vasectomized men, autoantibodies to spermatozoa may develop by resorption of sperm. Within a year after sterilization, antibodies to sperm can be demonstrated in 75 per cent of patients.⁹ Protamines are also found in human sperm

and in 22 per cent of vasectomized men an immunologic response develops to these protamines.¹⁰ Sera of infertile or vasectomized men which react strongly in the complement fixation test with human protamines also fix complement when protamine from salmon is used as antigen.¹¹ Because of this cross-reactivity, vasectomized men with autoantibodies to human protamines may develop an anaphylactic reaction when exposed to protamine from salmon. In our patient antibodies to human protamine were not expected as a cause for his anaphylactic reaction since he had not had a vasectomy. In conclusion, the possibility of an anaphylactoid reaction to protamine must be considered in a patient who is allergic to fish, infertile, or has had a vasectomy.

REFERENCES

1. Goldman, BS, Joison J, Austen WG: Cardiovascular effects of protamine sulphate. *Ann Thorac Surg* 7:459-471, 1969
2. Moorthy SS, Pond W, Rowland RG: Severe circulatory shock following protamine (an anaphylactic reaction). *Anesth Analg (Cleve)* 59:77-78, 1980
3. Nordström L, Fletcher R, Pavek K: Shock of anaphylactoid type induced by protamine: a continuous cardiorespiratory record. *Acta Anaesthesiol Scand* 22:195-201, 1978
4. de Haan P, Boorsma DM, Kalsbeek GL: Penicillin hypersensitivity. Determination and classification of anti-penicillin antibodies by the enzyme-linked immunosorbent assay. *Allergy* 34:111-119, 1979
5. Rosekrans PCM, Meyer CJLM, Cornelisse CJ, et al: Use of morphometry and immunohistochemistry of small intestinal biopsy specimens in the diagnosis of food allergy. *J Clin Pathol* 33:125-130, 1980
6. Kern RA, Langner PH: Protamine and allergy. *JAMA* 113:198-200, 1939
7. Caplan SN, Berkman EM: Protamine sulfate and fish allergy. *N Engl J Med* 295:172, 1976
8. Samuel T: Antibodies reacting with salmon and human protamines in sera from infertile men and from vasectomized men and monkeys. *Clin Exp Immunol* 30:181-187, 1977
9. Hellema HWJ, Rümke P: Sperm autoantibodies as a consequence of vasectomy. *Clin Exp Immunol* 31:18-29, 1978
10. Samuel T, Kolk AHJ, Rümke P, et al: Autoimmunity to sperm antigens in vasectomized men. *Clin Exp Immunol* 21:65-74, 1975
11. Samuel T, Kolk AHJ: Autoantigenicity of human protamines, Vasectomy. Immunologic and pathophysiologic effects in animals and man. Edited by Lepow IH, Crozier R. New York, Academic Press, 1979, pp 203-223