

CASE REPORTS

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Anaphylactoid Reaction to Protamine Confirmed by Plasma Tryptase in a Diabetic Patient during Open Heart Surgery

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ANAPHYLACTOID reactions to protamine during open heart surgery in diabetic patients who use insulin preoperatively have been reported.¹ We describe a similar case in which the anaphylactoid reaction to protamine was confirmed by increased plasma tryptase concentration and a positive skin test.

Case Report

A 53-yr-old, 171-cm, 52-kg man was scheduled for a patch closure of an atrial septal defect. No transfusion was expected. Preoperative

hemodynamics included; blood pressure 110/70 mmHg, heart rate 64 beats/min, cardiac index $2.4 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$, Qp/Qs 2.8, and ejection fraction 47%. Medical history included diabetes mellitus treated with diet control and oral hypoglycemics until 6 months earlier, when NPH insulin had been added. He claimed no allergy to food or drugs.

Anesthesia was induced with diazepam and fentanyl and maintained with 33% N₂O, fentanyl, and pancuronium bromide before cardiopulmonary bypass. Duration of cardiopulmonary bypass was 55 min, and no blood was transfused. About 15 min after cardiopulmonary bypass, an injection of protamine (protamine sulfate, 10 mg/ml, Shimizu) was started *via* the peripheral vein. Within about 10 min, when 12.5 ml protamine had been injected, the systolic blood pressure decreased from approximately 100 to 40 mmHg. The heart rate increased from 105 to 135 beats/min. Initially, hypovolemia was assumed to be the cause of the hypotension and the remaining fluid in the oxygenator and plasma protein fraction (PPF) was infused rapidly. Within 10 min, systolic blood pressure recovered gradually but remained at 70-80 mmHg, and dopamine ($3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) was given. Edema on the face, ears, lips, and conjunctiva were noticed. The end-tidal carbon dioxide, sampled from the distal end of the endotracheal tube, decreased from 30-35 to 15-20 mmHg. Peak inspiratory pressure increased, and decreased deflation of the lungs was observed. Within 10 min after administering protamine, SpO₂ gradually decreased from 100% to 84% and recovered to 100% about 40 min after protamine. Arterial blood gas analyses (table 1) demonstrated hypoxia, hypercarbia, and hemoconcentration. Although

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Table 1. Arterial Blood Gas Analyses during the Anaphylactoid Reaction

Time	FiO ₂	pH	P _{O₂} (mmHg)	P _{CO₂} (mmHg)	BE (mEq/L)	Hb (g/dl)
5 min before protamine	1.0	7.44	296	38	2.2	8.7
20 min after protamine	1.0	7.20	59	68	-3.7	13.4
45 min after protamine	1.0	7.18	197	67	-1.9	13.0
58 min after protamine	1.0	7.22	278	63	-0.6	12.8
1 h 30 min after protamine	0.6	7.31	215	51	0.6	12.8
2 h 18 min after protamine	0.6	7.33	130	48	0.3	12.2

FiO₂ = fractional inspired oxygen tension; P_{O₂} = arterial oxygen tension; P_{CO₂} = arterial carbon dioxide tension; BE = base excess; Hb = hemoglobin.

2,000 ml of PPF was rapidly infused within 1 h after protamine, central venous pressure remained 1–3 mmHg, and the right atrium and ventricle remained small, as observed in the operating field. Based on these observations, an anaphylactoid reaction was suspected. Methylprednisolone (1,000 mg) was injected. The blood was sampled about 1 h after the protamine injection and centrifuged, and the serum was frozen for tryptase measurement. Systolic blood pressure increased to greater than 100 mmHg with dopamine. Fluid balance during anesthesia (including cardiopulmonary bypass) was as follows: blood loss 460 g, PPF 3,250 ml, lactated Ringer's solution 5,040 ml, and urine 970 ml. The trachea was extubated the following morning.

Serum tryptase was 26.1 ng/ml (normal value < 2.0 ng/ml, RIA method, Mitsubishi Yuka BCL, Osaka, Japan). The skin test for protamine was performed twice, 53 and 518 days after the operation. In the first test, protamine sulfate (10 mg/ml) was diluted 50 times with saline, and 0.1 ml (0.02 mg) was injected intradermally, resulting in a wheal (W, 6 × 11 mm) and a flare (F, 25 × 30 mm) in 20 min. Saline was used as a negative control, and there was no flare. In the second test, 0.02 ml of each material was injected intradermally, and the diameters of W and F were measured 15 min after the injection. Each drug was diluted with saline. Protamine was positive: 0.01 mg/ml protamine sulfate (W 4 × 5 mm, F 20 × 22 mm) and 0.1 mg/ml protamine sulfate (W 6 × 7 mm, F 22 × 32 mm). Heparin was negative: 1,000 U/ml heparin sodium (W 0 × 0 mm, F 0 × 0 mm). Saline was used as a negative control (W 0 × 0 mm, F 0 × 0 mm). Tubocurarine and histamine were used as positive controls: 0.003 mg/ml tubocurarine chloride (W 0 × 0 mm, F 3 × 4 mm), 0.03 mg/ml tubocurarine chloride (W 5 × 9 mm, F 25 × 28 mm), and 0.01 mg/ml histamine dihydrochloride (W 7 × 10 mm, F 25 × 50 mm).

Discussion

Catastrophic reactions to protamine during cardiovascular surgery are reported to be rare (0.13%).² However, in patients with diabetes using NPH insulin, which contains protamine, the incidence is 50 times greater compared to the nondiabetic population.¹ In the current case, the patient had been treated with NPH

insulin (14–20 U/day) for 5 months and appeared to have developed allergy to protamine before the cardiac surgery. His sensitivity to protamine was confirmed by the skin test performed 53 and 518 days after the operation. PPF has been reported to cause similar reactions,³ but in this case, PPF was started after the onset of hypotension. However, it is possible that PPF could have influenced the adverse hemodynamic effects.

Serum tryptase is an important indicator of mast cell involvement⁴ and anaphylactoid reactions.⁵ The increased serum tryptase concentration observed 1 h after the protamine injection in the current case, with the hypotension, hypovolemia, persistent hemoconcentration, edema, hypoxia, and hypercarbia, suggested that an anaphylactoid reaction had occurred.

Plasma histamine concentration is another indicator of anaphylactoid reactions, but tryptase measurement has some advantages over histamine measurement.⁵ First, because of the short half-life of histamine in the circulation after release from mast cells (half-life is several minutes), the blood must be sampled within 30 min. Tryptase (half-life is about 2 h) can be sampled 1 h after the life-threatening events. Second, because of the presence of histamine in basophils, hemolyzed or clotted blood cannot be used for histamine measurement but can be used for tryptase measurement. Third, the blood sample should be centrifuged at low temperature immediately, and the plasma should be frozen for histamine measurement, but the sample can be left at room temperature up to several days for tryptase measurement.⁴

In summary, we report an anaphylactoid reaction to protamine, confirmed by increased plasma tryptase concentration and a positive skin test, during open heart surgery in a patient with diabetes treated preoperatively with NPH insulin.

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