Cardiac arrest following protamine administration

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A case report of fatal cardiac arrest following protamine reversal of systemic heparinization during vascular surgery is presented. Patients who have received protamine zinc insulin, NPH insulin, and those with previous exposure to protamine sulphate or allergy to fish are more likely to have a reaction to protamine. Protamine-induced hypotension can be mediated by immunological or non-immunological mechanisms. Several alternative methods of heparin reversal which may avoid similar catastrophes are presented.

Key words

ANAPHYLAXIS: protamine; SURGERY: cardiovascular, peripheral vascular.

Protamine sulphate, a strong polycationic polypeptide, combines with acidic heparin to form a neutral salt, thus eliminating the anticoagulating properties of heparin. It is widely used in cardiac and vascular surgical procedures, and in donations of blood components when a cell separator is used. Severe anaphylactic reactions to protamine have been reported rarely. We recently observed a case of fatal hypotension following slow intravenous administration of 60 mg of protamine in a diabetic patient receiving isophane insulin who had had prior exposure to protamine during vascular surgery.

Case report

A sixty-one-year-old male presented with a four-week history of dysphasia, clumsiness, and pares-

thesias of right upper and lower extremities. He also had severe intermittent claudication and rest pain in his right lower leg for six months and a history of hypertension and diabetes for 30 years. Left femoro-popliteal bypass had been done six months prior to this admission. His medications were metoprolol 50 mg b.i.d., NPH insulin 24 u q.a.m., 15 u q.p.m. and Toronto insulin 12 u q.a.m. He had no history of allergy.

His weight was 60 kg and physical examination was unremarkable except for bilateral carotid bruit, and absent or reduced peripheral arterial pulses. His blood pressure on the ward was labile, ranging from 100/70 to 200/100 mmHg. Laboratory investigations were normal, except for ST depression in ECG leads II, III, AVF, V₄-V₆. Angiography revealed 90 per cent stenosis of the left internal carotid artery, and 60 per cent stenosis of the right internal carotid artery and occlusion of the right superficial femoral artery.

He was scheduled for left carotid endarterectomy. Premedication was 10 mg valium, orally. Blood pressure was monitored with an arterial line. He was induced with fentanyl 200 µg, lidocaine 100 mg, thiopentone 150 mg, and pancuronium 5 mg, intravenously. Maintenance of anaesthesia was with oxygen, nitrous oxide and $\pm$ 0.5 per cent enflurane. The blood pressure was stable at about 150 mmHg systolic throughout the procedure. Heparin 6000 units was given, followed 25 minutes later by intravenous protamine 50 mg, after the endarterectomy. The blood pressure immediately fell to 80-90 mmHg, and a neosynephrine drip was required for one to two minutes to increase the blood pressure. The patient recovered uneventfully.

Seven days later the patient was scheduled for right femoro-popliteal bypass and right lumbar sympathectomy. A preoperative electrocardiogram showed no new findings. He received a spinal anaesthetic. Tetracaine 14 mg was given at L₃₋₄, which produced loss of sensation to the T8 level. He

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TABLE I Protamine reactions

Author	Sex/Age	Surgery	Pulmonary changes	Skin changes	Cardiac arrest
Jackson ⁴	F/63	Ileofemoral endarterectomy	—	—	Yes, resuscitated
Lakin ⁴	M/29	Blood component donation	Dyspnoea, wheezing	Urticaria	—
Moorthy ⁶	F/26	Nephrolithotomy	—	Skin flush	—
Knappe ⁷	M/55	Aorto coronary bypass	Bronchospasm	—	—
Doolan ⁸	M	Cardiac catheterization	Apnoea	—	Yes, resuscitated
	M	Carotid endarterectomy	Bronchospasm	—	Yes, resuscitated
	M	Cardiac catheterization	Facial oedema stridor	—	Yes, resuscitated
Cobb ⁹	M/51	Carotid endarterectomy	—	Skin flush	—
Vontz ¹⁰	M/52	Carotid endarterectomy	Bronchospasm	Angioneurotic oedema	Neurological deficit
Nordstrom ¹⁹	F/7	Open heart surgery	Bronchospasm	—	—

*All cases included severe and prolonged hypotension.

was awake and conversed with the surgeon intermittently throughout the procedure. Right lumbar sympathectomy was done first. He then received 6000 units of heparin, and right femoro-popliteal bypass was done. Following release of the clamps good flow was noted in the graft, and the systemic blood pressure was 160 mmHg. At this time estimated blood loss was about 200 ml, and the fluids administered were 1000 ml of plasmalyte solution, one unit of packed cells, and 100 cc dextrose-insulin solution with 20 units of insulin in 1000 ml of five per cent dextrose solution. Protamine 60 mg was injected over one to two minutes and shortly thereafter the patient complained of difficulty breathing. Systolic blood pressure dropped precipitously to 40 mmHg. Despite prompt injections of neosynephrine, 0.5 mg twice, 1 mg adrenaline twice and intubation and ventilation with oxygen, the patient remained severely hypotensive. Peak airway pressure was 30 mmHg. The electrocardiogram still showed sinus rhythm at 60/min with no new ST-T wave changes. Despite cardiac massage, severe hypotension persisted and he developed ventricular fibrillation. He was defibrillated, and the electrocardiogram now showed marked ST elevation in the modified V₅ lead. A central line was inserted into the femoral vein and an arterial line was inserted into the femoral artery. Isoproterenol and dopamine drops were started. However, the patient again developed ventricular fibrillation and could not be resuscitated despite major efforts.

Discussion

Clinically, protamine is widely used without major complication. Recently, Milne observed that intra-

venous protamine produced no significant change in blood pressure, heart rate, left atrial pressure, central venous pressure, systemic vascular resistance or cardiac index.¹ However, hypotension can occur in some patients and there appear to be two types of reactions after protamine administration in humans. The first, seen in many patients, is a mild to moderate fall in blood pressure. This is due to a vasodilation effect of protamine as well as the possibility of depressed myocardial contractility.^{2,3}

The second type of reaction is severe. Most of the case reports had clinical features suggestive of a type I anaphylactic response to protamine.⁴⁻¹⁰ In certain patients, IgE or IgG reaginic antibodies are produced in response to protamine. The IgE antibodies are attached to mast cells. The second exposure to protamine results in a combination of the antigen with IgE or IgG complexes which trigger the degranulation of mast cells, releasing histamine and other vasoactive amines. Most of the cases reported either note previous exposure to protamine, diabetics on protamine zinc insulin, or isophane insulin, or allergy to fish.

Protamine is produced from sperm or mature testes of salmon, or related species belonging to the family salmonidae or clupeidae. Caplan and Berman described four patients who experienced an allergic reaction to protamine.¹¹ Two of these patients were allergic to fish. Knappe reported a patient who was allergic to fish and developed a severe anaphylactic reaction after receiving protamine.⁷

In infertile or vasectomized men, sperm was absorbed into the circulation. Protamine in the sperm acts as a chronic antigenic stimulus, and

TABLE II Protamine reaction

Author	Protamine dosage	Onset	Prior protamine exposure	Allergy to fish	Test
Jackson ⁴	40 mg over 1-3'	Immediate	Exposed to protamine 4 years ago	—	—
Lakin ⁵	6.5 mg over 30 sec.	½ minute	Exposure to protamine 5 months ago	—	IgG ↑
Moorthy ⁶	20 mg over 5 minutes	1 minute	Protamine zinc insulin for 5 years	—	IgE ↑
Knappe ⁷	50 mg	1 minute	—	Yes	IgE ↑
Doolan ⁸	35 mg	Immediate	Reaction on the 4th exposure	—	Positive skin test
	15 mg	Immediate	Exposure to protamine 6 weeks ago	—	Positive skin test
	10 mg	Immediate	NPH Insulin	—	Positive skin test
Cobb ⁹	25 mg over 1-2'	Immediate	NPH Insulin	—	—
Vontz ¹⁰	10 mg	Immediate	NPH Insulin	—	IgE ↑
Nordstrom ¹⁹	60 mg IV slowly	1 minute	—	—	—

auto-antibodies to sperm occur. These patients may therefore be at increased risk to allergic reactions to protamine.^{12,13}

The repeated administration of intravenous protamine could result in an anaphylactic reaction. Doolan reported a patient who had a severe reaction on his fourth exposure to protamine within two years.⁸ In a retrospective study of blood component donors, Lakin found that prior exposure to protamine is associated with an increased risk of adverse reaction.⁵ Of twenty-two initial protamine injections, no adverse reactions were observed. Of eleven donors receiving protamine a second time, four urticarial episodes with or without bronchospasm or hypotension were noted. There is evidence that the immunologic anaphylactic reaction is mediated by a complement dependent IgG skin sensitizing antibody.

In diabetic patients treated with protamine zinc insulin or NPH insulin, four case reports of anaphylactic reactions to protamine have been reported.^{6,8,10} The reactions were usually severe, with hypotension being prolonged in spite of vigorous treatment. Grant studied four diabetics on NPH insulin who had anaphylactic reactions to protamine during open heart surgery, and their findings were compatible with an immunological basis. Sensitization was probably induced by prior chronic exposure to protamine in NPH insulin or protamine zinc insulin.

Our patient had previously received 60 mg protamine intravenously during left femoro-popliteal bypass, with no change in blood pressure. Six months later, he developed some degree of hypotension (which lasted for 1-2 minutes) following protamine injection. The blood pressure was easily

elevated with a neosynephrine drip. Seven days later, following intravenous protamine he developed severe hypotension resistant to treatment and subsequently suffered massive myocardial infarction and cardiac arrest. It is possible that prior exposure to protamine with the previous vascular surgery and the protamine content of isophane insulin (NPH insulin 0.3-0.6 mg of protamine per 100 units of insulin) sensitized our patient to protamine. The interval between exposure is said to be important, with a short incubation period of two weeks being most optimal for development and expression of drug allergy.¹⁶ The interval in our case was seven days.

The manifestation of this allergic reaction may have been accentuated by the co-existence of a peripheral sympathetic block due to the spinal anaesthesia. The spinal anaesthetic might have impaired the endogenous release of epinephrine from the adrenal glands;¹⁷ epinephrine normally acts to increase intracellular concentrations of cyclic adenosine monophosphate and thus inhibit degranulation of mast cells and reduce the release of chemical mediators. Furthermore, peripheral sympathetic block would prevent compensatory vasoconstriction during an allergic reaction and thus exaggerate the magnitude of hypotension.¹⁸

Only one case of non-immune anaphylactoid response has been reported. Nordstrom observed an anaphylactoid response in a six-year-old girl who had no prior exposure to protamine. She developed hypotension and bronchospasm after protamine chloride, which was treated with intravenous isoproterenol.¹⁹ Protamine, being a polycationic polypeptide, releases histamine from mast cells, and basophils.²⁰ Complement consumption can be

mediated by protamine²¹ or protamine-heparin complexes,²² and this may produce anaphylactoid symptoms. Rent found *in vitro* complement consumption to be most pronounced when protamine is in "excess" of heparin.

Increased protamine sensitivity should be kept in mind in patients who are receiving protamine zinc or isophane insulin, patients with previous exposure to protamine, or allergy to fish. During peripheral vascular surgery with small doses of heparin, the use of protamine should rarely be required. Spontaneous reversal of anticoagulation is strongly encouraged. If protamine must be used, it is recommended that 5–10 mg as a small test dose be given,⁸ with intravenous adrenaline, vasopressors, and plasma volume expanding agents available. If a patient has a history of reaction to protamine, they should be appropriately premedicated with 50 mg of prednisone orally every six hours for one day, and 50 mg of intravenous diphenhydramine one hour before protamine. This regimen has been found to prevent severe reactions to contrast in patients with a past history of allergy to radiographic dye.²³

As another approach in patients who have documented protamine allergy, hexadimethrine can be used as a safe alternative to protamine.⁹ Hexadimethrine is not supplied by the pharmaceutical industry and must be prepared from a powder by the hospital pharmacy. The powder is available in Canada. Parsons has reported on eleven patients who were allergic to protamine. When hexadimethrine was used, there was 100 per cent success in reversal of heparin anti-coagulation without adverse reaction.*

Those patients who have developed a reaction to protamine should have intradermal skin testing, and their IgE and IgG antibodies and complement assessed. This should further elucidate the mechanism of the reaction.

In summary, we have attempted to draw attention to the possible precipitating factors, and the clinical clues to the existence of protamine sensitivity in a given patient. Avoidance of protamine reversal by natural degradation of heparin is often possible, but failing this, a small test dose of protamine with adrenaline on stand-by, or use of hexadimethrine may be lifesaving.

*Parsons, B. Personal communication. Austin Hospital, Heidelberg, Australia.

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Résumé

On rapporte l'observation d'un arrêt cardiaque fatal à la suite d'administration de protamine durant un cas de chirurgie cardiovasculaire. Les malades qui reçoivent déjà de l'insuline-protamine-zinc ou de l'insuline NPH, ceux qui ont reçu antérieurement du sulfate de protamine et ceux allergiques au poisson sont plus susceptibles de présenter une réaction à la protamine. L'hypotension attribuable à l'administration de protamine peut s'expliquer par un mécanisme immunologique et un mécanisme non-immunologique. On discute de nombreuses autres méthodes utilisables pour renverser l'effet de l'héparine chez des malades susceptibles de présenter de telles complications.