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Management of the Patient with Protamine Hypersensitivity for Cardiac Surgery

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Patients may present for cardiac surgery with a history of protamine hypersensitivity occurring during cardiac catheterization or previous cardiac surgery.1–10 Over a recent 24-month period, four patients of the 1,452 requiring open-heart surgery at our hospital presented with a history of protamine hypersensitivity (incidence 0.28%). This report describes the first two cases and discusses the evaluation of these patients and management options during cardiac surgery.

REPORT OF TWO CASES

Patient 1: A 42-year-old, 58-kg woman with unstable angina pectoris and an uncomplicated myocardial infarction 7 months previously was admitted for cardiac catheterization. She had no history of asthma, food or drug allergies, or other atopic disorders. Premedication for cardiac catheterization was im meperidine, scopolamine, diphenhydramine, and cefazolin. She received heparin, 5,000 units, iv, and procaine local anesthesia at the time of catheterization. Coronary arteriography, performed using radiopaque contrast media (Hypaque-76®, Winthrop) without incident, demonstrated two-vessel coronary artery disease, and normal left ventricular function. At the conclusion of the study, the administration of protamine sulfate, 50 
mg. iv, was immediately followed by hypotension (systolic blood pressure 50 mmHg), dyspnea, urticaria, and pruritis. Resuscitation was accomplished within minutes with oxygen, epinephrine, iv fluids, diphenhydramine, and hydrocortisone.

The patient was re-admitted 6 weeks later for double aorticcoronary bypass surgery. Preoperative hematologic and coagulation values were normal. Intradermal testing to 100 μg of intradermal protamine sulfate was negative. The plan for management was avoidance of protamine administration and omission of heparin neutralization.

Prior to the institution of cardiopulmonary bypass (CPB), heparin was titrated to bring the activated clotting time (ACT) over 400 s. Twenty-five thousand units (4,500 units/kg) of heparin were administered in divided doses, and an ACT of 670 s achieved. No further heparin was administered, and after 94 min of hypothermic CPB the ACT was 386 s. The patient was weaned from CPB, and surgical hemostasis was accomplished using electrocautery and thrombin-soaked Gelfoam® (Upjohn Co.). During chest closure, the oxygenator contents were washed and concentrated in a Dideco model BT 795 Autotrans™ cell washer and 480 ml of autologous erythrocytes reinfused. In addition, 400 ml of lactated Ringer’s solution, 500 ml of homologous packed erythrocytes, and 355 ml of fresh-frozen plasma were administered in the operating room. At the conclusion of the operative procedure the ACT was 366 s.

In the intensive care unit, the prothrombin time was 17.2 s, partial thromboplastin time greater than 150 s, platelet count 124,000/ 
mm³, and hemoglobin 9.2 g/dl. Mediastinal tube drainage was approximately 650 ml/h during the first 6 h. The drainage was collected, washed, and concentrated for reinfusion. Additional blood volume replacement was accomplished using homologous packed erythrocytes, fresh-frozen plasma, platelet concentrates, and colloid solutions. Calcium chloride was administered intermittently (total dose, 3 g) to maintain a normal blood ionized Ca²⁺ level. Mediastinal drainage slowed to 150 ml/hr after the initial 6 postoperative hours and to 25 ml/h 13 h after surgery. At that time, chest tube drainage was 4,985 ml, and replacement consisted of 2,000 ml autologous erythrocytes, 1,750 ml homologous packed erythrocytes, 1,500 ml fresh-frozen plasma, 450 ml platelet concentrates, and 250 ml 5%
partial protein fraction. The hemoglobin was 14.4 g/dl, PT 12.0 s, 
PTT 30.1 s, and platelet count 156,000/mm³.

On the second postoperative day, the mediastinal drainage tubes 
were removed and the patient transferred from the intensive care 
unit. Total tube drainage was 5.275 ml.

Patient 2: A 53-year-old, 89-kg man with crescendo angina pectoris 
underwent cardiac catheterization. He had no history of asthma, 
food or drug allergies, or other atopic disorders. Premedication 
and technique of catheterization were similar to those described for 
the patient above. Angiography demonstrated two-vessel coronary artery 
disease and inferior wall hypokinesis. Protranate sulfate, 50 mg, iv, 
administered at the conclusion of the study, was followed immediately 
by severe hypotension, urticaria, and facial numbness. Treatment 
consisted of oxygen, intravenous fluids, methoxamine, diphenylhydramine, 
and methylprednisolone.

Nine days later the patient underwent percutaneous transluminal 
coronary angioplasty. He received prednisone, 100 mg po, and 
cimetidine, 300 mg po, every 6 h during the 24 h prior to angioplasty 
and diphenhydramine, 50 mg im, on transport to the catheterization 
laboratory. Dissection of the left anterior descending coronary artery 
resulted in urgent coronary artery bypass surgery. Heparin, 3 mg/ 
kg, was administered prior to cardiopulmonary bypass. During re-
warming on CPB, hydrocortisone 200 mg and diphenhydramine 50 
mg were administered iv. CPB was terminated 30 min later without 
inotropic support. After a 5-mg test dose of protamine was injected 
iv without effect, heparin neutralization was accomplished with 250 
mg infused over 5 min. No adverse reaction occurred.

Steroid therapy was continued for 12 h. The patient received 2 
units of whole blood and 2 units of fresh frozen plasma postoperatively. 
Total chest tube drainage was 380 ml when the tubes were removed 
17 h after surgery.

Discussion

The protamines are a group of low molecular weight 
proteins found in the sperm of salmon or related species 
of the salmonidae or clupeidae family as well as in 
human sperm. Protamine is used clinically in insulin 
preparations as an absorption-delaying agent and as an 
intravenous preparation to neutralize heparin, the latter 
being associated with instances of profound cardiovas-
cular collapse.1-10 The etiology of this phenomenon may 
be immune-mediated anaphylaxis (type 1 hypersensitivity) 
or nonimmunologic (anaphylactoid).11

Immunologic anaphylactic reactions to protamine have 
been reported in the following: 1) patients presumably 
cross-sensitized to protamine because of sensitization 
with fish antigens to which they are allergic,1,2 2) patients 
sensitized by previous administration of protamine,3,4 
and 3) diabetic patients sensitized to protamine by 
previous exposure via protamine zinc or NPH insulin 
administration.5-6 There are approximately 2.8 mg of 
protamine per 100 units of protamine zinc insulin and 
0.5 mg per 100 units of NPH insulin. Vasectomized 
men also may be at risk. Twenty-two per cent of this 
population will contain antiprotamine antibodies to the 
protamine in human sperm.12 Some infertile men also 
may have antisperm antibodies that cross-react with 
protamine.13 Documentation of an immunologic, 
immediate hypersensitivity reaction to protamine has in-
cluded elevated protamine antibodies of the IgE, M, 
and G classes in one case2 and the demonstration of a 
complement dependent, skin-sensitizing IgG protamine 
antibody in another.3

More common are nonimmunologic anaphylactoid 
reactions to protamine sulfate.7-10 Mast cell and basophil 
activation and subsequent mediator release is triggered 
through pathways not involving IgE or IgG antibody, 
that is, activated complement fragments (C3a, C5a), calcium 
ionophores, or hyperosmolar stimuli. Support for non-
imunologic effects of protamine includes the ability of 
protamine to degranulate rat mast cells in vitro14 
and the activation of the complement system by prot-
amine in association with C-reactive protein15 and by 
protamine–heparin complexes with subsequent C3a, C5a 
generation.16

Evaluation of protamine hypersensitivity includes a 
clinical history, immediate hypersensitivity skin testing 
(intradermal or prick tests) and, possibly, in vitro diag-
nostic tests. The belief that protamine hypersensitivity 
caused the hypotensive episodes during cardiac cathe-
terization in the patients presented above is supported 
by the appearance of the clinical findings of a systemic 
hypersensitivity reaction: urticaria, hypotension, and 
angioedema; the temporal relationship to protamine injec-
tion; and the lack of a temporal relationship to the 
administration of radiographic contrast media (RCM), 
procaine, or heparin. The absence of a history of fish 
allergy or previous protamine exposure, including in-
sulins, suggested that the mechanism of response in both 
patients was nonimmunologic, i.e., anaphylactoid.

The role of immediate hypersensitivity skin tests for 
purposes other than confirmation of penicillin or insulin 
hypersensitivity is controversial17,18 and their predictive 
accuracy in those at risk for immediate reactions to 
protamine is unstudied. Reports of positive intradermal 
skin tests to protamine from 1 ng/ml to 1 mg/ml 
following clinical hypersensitivity reactions have been 
used as evidence for an anaphylactic phenomenon.2-5 
Thus, patients suspected of a previous IgG- or IgE-
mediated reaction who react on intradermal testing with 
low concentrations of protamine may be at risk for 
another anaphylactic response if rechallenged.

Less is known about the interpretation of skin test 
results in suspected nonimmunologic reactors. The ma-
majority of subjects who have had an anaphylactoid reaction 
will demonstrate a positive wheal and flare response if 
skin tested with the inciting agent. However, in a study 
of intradermal testing after hypersensitivity reactions to 
anesthetic agents, five of 40 subjects had negative results 
after significant clinical reactions.17 In the case of RCM, 
the likelihood of another reaction upon reexposure can 
not be predicted by intradermal testing.18 Furthermore, 
RCM19 and protamine14 may cause false-positive intra-
dermal tests in normal subjects by direct non-specific mast cell degranulation. Because skin testing appears to be of little value in predicting the likelihood of anaphylactoid response, the negative result in the first patient was disregarded and intradermal testing was not performed in the three subsequent cases.

Of the in vitro diagnostic tests, the basophil histamine release test is principally a research tool, and use of the radioallergosorbent test (RAST) is prevented by the lack of a commercially available protamine antigen.

At the present time we would recommend avoiding use of protamine in patients suspected of previous anaphylactic reactions on the basis of the clinical history who currently react on intradermal skin tests with low concentrations of protamine (1 mg/ml or less). Heparin neutralization following cardiopulmonary bypass may be accomplished using hexadimethrine or omitted entirely in selected cases. Castenada et al. described the management of 204 patients with omission of heparin neutralization after cardiopulmonary bypass following surgery for acquired valvular and congenital heart disease. Only four patients later required the administration of protamine or reoperation for bleeding. Hexadimethrine bromide (polybrene) is a synthetic heparin antagonist. Hypotension, reduced cardiac output, and increased pulmonary vascular resistance have been demonstrated in dogs following its use and are more marked than those hemodynamic derangements produced by protamine. In addition, hexadimethrine has an anticoagulant action resulting from the inhibition of Factor XII activation and must be administered by careful titration to avoid continued bleeding. Although not commercially available in the United States, this drug can be prepared for clinical use.

In addition to these alternatives, management of the potential anaphylactoid reactor may include steroid–antihistamine pretreatment and cautious protamine administration. Pretreatment with steroids and histamine (H₁ and H₂) receptor blockers has been shown to attenuate anaphylactoid responses to RCM and chymopapain. The incidence of a second anaphylactoid reaction to RCM in untreated reactors is 17–55% and is reduced to 5–7.5% by pretreatment. In addition, reactions following pretreatment are generally less severe in nature. However, there have been no prospective trials of steroid–antihistamine pharmacoprophylaxis prior to protamine administration, and our limited experience with three patients is insufficient to establish its effectiveness. If protamine administration is intended following pretreatment, a small initial test dose, 5–10 mg, has been recommended. Sympathomimetics, rapid fluid infusion, antihistamines, and steroids should be immediately available for treatment of a hypersensitivity reaction. Immediate systemic reactions to protamine following cardiopulmonary bypass must be distinguished from hypovolemic and cardiogenic shock and cardiac tamponade.

In our initial experience (patient 1), omission of protamine neutralization of heparin following cardiopulmonary bypass was elected on the basis of the patient’s strong clinical history of hypersensitivity reaction, the unavailability of hexadimethrine, and uncertainty regarding the efficacy of steroid–antihistamine pretreatment prior to protamine reexposure. In the second patient with a history of anaphylactoid protamine hypersensitivity and in two subsequent cases protamine administration was performed without incident following steroid–antihistamine prophylaxis. Postoperative blood loss and transfusion were routine in contrast to the postoperative course following omission of heparin neutralization. The transfusion of 29 units of homologous blood products in the first patient (vs. four in the second case) created a significant potential for transfusion reaction, acquired infection, and metabolic disorders related to massive blood transfusion. Given the frequency of posttransfusion hepatitis, including asymptomatic cases, is 3–6 cases/1,000 units transfused, the risk of postransfusion hepatitis to the first patient following omission of heparin neutralization was 8.7–17.4%. This may be contrasted to the unknown frequency and morbidity of hypersensitivity response to protamine in a pretreated individual. In the case of RCM, 5–7.5% of pretreated potential reactors experience mild symptoms.

Management of the patient with protamine hypersensitivity during cardiac surgery requires assessment of the relative risks of protamine reexposure, hexadimethrine administration, and omission of heparin neutralization. Avoidance of protamine may be preferable for the suspected immunologic reactor; however, the choice of management is less clear for the nonimmunologic reactor. This report presents two patients with previous anaphylactoid reactions to protamine sulfate and discusses their management during cardiac surgery.

The authors acknowledge the valuable contributions provided by Norg Ellison, M.D., and L. Henry Edmunds, M.D., by their editorial review of this manuscript.

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61:764–767, 1984

Migrating Disc Complicating Spinal Decompression in an Achondroplastic Dwarf: Intraoperative Demonstration of Spinal Cord Compression by Somatosensory Evoked Potentials

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Achondroplasia, a dysplasia of endochondral bone formation, involves both the vertebral column and long bones. Approximately 50% of achondroplastic dwarfs have symptomatic spinal stenosis.1 Although stenosis of the vertebral canal is most common in the thoracolumbar region, cervical and generalized stenosis also can occur.2 In achondroplastic dwarfs, the intervertebral discs are relatively hyperplastic and have a tendency to bulge laterally and posteriorly.3 Although routine extradural

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Accepted for publication May 22, 1984.