Suspected Protamine Allergy: Diagnosis and Management for Coronary Artery Surgery

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Anaphylactic reactions, although very rare, present a major problem in medicine because they are associated with significant morbidity and mortality. In France, anaphylaxis occurs in 1 of 1500 anesthetics with a mortality of 6% (1). The incidence of anaphylaxis during anesthesia in Australia in the late 1970s was 1 in 5000 (2). Identification of the drug responsible for anaphylaxis becomes more difficult when the patient receives multiple drugs. Inappropriate “allergy” designation complicates future care of the patient, thus underscoring the importance of diagnostic techniques to identify the drug responsible. In this report of a patient suspected to have allergy to protamine, the diagnostic information and clinical course upon reexposure suggested an alternative diagnosis.

Case Report

A 56-yr-old male presented for cardiac catheterization because of a positive stress test and new anginal pattern. Past medical history included reactive airway disease, hypercholesterolemia, and a “silent” myocardial infarction 2 yr before admission. Past surgical history included bilateral carpal tunnel release and bilateral inguinal herniorrhaphies.

After cardiac catheterization via the right femoral artery and vein, the patient received 15 mg of protamine intravenously to neutralize administered heparin. Within 15 min, the patient developed severe hypotension and bradycardia. Treatment consisted of atropine 1 mg intravenously and rapid colloid administration. The patient complained of pruritus and dyspnea. Physical examination revealed diffuse urticaria and bilateral wheezing. Subsequent treatment included 50 mg of diphenhydramine and 100 mg of hydrocortisone intravenously every 8 h and 50 mg of ranitidine every 12 h, for 2 days, after which he required urgent coronary artery bypass surgery.

Further discussion with the patient revealed that he had undergone vasectomy for voluntary sterilization. To evaluate further an allergy to protamine, the patient received intradermal tests according to Fisher’s protocol (3). Results of the intradermal test to protamine were negative. (See Table 1). Serum for radioallerosorbent (RAST) testing for antiprotamine IgE and IgG was secured for subsequent analysis (4). The patient received 10 mg of diazepam orally and 2 g of cefazolin intravenously before operation and was monitored using noninvasive modalities, a radial arterial catheter, and an oximeter pulmonary arterial catheter. The induction of anesthesia employed intravenous sufentanil, 2 μg/kg, and vecuronium, 10 mg, with maintenance provided by isoflurane in oxygen and intravenous sufentanil. Heparin (300 U/kg) administration achieved an activated clotting time of 504 s. After initiation of cardiopulmonary bypass, the patient received 50 mg of diphenhydramine and 250 mg of methylprednisolone intravenously.

After successful termination of cardiopulmonary bypass with lidocaine and nitroglycerin infusions, protamine administration began in step-wise fashion. First, a challenge dose, 1 mg of protamine in 50 mL of diluent, was infused over 2 min 45 s without subsequent hemodynamic changes over 5 min. Then, 10 mg was infused over several minutes. Again hemodynamics did not alter. Finally, the full neutralization dose, 400 mg, was infused over 12 min to neutralize the total heparin dose of 40,000 U. Figure 1 summarizes these events. Blood specimens were obtained for plasma histamine concentration just prior to protamine administration and 1, 3, and 5 min after both the 1-mg challenge and the neutralizing dose. Table 2 displays these results. Airway pressures did not deivate with or after protamine administration. No cutaneous changes occurred perioperatively, nor did any other significant adverse sequelae.

The patient was discharged on the ninth postoperative day and returned 2 mo later for collection of serum. Repeat RAST remained negative to IgG and IgE. In addition, no antibodies of the IgA, IgG, and IgM classes were present to sperm determinants.

Discussion

Anaphylactic reactions occur with a wide range of drugs used during anesthesia. These include antibiotics, induction drugs muscle relaxants, opiates, local anesthetics, latex, radiocontrast dye, protamine, blood products, and most other drugs employed during anesthesia. In a review of the French and English literature between 1964–1984, Levy (5) found 975 cases of

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Table 1. Results of Skin Testing

<table>
<thead>
<tr>
<th>Material</th>
<th>Concentration</th>
<th>Skin Induration (mm)</th>
<th>Pruritus</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.9%</td>
<td>4.0</td>
<td>None</td>
<td>Negative</td>
</tr>
<tr>
<td>Tubocurarine&lt;sup&gt;b&lt;/sup&gt;</td>
<td>100.0 µg/mL</td>
<td>14.0</td>
<td>Intense</td>
<td>Positive&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Protamine&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1.0 µg/mL</td>
<td>5.5</td>
<td>None</td>
<td>Negative</td>
</tr>
<tr>
<td>Protamine&lt;sup&gt;e&lt;/sup&gt;</td>
<td>10.0 µg/mL</td>
<td>7.0</td>
<td>Mild</td>
<td>Negative</td>
</tr>
</tbody>
</table>

<sup>a</sup> Saline 0.9% used as a negative control to rule out dermatographia.

<sup>b</sup> d-Tubocurarine HCl 3 mg/mL (Squibb, Princeton, NJ) diluted with preservative-free saline. Used as a positive control positive result to exclude impaired responsiveness.

<sup>c</sup> Skin induration >10.0 mm in largest diameter measured after 10 min and persisting at least 30 min constitutes a positive result.

<sup>d</sup> Protamine sulfate 10 mg/mL (Elkins-Sinn, Cherry Hill, NJ) diluted with preservative-free saline. The recommended dilution for protamine is 1 µg/mL (3).

<sup>e</sup> Protamine sulfate, tenfold more concentrated than initial dilution, used to exclude inadequate allergen exposure.

Figure 1. Hemodynamic and histamine concentration measurements during protamine infusions. Arrows labeled 1 indicate beginning and termination of intravenous infusion of 1 mg of protamine in 50 mL of diluent. Arrows labeled 2 indicate beginning and termination of 400-mg protamine infusion (total volume, 90 mL). The relative time scale begins 1 min before the first protamine infusion. Histamine concentrations appear as columns. Connecting lines for mean systemic blood pressure (BP; closed circles) and mean pulmonary arterial blood pressure (PAP; open circles) are for visual ease.

anaphylactic reactions to anesthetics. The incidence reported was 42.3% hypnotic drugs, 50% muscle relaxants, 32% opiates, 2.3% benzodiazepines, and 1% neuroleptics. During anesthesia, several drugs may be given concurrently, any of which may present a problem. When an anaphylactic reaction occurs, the offending drug should be identified. This case report deals with a suspected anaphylactic reaction to protamine following cardiac catheterization in a patient with a prior vasectomy.

Protamine sulfate, a strongly alkaline polycationic molecule used either to neutralize the anticoagulant effects of heparin or to slow the absorption of insulin, derives from salmon sperm through a protein purification process. The adverse reactions to intravenous administration of protamine may include rash, urticaria, bronchospasm, pulmonary hypertension, and systemic hypotension leading to circulatory collapse or death (6).

Allergic or anaphylactic reactions occur more frequently in those patients previously sensitized to the allergen. Insulin-dependent diabetic patients, treated with either neutral protamine Hagedorn or protamine zinc insulin, are sensitized daily by subcutaneous injections. Diabetic patients treated with either of these preparations may be at increased risk for allergic reaction to protamine (7–10). The rarity of allergy to protamine renders difficult the demonstration of increased risk in the diabetic population or one of its subsets. Large prospective studies fail to show any statistically significant increase in risk (11). One case control study validates increase risk, but carries with it the bias and shortcomings inherent in a case control study (12).

Patients who have undergone vasectomy may also be at increased risk of protamine allergy (13). The disruption of the blood-testis barrier after vasectomy produces antibodies to sperm in more than 60% of patients and to human protamine in 22% to 29% of patients (14,15). These antibodies to human protamine can cross-react with medicinal protamine (14). No prospective study to date has demonstrated whether patients who have undergone vasectomy have increased risk of
Allergic response to protamine (11,14,16). Anecdotal reports imply that patients who have undergone vasectomy are at increased risk for allergic response to protamine (13). However, two studies prospectively observed 16 and 20 patients, respectively, with a history of vasectomy undergoing subsequent protamine reversal of heparin after bypass. No patient experienced an adverse response to protamine (11,16).

Skin testing provides a quick and inexpensive method for evaluating an allergen's effect. Fisher employed skin tests for diagnosing patients with a history of anaphylaxis during surgery (3). False-negative responses, although rare, can occur, especially in patients taking antihistamines or in patients with IgG antibodies (17). Despite receiving antihistamines, the patient in our study displayed a positive response to skin testing with curare, ruling out the possibility of a false-negative response to protamine owing to antihistamine administration.

Histamine concentrations measured serially did not rise above the normal physiologic values. Antihistamines attenuate the effects of histamine on receptors, but do not affect the release of histamine from mast cells upon exposure to an antigen. However, steroids stabilize membranes and thus may prevent degranulation of mast cells. Steroid pretreatment may explain the absence of increased histamine concentrations in this patient.

Serum collected before surgery for RAST failed to demonstrate IgG or IgE to protamine. However, after an acute reaction, antibodies may be undetectable, mandating repeat testing several months later (17). After a 2-mo interval in this patient, results of RAST testing remained negative. The patient also tested negative for antibodies to sperm. Stabile hemodynamics following a neutralizing dose of protamine, no increase in histamine concentrations, a negative response of RAST to protamine, and no antibodies to sperm lead one to conclude that this patient was not allergic to protamine. The event after catheterization more likely represents an anaphylactoid reaction to intravenous contrast drug, although this possibility has not been explored further. Contrast drug reactions may occur without prior exposure, may be delayed, and are not predicted by skin tests (19). Prevention of contrast reactions with steroid pretreatment has been well documented (20).

The potential for an anaphylactoid reaction to protamine represented the primary concern during this patient’s surgery. Unneutralized heparin increases unacceptably the need for blood product transfusion (21,22). The technique of a graded exposure to protamine helps minimize allergen exposure should an adverse response occur. Another possible approach might have been preoperative desensitization; this has not been reported with protamine and was not possible due to the urgency for surgical intervention in this patient.

Protamine allergy, although often cited, is rarely documented. This case highlights the importance of vigorous followup to ascertain or rule out the diagnosis when protamine allergy is suspected. Just as vasectomy alone does not always yield antibodies to sperm or protamine (14,15), and just as IgG antibodies to protamine does not always result in an adverse clinical response to protamine (12,14), vasectomy and a suspicious clinical event following protamine administration do not ensure that the offending drug was indeed protamine.

References


