Increased risk of severe protamine reactions in NPH insulin–dependent diabetics undergoing cardiac catheterization

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ABSTRACT Protamine is widely used for reversing systemic heparinization after cardiac catheterization. Although rare, major reactions to protamine that simulate anaphylaxis occasionally occur and have previously been associated only with an allergic reaction to fish. Because neutral protamine Hagedorn (NPH) insulin includes protamine, it might be anticipated that NPH insulin–dependent diabetic patients would develop sensitivity to protamine. Of 866 consecutive patients undergoing cardiac catheterization over a 20 month period, 651 received protamine for reversal of heparinization. Of these, 8.5% (56/651) were diabetics and 2.3% (15/651) were NPH insulin–dependent diabetics. During this period seven patients were observed immediately after administration of protamine to have major adverse reactions that required the administration of catecholamines. One death ensued. Of the seven major reactions, four occurred in NPH insulin–dependent diabetics and one occurred in a patient with an allergy to fish. The incidence of major protamine reactions was 27% (4/15) in the NPH insulin–dependent diabetics vs 0.5% (3/636) in those with no history of NPH insulin use (p < .001). This represents a 50-fold increased risk of a major reaction to protamine if the patient was receiving NPH insulin. Accordingly, we recommend that diabetics on NPH insulin and patients with allergies to fish undergo cardiac catheterization without the use of protamine or, when necessary, that protamine be administered cautiously in anticipation of a major adverse reaction.


SINCE its introduction in 1939, protamine has been used for reversal of the effects of heparin in situations requiring short-term anticoagulation. Its use in cardiac catheterizations performed with the femoral approach has become routine in many laboratories. Used according to established guidelines, protamine is a relatively safe and effective drug. However, severe reactions to intravenous protamine have been reported, documenting respiratory compromise, hypotension, and shock immediately after its administration. The only factor previously reported to predispose to such protamine reactions is a history of allergic reactions to ingestion of fish.

Many insulin-dependent diabetic patients have had long-term exposure to protamine in the form of neutral protamine Hagedorn (NPH) insulin. The purpose of this study was to investigate the relationship between NPH insulin use and severe adverse reactions to intravenous protamine given in the course of cardiac catheterization.

Methods

The records of 866 consecutive patients undergoing cardiac catheterizations at Boston University Medical Center over a 20 month period from September 1980 to May 1982 were reviewed retrospectively. The mean age was 56 years, with 73% men and 27% women. Of these, 98 were diabetic and 30 were diabetics with histories of NPH insulin use.

All patients underwent cardiac catheterization in the fasting state, after premedication with diazepam and diphenhydramine. In all cases an intravenous bolus of 100 U/kg heparin was given after the introduction of the arterial catheter. Of the 866 consecutive catheterizations, 215 were performed with the brachial approach and 651 were performed with the femoral approach. No protamine was given to those whose catheterizations were performed from the brachial artery. At the end of each femoral procedure, the total effective heparin dose was calculated, taking into account the initial dose, all heparin in the flushing solutions, and the disappearance half-life of heparin. With the use of 1 mg of protamine for each 100 U of heparin effective at that time, the protamine dose needed for reversal was estimated and given as an intravenous bolus at a rate of 5 to 10 mg each minute. As long as the patient remained stable...
thereafter, the arterial catheter was removed and hemostasis was achieved by direct femoral pressure.

**Prospective control group.** To prospectively study the normal blood pressure response to protamine, 10 additional patients who had cardiac catheterization from the femoral approach were chosen at random. Blood pressure was recorded every minute for 15 min after intravenous administration of protamine. In this group no adverse symptoms or signs were noted in response to the drug.

**Statistical analysis.** Comparison between the incidence of major reactions in patients with and without a history of NPH insulin use was made by Fisher’s exact test. A comparison of the changes in blood pressure between groups of patients was made with an unpaired t test.

**Results**

**Major protamine reactions.** During this 20 month period there were seven instances in which the administration of protamine was followed immediately by a severe reaction that simulated anaphylaxis, characterized by hypotension and sufficient symptoms to require intravenous catecholamines. We considered these the “major protamine reactions.” All seven had significant respiratory embarrassment. Other symptoms are summarized in table 1.

In each of these seven patients, clinical deterioration occurred immediately after the administration of intravenous protamine. Although this was a retrospective study, this close temporal relationship was obvious from detailed notes in the cardiac catheterization logbook. The nadir of systolic blood pressure ranged from 0 to 106 mm Hg and occurred a mean of 3.1 min after administration of protamine (range 1 to 6 min). This represented an average decline of 47% (range 15% to 100%) from the baseline level. In several of these patients only half the dose had been administered at the onset of clinical deterioration and the total dose given was therefore even less than the standard dose.

The treatment required in the seven cases of major protamine reaction included bolus administration of epinephrine in all patients (see table 1). The infusion of additional pressor agents was required because of persistent hypotension in three of the seven patients.

**Minor protamine reactions.** An additional 10 of the 866 patients in the consecutive series developed minor protamine reactions that did not require the use of intravenous catecholamines. The symptoms experienced by this group are listed in table 2. No treatment was required in eight patients. Two of the 10 patients were given additional diphenhydramine.

The nadir of blood pressure in the 10 cases of minor protamine reaction occurred a mean of 2.4 min after administration of protamine. The systolic blood pressure fell a mean of 13% (range 0% to 27%) from its baseline level (p < .01 vs the group with major reactions).

In the remaining 849 patients, no adverse symptoms were noted in response to protamine.

**Control group.** In the 10 prospective patients whose blood pressure was measured every minute after the administration of protamine and in whom no adverse reactions were clinically apparent, the nadir of blood pressure occurred a mean of 8.4 min after protamine. The mean decrease in systolic blood pressure was 5% (range 0% to 15%) (p < .02 vs the group with major reactions; p < .04 vs the group with minor reactions).

**The incidence of major protamine reactions in NPH insulin–dependent diabetics.** Of the 651 patients given protamine, 56 were diabetic and 15 were receiving or had received NPH insulin. Four of these 15 developed major protamine reactions (figure 1). The incidence of major reactions in NPH insulin–dependent diabetics, therefore, was 27% (4/15) with a 95% confidence interval of 5% to 49%.

**Major protamine reactions in patients not taking NPH insulin.** In this entire series there were 636 patients given protamine who had no history of NPH insulin use, including 41 diabetics and 595 nondiabetics. Among these patients, three major protamine reactions were observed, all of which occurred in nondiabetics. Therefore the incidence of major protamine reactions in patients without histories of NPH insulin use was 0.5% (3/636) with a 95% confidence interval of 0% to 1.0%. This was less than one-fiftieth of the 27% incidence in the insulin–dependent diabetic group (p = .001).

Of the three nondiabetics who had major protamine

**Table 1**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea, wheezing, cyanosis</td>
<td>Epinephrine (n = 7)</td>
</tr>
<tr>
<td>(n = 7)</td>
<td></td>
</tr>
<tr>
<td>Flushing, urticaria (n = 4)</td>
<td>Diphenhydramine (n = 6)</td>
</tr>
<tr>
<td>Chills (n = 4)</td>
<td>Oxygen (n = 6)</td>
</tr>
<tr>
<td>Chest pain (n = 3)</td>
<td>Catecholamine drip (n = 3)</td>
</tr>
<tr>
<td>Nausea, vomiting (n = 2)</td>
<td>Hydrocortisone (n = 2)</td>
</tr>
<tr>
<td>Respiratory arrest, death (n = 1)</td>
<td>Bronchodilators (n = 1)</td>
</tr>
<tr>
<td></td>
<td>Intra-aortic balloon (n = 1)</td>
</tr>
</tbody>
</table>

**Table 2**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flushing (n = 10)</td>
<td>Diphenhydramine (n = 2)</td>
</tr>
<tr>
<td>Urticaria (n = 5)</td>
<td></td>
</tr>
<tr>
<td>Dyspnea (n = 1)</td>
<td></td>
</tr>
</tbody>
</table>
reactions, one patient, in retrospect, recalled urticarial reactions after eating fish. The remaining two patients both had significant exposure to protamine in the course of a previous cardiac catheterization and/or coronary bypass operation within the preceding 3 months.

Rechallenge with protamine. Four of the seven patients who had major protamine reactions were subsequently reexposed, either intentionally or unintentionally, to protamine.

The first patient to have a major protamine reaction in this series was a 55-year-old NPH insulin-dependent diabetic who developed total cardiovascular collapse 90 sec after an uneventful catheterization had shown left main coronary disease. After resuscitation and intra-aortic balloon insertion, an emergency coronary bypass was performed. The patient did surprisingly well until he was given protamine at the end of the operation, when he again developed severe hypotension and could not be resuscitated. Only later was it realized that both of his arrests coincided with protamine administration.

The second patient to be reexposed to protamine after a major reaction was a nondiabetic patient who had a history of allergic reactions to fish. He underwent desensitization with incremental protamine doses before coronary bypass surgery, after which protamine was cautiously given with no ill effects.

A third patient in the major reaction group also underwent a subsequent attempt at desensitization. This NPH insulin-dependent diabetic was given incremental doses of protamine, until a moderate dose precipitated another severe protamine reaction and a major ischemic episode.

The fourth patient to be reexposed to protamine after a major reaction in the catheterization laboratory was an NPH insulin-dependent diabetic. He had a subsequent uneventful cardiac catheterization without the use of protamine. Thereafter he underwent desensitization with incremental doses of protamine immediately before coronary bypass surgery. When given protamine after the operation, no adverse response occurred.

Patients not given protamine. Of the 215 patients undergoing cardiac catheterizations via the brachial approach without protamine administration, 42 were diabetics, 15 of whom were insulin-dependent diabetics (see figure 1). There were no unexplained episodes of hypotension or symptoms simulating anaphylaxis in any of the 215 cases.

Minor reactions. Of the 10 cases of minor reaction to protamine, nine occurred in nondiabetic patients and one in a diabetic with no history of NPH insulin use.

Discussion

Protamine has been used as a procoagulant since 1939. As a protein of low molecular weight that is highly concentrated in the genital tissue of some species of fish, protamine is commercially prepared from

FIGURE 1. The schema of patients in our consecutive series undergoing cardiac catheterization showing the incidence rates of adverse reactions to protamine. The number of patients in each category is shown in parentheses. The 27% incidence in 15 NPH insulin-dependent diabetics who received protamine is in contrast to the absence of reactions in the diabetics not on NPH insulin who received protamine and to the 0.5% incidence in the 592 nondiabetics who received protamine.
the sperm of salmon.\textsuperscript{4, 14} This may explain the propensity for protamine reactions in those with histories of allergies to fish.\textsuperscript{9, 10} Because it is high in arginine and is cationic, protamine binds tightly to heparin, which is highly anionic. This neutralizes the anticoagulant effects of both substances.

The cardiovascular effects of intravenous protamine are mainly those of peripheral vasodilation with some negative inotropic effects.\textsuperscript{15-18} Protamine can cause aggregation of platelets,\textsuperscript{19} which may be the mediator of its tendency to cause increases in pulmonary arterial pressure,\textsuperscript{20} particularly when it is administered on the systemic venous side of the pulmonary vascular bed.\textsuperscript{21}

Current patterns of the use of protamine in cardiac catheterization have resulted from the way coronary arteriography developed in this country and the analysis of complications thereof. In the original protocol for arterial catheterization published by Seldinger in 1953, neither protamine nor heparin was suggested,\textsuperscript{22} nor were they used by Judkins in his technique of coronary arteriography via the percutaneous approach.\textsuperscript{12} In several studies before 1975, thromboembolic complications were found to be higher with the femoral approach than with the brachial approach.\textsuperscript{23-25} Later studies have shown a less marked difference between the complication rates of the two methods, a phenomenon largely credited to the addition of heparin to the femoral protocol.\textsuperscript{26-31}

Walker et al.,\textsuperscript{29} in comparing femoral catheterization performed with and without heparin, found fewer thromboembolic complications in those performed with systemic heparinization. This study, however, was done with historical controls, comparing results from the early years when femoral catheterizations were done without heparin to those of subsequent years when heparin was added. Thus the relative inexperience with the newer femoral technique in the earlier years may have also had an influence.

Concomitant with systemic heparinization of patients undergoing catheterization by the femoral approach has been the routine use of protamine to reverse anticoagulation at the termination of the procedure. Protamine was professed to be efficacious without any systemic proof of its safety in this setting.\textsuperscript{26, 27, 29}

In our study, the overall incidence of major adverse reactions to protamine was low. However, in a small subgroup of patients with previous exposure to the drug in the form of NPH insulin, the incidence of major protamine reactions was four of 15 or 27%. In NPH insulin–dependent diabetics with coronary disease, this is a caveat of utmost importance.

Although infrequent, episodes of major hemodynamic deterioration that stimulated anaphylaxis and temporally followed the administration of protamine have been discussed in a number of reports.\textsuperscript{5-10} Several biochemical mechanisms have been postulated, although this may vary from case to case.

Nonimmunologic anaphylactoid reactions may be responsible. In some cases the complement pathway may be activated, either directly\textsuperscript{32} or via nonspecific mediators dependent on mast cell degranulation, platelet aggregation, or interaction with C-reactive protein.\textsuperscript{33}

In one patient with a history of allergy to fish\textsuperscript{7} who had a severe reaction to protamine, the mechanism was proved to be true anaphylaxis mediated by immunoglobulin E. There have also been two isolated case reports of severe reactions in diabetics with histories of exposure to NPH insulin.\textsuperscript{5, 8} Although one of these patients developed elevation of total immunoglobulin E, no detailed immunologic testing was carried out in either study.

To our knowledge, no studies prior to this report have shown a relationship between major protamine reactions and NPH insulin use. The strong statistical relationship in this series between major protamine reactions and exposure to protamine in the form of NPH insulin implies that the patients had been specifically sensitized. Unfortunately, no specific immunologic mechanism can be elucidated because this series of protamine reactions occurring during cardiac catheterization was studied retrospectively.

It is of interest to consider the two nondiabetic patients without histories of allergic reactions to fish in this series who had severe protamine reactions. Both of these patients had been recently exposed to protamine in the course of cardiac catheterization and/or coronary bypass surgery within the 3 months preceding the major protamine reaction. One might surmise that these patients were sensitized to the protamine given to them in the course of their earlier cardiac catheterization. If so, this has significant implications for any patient who is likely to undergo cardiac surgery, in which protamine is often, although not always,\textsuperscript{34} used for heparin reversal at the termination of cardiopulmonary bypass. Indeed, postoperative severe hypotension has been previously suspected to be caused by an adverse response to protamine.\textsuperscript{3}

Lakin et al.\textsuperscript{7} reported a severe reaction in a patient who was repeatedly exposed to protamine in the setting of filtration leukapheresis. In that case, immunoglobulin G antibodies specific for protamine were found in the patient’s serum. Additionally, patients with a recent exposure to protamine had an increased incidence.
of urticarial and bronchospastic reactions to protamine given after leukapheresis.

Several alternatives exist in performing cardiac catheterization without the use of protamine. The femoral approach can be used with heparin administered according to the standard procedure without protamine, achieving hemostasis either by direct pressure or by leaving a sheath in the artery until the heparin effect is reduced. Alternatively, the Judkins approach can be used without heparin and protamine. If the physician is trained to do so, the procedure can be done by the Sones approach. Finally, high-risk patients can be desensitized with incremental protamine doses, monitoring carefully for adverse effects. The relative risks of each approach should be evaluated individually for each patient.

Recently, the Collaborative Study of Coronary Artery Surgery showed no difference in mortality between patients undergoing catheterizations with and without heparin. They did not report statistics regarding use of protamine.

In conclusion, this study showed a 50-fold (27% vs 0.5%) increase in risk of major protamine reactions in NPH insulin–dependent diabetics compared with those without histories of NPH insulin use. In our catheterization laboratory, we no longer give protamine routinely to NPH insulin–dependent diabetics.

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