

Protamine Allergy Reactions During Cardiac Catheterization and Cardiac Surgery: Risk in Patients Taking Protamine-Insulin Preparations

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Protamine insulin use may immunologically sensitize patients to protamine, leading to anaphylactoid reactions upon subsequent exposure to protamine sulfate during cardiac catheterization or cardiovascular surgery. The risk of such reactions in protamine insulin-dependent patients is uncertain. One catheterization study reported a 50-fold greater risk while a second showed no increased risk! To clarify the risk, the records of 7,750 cardiac catheterization procedures between 1984 and 1987 were analyzed for presence of NPH or PZI insulin use, protamine administration, and any complications or adverse reactions. Protamine was administered in 3,341/7,750 procedures (43%), including 171 in diabetics receiving NPH insulin. Adverse reactions to protamine occurred in 2/3,170 non-insulin patients, 0.06%, and adverse reactions due to probable NPH insulin sensitization occurred in 1/171, 0.6%, of NPH diabetics, $p = .034$. Meta-analysis of risk showed an odds ratio of 7.96 for the NPH diabetic patients, and combining these results with the other large series in the literature (269 NPH diabetics total) showed an odds ratio of 4.19 compared to a non-NPH insulin group. Meta-analysis of the surgical literature showed the risk in surgical patients to be 2.1% in NPH patients versus 0.12% with no NPH, with an odds ratio of 15.52. The greater incidence in surgical patients may be due to protamine sensitization at prior catheterization and to the larger dose of protamine administered to surgical patients.

Key words: anaphylaxis, IgE antibodies, NPH

INTRODUCTION

The use of protamine sulfate to reverse heparin during cardiac catheterization in NPH insulin-dependent diabetics is controversial [1,2]. A number of reports, mostly case reports in cardiac surgical populations, have suggested that protamine containing insulins may immunologically sensitize patients to protamine resulting in serious anaphylactoid reactions upon subsequent exposure at surgery or catheterization [3–9]. IgE and IgG antiprotamine antibodies have been identified and linked to the anaphylactoid reactions [9–11]. However, the frequency of such adverse reactions, and the risk in NPH taking diabetics is unclear. The two reports concerning cardiac catheterization have shown markedly disparate results. Stewart et al. retrospectively reviewed the results in 15 NPH diabetics and found reactions in 27%, representing a 50-fold greater risk than in non-NPH patients [1]. Reed and Gascho reported on a combined retrospective and prospective evaluation in 98 NPH diabetics undergoing catheterization and found no adverse reactions to protamine sulfate administration, and concluded the NPH diabetic was at no greater risk than other patients [2]. Several large studies in patients undergoing cardiovascular

surgical procedures have also shown variability of risk of reactions [12–15], and, thus, in both catheterization and surgical groups the risk of adverse reactions remains uncertain.

Because of the markedly diverse results of the two catheterization studies, and the variability of the several surgical studies, we reviewed our experience with diabetic patients undergoing cardiac catheterization over a 4 year period. We report the largest series of catheterization patients studied to date, and compare the risk to that of cardiovascular surgical patients as determined from the literature.

MATERIALS AND METHODS

A retrospective review of the records of all patients undergoing cardiac catheterization at LDS Hospital in

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the years 1984 through 1987 inclusive was undertaken. This retrospective chart review protocol was approved by the LDS Hospital Institutional Review Committee for Human Research. All records were computer searched for codes for cardiac catheterization procedures, diabetes mellitus diagnosis, and any complications. The written medical records of all diabetic patients undergoing cardiac catheterization during those 4 years were reviewed for type of insulin or oral hypoglycemic administration, whether protamine sulfate was administered and at what dose, and for any adverse reaction to protamine. The records of all cardiac catheterization patients, diabetic and non-diabetic, with any coded adverse event during or following the cardiac catheterization were reviewed; the type and severity of complication was recorded, and the relationship to protamine administration was noted. All patients with hypotensive episodes, defined as a fall in systolic BP to less than 90 mm Hg accompanied by symptoms/signs of hypoperfusion, or anaphylactoid reactions within 10 minutes of protamine administration were considered to have a protamine reaction.

The results were compared to those of the two disparate previous studies of catheterization patients, and the combined results of the three large surgical reports of protamine reaction risk were evaluated, using statistical techniques as described below.

Statistical Analysis

A meta-analysis [16] of the risk of protamine reactions in NPH insulin-exposed and -unexposed patients from the present study and other studies from the literature was performed. The results of the present study are reported as the percentage of patients with adverse reactions to protamine in both the NPH-exposed and -unexposed groups (percent risk). Comparison of the two risks used the odds ratio, which approximately equals the risk ratio in our case where the prevalence of adverse reactions is low. The association between adverse reactions and NPH exposure was evaluated using the X^2 test based on the log odds ratio [17]. The combination of the logarithms of odds ratios described by Fleiss [17] and by DerSimonian and Laird [18] was used to evaluate the risk in exposed and unexposed patients from the present study combined with the data from the other two studies of catheterization patients from the literature [1,2] and from the combined surgical literature [13–15]. In this procedure, the log of the odds ratio, the standard error of the odds ratio, and a weight based on the inverse of the standard error are obtained from each study. Then, weighted averages of the log odds ratio and standard errors are obtained. These measures are used to construct a test of heterogeneity of odds ratios among the studies and a global test of association for the weighted average of the odds ratio. This global test of association identifies

significance of a departure from the null hypothesis that the odds ratio equals 1.

RESULTS

During the 4 years included in the study 7,750 cardiac catheterization procedures were performed. Protamine sulfate was administered at the end of cardiac catheterization in 3,341 of the 7,750 procedures (43%). The dose ranged from 30 to 50 mg, except for one patient who received 100 mg after 10,000 units of heparin. There were 388 diabetic patients who received protamine sulfate representing 11.6% (388/3341) of all who received protamine; 217 of the 388 had no current or prior exposure to protamine insulins and 171 were receiving NPH or protamine zinc insulins.

There were two hypotensive reactions in the 3,170 patients (0.06%) not receiving protamine insulins. There were also two reactions, 1.2%, in the 171 patients on protamine-containing insulins. One was an anaphylactoid reaction which occurred in a patient who had received 50 mg of protamine sulfate IV during a cardiac catheterization 6 months earlier. The patient was taking NPH insulin then and had no adverse reaction, suggesting they were not sensitized by the NPH insulin at that time. The reaction to protamine sulfate at the subsequent catheterization, therefore, if immunologic, was most likely due to sensitization from the protamine administered at the prior cardiac catheterization rather than from the NPH insulin use. The second patient, with a severe and fatal hypotensive response, had no prior exposure to protamine except for NPH insulin use. Thus, 0.6% (1/171) of patients receiving protamine-containing insulins had an anaphylactoid type reaction which might be most likely ascribed to NPH insulin sensitization, compared to reactions of 0.06% in non-exposed patients, $p = .034$. Meta-analysis revealed an odds ratio of 7.96 for the NPH exposed patients compared to non-exposed, and this odds ratio was significantly different from 1, $p = .01$. Table I shows the results of the meta-analysis of the data from the current study, the current study combined with the two other catheterization studies [1,2], and the combined data of the three large cardiovascular surgical studies [13–15]. Testing the results of the present study and those of Reed and Gascho [2] for heterogeneity showed a p value of .346 indicating that these data represented similar populations. When the Stewart et al. [1] data was added the p value for heterogeneity was .0001, showing the Stewart et al. data to be highly inconsistent with the two homogeneous larger studies. Since the present study and that of Reed and Gascho were homogeneous, the data from the two studies were combined, and the combined results showed there was one reaction in the 269 NPH patients, yielding an odds ratio of 4.19.

TABLE I. Analysis of Risk of Protamine Reactions in NPH Insulin or Protamine Sulfate Exposed Patients*

Study group(s)	X ² heterogeneity	<i>p</i>	Odds ratio	X ² association	<i>p</i>
Catheterization					
Vincent et al. ^a			7.96	4.49	.01
Vincent et al. ^a	+ 0.886	.346	4.19	4.16	.04
Reed and Gascho [2]					
Vincent et al. ^a					
Reed and Gascho [2]	129.08	<.0001			
Stewart et al. [1]					
Surgical					
Levy et al. [12]					
Gupta et al. [14]	1.476	.224	15.52	28.06	.00001
Gottschlich et al. [13]					

*X² heterogeneity: Test for heterogeneity of data sets. A *p* value < .05 suggests data sets are from different populations. X² association: The *p* value identifies the significance of a departure from the null hypothesis that the odds ratio equals 1.

^aRefers to the data in this article.

Statistical analysis of the three large surgical series showed the data to be homogeneous, Table I, *p* = .224. There were 13 reactions in 603 NPH diabetics, 2.1%, versus 6 reactions in 6,511 non-exposed patients, 0.12%, an odds ratio of 15.52.

DISCUSSION

Several case reports between 1980 and 1984 suggested that protamine administered in protamine-containing insulins or intravenously at cardiac catheterization might sensitize patients to protamine, resulting in anaphylactoid reactions upon re-exposure during vascular or cardiac surgery, or cardiac catheterization [4–9]. However, a study by Stewart et al. [1] was the first to systematically evaluate the risk of anaphylactoid reactions caused by NPH insulin sensitization in NPH insulin-dependent diabetic patients receiving protamine sulfate at the time of cardiac catheterization. In that retrospective study there were 15 NPH insulin-dependent diabetics among the 651 patients who received protamine. Major reactions occurred in 4/15 (27%) of the NPH insulin diabetics versus 3/636 (0.5%) of patients with no prior history of NPH insulin use, a 50-fold greater incidence. A substantially different conclusion was reached by Reed and Gascho [2], in a combined retrospective and prospective study of a larger population of catheterization patients. In their retrospective study of 74 NPH-requiring diabetics who were exposed to protamine during catheterization no reactions occurred, nor were there any adverse reactions in a prospective study of 24 NPH insulin-dependent diabetics. Thus, there were no reactions in their total of 98 NPH insulin-requiring diabetics. Reed and Gascho, therefore, concluded that diabetics with prior exposure to

protamine insulins were not at increased risk of anaphylactoid reactions during administration of protamine sulfate at the time of cardiac catheterization. Our study reports the largest group of NPH diabetics studied, with a 0.6% incidence of anaphylactoid reactions in protamine insulin-dependent diabetics compared to 0.06% in unexposed patients, with an odds ratio of 7.96. Probably the most accurate estimate of risk results from the combination of the present study and that of Reed and Gascho representing 269 diabetics, with an odds ratio of 4.19 and relative risk of 4.

A review of the surgical literature is also instructive. In an indepth review of protamine toxicity reported in 1985, Horrow [3] described the several types of adverse responses to protamine including hypotension related to rapid administration, antibody-mediated anaphylaxis, immediate anaphylactoid responses without antibody involvement, the possibility of delayed anaphylactoid responses, and severe pulmonary vasoconstriction. He reviewed the data of 13 patients in the literature reported to have had anaphylactoid reactions due to prior exposure to protamine-containing insulins. The four patients reported by Stewart et al. in 1984 [1] were not included in Horrow's review. He determined that only one case, reported by Doolan et al. [6] provided convincing evidence of an immune-mediated phenomenon to support the hypothesis of NPH insulin sensitization. He concluded that sensitization to protamine secondary to the use of insulin preparations was an uncommon but serious occurrence. Weiss et al. [11] recently reviewed the increasing evidence of IgE antibodies to protamine occurring in NPH insulin-dependent diabetics and IgG antibodies in other sensitized patients. They discussed the mechanisms of adverse reactions to protamine which include protamine-

heparin complexes (which may activate the alternate complement pathway leading to hypotension, platelet aggregation, and thrombosis, Click et al. [20]), protamine-antiprotamine IgG-antibody interaction, inhibition of serum carboxypeptidase N, and thromboxane production, but concluded that humorally mediated IgE immune responses are the likely cause of the reactions in diabetics taking protamine insulins. Levy et al. [12] reported the results of a prospective evaluation of protamine administration to NPH-requiring diabetics undergoing cardiac surgery procedures. There were 50 NPH diabetics out of 1,551 surgical patients. Reactions occurred in 1/50 (2%). It should be noted that the patients in Levy's study all had prior catheterization and, while not stated in the report, some undoubtedly had protamine during catheterization. The sensitization in the 1 of 50 patients might have occurred from that exposure rather than NPH sensitization. Gottschlich et al. [13] performed a retrospective analysis of 2,996 patients undergoing cardiac bypass surgery. Four of the subjects experienced an adverse reaction due to protamine (0.13%). Two occurred in non-diabetic patients, 0.07% (2/2,601), and both patients had prior exposure to protamine sulfate during cardiac catheterization. There were 68 diabetics receiving NPH insulin and adverse reactions to protamine occurred in 2.9% (2/68). One of the two diabetics with protamine reactions had a prior exposure to protamine during cardiac catheterization. Whether the other diabetic patient with a reaction also received protamine sulfate during cardiac catheterization was not stated. Thus, it is not possible to conclude that both patients had NPH insulin sensitization; one or both may have had sensitization from protamine given at prior cardiac catheterization. A brief report by Gupta et al. [14] described the incidence of protamine reactions in 1,150 arterial surgery patients. Reactions occurred in 9/325, 2.8%, of NPH insulin-taking patients, compared to 2/825, 0.24% in non-diabetic patients. Three patients required cardiopulmonary resuscitation and one died. No mention was made of possible prior protamine exposure during angiography. Levy et al. [15] reported on 3,245 consecutive cardiac surgery patients requiring cardiopulmonary bypass. There were 160 patients with NPH insulin-dependent diabetes, and there was one reaction, 0.6%, (1/160). Adverse reactions occurred in 2/3,085 (0.06%) of non-insulin-dependent diabetics. They concluded that the incidence of clinical reactions in patients taking NPH insulin was not significantly different from that in other patients. They further concluded that prior NPH insulin use did not represent a contraindication to protamine after cardiopulmonary bypass.

An important point, noted above, is the possible sensitization of patients by protamine administered IV at the time of catheterization and the role this might play in the

reported incidence of reactions, including the NPH insulin patients. Several of the early reports of protamine hypersensitivity were in patients who had received protamine at prior catheterization as the only source of exposure [6,8,10]. One of these reports, by Sharath et al. [10] is particularly pertinent in that anti-protamine IgE antibodies were identified in the patient with an anaphylactoid reaction, confirming that protamine given at catheterization can produce the same immune response and sensitization as has been described in NPH insulin diabetics [10,11]. One of two of the NPH diabetics with a protamine reaction in our study had protamine at a prior catheterization, one of two with reactions reported by Weiler et al. [9] had previous protamine exposures during each of 3 catheterizations, and in Gottschlich et al.'s study [13] both of the non-diabetics and one of two of the diabetics having reactions had protamine administered IV at prior catheterization. In the vascular and cardiac surgery studies [12–15] probably a large number of study subjects had received protamine at prior peripheral or coronary angiography. Similarly, while not stated, some of the patients in the study of Stewart et al. [1] may have been sensitized by IV protamine at previous catheterization, and this, along with the small number of NPH diabetic patients in the study may have contributed to the unusually high number of observed reactions. The actual source of sensitization in the patients reported in the literature is somewhat uncertain, therefore, and the incidence of reactions ascribed to NPH sensitization may be artifactually high, with some of the reactions due, instead, to sensitization from protamine sulfate administered at prior catheterization.

While the risk of protamine reactions during catheterization in diabetic patients exposed to protamine containing insulins is low, 0.6% or less, it is 4- to 8-fold greater than in patients without NPH exposure. Most catheterization procedures are now performed using no heparin or only low dose (3,000–4,000 units) heparin which does not require reversal for adequate hemostasis upon catheter withdrawal, and this has markedly lessened the problem of protamine allergy. When full anticoagulation with heparin and subsequent protamine reversal are required, protamine can be administered with an acceptable risk providing appropriate facilities and personnel are available for treatment of the uncommon anaphylactic reaction. If potential or active bleeding is not a problem and protamine reversal is not mandatory, an alternative approach, commonly used in patients undergoing percutaneous transluminal angioplasty, is to leave a sheath in the femoral vessel(s) until the heparin effect has decreased, usually 3 to 4 hours after cessation of heparin. In surgical patients the risk is higher for both NPH and non-NPH patients compared to catheterization patients: 2.1% vs. 0.6% for NPH-receiving patients and 0.12%

vs. 0.06% for non-NPH patients, perhaps due to a higher rate of sensitization of surgical patients by IV protamine sulfate during prior angiography, and also the larger dose of protamine used at surgery compared to catheterization. The relationship of dose to risk of allergic reactions has been described for penicillin allergy [19], and may be similar in protamine allergy. In cardiac surgical procedures protamine reversal is required in most instances. In NPH insulin-dependent patients a small test dose of protamine is often given, followed by an appropriate reversal dose if no reaction occurs with the test dose. When a reaction does occur, the heparin effect may be allowed to diminish naturally, with careful observation for excessive bleeding. As IgE and IgG protamine allergy testing [11,12] becomes more generally available, this test may be used to prospectively identify those to whom protamine can be safely given, and those who should be cautiously observed without protamine administration. Kambam et al. [21] recently reported that suspected protamine reactions at cardiac surgery were successfully treated by intravenous H₂ receptor blocker (Cimetidine) administration in two patients. The mechanism of the anaphylactoid reaction in these two patients may not have been protamine immune sensitization, however; neither patient was receiving NPH or PZI insulin, nor was protamine administration at prior catheterization mentioned. Whether this treatment will be useful in treating reactions in protamine-sensitized patients is, therefore, unknown.

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