Catheterization and Cardiovascular Diagnosis 14:19–23 (1988)

The Safety of Protamine Sulfate in Diabetics Undergoing Cardiac Catheterization

David C. Reed, MD, and Joseph A. Gascho, MD

The frequency of anaphylactoid reactions to protamine sulfate was examined by reviewing the records of diabetic patients undergoing cardiac catheterization over a 5-year period, and by prospectively monitoring diabetic patients receiving NPH insulin during the infusion of protamine sulfate.

No anaphylactoid reactions were noted after protamine administration (48 ± 5 mg) in the retrospective study in either patients with prior exposure to protamine (74 catheterizations) or in diabetics with no exposure to protamine (132 catheterizations). In the prospective study, no anaphylactoid reactions were seen in the 24 NPH insulin-dependent diabetics during the infusion of protamine sulfate (45 ± 5 mg). Five of the 42 patients (12%) from the retrospective study who underwent vascular surgery developed severe reactions to much larger doses of protamine (380 ± 118 mg).

Diabetics with prior exposure to protamine sulfate do not appear to be at increased risk of anaphylactoid reaction after the administration of protamine sulfate in the dose range of < 50 mg at the time of cardiac catheterization.

Key words: diabetes mellitus, cardiac catheterization, protamine sulfate, anaphylactoid reaction

INTRODUCTION

Several reports of major adverse responses to the administration of protamine sulfate have been made [1–7]. Most of these reactions have occurred after vascular surgery or cardiopulmonary bypass. However, recently similar reactions were noted in the setting of cardiac catheterization, where intravenous protamine sulfate is used to reverse systematic heparinization [5,6]. The majority of catheterization patients with reactions to protamine sulfate had a history of prior exposure to protamine in the form of natural protamine Hagedorn (NPH) insulin. On this basis it has been recommended that diabetics receiving NPH insulin not be given protamine sulfate [3,7,8].

The purpose of this study was to examine the safety of protamine sulfate administration during cardiac catheterization in patients with previous exposure to protamine. Because the most common form of exposure to protamine is in NPH insulin, we specifically examined diabetics with exposure to NPH insulin, and used as controls diabetics without known exposure to protamine (in the retrospective portion of the study) or nondiabetics (in the prospective portion of the study).

METHODS

Retrospective Study

The hospital records and catheterization reports of all patients with diabetes mellitus undergoing cardiac catheterization at the University of Virginia Hospital for a 5-year period, from 1980 through 1984, were reviewed retrospectively. Catheterizations were performed in the fasting state. Patients were not routinely premedicated prior to catheterization, although diazepam was frequently administered as needed for anxiety at the time of catheterization. Three patients received diphendydramine and hydrocortisone as premedications because of previous reactions to contrast agents. The diagnosis of diabetes mellitus was made on the basis of the discharge diagnosis listed in the hospital record. The age, gender, and weight of each patient was recorded. The present or past use of protamine-containing compounds, including NPH insulin and protamine sulfate, was assessed. The catheterization reports were evaluated to determine if heparin sulfate and protamine sulfate were administered at the time of catheterization. Depending upon the preference of the attending physicians, heparin sulfate was or was not given after arterial access was achieved. When administered, the dose was routinely 5,000 units intravenously. In patients receiving protamine sulfate, the

From the University of Virginia School of Medicine, Charlottesville, Virginia.

Received March 17, 1987; revision accepted May 30, 1987.

Dr. Joseph A. Gascho is now at the Division of Cardiology, The Milton S. Hershey Medical Center, The Pennsylvania State University, PO Box 850, Hershey, PA 17033. Address reprint requests there.

dose was noted. (Generally, in our laboratory, the maximum dose of protamine sulfate administered to reverse the effects of systemic heparinization is 50 mg. The dose of protamine sulfate is reduced in relation to the length of the procedure and is given intravenously over a 2–5-min period.)

The catheterization records, procedure and postprocedure notes recorded by nurses and physicians, and hospital records were carefully reviewed to determine if any adverse reactions occurred after the administration of protamine sulfate. Mild reactions were those characterized by urticaria or rashes, while moderate reactions were defined as chest pain, breathlessness, or anxiety. Those reactions did not require the administration of catecholamines. Major reactions were considered to be characterized by the development of hypotension or wheezing and requiring catecholamines and/or intubation. All subsequent records of patients receiving protamine sulfate were reviewed to determine if reactions occurred when the patient was rechallenged with protamine sulfate.

Prospective Study

Prospectively, continuous electrocardiographic and hemodynamic monitoring was performed during and after the infusion of protamine sulfate in 24 consecutive patients with diabetes mellitus with current or prior exposure to NPH insulin. These hemodynamic parameters were compared to hemodynamic parameters recorded after protamine sulfate administration in 50 consecutive nondiabetic patients, without previous known exposure to protamine, who underwent cardiac catheterization.

RESULTS

Retrospective Study

From 1980 through 1984, 5,131 cardiac catheterizations were performed at the University of Virginia Hospital. Of these procedures, 409 (8.0%) were performed in 386 patients with diabetes mellitus (Table I). This report is based upon the analysis of the records of these 409 catheterizations. The mean age of patients was 57 ± 10 SD (range 9 to 87) years; 247 of the 409 catheterizations (60.4%) were in males, and 162 (39.6%) were in females. At the time of the procedure, 145 of 409 patients (35.5%) were receiving NPH insulin, and an additional 13 patients had previous known exposure to protamine sulfate alone. Thus a total of 158 patients had been exposed to protamine prior to catheterization.

In 206 of 409 catheterizations (50.4%) protamine sulfate was administered at the end of the procedure. The mean dose was 48.0 ± 4.9 (range 15 to 70) mg, and the mean dose per unit weight was 0.66 mg/kg. Only one patient received more than 50 mg protamine sulfate. Four patients received more than 1 mg/kg (range 1.03 to 1.13 mg/kg); two of these patients weighed less than 50 kg, and the other two received doses of 8,000 and 13,000 units of heparin sulfate. Protamine sulfate was given at the end of the procedure to 74 of 158 patients (46.8%) with previous exposure to protamine, and to 132 of 251 patients (52.6%) with no known exposure to protamine. There was no significant difference in the frequency of administration of protamine sulfate between the group with exposure to protamine and the group with no known exposure to protamine ($X^2 = 0.92$, $p = 0.25$).

A total of eight attending physicians performed cardiac catheterizations on the patients of this study. Four of these physicians did not routinely administer heparin sulfate after arterial access was obtained, and a fifth physician began using heparin sulfate in 1982. Of the 84 diabetic patients with exposure to protamine who did not receive protamine sulfate after catherization, 58 did not receive heparin sulfate because of the attending physician preference. Of the remaining 26 patients, in 25 protamine sulfate was not given because of unstable angina pectoris leading to emergency surgery (11), indwelling arterial sheaths (7), transseptal approaches that were not heparinized (5), or inadvertant omission (2). One patient did not receive heparin sulfate or protamine sulfate because of a previous adverse reaction to protamine.

None of the 206 patients given protamine sulfate, nor any of the 203 patients not given protamine sulfate at the end of the procedure had anaphylactoid reactions.

Two patients experienced moderate reactions, possibly related to the administration of protamine sulfate, one from the group with previous protamine exposure, and one from the group without known previous exposure to protamine. An NPH insulin-dependent diabetic developed chest pain, cough, and dyspnea without pulmonary edema (pulmonary capillary wedge pressure = 18 mmHg) within several minutes after receiving protamine sulfate 45 mg. The second patient, a diabetic treated with an oral hypoglycemic agent without known exposure to NPH insulin or protamine sulfate, experienced dyspnea, wheezing, and chest pain 10 min after the administration of protamine sulfate, 50 mg. Neither of these patients became hypotensive, both responded to diphenhydramine

TABLE I. Profile of Retrospective Patient Population*

	No. (%)
Procedures	409
Males	247 (60.4)
Females	162 (39.6)
Exposure to protamine	
Present NPH insulin use	145 (35.5)
Previous protamine exposure	13 (3.1)
Total exposure	158 (38.6)

*Average age in years was 57.2.

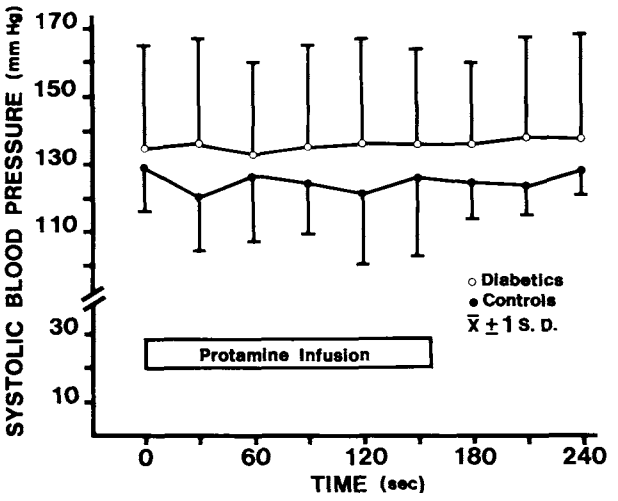

Fig. 1. Blood pressure response during and immediately after protamine sulfate infusion in 24 NPH insulin-dependent diabetics and 50 nondiabetic patients.

TABLE II. Prospective Patient Population

	No.	Protamine dosage (mg)
Procedures	74	—
Nondiabetics	50	46.7 ± 3.9
Diabetics	24	45.7 ± 3.0

and oxygen, and neither required catecholamine support, bronchodilators, or ventilatory or blood pressure support.

Three other patients developed urticaria shortly after the procedure, attributed in each case to be minor reactions to the intravenous contrast agent, but possibly related to protamine sulfate. Two of those three patients had no known exposure to protamine, and all were treated successfully with diphenhydramine.

Rechallenge With Protamine Sulfate in NPH Insulin-Dependent Diabetics

Both of the patients with reactions to protamine were later challenged with protamine sulfate at coronary artery bypass surgery. One was treated with diphehydramine hydrochloride, 50 mg, and hydrocortisone, 100 mg, prior to surgery. They experienced no untoward reactions after surgery. The doses of protamine sulfate administered were 340 and 395 mg. Of the 72 other diabetic patients previously exposed to protamine who received protamine sulfate during catheterization, 38 were reexposed at the time of cardiac surgery, where the average dose of protamine sulfate was 412 ± 72 mg. Of these patients, four (11%) experienced an adverse response. Hypotension occurred in three patients, and two of these three required catecholamine support. In the fourth patient, an immediate dramatic fall in cardiac output without hypotension was noted after protamine sulfate administration. The low output state responded to a brief course of dobutamine. Three other patients underwent peripheral or carotid vascular surgery with reversal of heparinization by protamine sulfate; one of these three patients experienced the abrupt onset of hypotension requiring multiple pressors after a 60-mg infusion of protamine sulfate. Finally, 7 of the patients underwent 11 cardiac catheterization procedures utilizing protamine sulfate after the study period ended but prior to the beginning of the prospective monitoring. None suffered adverse responses.

Prospective Study

Twenty-four consecutive diabetic patients, who were receiving NPH insulin, and 50 consecutive nondiabetic patients with no exposure to protamine were observed and monitored hemodynamically after the administration of protamine sulfate (45 ± 6 mg) at the end of the catheterization procedures (Table II). No mild, moderate, or major reactions were recorded in either group of patients. A clinically unimportant fall in the average value of systolic pressure of 5–8 mmHg was noted in both groups during the first minute of protamine sulfate administration (Fig. 1). Diastolic pressure and heart rate were unchanged.

One patient in each group experienced a decrease in systolic blood pressure of > 20 mmHg, but the decreases were transient and did not require the termination of the infusion of protamine sulfate.

DISCUSSION

It is generally recommended that patients undergoing cardiac catheterization receive heparin sulfate after catheters have been inserted [9]. These patients usually are given protamine sulfate at the end of the procedure to reverse the anticoagulation effects of the heparin sulfate. Rarely, adverse effects have been noted after the administration of protamine sulfate. Of major concern is a recent report suggesting that patients with prior exposure to protamine have a substantial risk of anaphylactoid reactions after receiving protamine sulfate after cardiac catheterization [7]. Four of 15 patients with prior exposure to protamine experienced anaplylactoid reactions after the administration of protamine sulfate after catheterization, and one of these four patients died. The authors of this report recommend that diabetics exposed to NPH insulin not be given protamine sulfate after catheterization [7], and on the basis of this report it is now recommended in one catheterization textbook that "Patients who have been receiving NPH insulin...should not receive protamine if at all possible" [8].

It was our impression that major reactions to protamine sulfate, even in patients with diabetes mellitus and pre-

vious exposure to protamine, were rare. We therefore determined the incidence of reactions to protamine sulfate, first by retrospectively examining the records of cardiac catheterizations undertaken over 5-year period of time, and second by prospectively monitoring patients during and after the infusion of protamine sulfate. Because one of the most common forms of exposure to protamine is NPH insulin, we specifically evaluated patients with diabetes mellitus with previous or current exposure to NPH insulin. Diabetics without protamine exposure served as controls.

Our data suggest that in patients generally receiving $\leqslant$ 50 mg and $\leqslant$ 1 mg/kg of protamine sulfate: 1) the incidence of reactions to protamine sulfate after cardiac catheterization is very low; and 2) the incidence of reactions to protamine sulfate is not increased by prior exposure to protamine. Anaphylactoid reactions to protamine sulfate administration were noted in neither the retrospective analysis of 74 diabetics with previous exposure to protamine nor in the prospective analysis of 24 diabetics, also with prior exposure to protamine. One patient with prior exposure to protamine had a reaction that might have been related to protamine sulfate. However, a similar reaction occurred in one patient from the group without known exposure to protamine. Thus it did not appear that previous exposure to protamine was associated with an increased frequency of even moderate reactions to protamine sulfate. In addition, the hemodynamic response to protamine sulfate was minor, and was similar in diabetic patients with previous exposure to protamine and in nondiabetics without protamine exposure.

It is unclear why we noted a low incidence of protamine reactions, while Stewart et al [7] describe a frequency of 27%. There were several differences between the two studies. The study by Stewart et al was retrospective, while our study had both a retrospective and a prospective arm. We might have noted a falsely low incidence of reactions to protamine in the retrospective portion of our study if reactions were not recorded in the patients' records. However, in the prospective trial, no reactions occurred.

Of potential concern in the retrospective part of our study is that some diabetic patients exposed to protamine did not receive protamine sulfate at the time of catheterization. However, diabetics with previous known exposure to protamine received protamine sulfate as often as diabetics without known exposure to protamine (46.8% vs 52.6%, $p = 0.25$, Chi Square test). The reason most patients did not receive protamine sulfate was based on the preference of the attending cardiologist. This decision was not based upon the concern for a possible reaction to protamine except in one patient, who was not given protamine sulfate because of a previous reaction to that agent. Thus it is unlikely that a significantly higher incidence of reactions would have been noted had all protamine-exposed diabetics received protamine sulfate.

In this study of Stewart et al [7], the total number of patients at increased risk for anaphylactoid reactions (patients with previous exposure to protamine who received protamine sulfate after catheterization) is not known. These investigators noted that 15 patients were receiving NPH insulin at the time of study, and several additional patients apparently had previous exposure to protamine. The number at risk in our report (98; 74 from the retrospective analysis and 24 from the prospective analysis) is much larger than the number at risk in the study by Stewart et al. This makes a type I error unlikely in our report.

It is possible that the dose of protamine sulfate given in the study by Stewart et al was larger than the dose given to our patients. In the report by Stewart et al, 1 mg of protamine sulfate was given for each 100 units of heparin sulfate considered effective at the end of the procedure. One hundred units/kg of heparin sulfate were administered after arterial access had been obtained at the beginning of the case. Although the exact dose of protamine sulfate is not known, it is possible that it was a larger dose than given to patients in our study.

However, despite these observations, the differences between this study and the study by Stewart et al are not fully explained.

CONCLUSIONS

No major reactions to protamine sulfate in doses of generally $\leqslant$ 50 mg and $\leqslant$ 1 mg/kg were noted after catheterization in 98 cardiac catheterizations performed in diabetics with previous exposure to protamine. Anaphylactoid reactions to protamine sulfate necessitate immediate, appropriate treatment. Slow infusion of protamine sulfate and vigilance for reaction occurrence is warranted as good medical practice, and a patient with a prior history of anaphylactoid reaction to protamine should not receive the agent. It is not known if the frequency of thrombotic complications is increased if heparin is not used. Even when heparin is administered, the use of protamine sulfate after cardiac catheterization can be avoided by applying the pressure over the puncture site for prolonged periods of time, or by delaying withdrawal of the catheter until the effects of heparin sulfate have abated. However, as shown in these data, in the largest series to date, the active or prior use of NPH insulin does not appear to be associated with an increased incidence of anaphylactoid reactions to protamine sulfate after cardiac catheterization. Our data would suggest that exposure to NPH insulin per se in not a contraindication to the use of protamine sulfate in doses of $\leqslant$ 50 mg or $\leqslant$ 1 mg/kg.

REFERENCES

1. Jackson DR: Sustained hypotension secondary to protamine sulfate. Angiology 21:295–298, 1970.
2. Moorthy SS, Pond W, Rowland RG: Severe circulatory shock following protamine (an anaphylactoid rection). Anesth Analg 59:77–78, 1980.
3. Cobb CA, Fung DL: Shock due to protamine hypersensitivity. Surg Neurol 17:245–246, 1981.
4. Vontz FK, Prestow EC, Cahill DJ: Anaphylactoid shock following protamine administration. Am Surg 48:549–551, 1982.
5. Lowenstein E, Johnston WE, Lappas DG, D'Ambra MN, Schneider RC, Daggett WM, Akins CW, Philbin DM: Catastrophic pulmonary vasoconstriction associated with protamine reversal of heparin sulfate. Anesthiology 59:470–473, 1983.
6. Holland CL, Singh AK, McMaster PR, Fang W: Adverse reactions to protamine sulfate following cardiac surgery. Clin Cardiol 7:157–162, 1984.
7. Stewart WJ, McSweeney SM, Kellett MA, Faxon DP, Ryan TJ: Increased risk of severe protamine reactions in NPH insulin-dependent diabetics undergoing cardiac catheterization. Circulation 70:788–792, 1984.
8. Grossman W: Complications of cardiac catheterization: Incidence, causes and prevention. In Grossman W (ed): "Cardiac Catheterization and Angiography." Philadelphia: Lea and Febiger, 1986, p. 39.
9. Baim DS, Grossman W: Percutaneous approach and transseptal catheterization. In Grossman W (ed): "Cardiac Catheterization and Angiography." Philadelphia: Lea and Febiger, 1986, p. 86.