

Protamine allergy as a complication of insulin hypersensitivity: A case report

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Background: Although most patients receiving insulin produce insulin-specific IgE, significant allergic symptoms develop in very few of them. Patients receiving neutral protamine Hagedorn (NPH) insulin are at increased risk for the development of protamine hypersensitivity. The case of a 19-year-old woman with insulin-dependent diabetes and regular and NPH insulin hypersensitivity is presented.

Objective: The purpose of this study was to determine whether desensitization to NPH insulin, as well as standard insulin desensitization, could control allergic symptoms in a patient allergic to both NPH and regular insulin.

Methods: The patient required insulin desensitization for severe urticaria, angioedema, and occasional wheezing resulting from her insulin dose. She underwent a standard protocol for insulin desensitization twice in a 2-month period, with persistence in her symptoms. She was found to have high protamine-specific, as well as insulin-specific, IgE levels, and because of her poor response to regular insulin desensitization, she was desensitized to both regular and NPH insulin.

Results: Dual desensitization resulted in marked improvement in her symptoms. The patient had recurrence of urticaria and angioedema a year and a half later, at which point the NPH was stopped and she was desensitized to regular insulin. She continued to receive regular insulin 4 times per day over the following 3 years with only occasional hives.

Conclusion: Patients with insulin allergy may not have complete resolution of their symptoms after standard desensitization, particularly those patients with concomitant protamine allergy. These patients may require protamine/NPH desensitization, an alternative insulin preparation, or both. (*J Allergy Clin Immunol* 1999;104:462-5.)

Key words: Insulin allergy, protamine allergy, desensitization, IgE, IgG

Before the more common use of human insulin, bovine and porcine insulin-specific IgE could be found in up to 80% of patients with insulin-dependent diabetes mellitus (IDDM).^{1,2} Insulin-specific IgE develops in

Abbreviations used

IDDM: Insulin-dependent diabetes mellitus

NPH: Neutral protamine Hagedorn

approximately half of insulin-treated patients.³ Insulin-specific IgG is present in virtually all patients with IDDM.⁴ Local allergic reactions to insulin occur in 15% to 55% of patients, but only 5% to 15% of patients actually require treatment for these reactions.^{5,6} Systemic allergic reactions to insulin only occur in 0.1% to 2% of patients.⁷⁻⁹

Neutral protamine Hagedorn (NPH) insulin contains protamine to prolong its metabolism, leading to its longer therapeutic effect compared with that of regular insulin.¹⁰ Patients receiving NPH insulin are also at increased risk for the development of protamine hypersensitivity.¹¹⁻¹³ One study found a 50-fold increased risk of a major reaction to protamine used for heparin reversal during cardiac catheterization or cardiac bypass if the patient was receiving NPH insulin.¹¹ There are only a few reports in the literature of diabetic patients with immediate-type hypersensitivity reactions to NPH insulin.¹⁴⁻¹⁶

CASE REPORT

Our patient is a 19-year-old white female who was diagnosed with IDDM in 1986. Since the beginning of her treatment with insulin, she experienced local hives at injection sites. A variety of measures were undertaken to reduce her reactions, including split dosing, administration of alternative preparations (eg, Lente and porcine insulin), and pretreatment with antihistamines, with no improvement in her symptoms. In March 1993, recurrent angioedema, wheezing, and laryngeal edema developed in the patient while she was receiving Humulin regular and NPH insulin (Eli Lilly, Indianapolis, Ind). She was treated with antihistamines and steroids with no improvement. In May 1993, she underwent desensitization with regular Humulin insulin, as outlined in Table I. Although she experienced a transient improvement after desensitization, angioedema and generalized urticaria recurred within a few weeks while she was being treated with Humulin regular and NPH insulin. A second desensitization with regular insulin was performed in July 1993 with similar results. She was found to have high protamine-specific, as well as insulin-specific, IgE levels, and because of her poor response to regular insulin desensitization, she was desensitized with both NPH and regular human insulin in September 1993. The NPH desensitization protocol is outlined in Table I. The patient had marked improvement in her symptoms with only intermittent hives over the following year and a half.

In March 1995, she had recurrence of severe hives and angioedema. At this point, the decision was made to stop the NPH insulin to

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remove the continued protamine exposure. She underwent regular insulin desensitization and began a 4 times daily regimen of regular insulin. It has been 3 years since her last desensitization, and the patient continues to receive regular insulin alone with only occasional hives.

METHODS

The insulin desensitization was undertaken in a hospital setting. Informed consent was obtained before each desensitization. The patient was allowed nothing by mouth other than sugar-free liquids 8 hours before and during the desensitization. The patient stopped receiving antihistamines at least 24 hours before desensitization. Vital signs were monitored every 30 minutes, and blood glucose levels were obtained every 2 hours. Insulin doses were given every 20 to 30 minutes. If any reaction occurred, then the previous one or two doses were repeated until no further reaction was observed. The regular and NPH insulin desensitization protocols are presented in Table I. The regimen started at an insulin dose of 0.001 U, with each subsequent dose being twice that of the previous one. Doses were initially given intradermally until 0.1 U, and all remaining doses were given subcutaneously. At the end of the protocol, the patient was given her usual insulin dose minus the total amount given during the desensitization.

Insulin- and protamine-specific IgE and IgG antibody levels were measured in serum before and after most of the desensitizations by using previously described immunoassay methods.¹⁷ All levels were measured by the Johns Hopkins Dermatology, Allergy, and Clinical Immunology Reference Laboratory (Baltimore, Md). Of note, the patient could not be skin tested because she was unable to stop her antihistamine use for a sufficient length of time.

RESULTS

The effect of insulin desensitization on insulin- and protamine-specific IgE levels is shown in Fig 1. There was very little change in insulin-specific IgE levels with any of the desensitization procedures. There was a significant decrease in the protamine IgE level after desensitization with NPH and regular insulin and a smaller, further decrease after NPH was stopped. The effect of insulin desensitization on insulin- and protamine-specific IgG levels is shown in Fig 2. There was very little response in either insulin or protamine IgG levels with any of the interventions until the NPH was stopped and the fourth regular insulin desensitization was performed, at which point a slight decrease in the protamine IgG level was noted.

DISCUSSION

There have been few reports in the literature describing the efficacy of insulin desensitization in patients receiving insulin. Galloway¹⁸ reported that 90% of patients with systemic insulin allergy can be successfully desensitized. Wentworth et al¹⁹ reported only 6 unsuccessful insulin desensitizations in a group of 129 patients. Neither protocol used human insulin. Others have described the need for more prolonged desensitization protocols for some patients who are nonresponsive to conventional protocols.^{11,20} A recent case report describes a patient who required a pancreatic transplant to control insulin allergy.²¹

Protamine-specific IgE antibody develops in approxi-

TABLE I. Regular and NPH insulin desensitization protocol

Insulin dose (mL)	Concentration (U/mL)	Route of administration	Unit dose
0.02	0.05	ID	0.001
0.04	0.05	ID	0.002
0.08	0.05	ID	0.004
0.02	0.5	ID	0.01
0.04	0.5	ID	0.02
0.08	0.5	ID	0.04
0.02	5	SQ	0.1
0.04	5	SQ	0.2
0.08	5	SQ	0.4
0.02	50	SQ	1
0.04	50	SQ	2
0.08	50	SQ	4

Modified from Eli Lilly Pharmaceutical Company protocol. Doses are given every 20 to 30 minutes. NPH insulin desensitization was run in parallel with regular insulin desensitization.

ID, Intradermal; SQ, subcutaneous.

mately 50% of patients treated with protamine-containing insulin.²² Weiss et al²³ found that patients with protamine-specific IgE had a 95-fold increased risk of experiencing a severe reaction to protamine, and patients with protamine-specific IgG had a 35-fold increased risk of a severe reaction. Stewart et al¹² found that 27% of diabetic subjects receiving NPH insulin and undergoing cardiac catheterization had major allergic reactions to protamine compared with 0.5% of those not receiving protamine-containing insulin. Thompson and Ronco¹¹ found a 50-fold increased risk of a major reaction to protamine used for heparin reversal during cardiac catheterization or cardiac bypass if the patient was receiving NPH insulin.

Blanco et al¹⁶ reported on a subject who was allergic to both NPH and regular insulin; however, that subject was successfully treated with an alternative insulin preparation (Lente). They reported initial insulin-specific IgE levels of 12.4 kU/L and protamine-specific IgE levels 6 months after initial presentation of 1.7 kU/L. Because the time sequence during which the levels were drawn and the units in which the levels were expressed are different, comparisons with our subject's levels are difficult. Dykewicz et al¹⁵ reported on 2 subjects who were allergic to NPH insulin alone and who were successfully treated with Lente insulin. They reported protamine-specific IgE levels of 9 ng/mL and 24 ng/mL, respectively, in their subjects, which are higher than the levels found in our patient (ie, 0.2 to 4.2 ng/mL). There is one report in the literature of a patient who was allergic to NPH insulin and was desensitized to protamine who remained symptom-free for 9 months after desensitization.¹⁴ Long-term symptom-free periods and specific IgE and IgG results were not published. There are no previous reports in the literature of NPH insulin desensitization.

Other groups have reported that serologic testing for insulin-specific IgE is not very helpful in the diagnosis and management of patients with insulin allergy.²⁴

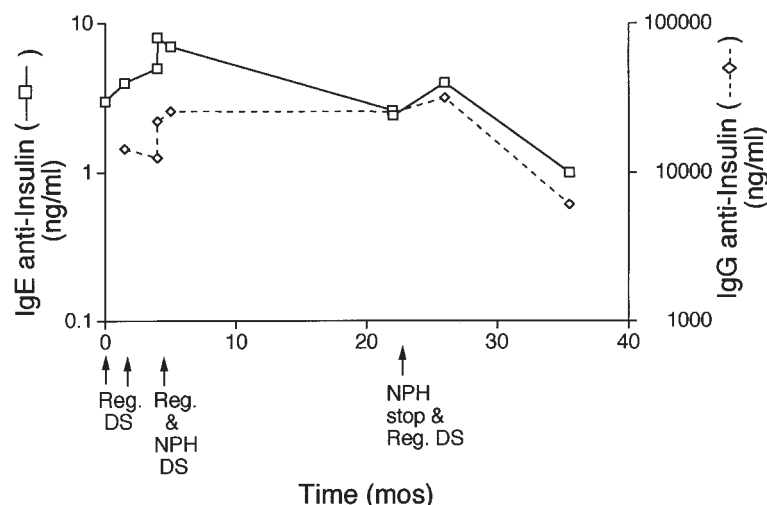


FIG 1. Insulin-specific IgE (open squares) and insulin-specific IgG (open diamonds) levels after desensitization (DS) with regular (Reg.) human insulin, NPH insulin, or both. Arrows denote desensitization times and time of NPH cessation.

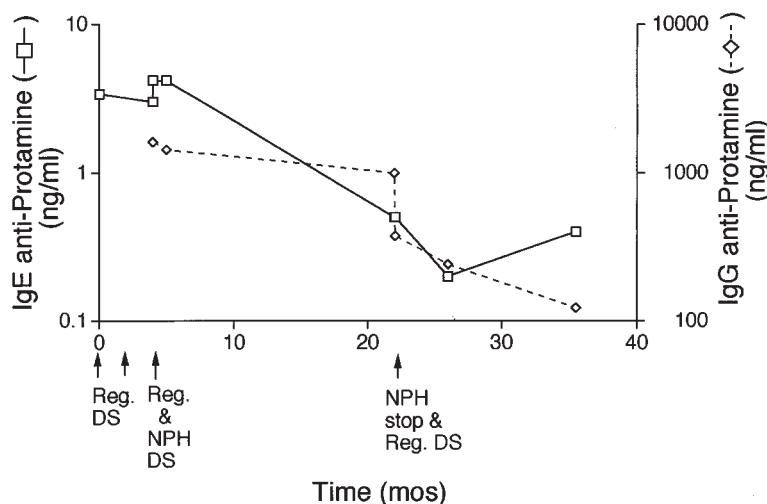


FIG 2. Protamine-specific IgE (open squares) and protamine-specific IgG (open diamonds) levels after desensitization (DS) with regular (Reg.) human insulin, NPH insulin, or both. Arrows denote desensitization times and time of NPH cessation.

Although skin testing with both regular and NPH insulin may be useful for identifying dual sensitivity to insulin and protamine in NPH insulin, we were unable to perform skin testing in our patient because of an inability to stop antihistamines for a sufficient interval before testing. In her case anti-insulin- and antiprotamine-specific IgE levels, in addition to history, were helpful in making the diagnosis. Although there was a decline in specific IgE to protamine after desensitization, the levels of specific IgE for insulin and protamine were not predictive of changes in her reactivity after desensitization.

This case report illustrates that desensitization with regular insulin may not always be successful in relieving symptoms of insulin allergy. In this case we believe the failure of conventional desensitization was the result of

protamine sensitivity, although it is possible that use of a slower desensitization protocol could have been of benefit, albeit not necessarily possible in a patient with labile blood sugars. Any patient who has failed standard insulin desensitization and is receiving NPH insulin should be assessed for protamine allergy. Patients who do not respond to conventional insulin desensitization protocols may require repeated desensitizations, as well as use of alternative long-acting insulin preparations (eg, Lente), desensitization with protamine or NPH insulin, very slow desensitization protocols, or use of frequent regular insulin dosing. Our patient was unable to tolerate Lente insulin from previous trials. She initially responded well to desensitization to NPH insulin but eventually required cessation of NPH insulin to provide long-term relief.

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