

Type I Allergy to Insulin: Case Report and Review of Localized and Systemic Reactions to Insulin

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Allergic reactions to insulin preparations are not uncommon. Although patients often present with skin symptoms, most articles on insulin allergy are published in endocrinology and allergy journals. The purpose of this report is to describe a case of localized type I allergy to insulin as well as provide a review of the classification of insulin allergy, methods of evaluation, and management options.

Case Presentation

A 74-year-old Caucasian male with a 7-year history of type 2 diabetes mellitus presented to the Minneapolis Veterans Affairs Medical Center dermatology clinic for evaluation of a 2-year history of pruritic erythematous papules at insulin injection sites. A single urticarial papule of 5 to 15 mm developed within 10 minutes at the site of each injection and persisted for 4 to 5 days before spontaneous resolution. There was no history of vesiculation, and the patient denied having dyspnea, dysphagia, or any other skin problems.

Four different types of insulin (Neutral Protamine Hagedorn, lispro, glargine, and aspart) as well as different syringes had been tried without change in the intensity or duration of the reactions. Topical triamcinolone ointment was not helpful. Other medical history included gastroesophageal reflux disease, hypercholesterolemia, hypertension, prostate cancer treated with radiation, and a history of stroke. He had no history of eczema, seasonal allergies, or reactive airway disease.

Physical examination of the abdomen revealed pink indurated wheals of 0.5 to 1.5 cm at sites of previous insulin injections. No angioedema was present, and a full skin examination revealed no other pertinent skin conditions.

Patch testing was performed with the North American Contact Dermatitis Group Standard Tray (65 antigens), 24

additional antigens, and 13 different types of undiluted commercially available insulin preparations (Table 1). Readings were negative at 48 and 72 hours.

Intradermal testing was then performed with the same 13 insulin types, with histamine and saline as positive and negative controls, respectively; 0.05 mL of each undiluted insulin solution was injected intradermally in the forearms. Pruritic wheals ranging in size from 8 to 10 mm developed within 5 minutes at all insulin sites as well as at the histamine site; no reaction developed at the site of the

Table 1. Tested Insulin Types

<i>Insulin Type*</i>	<i>Inactive Ingredients</i>
Vial Formulations	
Humulin L Lente [†]	Methylparaben
Humulin U Ultralente [†]	Methylparaben
Novolin 70/30 [‡]	m-Cresol, phenol
Lantus (glargine) [§]	m-Cresol, zinc, glycerol
Novolin N [‡]	m-Cresol, phenol
Novolog (aspart) [‡]	Glycerin, phenol, m-cresol, zinc, disodium hydrogen phosphate dehydrate, sodium chloride
Novolin R [‡]	m-Cresol
Humalog (lispro) [†]	Glycerin, dibasic sodium phosphate, m-cresol, zinc, phenol
Cartridge Formulations	
Novolin 70/30 [‡]	m-Cresol, phenol
Lantus (glargine) [§]	Zinc, m-cresol, glycerol
Novolin N [‡]	m-Cresol, phenol
Novolog (aspart) [‡]	m-Cresol, zinc, glycerin, phenol, disodium hydrogen phosphate dehydrate, sodium chloride
Novolin R [‡]	m-Cresol

*All 100 units per milliliter.

[†]Eli Lilly and Company (Indianapolis, IN).

[‡]Novo Nordisk Pharmaceuticals (Princeton, NJ).

[§]Aventis Pharmaceuticals (Kansas City, MO).

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normal saline injection (Figs 1 and 2). Pertinent laboratory studies included an antiinsulin immunoglobulin E (IgE) antibody of greater than 100 kU/L (positive) and antilatex IgE antibody of less than 0.35 kU/L (negative).

Based on the history, clinical examination, and intradermal testing results, the patient was diagnosed with a localized type I allergy to insulin. Protein contact dermatitis was also considered although this patient did not have eczematous dermatitis and was not atopic. Although we were unable to obtain the inactive ingredients of the insulin preparations for additional intradermal testing, an allergy to an inert ingredient was thought to be unlikely given the positive results to all 13 insulin types, which had different inactive components (see Table 1).

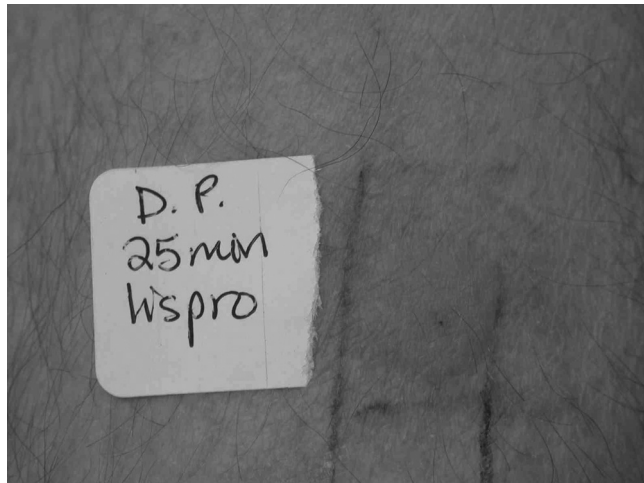


Figure 1. Wheal formation from insulin during intradermal testing.

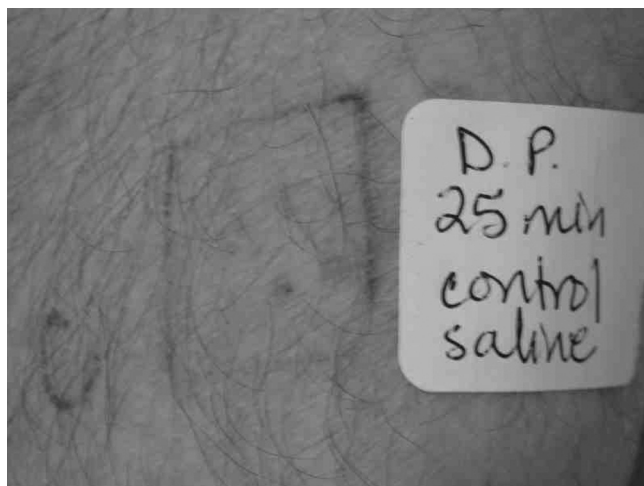


Figure 2. Testing showed no reaction at the site of negative control.

Insulin therapy was discontinued, and a combination of exenatide (an injectable glucagon-like peptide agonist), glyburide, metformin, and rosiglitazone was administered, resulting in adequate glucose control.

Insulin Allergy

Allergic reactions to insulin preparations have been recognized since treatment with insulin began in the 1920s.^{1,2} Although the prevalence of allergy to insulin has decreased since recombinant human insulin became widely available in the 1980s,^{3,4} recognition of this entity is important because systemic insulin allergies may be life threatening and because both systemic and localized reactions may have an impact on diabetes management. Although the exact prevalence of insulin allergy is unknown, 5 to 15% of patients treated with insulin who are referred for possible allergy are estimated have this condition⁵; less than 1% experience systemic reactions.^{4,6–8}

Localized insulin allergy may occur to (1) the insulin molecule or aggregates of insulin molecules formed during storage,⁹ (2) additives in the insulin preparation, or (3) components of the injection materials.⁶ Common antigenic additives include zinc and protamine. Bovine insulin is thought to be more immunogenic than porcine insulin, and both are more immunogenic than human insulin.^{10,11} It is common for patients to give a history of a medication “holiday” preceding a reaction.⁴ There are, however, reports of patients’ developing insulin allergy without a lapse of treatment.^{12,13} Other risk factors for the development of insulin allergy include type of insulin delivery; frequency of insulin administration; medication pH; solubility; additives; purity; and patient-specific factors such as age, sex, and human leukocyte antigen (HLA) type.^{10,14} HLA-DR4 and -DR7 have been associated with an increased risk of the development of insulin immunoglobulin G (IgG) antibodies whereas HLA-DR3 may be protective.^{15–18}

Type I, type III, and type IV hypersensitivity reactions to insulin have been reported.^{4,6,19} The most common reactions are type I IgE-mediated hypersensitivity reactions, either immediate reactions only or both immediate and late reactions. Patients with an immediate response typically report the development of a wheal and flare reaction within 10 to 20 minutes of allergen exposure. Individuals experiencing both immediate and late reactions initially develop a wheal and flare; these are followed by diffuse swelling and erythema, beginning 2 to 3 hours after injection, peaking at 6 to 12 hours, and disappearing within 12 to 24 hours. The reactions are generally

localized^{6,20,21} although there have been rare reports of anaphylaxis.²²

Evaluation

Evaluation of a patient suspected of having a localized insulin allergy should begin with a thorough history and physical examination to rule out other causes of symptoms, such as noninsulin allergy (eg, allergy to latex, nickel, disinfectants, or additives) or skin disease.²³ The insulin injection should be observed for proper technique.²⁴ Prick testing is not useful, owing to low sensitivity.⁷ Intradermal testing is helpful for confirming a suspected allergy, allowing identification of a specific allergen, and comparing the degree of sensitivity to particular insulins. Although several methods have been described, the procedure has not been standardized.⁷ Intradermal testing is typically performed on the flexor forearms. Testing should be performed for various insulin types, additives, and controls (usually histamine and saline). The choice of insulin used for testing may vary. In general, insulin suspected of causing a reaction should be tested, as well as those insulins considered as potential substitutes. Insulin test kits that included specific insulin types and additives (Aventis test kit, Novo Insulin Allergy Kit, Aventis Bridgewater, NJ) were available in the past.^{21,25} Common additives that may also be used for testing include paraben, phenol, metacresol, zinc chloride, isophane, and protamine sulfate.²³ However, the value of testing with protamine is debated because nonspecific reactions can occur.²⁶ The exact dilutions used for testing and monitoring guidelines vary.^{21,23} It is important to closely monitor the patient for symptoms of anaphylaxis during intradermal testing. Injection sites should be evaluated 10 to 15 minutes after testing begins and again at approximately 30 minutes. The patient should be asked to monitor the sites for up to 2 days following the testing, to evaluate for type III and type IV hypersensitivity reactions.²¹ Test sites are considered positive if the diameter of the wheal is at least half that of those of the positive control.⁷ All positive test results should be carefully correlated with the clinical history since up to 50% of diabetic patients treated with insulin will have positive intradermal testing results without clinical relevance.^{27–29}

Laboratory studies may be considered in addition to intradermal testing for patients with suspected insulin allergy. Latex may be present in the vials and syringes of insulin injection supplies; thus, antilatex IgE antibodies should be measured.³⁰ Antiinsulin IgE antibodies can be measured although the clinical relevance is unclear.

Insulin-dependent diabetic persons without clinical manifestations of insulin allergy often have elevated antiinsulin IgE levels.^{6,29,31–34} An association of insulin resistance and elevated antiinsulin IgG antibodies has been suggested although false positives are frequently present.^{4,14,21} If cutaneous symptoms persist and if intradermal test results are negative and antilatex IgE antibodies are normal, a skin biopsy may also be helpful.²⁴

Treatment

Insulin Substitution

Most individuals with insulin allergy do not require intervention; spontaneous resolution is not uncommon.^{6,35,36} For those patients who remain symptomatic, the results of intradermal skin testing with insulin preparations and additives will guide therapy.^{21,23}

If the patient is insulin dependent, the results of intradermal testing will guide the choice of insulin. The newer insulin analogues and crystalline zinc insulin may be less allergenic for patients allergic to other human insulins. Many case reports describe the use of the short-acting human insulin analogues lispro and aspart in the management of patients with cutaneous allergies to insulin.^{37–43} The amino acid substitutions in lispro and aspart result in less self-association than in other human insulins, and it is felt that these molecules are less antigenic as monomers.^{31,38,44} Glargine, a long-acting human insulin analogue, has also been successfully used in some patients with insulin allergy.^{40,45} Unfortunately, allergies to lispro, aspart, and glargine, as in our patient, have also been reported.^{42,46–48}

There have been several case reports of patients allergic to short- and intermediate-acting insulins but not to long-acting crystalline zinc insulin.^{49–51} Takatsuki and colleagues reported on a patient who had a negative skin test result for Novolin U semisynthetic crystalline zinc human insulin (Novo Nordisk, Princeton, NJ) but a positive result for decrystallized Novolin U. They hypothesized that the crystallized structure may mask the antigenicity of the insulin molecule.⁵¹ Crystalline zinc insulin may be considered as a long-acting insulin option for patients with insulin allergy who are not also allergic to zinc. The inhaled insulin Exubera (Pfizer, New York, NY) was recently approved by the US Food and Drug Administration. Although it does not replace long-acting insulin, it may be a useful tool in patients with local cutaneous reactions to short-acting insulin.

Continuous subcutaneous insulin infusion, typically with lispro or aspart analogue insulins, has been used with success since the 1980s in patients with insulin allergies.^{52–55} Valentini and colleagues hypothesized that continuous infusion maintains mast cells at the injection site in a state of degranulation, thereby blocking the immunologic reaction.⁵² Other investigators feel that continuous infusion prevents an allergic reaction by delivering a smaller insulin dose at the injection site⁵³ or by acting to slowly desensitize the patient.^{54,55}

Desensitization to Insulin

When substitution of insulin preparations and change in delivery methods do not resolve symptoms or when patients are unable or unwilling to make these changes, an insulin desensitization protocol may be initiated. Insulin desensitization has been used as a treatment for insulin allergy since the 1920s.⁵⁶ Many different protocols have been suggested,^{28,31,57–59} some of which include the injection of steroids with insulin⁶⁰ or the use of a subcutaneous pump.⁶¹ One of the first protocols for rapid desensitization with human insulin was published by Bodendorfer and colleagues in 1985.⁶² The current protocol recommended by Eli Lilly is described in Table 2. In general, modern rapid desensitization protocols have the following characteristics: (1) very small doses initially given intradermally gradually proceed to larger, subcutaneous doses; (2) the dose increases with each injection; (3) doses are administered every 15 to 30 minutes; (4) when a reaction occurs, the protocol is reinitiated one to two steps prior to the reaction; and (5) desensitization is performed in a hospital setting with resuscitative equipment on hand.

During insulin desensitization, total serum IgE and antiinsulin IgE antibodies will generally decrease.³⁵ The mechanism of desensitization is not completely understood, but it has been suggested that desensitization involves IgE antibody neutralization, the production of IgG blocking antibodies, or possibly the depletion of mast-cell mediators.^{25,61} There are many reports of successful desensitization in the literature.^{7,28,31,57–59,61–65} However, in some cases desensitization requires multiple or extended courses, and allergic symptoms may recur.^{37,38,66,67} Desensitization with oral insulin and aspirin has also been reported.⁶⁸

Other Treatment Options

Nonspecific antiinflammatory and immunosuppressive treatments or dividing the insulin dose between two or more injection sites may be helpful for some patients.^{23,35} Intraluminal antihistamines have been used since at least the 1950s.³⁶ Loeb and colleagues reported on a patient with local immediate and delayed-type hypersensitivity reactions to insulin who was treated with diphenhydramine and hydrocortisone. Injection of 1 mg of diphenhydramine with insulin prevented the immediate reaction whereas injection of 1 mg of hydrocortisone with insulin prevented the delayed reaction. When both medications were injected together, both reactions were prevented.⁶⁹ Oral antihistamines may also provide relief from local symptoms. One patient with a local reaction to insulin was successfully treated with 10 mg of cetirizine per day.⁷⁰ Ganz and colleagues reported treating systemic insulin allergy and resistance with 40 mg of oral prednisone and 50 mg of oral diphenhydramine daily.¹³ Jaeger and

Table 2. Protocol for Rapid Desensitization

<i>Insulin Volume (mL)</i>	<i>Insulin Concentration (U/mL)</i>	<i>Dose (U)</i>	<i>Route of Administration</i>
0.02	0.05	0.001	ID
0.04	0.05	0.002	ID
0.08	0.05	0.004	ID
0.02	0.5	0.01	ID
0.04	0.5	0.02	ID
0.08	0.5	0.04	ID
0.02	5	0.1	SQ
0.04	5	0.2	SQ
0.08	5	0.4	SQ
0.02	50	1	SQ
0.04	50	2	SQ
0.08	50	4	SQ

Adapted from the protocol available from Eli Lilly (Indianapolis, IN): data on file, supplied by The Lilly Answers Center on December 6, 2005. ID = intradermal, SQ = subcutaneous.

colleagues reported similar success in treating systemic allergy and resistance with corticosteroid (1 mg/kg) and oral antihistamine; the steroid dose was later tapered to 12.5 mg per day.²¹

Some patients may be able to maintain adequate glycemic control with more aggressive oral therapies and nutrition, thus obviating the need for insulin.^{6,23,46} For patients with type 2 diabetes, exenatide (Amylin Pharmaceuticals, San Diego, CA), a glucagon-like peptide 1 (GLP-1), may be another alternative. The biologic functions of GLP-1 include enhanced glucose-stimulated insulin secretion from pancreatic beta cells, up-regulated insulin gene expression, slower gastric emptying, lower basal glucagon secretion from pancreatic alpha cells, decreased appetite, and an increased sense of satiety.⁷¹ In several placebo-controlled trials, patients treated with exenatide plus sulfonylurea, metformin, or sulfonylurea and metformin exhibited a decrease in HbA1c of 0.4 to 0.9% and a statistically significant decrease in body weight.^{72–75} Exenatide is administered as twice-daily subcutaneous injections.

Summary

Localized reactions to insulin are not uncommon. The management of insulin allergy includes formulation substitution, desensitization, or the use of noninsulin hypoglycemic medications.

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