

A Case of Skin, and Secondarily Generalized, Reaction to Insulin Injection

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PRESENTATION

R.J. is a 51-year-old man who has had type 2 diabetes for 18 years. Because of poor metabolic control with oral agents, he was prescribed a premixed formulation of regular and NPH insulin (Novo Nordisk, Madrid, Spain). Two weeks later, he developed pruritic lesions at the injection site. As treatment continued, lesions of similar characteristics developed in previous injection sites. He was switched to a different brand of the same mixture of insulins (Eli Lilly, Madrid, Spain).

He presented to the emergency department when, after injecting a dose of insulin, he developed nausea, labial edema, shortness of breath, and urticaria lesions progressing from trunk to extremities. He improved rapidly with oral antihistamines and intravenous corticosteroids.

R.J. was then evaluated by the Allergology Department and was diagnosed with having experienced an anaphylactic reaction. Three days

later, blood samples were taken for laboratory testing (Table 1).

Skin prick and intradermal tests revealed sensitization to all insulins tested: regular, NPH, and premixed formulations (Novo Nordisk and Eli Lilly), as well as lispro, aspart, glulisine, glargine, detemir, aspart/aspart protamine, and lispro/lispro protamine. Results were considered positive when the diameter of the wheal was ≥ 3 mm larger than the negative control. Saline solution and histamine were used as negative and positive controls, respectively. Tests against other potential allergens were not deemed necessary because he showed reaction to all the preparations tested, which had different excipients.

A diagnosis of type I hypersensitivity to insulin was established. R.J. underwent a rapid subcutaneous desensitization to the initial mixture of insulins (regular and NPH [Novo Nordisk]) uneventfully, tolerating increasing concentrations of the

preparation to a maximum dose of 18 units. He was discharged with a prescription for this mixture, 22 units before breakfast and 16 units before dinner. Eight months later, he had had two mild generalized reactions that were controlled with oral antihistamines.

QUESTIONS

1. Is this patient allergic to insulin?
2. What is the differential diagnosis of insulin allergy?
3. What is the therapeutic approach to patients with type I allergy to insulin preparations?

COMMENTARY

Insulin allergy is a rare complication of a common disease. Since the commercialization of recombinant human insulin and its analogs, allergic reactions have become far less common, with an estimated prevalence of $\sim 2\%$,¹ but less than one-third of these cases are really caused by insulin itself. Insulin preparations contain several allergens. Additives (zinc and protamine), solvents (metacresol, glycerol, phenol, and sodium phosphate), local disinfectants,¹ and even latex² may be responsible for the allergic reaction.

In addition, skin reactions after drug injection that can resemble an allergic reaction may instead be the result of other causes, such as poor injection technique. In one study,³ insulin allergy was diagnosed in 41% of the patients studied, but in another 41% of cases, noninsulin-related causes were discovered (e.g.,

Table 1. R.J.'s Allergy Blood Testing Results

	Results	Normal Values
Total immunoglobulin E (IgE) (IU/ml)	41.2	0.0–100.0
Basal tryptase ($\mu\text{g/l}$)	1.89	0.0–11.0
Specific IgE rc207 (protamine) (IU/ml)	< 0.35	< 0.35
Specific IgE c70 (porcine insulin) (IU/ml)	5.24	< 0.35
Specific Ig E c71 (bovine insulin) (IU/ml)	3.35	< 0.35
Specific Ig Ec73 (human insulin) (IU/ml)	4.17	< 0.35
Latex	Negative	

poor injection technique, skin disease, or other systemic allergy). The remainder of the patients had local reactions of unknown cause, but symptom relief was achieved in some cases by unspecific therapy.

Insulin injected in the subcutaneous tissue may elicit various immune system reactions.⁴ Type I drug-induced hypersensitivity reactions, which mediate most insulin allergies, result from the release of mediators from immunoglobulin E-sensitized mast cells or basophiles. Type III reactions are the result of the formation of insulin-antibody immune complexes, which activate the immune response. They generally present as subdermal, more or less hot, erythematous nodules at the injection site 4–8 hours after the puncture and last for ~48 hours. In type IV reactions, which are mediated by T cells, skin reactions often appear 8–12 hours after injection but can appear as long as 24 hours after injection and last up to 7 days. The pathophysiological mechanism involved determines the clinical manifestations.

In most cases, allergic reactions appear a few minutes after injection and are restricted to the skin (i.e., red blotches, induration, pruritus, burning sensation, flushing, and urticaria). These reactions are often self-limited under continuation of therapy. However, local forms can progress to systemic symptoms (i.e., sneezing, sinus and nasal congestion, coughing, shortness of breath, wheezing, abdominal pain, nausea, vomiting, and diarrhea) and occasionally potentially life-threatening reactions such as anaphylaxis.

When patients present with cutaneous reactions to insulin injections, the first step is to confirm the diagnosis of allergy to insulin with the proper tests. Diagnosis of type I reactions is based on a meticulous

clinical history, supported by specific skin tests, serologic tests, or both.¹

If the patient is allergic to an additive, using a preparation without that additive should solve the problem.⁵ Should the diagnosis of insulin allergy be confirmed, there are various treatment options. Switching to antidiabetic oral drugs is nonviable in many cases of type 2 diabetes (and never in type 1 diabetes). In such cases, prescribing other types of insulin against which the patient is not sensitized is the most logical approach. If this is not an option, symptomatic treatment for local reactions is recommended.

Desensitization under close monitoring (in an intensive care unit, where resuscitation maneuvers can be immediately undertaken, if necessary) is the treatment of choice for patients with drug-induced type I hypersensitivity systemic reactions who require the insulin to which they are sensitized. Desensitization can also improve tolerance to insulin in local type I reactions, if deemed necessary.^{6,7}

Our patient suffered a life-threatening systemic reaction and had positive cutaneous tests to all commercially available insulins. We decided to desensitize him to a mixture of regular and NPH insulin in an attempt to control both basal and postprandial glycemia with a single preparation.

Corticosteroids and antihistamines are usually used as premedication in desensitization. We used only cetirizine as premedication because our patient already had difficulties with glycaemic control. Blood glucose levels should be closely monitored by an endocrinologist throughout the desensitization protocol.

All clinical desensitization protocols are empiric. During desensitization, drug antigens are reintroduced in an incremental

manner, allowing for full therapeutic doses to be delivered with minor or no side effects.⁸ Toleration can be maintained as long as drug antigens are administered at regular intervals because the presence of antigens at all times is crucial to maintaining the desensitized state. Another way to induce desensitization is by delivering progressively increasing doses of the allergen (i.e., regular, aspart, or lispro insulin) by continuous subcutaneous infusion via an insulin pump.⁹

Corticosteroids and immunosuppressives have been used.¹ They are not unambiguously associated with a full recovery and are not free of side effects. In refractory cases, biological therapies with rituximab and omalizumab have been described. This approach is expensive, and, again, can cause side effects. Two cases have been reported of patients who underwent pancreas transplantation for generalized allergy to insulin.^{10,11} The morbidity associated with this process and its costs continue to be of concern.¹²

CLINICAL PEARLS

- Insulin allergy is a rare complication of a common disease.
- In most cases, allergic reactions are restricted to the skin and are often self-limiting under continuation of therapy. However, local forms can progress to systemic, occasionally potentially life-threatening reactions.
- When patients present with cutaneous reactions to insulin injections, allergy to insulin and to other components of the preparation should be ruled out. Other causes of skin reactions after drug injection must also be ruled out.
- Treatment should be individualized, depending on each patient's characteristics.
- Effective and close cooperation between the endocrinologist and

the allergist to achieve a quick diagnosis and timely treatment of suspected cases of insulin allergy is especially important.

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