



Insulin allergy

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Abstract Insulin reactions occur rarely but are of tremendous clinical importance. The first was reported in 1922 as a callus reaction at the injection site of insufficiently purified bovine insulin. Porcine insulin was subsequently found to be less allergenic than bovine insulin. Increasingly pure insulins have decreased the risk of adverse reactions, and the production of recombinant insulin with the same amino sequence as human insulin saw a large decrease in adverse reactions. Currently, the prevalence of allergic reactions to insulin products appears to be approximately 2%, and less than one-third of these events have been considered related to the insulin itself. Other reactions occur due to the preservatives added to insulin, including zinc, protamine, and meta-cresol. Allergic reactions can be type I or immunoglobulin E-mediated, type III or Arthus, and type IV or delayed-type hypersensitivity reactions. Type I reactions are the most common and can, rarely, cause anaphylaxis. In contrast, type IV reactions can occur after a delay of several days. Investigations include skin prick testing, patch testing, intradermal testing, and occasionally, skin biopsy.

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Introduction

Diabetes is increasingly common, and recombinant human insulin is essential in the management of patients with type 1 and in some patients with type 2 diabetes mellitus. Insulin is also used in the acute medical setting where maintaining a normal blood glucose level improves the outcomes in medical emergencies, such as cerebrovascular accidents and acute myocardial infarction.

We shall explain the different types of allergic reactions reported for insulin itself and those reported for the components used in insulin administration. We shall consider the investigation of these different types of reaction and make recommendations for their management. We have reviewed relevant reports published since 1970 to provide a comprehensive review of information on this subject.

Background

In 1922, two Canadians, Banting and Best, extracted insulin from animal pancreatic islets. Bovine insulin was then injected into human volunteers. It was still so impure at this stage that as a result of the injection, a 7.5-cm callus developed at the injection site on the patient's left buttock.¹

Protamine, a low-molecular-weight protein, was used with zinc to develop slow-release insulin in 1936, and isophane neutral protamine Hagedorn insulin, which is also bound to protamine, was introduced in 1950. This has a maximal effect of 24 hours and can be mixed with any proportion of fast-acting regular insulin.²

By the 1970s, chromatographic purification techniques allowed the production of highly purified animal insulin. Before this development, porcine and bovine insulin had been frequently reported to cause allergic reactions and lipoatrophy.³

Human insulin was chemically synthesized in 1966, and a fully synthetic insulin (CGP 12 831) was produced by Ciba-

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Geigy in Basel in 1975. In 1978, scientists from the biotechnology corporation Genentech in San Francisco, California, working with a genetically manipulated plasmid of *Escherichia coli* bacteria, succeeded in producing insulin with the same amino sequence as seen in humans.⁴

Insulin antibodies at high titers were observed in many patients treated with early insulin preparations containing proinsulin, C-peptide, and other peptide contaminants. High levels of immunoglobulin (Ig) G anti-insulin antibodies can lead to immune-mediated insulin resistance; this is now rare due to the widespread use of highly purified porcine insulin and human insulin preparations. Lipoatrophy, which was reported in 10% to 55% of patients treated with nonpurified bovine or porcine insulin preparations, has almost disappeared since the advent of exclusive human insulin treatment. The current prevalence of reactions during insulin treatment appears to be about 2%, and less than one-third of these reported events have been considered to be related to the insulin therapy.^{3,5}

Alternatively, the noninsulin components of the injection or infusion can cause reactions to develop in patients. This has been reported to occur with local disinfectants, nickel, zinc, protamine, and preservatives and solvents such as metacresol, glycerol, phenol, and sodium phosphate.⁶

Reactions to insulin preparations range from local injection site reactions to severe generalized anaphylactic reactions. The pathologic type of allergic reactions described for insulin injections and its components include immediate type I IgE-mediated reactions, type III immune complex-type (Arthus reaction-localized or serum sickness-generalized), or type IV delayed-type hypersensitivity (DTH) reactions. These reactions can present clinically as immediate, they may have a short delay in onset with induration at the injection site and histologic evidence of leukocytoclastic vasculitis up to 6 hours after injection, or there may be a longer delay, with onset after 8 to 24 hours because of a delayed type hypersensitivity process.⁷ Most reactions are usually type I hypersensitivity, but there are no specific reports on the frequency of other types of insulin allergy.

Diagnosis of insulin reactions

Type I hypersensitivity

IgE-mediated reactions have been reported with animal and human insulin, including semisynthetic and biosynthetic insulins. The switch to insulin analogs has markedly decreased the number of allergic episodes, because the allergenicity of insulin has been proposed to be altered by chemical changes in the terminal of the β chain, where the structure is modified in insulin analogs. For instance, lispro is insulin with lysine and proline in positions 28 and 29, respectively, of the β -chain, instead of proline and lysine, as in human insulin; aspart has aspartate in position 28 of the

β -chain instead of praline; and glargine is insulin with arginine and proline in positions 28 and 29, respectively. These analogs also have ability to induce allergic reactions, however, and reduced immunogenicity has been suggested to be more associated with its faster absorption than any changes in the immunogenic epitopes.^{3,5}

IgE-mediated symptoms occur immediately after insulin injection, either intravenously or subcutaneously. Skin reactions vary from local erythema and swelling at the injection site to generalized reactions such as urticaria and angioedema. Type I reactions are the most common type of insulin allergy, with more than 300 case reports since 1950.^{8,9}

In rare, severe cases, anaphylaxis with dyspnea and hypotension has been recorded. For example, 3 severe anaphylactic reactions developed in an insulin-treated diabetic patient immediately after self-administered subcutaneous injections of neutral protamine Hagedorn human recombinant-DNA insulin within a 2-month period. These reactions consisted of local and systemic symptoms, including dyspnea and hypotension. Simultaneous sensitizations to human insulin and to protamine were demonstrated, both by skin prick testing and by the determination of serum-specific IgE. The patient was treated with human lente insulin, which was tolerated well with no reaction.^{10,11}

Accurate diagnosis is based on a meticulous clinical history, but it needs to be supported by specific skin or serologic tests, or both. In cases of diagnostic doubt, drug provocation tests can be useful, because insulin preparations contain multiple potential allergens that can trigger reactions, including carrier proteins and additives.⁵

The presence of insulin sensitization can be proven by skin prick testing and determination of the specific IgE; however, skin test results must be evaluated with care because nonallergic diabetic individuals have also been documented to have a positive skin prick test to protamine and less frequently to human insulin.¹²

First-line management of insulin allergy centers on symptomatic therapy with antihistamines. The patient should then be switched to a different insulin preparation. In patients who demonstrate allergic reactions to individual preservative components, a switch to a preparation that does not contain the specific agent can lead to a complete cessation of signs and symptoms.¹³

A further approach is to attempt to permit the patient to tolerate the insulin that causes the reaction. One method of inducing tolerance is the administration of insulin as a continuous subcutaneous insulin infusion. Several case reports describe the beneficial effect of this form of administration in diabetic patients who are allergic to insulin or to the added components such as protamine.¹⁴⁻¹⁸

The successful use of specific immunotherapy for the treatment of insulin allergy has been reported in several cases. Patients are reported in whom various treatment options, including a change of insulin, change of insulin application, and symptomatic treatment with antihistamines had been attempted, without success. Specific immunotherapy

consisting of successive subcutaneous injections of insulin was undertaken with close monitoring in an inpatient setting. The initial insulin dose was 0.00001 units and was subsequently increased 10-fold up to 1 unit, then 2, 4, 8, 16, and 20 units. If a local allergic reaction developed, the last dose was repeated until no further reaction occurred, and then the dose increases were continued. If systemic reactions occurred the dose was halved.

During immunotherapy, blood glucose was closely monitored and controlled by diet, oral antidiabetic medications in type 2 diabetic patients, or insulin pump treatment using insulin analogs different from the insulin preparations being used for immunotherapy. Specific immunotherapy was often effective, although the effects may not have been permanent, because signs and symptoms did recur.¹⁹

The use of intravenous insulin injection to induce insulin tolerability was reported in a severely insulin allergic diabetic patient. Skin tests were positive to all forms of commercially available insulin and insulin analogs but negative for solvent and additives. Attempted desensitization with the subcutaneous administration of insulin, with continuous subcutaneous injection of insulin lispro, or with oral antiallergic agents did not prevent frequent life-threatening allergic symptoms, especially after bolus injections with meals. No allergic reactions were observed after intravenous injection of 100 units of regular insulin per 500 mL through a central catheter with a portable pump delivering 5 to 10 mL/h, adjusted according to self-monitored blood glucose level.²⁰

Type III hypersensitivity

The injection of insulin has also been reported to cause a late type III Arthus reaction. This is characterized by the development of subcutaneous nodules at the injection site 2 to 6 hours after administration.²¹ This reaction necessitates immediate withdrawal of the insulin and consideration for commencement of systemic steroid treatment; however, it remains an extremely rare phenomenon.

One report documented a 31-year-old man with type 1 diabetes mellitus who presented with a small subcutaneous, slightly painful nonerythematous nodule with a central hematoma at the injection site 4 to 6 hours after injection with detemir, a long-acting insulin analog (Levemir®, Novo Nordisk).²² Detemir was switched to glargine, another long-acting basal insulin analog. The nodules spontaneously disappeared within 48 hours. The diagnosis of a type III allergic reaction was made clinically without formal confirmatory skin testing due to concern about the development of serum sickness on reintroducing the allergenic insulin.²²

Type IV hypersensitivity

Type IV hypersensitivity reactions to insulin do not appear to have been reported. Type IV reactions usually

occur to the components added to insulin preparations, including meta-cresol, protamine, and epoxy resin. Some components, such as protamine, can also be involved in type I hypersensitivity reactions.

Cresol

Cresols are a widely occurring natural and manufactured group of aromatic organic compounds that are categorized as phenols (sometimes called *phenolics*). Cresols are used as solvents, disinfectants, deodorizers, and as insecticides. Cresols are found in many foods, wood and tobacco smoke, crude oil, coal tar, and wood preservatives such as creosote, cresolene, and cresylic acids. In its chemical structure, a cresol molecule consists of a methyl group substituted onto the benzene ring of a phenol molecule. There are 3 forms of cresols that vary only slightly in their chemical structure: *ortho*-cresol (o-cresol), *meta*-cresol (m-cresol), and *para*-cresol (p-cresol). These forms occur separately or as a mixture. The word tricresol can be used as a synonym for cresol where it means a mixture of o-cresols, m-cresols, and p-cresols. Some types of insulin solution are preserved with meta-cresol. For example, 1 mL of Humalog® injection contains 3.15 mg meta-cresol.²³

DTH reactions to meta-cresol present as erythematous burning lesions at the injection sites on the day after the subcutaneous administration of insulin. Mild headache and gastric pain, along with erythematous burning lesions over the injection sites of the abdomen, developed in an older woman with type 1 diabetes the day after each insulin injection. These lesions lasted up to 2 weeks and were independent of the type of human insulin used or the site of the injection. She had been using various human insulins with no adverse effects for the preceding 3 years.

A skin biopsy specimen showed significant nonspecific inflammation compatible with a toxic drug reaction. Results of intradermal testing to human insulin, parahydroxybenzoate, esters, phenol, meta-cresol, zinc insulin, isophane insulin, and protamine were all negative. Subcutaneous injections with a sodium chloride control, meta-cresol, insulin, and glycerol were also negative after 20 minutes. Patch tests were positive to nickel sulfate 5% in petrolatum and to human, pork, and isophane insulin. A positive patch test was also seen to the meta-cresol, which was present in all insulins tested, suggesting that the preceding insulin reactions were explained by the meta-cresol contained in these preparations. This was confirmed by the fact that her skin lesions improved completely after she was treated with human insulin free of meta-cresol.

Two more patients have been reported recently. A local reaction not only developed at the injection sites, but the patients also complained of systemic symptoms, including nausea, headache, sweating, and diarrhea. They were reported to Novo Nordisk A/S, Bagsvaerd, Denmark, a producer of human insulin.

Monotard® and Ultratard®, also from Novo Nordisk, can be used in diabetic patients with meta-cresol allergy. In

response to these reactions, Novo Nordisk produced a short-acting insulin using methylparaben rather than meta-cresol as a preservative.^{24,25}

Epoxy resin

Epoxy or polyepoxide is a thermosetting polymer formed from the reaction of an epoxide “resin” with a polyamine “hardener.” Epoxy has a wide range of applications, including in fiber-reinforced plastic materials and general-purpose adhesives. The most common source of skin exposure to epoxy resin is uncured epoxy glue.²⁶

Reports of allergic contact dermatitis from unusual sources of epoxy resin have been described. Dermatitis developed in 2 patients at their insulin infusion site due to the presence of epoxy resin in the infusion set of an insulin pump. Dermatitis developed in both hands of a 15-year old boy with type 1 diabetes after the use of a portable insulin pump for continuous subcutaneous insulin administration. The needle of the pump, which was inserted in the subcutaneous tissue of the abdomen, was attached to the tube with epoxy resin glue. Patch testing showed a +++ positive reaction to epoxy resin and a ++ positive reaction to the glue-containing tube. It was not clear whether dermatitis had ever been present at the infusion site, although this appears probable. The dermatitis persisted despite avoidance of glues containing epoxy resin and disappeared only when he stopped using the insulin pump.²⁷⁻³⁰

Protamine

Protamine is a low-molecular-weight polycationic protein purified commercially from the sperm of the matured testes of salmon or related fish. It is complexed to insulin to delay absorption, thereby prolonging its pharmacologic effect. Reactions to protamine-containing insulins can be caused by the protamine component in the insulin preparation rather than by the insulin itself.³¹

Protamine acts as an adjuvant and the crystalline zinc solutions can alter immunogenicity by changing the structure of the β chain in insulin. A patient was reported with an immediate type of localized nodular reaction at the injection sites after insulin injection. Radioallergosorbent testing demonstrated a high IgE titre to insulin, and a skin biopsy specimen showed an intense eosinophilic infiltration. The reaction resolved after prescription of a zinc-free insulin preparation.³²⁻³⁵

An anaphylactic reaction to protamine sulfate during cardiac surgery is a rare but known entity. How to preoperatively predict such a reaction is still unclear.^{36,37}

The mechanisms of protamine-induced toxicity are complex and are still not yet completely clarified. Available data indicate that severe adverse reactions could be mediated by the immune response because protamine is a nonhuman protein. A large population of diabetic patients who had previously received protamine-containing insulins, and who developed antiprotamine antibodies, were considered at high risk for this immunoglobulin-mediated protamine response.

Protamine reactions, however, could also be triggered by a nonimmunologic mechanism. The heparin-protamine complexes, such as the antigen-antibody complexes, could activate the classical complement pathway, leading to sequestration of neutrophils in the lungs, formation of thromboxane A₂, and release of vasoactive histamine.³⁸

Management of insulin reactions

A diagnostic algorithm for patients suspected of having an insulin allergy has been proposed (Figure 1). In approaching a patient with suspected insulin allergy, a careful history is required to determine whether the reaction is clinically a type I, II, or III hypersensitivity and which agent is most likely to be the cause. Skin prick testing and a specific IgE titre are the mainstay of the diagnostic workup in suspected type I reactions. Positive prick test results and low specific IgE titers, however, may occur in up to 28% of diabetic patients without any clinical relevance. Antibody titers always should be assessed along with the clinical history. Two known reports showed that IgE-related mediated reaction to penicillin has a higher prevalence in insulin-allergic patients.^{7,39-41}

When performing either radioallergosorbent or prick testing, one should also consider type I hypersensitivity reactions to natural rubber latex. Allergic reactions have been reported to be caused by trace amounts of natural rubber latex from the vial membranes.^{42,43}

Human insulin is less immunogenic than animal insulin, and porcine insulin is less immunogenic than bovine insulin. Bovine insulin differs from human insulin in 3 amino acids and porcine insulin in only 1.⁷

In investigating suspected delayed-type reactions, investigations such as specific IgG and immune complex titres and patch testing are more useful. A skin biopsy specimen may also be helpful because it can give information about the type of inflammation in Arthus and delayed hypersensitivity reactions, especially if the clinical manifestations are limited to the skin.⁴⁴ When sensitization is limited to one type of insulin or specific preservative, the allergen can be avoided by choosing a different preparation suitable for the patient (Table 1).⁷ In addition, desensitization techniques and changes in the route or the rate of administration of insulin can be beneficial, especially in type I allergic reactions.^{8,19,20}

Conclusions

The diagnosis of insulin reactions requires a careful history and targeted testing, depending upon the type of reaction suspected. Type I reactions are more common to insulin itself, and type IV reactions occur mainly to the additives in commercial insulin preparations. Taking into

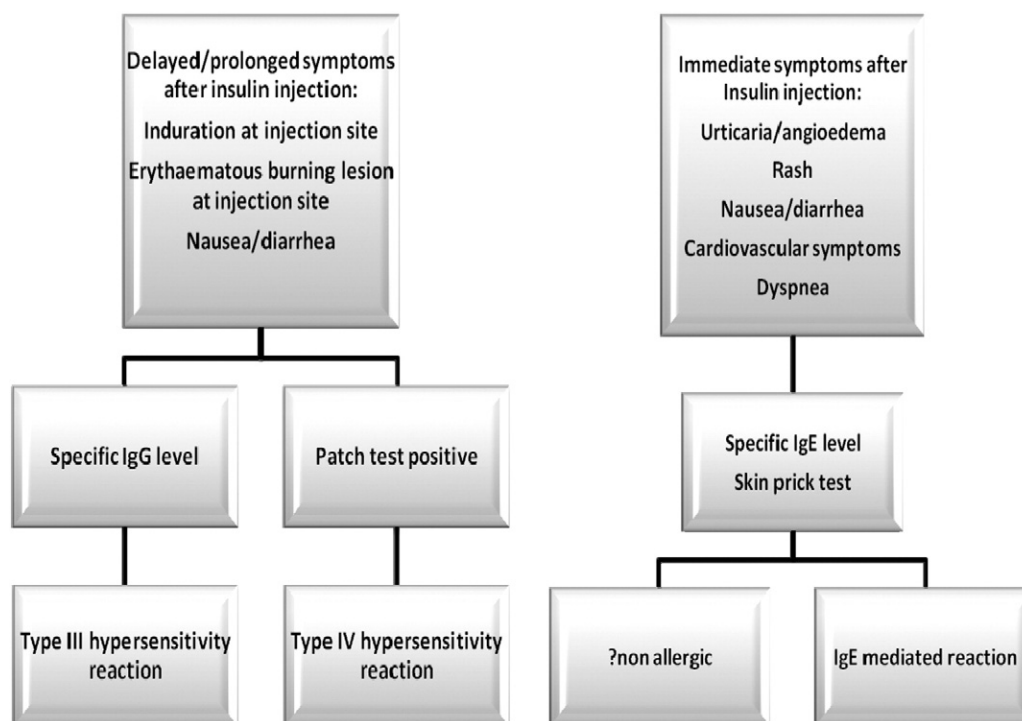


Fig. 1 A diagnostic algorithm for patients suspected of having an insulin allergy. IgE, immunoglobulin E. (Reproduced from Heinzerling et al with permission by John Wiley and Sons).

Table 1 Insulin preparations with respective additives

Preparation	Type	Zinc	Protamine	Cresol	Other
Actrapid	Human	X		X	Glycerol
Berlinsulin H Normal	Human			X	Glycerol
Huminsulin Normal	Human			X	Glycerol
Insuman Rapid	Human			X	Glycerol
Insulin B Braun	Human			X	Glycerol
Velosulin	Human	X		X	Glycerol
Insulin S Berlin Chemie	Porcine				Methyl-4-hydroxybenzoate
Insulin S.N.C Berlin Chemie	Porcine			X	Glycerol
Novorapid	r-DNA insulin aspart	X		X	Phenol, Glycerol
Apidra Optiset	Analogum (glulisine)			X	Trometanol
Humalog	Analogum (lispro)	X		X	Glycerol
Actraphane	Human	X	X	X	Phenol, glycerol
Berlinsulin H	Human	X	X	X	Phenol, glycerol
Huminsulin Basal for Pen	Human		X	X	Phenol, glycerol
Huminsulin Basal	Human	X	X	X	Phenol, glycerol
Huminsulin Profil	Human		X	X	Phenol, glycerol
Insulin B Braun Basal	Human	X	X	X	Phenol, glycerol
Protaphane	Human	X	X	X	Phenol
Insuman Basal	Human	X	X	X	Phenol, glycerol
Monotard	Human	X			Methyl-4-hydroxybenzoate
B Insulin S	Porcine				Methyl-4-hydroxybenzoate, Aminoquinurid
Insulin Novo Semilente MC	Porcine	X			Methyl-4-hydroxybenzoate
Humalog Mix	Analogum (lispro)	X	X	X	Phenol, glycerol
NovoMix 30	Insulin aspart-protamine crystals	X	X	X	Phenol
Levemir	Insulin detemir	X		X	Phenol
Ultratard	Human	X			Methyl-4-hydroxybenzoate
Lantus	Analogum (glargine)	X		X	Glycerol

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account the significant number of people with diabetes who are dependent upon insulin, allergic reactions to insulin may occur more frequently than reported in the literature. An international data bank would be an option to record cases and consequently to develop a more effective approach.

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