Insulin Allergy: A Case Report and Review of Literature

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Abstract

Objective: A case of insulin allergy to insulin aspart, insulin aspart protamine/insulin aspart 70/30, insulin lispro, and insulin lispro protamine/insulin lispro 75/25 in a patient with type 2 diabetes mellitus is reported. **Case Summary:** A 76-year-old Caucasian male weighing 81 kg presented with complaints of burning, lumps, and a rash where his insulin aspart protamine/insulin aspart 70/30 was injected 2 months after initiation. Because poor injection technique can mimic insulin allergy, the patient was counseled again on proper injection technique. The patient presented 2 weeks later with the same complaints. Insulin aspart protamine/insulin aspart 70/30 was discontinued and insulin lispro protamine/insulin lispro 75/25 was initiated. The patient presented 3 months later with a localized reaction. Insulin lispro protamine/insulin lispro 75/25 was discontinued and insulin U100 glargine and insulin lispro were initiated. One week later, the patient still had complaints of a localized reaction and was referred to an allergist for testing. Skin prick tests revealed insulin allergy to insulin aspart and insulin lispro but not to insulin U100 glargine or insulin glulisine. The patient's regimen was changed to insulin U100 glargine and insulin glulisine, and he has not experienced any reaction since. **Discussion:** Allergic reactions to human insulin preparations are rare and may present as a localized reaction or a generalized reaction. Different types of allergic reactions to human insulin have been reported, including type I, type III, and type IV hypersensitivity reactions. If insulin allergy is suspected, the following steps should be taken to confirm such allergy: evaluation of injection technique, switching to a different insulin preparation, and referral to an allergist for allergy testing if necessary. **Conclusion:** A patient with type 2 diabetes mellitus experienced a type I hypersensitivity reaction to insulin aspart, insulin aspart protamine/insulin aspart 70/30, insulin lispro, and insulin lispro protamine/insulin lispro 75/25.

Keywords

insulin, allergy, diabetes, type 2 diabetes, hypersensitivity

Introduction

Prior to the introduction of recombinant human insulin to the market in 1982, insulin allergy was a common occurrence due to the use of bovine and porcine insulin preparations that were often impure.^{1,2} Today, bovine and porcine insulin preparations are no longer available in the United States and better purification processes exist.³ However, allergy to human insulin preparations, although rare, can still occur in those who inject with insulin.¹

When insulin allergy is suspected, it is important to rule out other causes such as improper injection technique; allergies to inactive ingredients in the insulin formulation such as protamine sulfate, zinc, and metacresol; and allergies to latex or alcohol swabs that are used in the insulin preparation and injection process.⁴ Allergies to inactive ingredients in the insulin formulation can typically be resolved by switching to a different type of insulin that does not contain the offending inactive ingredient.^{3–5} In rare cases, an individual can be allergic to the insulin molecule itself.

Insulin allergy may present as a localized reaction at the injection site or a more severe, generalized reaction that can range from urticaria to anaphylaxis.⁵ Different types of hypersensitivity reactions to insulin have been reported including type I hypersensitivity reactions, type III hypersensitivity reactions, and type IV hypersensitivity reactions.^{3–5}

Because it is rare for an individual to experience insulin allergy, it is important to report such incidences. We report a case of a patient who experienced insulin allergy to insulin aspart, insulin aspart protamine/insulin aspart 70/30, insulin lispro, and insulin lispro protamine/insulin lispro 75/25.

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Case Report

A 76-year-old Caucasian male weighing 81 kg presented to the practice with complaints of lumps and a rash forming where his insulin aspart protamine/insulin aspart 70/30 was injected and also burning from the insulin. Insulin aspart protamine/insulin aspart 70/30 was initiated 2 months prior to the visit. His medical history was significant for type 2 diabetes mellitus (T2DM), chronic hepatitis C infection, cirrhosis of the liver, chronic renal impairment, hypertension, prior cerebrovascular accident, asthma, chronic obstructive pulmonary disease, chronic cough secondary to gastroesophageal reflux disease, restless legs syndrome, and hypothyroidism. He had a history of previous intravenous drug and alcohol abuse. He had no known drug allergies at the time of presentation. Known drug intolerances included fluticasone/salmeterol in which he experienced headaches and spironolactone in which he experienced breast tenderness. His medications included insulin aspart protamine/insulin aspart 70/30 (60 units twice daily before breakfast and before dinner; Novo Nordisk), insulin lispro for correction (inject 6 units if blood sugar is 250-290, 8 units if blood sugar is 300-349, 10 units if blood sugar is 350-400, 15 units if blood sugar is greater than 400 or unreadable, check blood sugar every 3-4 hours and repeat if necessary; seek medical attention if blood sugar remains elevated; Eli Lilly), furosemide (40 mg daily), lactulose 10 g/15 mL solution (15-30 mL twice daily), clopidogrel (75 mg daily), levothyroxine (112 µg daily), omeprazole (20 mg daily 30 minutes before breakfast), pramipexole (0.125 mg 2-3 hours before bedtime), ranitidine (300 mg daily), potassium chloride (20 mEq twice daily), and rifaximin (550 mg twice daily). All of the patient's medications were at recommended doses.

The patient's weight, heart rate, and blood pressure were taken at the beginning of the initial visit and were as follows: weight 81 kg, blood pressure 124/77 mm Hg, and heart rate 83 bpm. Examination of the patient's abdomen revealed a rash as well as a small lump at the injection site. The patient reported the reaction occurred from insulin aspart protamine/insulin aspart 70/30 because he had not used insulin lispro for correction. Due to his past history of intravenous drug abuse he chose not to inject himself and his wife did it for him. Both the patient and his wife were illiterate, which had resulted in improper preparation and injection of insulin in the past. Because improper injection technique can mimic the signs and symptoms of an allergic reaction, they were counseled again on proper injection technique, including how to mix insulin aspart protamine/insulin aspart 70/30 by gently rolling it, the importance of rotating injection sites, and not to reuse pen needles.

The patient presented to the practice 2 weeks later with the same complaints from injecting with insulin aspart protamine/insulin aspart 70/30, despite injecting his thigh in

addition to his abdomen and rotating injection sites. Further interviewing of the patient and his wife revealed that his wife was injecting his insulin in the wrong area of the thigh. They were counseled on what areas of the body insulin can be injected and a visual demonstration was given. Because there was still no relief of symptoms and proper injection technique of the abdomen was confirmed, insulin allergy to insulin aspart protamine/insulin aspart 70/30 was suspected. Insulin aspart protamine/insulin aspart 70/30 was discontinued and insulin lispro protamine/insulin lispro 75/25 was initiated (60 units twice daily before breakfast and before dinner; Eli Lilly). He presented to the practice 1 week later for a follow-up visit with no reports of a reaction to insulin lispro protamine/insulin lispro 75/25.

Two months after insulin lispro protamine/insulin lispro 75/25 was initiated, the patient returned to the practice with complaints of occasional itchy, painful bumps on the buttocks and a burning sensation where his insulin was injected. Interview of the patient's wife revealed that she was injecting the insulin quickly rather than holding the insulin pen for 10 seconds. Because the patient's wife was still not injecting his insulin properly, they were counseled again on proper injection technique and pen needles were switched to BD Nano 4 mm pen needles to make the injection process less painful and reduce the occurrence of wheals. The patient was instructed to return in 1 week for follow-up.

The patient did not return the following week for his follow-up appointment, but returned 1 month later with worsening complaints from insulin lispro protamine/insulin lispro 75/25. Examination of the patient's buttocks revealed a similar erythematous reaction to the one he previously experienced with insulin aspart protamine/insulin aspart 70/30. Insulin lispro protamine/insulin lispro 75/25 was discontinued due to suspected insulin allergy and a basal-bolus regimen consisting of insulin U100 glargine (60 units at dinner time daily; Sanofi-Aventis) and insulin lispro (15 units 15 minutes before meals; Eli Lilly) was initiated. The basal-bolus regimen was initiated because insulin U100 glargine and insulin lispro do not contain protamine sulfate, unlike insulin lispro protamine/insulin lispro 75/25 and insulin aspart protamine/insulin aspart 70/30, which was thought to be causing the reaction.⁶⁻⁹

Two days after initiating insulin U100 glargine and insulin lispro the patient presented to the practice with similar complaints of painful, itchy bumps. Pharmacy referred the patient to an allergist for further testing. Skin prick tests for insulin lispro, insulin U100 glargine, and latex were performed by the allergist. The skin prick test for insulin lispro produced a large red wheal confirming an allergy to insulin lispro. The skin prick tests for insulin U100 glargine and latex were negative. Based on the results from the allergist, insulin U100 glargine (60 units at dinner time daily) was continued, insulin lispro for mealtime coverage and for correction was discontinued, and insulin glulisine for mealtime

coverage (15 units 15 minutes before meals; Sanofi-Aventis) and for correction if needed was initiated. One week later at the second allergist appointment, skin prick tests for insulin glulisine and insulin aspart were performed. The skin prick test for insulin glulisine was negative; however, the skin prick test for insulin aspart produced a large red wheal confirming an allergy to insulin aspart. The patient was continued on insulin U100 glargine and insulin glulisine and has not experienced any reaction since.

Discussion

Insulin is necessary for the treatment of those with type 1 diabetes and many with type 2 diabetes. In rare cases, an individual can experience insulin allergy to human insulin preparations.¹ Different types of allergic reactions to human insulin have been reported, including type I, type III, and type IV hypersensitivity reactions.³⁻⁵ Type I hypersensitivity reactions are immediate, IgE-mediated reactions and are the most common type for those with insulin allergy to have. This reaction is typically a localized reaction characterized by pruritus, erythema, and swelling at the injection site. In some cases, a more generalized reaction ranging from urticaria to anaphylaxis has been reported.^{3,4} Type I hypersensitivity reactions to insulin usually start several weeks after insulin has been started.⁴ Type III hypersensitivity reactions, also referred to as serum-sickness reactions, are delayed, IgG-mediated reactions characterized by local Arthus reactions. Arthus reactions are extremely rare and are characterized by localized subcutaneous nodules that appear 4 to 6 hours after insulin injection.^{3,4} Lastly, type IV hypersensitivity reactions are delayed, T-cell mediated reactions.⁴ It is rare to experience a type IV hypersensitivity reaction to human insulin.³

If insulin allergy is suspected in a patient, it is important to take the proper steps in identifying a true insulin allergy. These steps include taking a detailed patient history, ruling out improper injection technique, allergy to inactive ingredients in the insulin preparation, or allergy to alcohol swabs or latex, which are used in the insulin preparation and injection process.⁴ Improper injection technique of any injectable medication can mimic that of an allergic reaction, which is why it is important to rule this out first. If proper injection technique is confirmed, the next step is to switch to another type of insulin because it is common to be allergic to inactive ingredients in the insulin preparation such as protamine sulfate, zinc, metacresol, sodium phosphate, phenol, and glycerol.³⁻⁵ If switching to a different type of insulin does not resolve the problem, it is likely that the patient is allergic to the insulin molecule itself and should be referred to an allergist for further testing.⁴

To confirm type I hypersensitivity reactions to human insulin, skin prick tests or intradermal skin tests may be used. Both tests have their pros and cons, and the decision

should be left to the allergist. Skin prick tests are safer and easier to perform⁶; however, they are less sensitive compared to intradermal skin tests.^{6,7} Intradermal skin tests are more sensitive; however, they are more invasive and can cause skin irritation that can look like a positive reaction, thus resulting in a false-positive. Additionally, intradermal skin tests run the risk of causing anaphylactic reactions.⁶ Serum IgE tests may also be used to confirm IgE-mediated insulin allergy.⁵

The following steps were followed to confirm insulin allergy in our patient—evaluation of injection technique, avoidance of alcohol swabs and adhesives, switching to a different insulin preparation, and referral to an allergist for allergy testing. First, injection technique was confirmed. The patient's wife injected his insulin because of his past history of intravenous drug abuse. Additionally, the patient and his wife were both illiterate and had a history of improperly following directions. They were counseled again on proper injection technique to rule it out as the cause of his localized reactions. When proper injection technique was confirmed and localized reactions were still occurring, his insulin was switched to a different type. Insulin was switched to insulin lispro protamine/insulin lispro 75/25 because insulin allergy is often due to inactive ingredients in the insulin preparation rather than the insulin molecule itself. He was not switched to a non-protamine sulfate containing basal-bolus regimen at first, even though protamine sulfate often causes allergic reactions, because our patient did not want to be injected more than twice daily. After the patient returned with a localized reaction to insulin lispro protamine/insulin lispro 75/25,⁸ protamine sulfate allergy was suspected, which is why he was switched to a basal-bolus regimen consisting of insulin U100 glargine⁹ and insulin lispro.¹⁰ Lastly, our patient was referred to an allergist for skin testing after he returned to the practice with a localized reaction to insulin U100 glargine and insulin lispro, similar to the reactions he experienced with insulin aspart protamine/insulin aspart 70/30 and insulin lispro protamine/insulin lispro 75/25. Skin prick testing on our patient confirmed insulin allergy to insulin lispro and insulin aspart. Because insulin aspart is an active ingredient in insulin aspart protamine/insulin aspart 70/30¹¹ and insulin lispro is an active ingredient in insulin lispro protamine/insulin lispro 75/25,⁸ insulin allergy to insulin aspart protamine/insulin aspart 70/30 and insulin lispro protamine/insulin lispro 75/25 was confirmed as well. Recall that type I hypersensitivity reactions to insulin do not start until the patient has been injecting with the offending insulin for several weeks, occur immediately after injecting with the insulin once reactions have started to develop, are often characterized by localized erythema and pruritus, and can be confirmed by skin testing.^{3,4} The reactions that our patient experienced were localized, erythemic, and pruritic in nature immediately after being

Table 1. Published Cases of Insulin Allergy.

Reference	Patient Age/ Gender	Type of Diabetes Mellitus	Insulin Type(s)/ Reaction	Switched to Different Insulin Type(s)/Reaction	Allergy Testing	Allergy Testing Result(s)
12	59/male	2 ^a	NPH insulin— localized reaction	NPH insulin/insulin human regular 70/30, insulin aspart protamine/insulin aspart 70/30, insulin glargine, insulin detemir—all resulted in same reaction	Skin provocation test	Insulin allergy to all insulin preparations tested
13	65/male	Secondary to total pancreatectomy	NPH insulin, insulin lispro—localized reaction	NPH insulin (NovoNordisk, Mississauga, Ontario, Canada), insulin aspart (NovoNordisk)—resulted in same reaction	IDT	Insulin allergy to recombinant human insulin preparation
13	40/female	1 ^b	Insulin glargine, insulin lispro— generalized reaction	Insulin detemir, insulin aspart—anaphylaxis due to use of insulin lispro instead of insulin aspart	Elevated IgE levels, positive autoantibodies (anti-GAD and anti-insulin)	Lab results suggest insulin allergy
13	49/female	2	NPH insulin, regular insulin— generalized reaction	N/A	Elevated IgE levels, positive anti-insulin antibodies, IDT	Insulin allergy to all insulin preparations tested
14	89/male	1	NPH insulin, insulin lispro—generalized reaction	NPH insulin porcine and insulin aspart, insulin glargine and insulin lispro—resulted in same reaction	IDT	Insulin allergy to all insulin preparations tested
15	50/male	2	Insulin aspart protamine/insulin aspart—localized reaction	NPH insulin, human insulin, insulin lispro—resulted in same reaction	IDT	Insulin allergy to all types of insulin
16	61/male	2	NPH insulin— localized reaction which evolved to anaphylaxis	Human insulin regular, insulin detemir—resulted in same reaction	SPT	Allergy to zinc chloride in insulin preparation
17	32/male	2	Human regular insulin—generalized reaction	Other types of insulin were not tested due to previous history of hypersensitivity reactions to NPH insulin	SPT, elevated IgE levels	Insulin allergy to all insulin preparations tested
18	55/female	2	NPH insulin and human regular insulin—generalized reaction	N/A	SPT, IDT	SPT positive for insulin allergy, IDT revealed insulin allergy to all except insulin aspart and allergy to protamine sulfate
19	44/female	Secondary to hemochromatosis	Human regular insulin (Eli Lilly)— localized reaction	Insulin lispro—skin reaction improved but did not disappear; anaphylaxis occurred 1 year later	IDT	Insulin allergy to all insulin preparations tested; negative for protamine sulfate allergy
20	39/female	1	Insulin detemir— urticaria, fever, arthralgia, facial edema	N/A	Elevated CRP and ESR, skin biopsy revealed deep perivascular dermatitis	Serum sickness-like, type III reaction
21	53/female	Secondary to GDM	Insulin aspart protamine/insulin aspart 70/30— localized reaction	Insulin aspart and insulin detemir, insulin lispro protamine/insulin lispro 75/25, insulin glargine, NPH insulin—severe lipatrophy	SPT, IDT	Insulin allergy to all available insulin preparations

Abbreviations: IDT, intradermal skin test; N/A, not applicable; SPT, skin prick test; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GDM, gestational diabetes mellitus.

^aType 2 diabetes mellitus.

^bType 1 diabetes mellitus.

injected with insulin aspart protamine/insulin aspart 70/30, insulin lispro protamine/insulin lispro 75/25, and insulin lispro. Reactions did not develop to insulin aspart protamine/insulin aspart 70/30 and insulin lispro protamine/insulin lispro 75/25 until several weeks after initiation. Additionally skin prick tests were positive for insulin aspart and insulin lispro. Our patient therefore experienced type I, IgE-mediated hypersensitivity reactions to insulin aspart, insulin aspart protamine/insulin aspart 70/30, insulin lispro, and insulin lispro protamine/insulin lispro 75/25.

Using the Ovid Medline interface and the search terms “insulin” and “insulin allergy” or “drug hypersensitivity,” other case reports of insulin allergy were identified. The search was limited to case reports published in the past 5 years. Both case reports published in the United States and case reports published outside of the United States were included. Twelve cases of insulin allergy were identified (Table 1), most of which were type I hypersensitivity reactions to human insulin (91%), just like what our patient experienced.¹²⁻²¹ In the published case reports where type I hypersensitivity reactions to insulin were suspected, all except one case report¹³ confirmed insulin allergy with skin prick testing or intradermal skin testing. Out of the cases that were type I hypersensitivity reactions, 50% were localized reactions and 50% were generalized reactions. Additionally, most reported insulin allergy to multiple insulin preparations (90%), just like our patient. One case report of insulin allergy was not to the insulin molecule itself, but rather to zinc in the insulin preparation,¹⁶ which is not an uncommon phenomenon when insulin allergy is suspected. Another case report of insulin allergy was a type III hypersensitivity reaction to insulin detemir,²⁰ a rare reaction to have to human insulin.

The Naranjo et al²² method for estimating the probability of adverse drug reactions was used for insulin aspart protamine/insulin aspart 70/30, insulin lispro protamine/insulin lispro 75/25, and insulin lispro because our patient was injected with these 3 insulin preparations. Insulin allergy to insulin aspart protamine/insulin aspart 70/30 (6), insulin lispro protamine/insulin lispro 75/25 (5), and insulin lispro (5) is probable (score 5-8).

Conclusion

This case describes a patient with type 2 diabetes mellitus who experienced a type I hypersensitivity reaction to multiple insulin preparations. Insulin allergy to human insulin is rare, although cases still occur today. If insulin allergy is suspected a detailed history should be taken and other potential causes should be ruled out. The type of hypersensitivity reaction should be identified and proper testing should be performed for confirmation.

Authors' Note

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Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Kayla M. Natali has no conflicts of interest. Jennifer D. Goldman: speaker's bureau Novo Nordisk and Sanofi, consultant Becton Dickinson.

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