CASE REPORT

Hypersensitivity Reaction to Insulin Glargine and Insulin Detemir in a Pediatric Patient: A Case Report

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Allergy to human insulin or its analogs is rare, but it is still a significant issue in current diabetes care. Allergic reactions can range from localized injection site reactions to generalized anaphylaxis, and they can be caused by excipients or the insulin molecules themselves. We presented a case of a 14-year-old male patient with generalized allergic reactions to insulin glargine and insulin detemir. The patient was successfully managed by being switched to a continuous subcutaneous insulin infusion with insulin aspart. Allergic reactions to insulin detemir and insulin glargine have both been well described, with insulin detemir allergy appearing to be more common. There are several potential mechanisms for insulin allergy, and immunologic characteristics vary among different insulin analogs. After confirming insulin allergy in practice, management involves treating symptoms and switching insulin preparations. This is the first documented case of allergies to both insulin glargine and insulin detemir in a pediatric patient. Exact mechanism of insulin allergy is unknown, and management strategies must be individualized for each patient.

INDEX TERMS: hypersensitivity, insulin detemir, insulin glargine, pediatrics, type 1 diabetes mellitus

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INTRODUCTION

Allergy to human insulin or its analogs is rare, with an estimated incidence of <1% to 2.4% in insulin-treated diabetic patients.^{1,2} However, cases of insulin allergy continue to be reported and range from local injection site reactions to generalized life-threatening anaphylaxis.^{3–5} Individuals may be allergic to the insulin molecule itself or to pharmaceutical excipients, such as protamine, zinc, or metacresol.^{6–8} Immediate, immunoglobulin E (IgE)–mediated allergic reactions (type I) are most common, although immune complex (type III) and delayed hypersensitivity (type IV) reactions can also occur.³

Type I, IgE-dependent reactions are mediated by the release of vasoactive substances from basophils and mast cells.³ Local symptoms typically present immediately after insulin injection and include injection site swelling, erythema, and itching.^{3,4} The reaction may become general-

ized, featuring urticaria, angioedema, and even anaphylaxis.^{4,5} In some cases, type I reactions are associated with a late phase, which peaks at 4 to 6 hours but can feature injection site indurations lasting several days.³

Type III insulin allergy typically manifests as a local Arthus reaction, which is characterized by the development of subdermal, tender nodules at the injection site.^{3,9} The nodules typically appear 2 to 6 hours after insulin administration and last up to 48 hours.⁹ They represent insulin-antibody complexes, which lead to inflammation through complement fixation and leukocyte attraction.¹⁰ In rare cases, type III reactions may be associated with serum sickness, which is mediated by IgG antibodies.¹⁰

Type IV insulin allergy represents a delayed, T-cell-mediated reaction characterized by subcutaneous, inflammatory, non-pruritic nodules at the injection sites.¹¹ Type IV allergic reactions can be differentiated from type III reactions in

that they usually present at least 24 hours after injection and can last for 4 to 7 days.¹⁰ However, in some cases the reactions may manifest as early as 2 to 12 hours after administration.¹¹

Despite its rarity, insulin allergy is a significant clinical dilemma, both because of its immediate effects and the implications for diabetes management. It can be especially challenging in patients with type 1 diabetes mellitus (T1DM) who lack non-insulin treatment options. We present a case of an adolescent with newly diagnosed T1DM who had allergic reactions to both insulin glargine and insulin detemir. This article will then discuss potential mechanisms of the allergic reaction and management strategies.

CASE PRESENTATION

A 14-year-old white male (59.2 kg and 5 feet 10 inches) newly diagnosed with T1DM was admitted to the pediatric intensive care unit (PICU) from the emergency department (ED) after being sent from his primary pediatrician's office for possible diabetic ketoacidosis. Patient did not have any other significant past medical history, and he was not known to have any drug allergies prior to admission. In the PICU, it was noted that the patient had Kussmaul respirations, delayed capillary refill, dry mucous membranes, and abdominal tenderness to deep palpation. The patient's labs on admission were significant for capillary blood glucose (CBG) 423 mg/dL, venous pH 7.117, bicarbonate 8.4 mEq/L, and acid-base deficit 19 mmol/L. He was initially started on an insulin drip per protocol at 0.1 units/kg/hr. The insulin drip was discontinued at the end of hospital day 1. Four units of insulin glargine were administered during the first night of his hospitalization. Insulin aspart was initiated with a 1:15 carbohydrate ratio and a sliding scale (SS) of 1 unit of insulin for every 50 mg/dL of CBG greater than 150 mg/dL.

On hospital day 2, the patient reported 2 episodes of intense pruritus, urticaria, and burning sensation on his chest and back lasting an hour and a half each. This occurred at lunch and again at 11:30 pm, an hour and a half after his insulin glargine dose (4 units). Symptoms resolved after the administration of oral diphenhydramine (25 mg), oral loratadine (10 mg), and topical emollients cream application. On hospital day 3,

another episode of pruritus began about 2 hours after the administration of his insulin glargine dose (9 units). Along with the episode of itching and burning, the patient also began complaining of a "scratchy throat" and was given oral loratadine (10 mg), oral and intravenous (IV) diphenhydramine (25 mg), and intramuscular methylprednisolone (40 mg) between midnight and 5 am. On hospital day 4, the patient was switched to insulin detemir because of the concern of an allergic reaction to insulin glargine. Insulin detemir was scheduled to be administered twice daily at 10 am and 10 pm.

On hospital day 4, the patient had another intense episode of urticaria and pruritus 45 minutes after his second dose of insulin detemir (12 units) at 11 pm, involving his eyes, arms, chest, and back. The patient had previously received 8 units of insulin detemir that morning at 8:25 am and was able to tolerate the insulin with no adverse reaction. The patient reported that the itching began about an hour after the administration of his evening dose of insulin detemir. To relieve these symptoms, he was given oral diphenhydramine (25 mg), topical hydrocortisone 1% ointment, oral hydroxyzine (50 mg), and oral lorazepam (1 mg). The pruritus lasted for about 6 hours until 5 am on hospital day 6 when he was able to rest. Insulin detemir was discontinued the next morning and CBGs were subsequently managed using frequent administrations of SS with insulin aspart. During this admission, he required 21 to 39 units of insulin aspart daily without any observed trend of increasing requirement of this form of insulin. Our patient was discharged on hospital day 7 on an insulin pump after more than 24 hours of observation without allergic symptoms and with reasonable glycemic control.

The patient was seen by an allergist and immunologist during his inpatient stay who noted a large degree of dermatographism. The physicians also concluded that the allergic symptoms might have been related to a histaminergic reaction to the medication rather than a true allergy. Further testing was deferred by the parents to determine whether or not this occurrence was a true allergic reaction. The patient is currently being monitored regularly by his endocrinologist and managed with an insulin pump with insulin aspart. He has not exhibited any further symptoms consistent with allergy to insulin aspart.

DISCUSSION

Literature Review

To our knowledge, this is the first documented case of a pediatric patient allergic to both insulin detemir and insulin glargine. Both reactions have an estimated score of 7 on the Naranjo Adverse Drug Reaction (ADR) Probability Scale.¹² A score of 7 indicates that these reactions were probable ADRs. In contrast, the most recent rash the patient reported has an estimated score of 2, indicating that the reaction was likely viral induced rather than mediated by insulin aspart.

Allergy to insulin detemir and insulin glargine was previously reported by Sola-Gazagnes et al¹¹ in an adult patient with type 2 diabetes mellitus (T2DM). This 29-year-old male patient exhibited a type IV allergy to insulin detemir in addition to insulin glargine. The reaction to detemir was characterized as an inflammatory, non-pruritic nodule at the injection site that presented 12 days after the first insulin detemir injection. The insulin glargine allergy was not described. Of note, the patient also reacted to insulin lispro but not to insulin aspart or insulin neutral protamine Hagedorn (NPH).

Multiple cases of allergy to insulin detemir have been documented. In 2005, Darmon et al⁹ reported a patient's type III allergy to insulin detemir. The patient was a 31-year-old man with T1DM who had previously been treated with insulin glargine and insulin aspart. After insulin glargine was switched to insulin detemir, he repeatedly experienced an immune complex reaction 4 to 6 hours after the administration of insulin detemir. The reaction presented as a subcutaneous, nonerythematous, slightly painful nodule with a central hematoma at the injection site. The patient did not react to insulin aspart during this time, and the nodule spontaneously disappeared 48 hours after the cessation of insulin detemir. He reported no further issues after being switched back to insulin glargine.

In 2007, Sola-Gazagnes et al¹¹ described 4 cases of type IV allergy (including the previously mentioned patient with a concurrent insulin glargine allergy) and 2 cases of type I allergy to insulin detemir. The allergies were revealed upon intradermal testing with 12 commonly available insulin preparations, including insulin detemir. The patients with type IV allergy to insulin detemir presented with subcutaneous, inflammatory,

non-pruritic nodules that appeared 2 to 12 hours after injection and lasted for 2 to 3 days. The patients with type I allergy presented with immediate, erythematous papulae after the administration of insulin detemir. Notably, the patients with type I allergy also experienced immediate hypersensitivity to 11 other (undisclosed) insulin preparations upon testing, whereas the patients with type IV allergy to insulin detemir did not react to other insulin preparations. The authors also reported that 8 additional cases of insulin detemir allergy had been reported to the French regulatory agency, as confirmed by their personal communication with a regulatory official.

Pérez et al⁵ reported a case of insulin detemir-induced anaphylaxis in 2009. They described an 88-year-old patient who presented with sudden dyspnea, dysphagia, itching, and injection site edema occurring less than 1 hour after the administration of insulin detemir. The patient was stabilized with oxygen, parenteral corticosteroids, and antihistamines. He was later transitioned to insulin glargine and insulin glulisine, both of which he tolerated well.

Several additional reports of severe injection site reactions to insulin detemir have been published. In 2006, Blumer¹³ described a 37-year-old woman who developed injection site reactions within hours of starting insulin detemir. In 2007, Ghosh et al¹⁴ reported seeing 3 patients who experienced insulin detemir-mediated injection site reactions in the span of only few months. In 2008, Blumer¹⁵ described a 63-year-old man who suddenly developed severe injection site reactions to insulin detemir after tolerating it for 15 months before that. The reactions began 8 hours after each injection and were described as erythematous, indurated, tender, non-pruritic areas around the injection site. His symptoms completely resolved after his insulin detemir was switched to insulin glargine.

Insulin glargine allergy seems to be less commonly reported than insulin detemir allergy, which is particularly notable because insulin glargine was approved by the US Food and Drug Administration 5 years prior to insulin detemir. Insulin glargine has been used to manage insulin allergy in several published cases.^{16–18} However, there have also been documented cases of insulin glargine allergy, mostly in the setting of allergy to multiple insulin preparations. Castéra et al¹⁹ and Moyes et al²⁰ described patients who were each

allergic to insulin glargine, insulin lispro, and insulin aspart. Heinzerling et al⁴ described a patient allergic to regular insulin, insulin NPH, insulin glargine, insulin lispro, and insulin aspart.

In 2003, Durand-Gonzalez et al²¹ described a patient who initially reacted to a regular NPH insulin mix but was also shown to be allergic to insulin glargine with skin testing. Additionally, this patient was allergic to insulin lispro but tolerated insulin aspart. In 2004, Madero et al²² reported a patient's IgG4-mediated allergy to insulin glargine, which was determined using direct enzyme-linked immunosorbent assay. Most recently, Alfadhli²³ presented a 12-year-old patient with new-onset T1DM who developed a generalized erythematous rash with pruritis after starting insulin glargine; her symptoms completely resolved after switching to insulin NPH. Overall, these case reports gave good descriptions of the allergies, but they were not able to provide information on how to predict which patients might be at an increased risk of developing allergic reaction to these insulin preparations.

Proposed Mechanisms

The described case reports reflect the complexity and heterogeneity of insulin allergy in clinical practice. It is difficult to compare the cases because the testing methodology and reporting characteristics were highly variable. The reports did not provide definite answers as to why our patient reacted to insulin glargine and insulin detemir but not to insulin aspart. Furthermore, because we did not obtain skin or IgG/IgE tests from our case patient, we cannot confirm the true nature of his allergy. However, based on the clinical picture and the available information, we can evaluate the possible mechanisms for his presumably allergy-mediated reactions.

The first major aspect to consider is the allergenicity of excipients used in the different insulin preparations. The insulin excipients most commonly associated with allergy include zinc, metacresol, and protamine.³ Insulin glargine, insulin detemir, and insulin aspart each contain zinc and metacresol, but they do not contain protamine. This similarity among the insulin preparations makes an excipient allergy unlikely in our case patient.

The next consideration involves the structure of the insulin molecules themselves. Insulin glargine, insulin detemir, and insulin aspart are

all human insulin analogs. Although analogs present new epitopes for immune system recognition, current evidence suggests that they are not associated with an increased risk of allergic reactions compared with human insulin preparations.³ As demonstrated by the case reports, however, the analogs appear to have unique immunologic profiles.

There is some evidence that rapid-acting agents may be less antigenic than long-acting agents. Ratner et al²⁴ demonstrated that persistent cutaneous insulin allergy was a result of the aggregation of high-molecular weight insulin molecules. Therefore, because rapid-acting insulin analogs are rapidly dissociated into monomers, they may be less likely to induce allergy.³ This theory was supported by multiple case reports that demonstrated successful management of insulin allergy by transitioning to the rapid-acting agents insulin lispro,²⁵⁻²⁸ insulin aspart,^{29,30} or insulin glulisine.³¹ Conversely, Hara et al¹⁸ proposed that the long-acting analog insulin glargine might actually be less antigenic than other analogs, and its slow dissolution could mimic a desensitization process. Similarly, continuous subcutaneous insulin infusion (CSII) has also been associated with decreased allergenicity, perhaps because of the smaller amounts of insulin delivered.¹⁰

The duration of action alone does not explain the analogs' unique immunologic profiles. As an example, many of the patients in the described cases were allergic to the short-acting analog insulin lispro but not to insulin aspart. Insulin lispro and insulin aspart have similar pharmacokinetic and pharmacodynamic profiles, but their amino acid sequences differ slightly. At position B28, insulin lispro has a proline (inverted with respect to native insulin), whereas insulin aspart contains aspartic acid.³² Yasuda et al²⁹ hypothesized that this modification at B28 was responsible for insulin aspart's decreased immunogenicity. Additionally, insulin glargine and insulin detemir, both long-acting analogs, also appear to have different immunologic characteristics. Sola-Gazagnes et al¹¹ hypothesized that insulin detemir's myristic acid moiety could induce allergy in some patients.

The described theories suggest that there are several potential mechanisms for our case patient's allergic reactions. Because he reacted to both insulin glargine and insulin detemir, his allergies might have been mediated by aggregation

of insulin molecules in the subcutaneous tissue. This is plausible because he tolerated CSII with a short-acting insulin analog. Still, his allergies might have been related to the unique amino acid sequences or molecular moieties in each analog. Ultimately, even with allergy testing we would only be able to hypothesize on the true etiologies of his reactions.

Evaluation/Management of Insulin Allergy

Initial evaluation of insulin allergy involves excluding alternate causes, such as poor injection technique, reaction to alcohol wipes, or other allergic conditions.³ For example, some insulin vials contain latex, which can contaminate the needle and elicit reactions in patients allergic to latex.³³ Insulin allergy can be proven with skin testing and assessment of IgE and IgG,^{34,35} although testing is not always feasible at the point of care.

First-line management options of insulin allergy include symptomatic relief with antihistamines and switching insulin preparations (or transitioning to oral agents in the case of T2DM).³ More severe allergic reactions may be treated with combinations of antihistamines in addition to a histamine 2-antagonist and systemic steroids.³ One method to induce tolerance is the use of CSII, which was the approach in our case patient. The use of CSII for insulin allergy has been proven successful in several case reports.^{10,35-37}

Another approach for the management of insulin allergy is the use of specific immunotherapy with escalating insulin doses.⁴ This strategy, also known as desensitization, induces tolerance in many patients with type I, IgE-mediated reactions.⁴ The exact mechanism of tolerance induction is unknown, but it may be related to the depletion of specific T cells, the induction of T-regulatory cells, and the modulation of antibody production by cytokines.³⁸

In certain cases, immunologic insulin resistance may occur secondary to the formation of insulin antibodies.⁴ It is important to realize that positive antibody titers indicate sensitization alone and may be present in insulin-treated diabetic patients with little clinical relevance.³ However, for cases of clinically significant insulin resistance, prolonged courses of steroids or other immunosuppressants may be required.³ Plasmapheresis is another option for insulin resistance, and it also can be used for serum sickness associated with

type III reactions.³⁹ Rarely, pancreas transplantations may be considered for life-threatening, generalized insulin allergy with anaphylaxis.⁴⁰

CONCLUSIONS

In this article we reported the first documented case of a pediatric patient allergic to both insulin detemir and insulin glargine. A review of the current literature reveals that allergic reactions to insulin detemir or insulin glargine have been well described, although reactions to insulin detemir seem to be more common. There are several potential mechanisms for the allergies, and management strategies must be individualized for each patient. Our case patient has been successfully managed on a CSII with insulin aspart. However, because insulin allergy can sometimes develop after a prolonged duration of therapy, our patient must be carefully monitored for the development of any new reactions.

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Abbreviations ADR, adverse drug reaction; CBG, capillary blood glucose; CSII, continuous subcutaneous insulin infusion; IgE, immunoglobulin E; IV, intravenous; NPH, neutral protamine Hagedorn; PICU, pediatric intensive care unit; SS, sliding scale; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus

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