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Letter to the Editor

Long-acting insulin allergy in a diabetic child

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Abstract

Insulin allergy has been uncommon since the introduction of human recombinant insulin preparations; the prevalence is 2.4%. Insulin injection could elicit immediate reactions, which are usually induced by an IgE-mediated mechanism, within the first hour after drug administration. In the present study, we describe the case of a child who experienced immediate urticaria after long-acting insulin injection. A 9-year-old girl affected by type 1 diabetes mellitus referred a history of three episodes of urticaria 30 min after insulin subcutaneous injection. During the first week of insulin therapy, she developed generalized immediate urticaria twice after long-acting insulin glargine first and then once after insulin degludec administration. Symptoms resolved within a few hours after treatment with oral antihistamine. She tolerated rapid insulin lispro. Her personal allergological history was negative. Skin prick tests with degludec, glargine and detemir were performed, showing negative results. Intradermal 1:100000-diluted tests were immediately positive for both degludec and glargine but not for detemir. In light of these findings, detemir was administered without any reaction. Our results show that detemir is tolerated by patients with clinical hypersensitivity reactions to degludec and glargine. Although reactions could be attributable to additives allergy, such as zinc or metacresol, this was excluded since all three preparations contain the same components. So, insulin itself acted as offending allergen. Detemir differs from degludec and glargine in a few aminoacids. Therefore, it is possible that the conformational rather than the linear epitope may be responsible for the reaction. This result suggests integrating intradermal tests in the diagnostic flowchart for insulin allergy. Insulin allergy should always be suspected in patients with immediate symptoms after drug injection. As allergologic work-up, prick by prick test and intradermal test to insulin preparations should be performed. In case of negative results of cutaneous tests, insulin analogs may be administered.

Keywords

allergy, children, IgE-mediated reaction, insulin allergy, management, type 1 diabetes mellitus, urticaria

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Background

Insulin allergy has been uncommon since the introduction of human recombinant insulin preparations, with a prevalence of 2.4%.[1] Insulin injection could elicit immediate reactions, which are usually induced by an IgE-mediated mechanism, within the first hour after drug administration.[2] Clinical signs and symptoms might be erythema and swelling at site of injection, urticaria, angioedema, rhinitis, bronchospasm and anaphylaxis. In patients with insulin allergy, it is

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difficult to establish effective management strategies and achieve glycemic control. In the present study, we describe the case of a child who experienced immediate allergic reaction following injection of long-acting insulin analogs.

Case report

A 9-year-old girl, affected by type I diabetes mellitus (DM1), was treated with four injections of recombinant human insulin (one injection of long-acting insulin glargine and three injections of rapid-acting insulin lispro). During the first week of insulin therapy, she developed generalized immediate urticaria twice after subcutaneous injections of long-acting insulin glargine. She received oral anti-histamine anti-H1 and symptoms resolved within a few hours. Insulin glargine was substituted for insulin degludec. After the first administration, generalized urticaria occurred in a few minutes. She recovered after treatment with oral anti-H1. In all three episodes, she did not present other symptoms or signs; blood pressure was normal. She tolerated insulin lispro. Her personal allergological history was negative. She never suffered from urticaria or angioedema. There was no temporal relation between urticaria and intake of foods, other medications, insect sting, physical stimuli and infections. Skin prick tests with undiluted insulin degludec and insulin glargine were performed, showing negative results. Histamine (10 mg/mL) and saline solution were used as positive and negative controls. Intradermal tests with 0.03 ml of a 1:100,000 dilution resulted positive for both insulin degludec and insulin glargine (longest length × perpendicular length of the wheal of 7 × 6 mm and 10 × 9 mm, respectively) (Table 1). Subsequently, she underwent skin prick test with 1:1 dilution of long-acting insulin detemir, and intradermal test with 1:100,000, 1:10,000, 1:1,000, 1:100, 1:10 and 1:1 dilution of insulin detemir. All these tests showed negative results. In light of these findings, insulin detemir was administered and it did not trigger any allergic reaction. At 6 months follow-up, parents reported that insulin detemir was regularly given without any adverse reaction.

Table 1. Results of diagnostic tests.

Allergen	Skin prick tests[a]	Intradermal tests[a]
Degludec	Negative	7 × 6 mm[b]
Glargine	Negative	10 × 9 mm[b]
Detemir	Negative	Negative[c]
Histamine	4 × 4 mm	–
Saline	Negative	–

[a]Longest length x perpendicular length of the wheal.
[b]1:100,0000 dilution.
[c]1:100,0000, 1:10,000, 1:1,000, 1:100, 1:10, 1:1 dilution.

Discussion

Our results show that insulin detemir has been tolerated by a patient with clinical hypersensitivity reactions to insulin degludec and insulin glargine (Table 2). Insulin detemir differs from insulin degludec and insulin glargine in a few amino acids. Therefore, it is possible that a conformational rather than a linear epitope may have induced an allergic response. However, we do not have set of subjects and hence no statistical tests employed to claim all patients will have same outcome.

Heinzerling et al.[3] reviewed immediate allergic reactions to insulin and proposed a diagnostic flowchart, suggesting that acute manifestations are likely to be IgE-mediated. They recommended the need for skin prick testing and assessment of IgE-insulin-specific levels.

It is remarkable to comment on the results of diagnostic tests in our case report. Prick tests of insulin degludec and insulin glargine were negative, even though intradermal tests were positive. Although skin prick testing is considered adequate to confirm insulin allergy, our results show that intradermal testing may be more sensitive for insulin (Figure 1). From a practical point of view, it is important to underline that intradermal test should be routinely used in the allergological work-up instead of insulin-specific IgE/IgG antibodies detection, as this test is not commercially available.

Reactions to insulin analogs could be caused by additives allergy, such as zinc or metacresol.[3] This possibility was excluded since all three preparations contain the same components. So, insulin itself acted as the offending allergen.

Various therapeutic options have been proposed for allergy to long-acting insulin analogs (Figure 1).[4] In case of emergency, intravenous administration may be required. Premedication with anti-histamines or glucocorticoids has also been suggested. When results of IgE tests

Table 2. Overview of insulin formulations used in the case report.

	Name	Type	Daily dose	Form	Onset (min)	Peak (h)	Duration (h)	Excipients
1	Glargine	Long-acting	1	Analog	180–240	No	24	Zinc chloride, metacresol, glycerol, hydrochloric acid, polysorbate 20, sodium hydroxide, water for injections
2	Degludec	Ultra long	1	Analog	30–90	Flat	>40	Zinc acetate, metacresol, glycerol, hydrochloric acid, phenol, sodium hydroxide, water for injections
3	Detemir	Long-acting	1	Analog	180–240	No	12–20	Zinc acetate, metacresol, phenol, mannitol, sodium chloride, disodium phosphate dihydrate

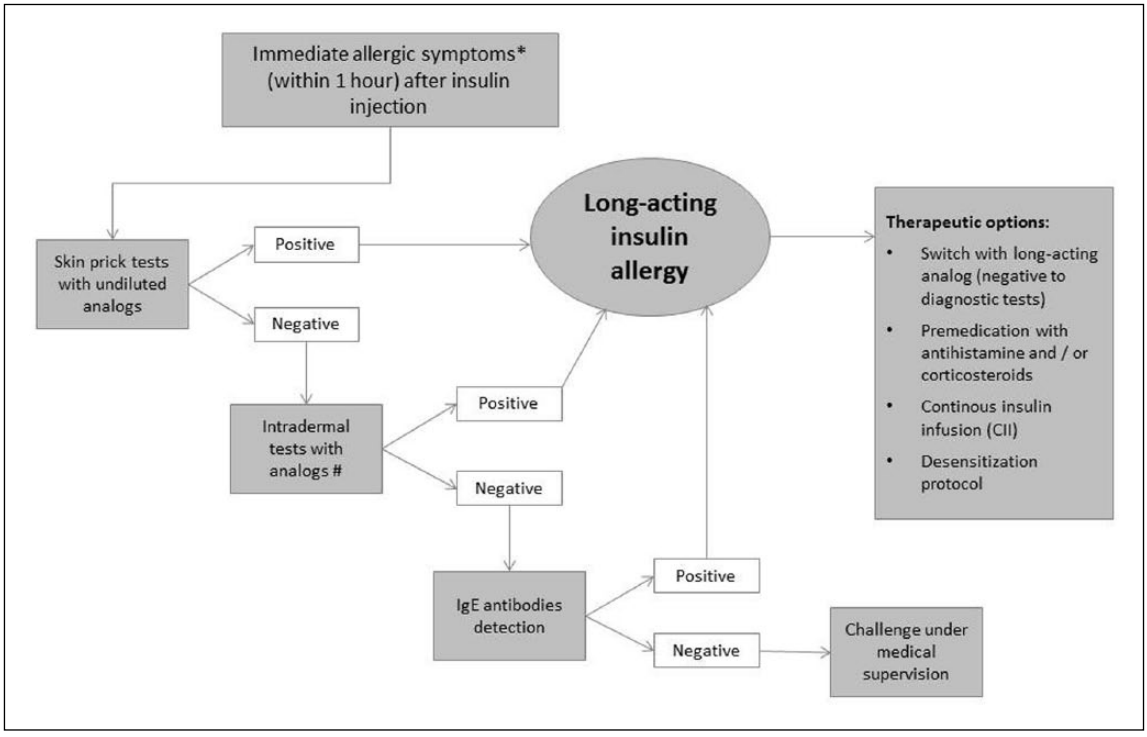

Figure 1. Diagnostic and therapeutic work-up of long-acting insulin allergy.
*Urticaria/angioedema, rhinitis, bronchospasm, anaphylaxis.
#1:100000, 1:10000, 1:1000, 1:100, 1:10, 1:1 dilution.

are negative, the long-acting analog should be administered under medical supervision to confirm tolerance. When IgE tests are positive, rapid-acting analogs may be used, since they have reduced antigenicity, due to increased clearance of monomeric analogs at injection sites which lessens mast cell stimulation. Recently, a continuous subcutaneous insulin infusion (CSII) with rapid-acting analogs in a pump system has been preferred. Another option is that patients perform a rapid desensitization protocol with long-acting analogs. A sequential dose increase causes a progressive stimulation of T-regulatory cells and the modulation of antibody production by cytokines, inhibiting both early and late mast cell activation responses.[5]

In conclusion, insulin allergy should always be suspected in patients with immediate symptoms after drug injection. An allergological work-up, including skin prick test and intradermal test to the culprit insulin analog and to different analogs must be performed. This would permit to choose a patient-tailored treatment.

Declaration of conflicting interests

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