

A CASE OF POSSIBLE HYPERSENSITIVITY REACTIONS TO HUMAN INSULIN

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Abstract

Background: *Insulin therapy is commonly used in diabetic patients. It represents the only option for patients with type 1 diabetes mellitus and could be part of the treatment plan for the patient with type 2 diabetes mellitus. Clinical appearance of hypersensitivity reactions to insulin vary significantly, depending on the immune mechanism involved. Many skin prick tests could be interpreted as positive reactions (either by using inappropriate concentrations or due to other mast cell degranulation causes). Case History:* Four weeks after initiation of insulin therapy, patient V.I. experienced a maculopapular rash, severe pruritus, induration at the injection site after 12-24 hours after administration. The presence of an insulin sensitization was proven by skin prick test and determination of specific IgE. **Discussions:** Patients suspected of insulin hypersensitivity should be evaluated by an allergologist in order to obtain a correct diagnosis and to identify other possible causes for the insulin intolerance. Desensitization should be undertaken only in real insulin hypersensitivity cases in patients who need it. **Conclusions:** Insulin allergy can be managed successfully with a good cooperation between the diabetologist and the allergologist.

key words: *diabetes mellitus, insulin therapy, insulin hypersensitivity, skin prick tests, desensitization.*

Background

Insulin therapy is commonly used in diabetic patients. It represents the only option for patients with type 1 diabetes mellitus and could be part of the treatment plan for the patients with type 2 diabetes mellitus, when diet and oral anti-diabetic medications do not succeed to control blood sugar levels or in some specific

conditions. Usually, in type 2 diabetes mellitus, insulin treatment initiation is done using a single shot of basal insulin (NPH, glargine or detemir). If treatment with basal insulin alone is not enough to reach glycemic control targets, supplementary shots of rapid acting regular human insulin or rapid insulin analog (lispro, aspart, glulisine) can be added.

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The prevalence of hypersensitivity reactions to insulin decreased significantly after the introduction in clinical practice of human insulin preparations (obtained by DNA recombination technology), being currently estimated at approximately 2.4% [1-3]. Clinical appearance of hypersensitivity reactions to insulin vary significantly, depending on the immune mechanism involved. Allergic reactions to insulin include IgE-mediated immediate type hypersensitivity, type III hypersensitivity (localized or generalized immune complex-mediated reactions) or delayed hypersensitivity type reactions. Furthermore, reactions with a delayed onset, e.g. 6 hours after injection of insulin may develop [4]. These delayed reactions include induration at the injection site with histological signs of leukocytoclastic vasculitis [5]. Finally, some reactions are even more delayed with onset after 8–24 h and may be put on account of delayed hypersensitivity. This has been reported most frequently for insulin preparations containing zinc [6] or protamine [7].

The presence of a rapid type I hypersensitivity reaction to insulin can be proven by skin prick test and determination of specific IgE [8]. A diagnostic algorithm in suspected insulin allergy has been suggested by Jaeger et al. in 2004 [9] and included intradermal skin testing, quantification of insulin-specific IgG and IgE in the serum, and analysis of the time-dependent binding/dissociation curves of the insulin-neutralizing antibodies in an *in vitro* assay.

Case History

Patient V.I. aged 52 years with history of recurrent autoreactive (positive autologous serum skin test) and cholinergic urticaria was diagnosed in September 2011 in the Diabetes Clinic of the "Nicolae Malaxa" Hospital with

type 2 diabetes mellitus and chronic C hepatitis. The therapy with insulin (human insulin-Humulin R and glargine- Lantus SoloStar) was initiated due to high levels of serum liver's enzymes. Four weeks after initiation of insulin therapy patient experienced a maculopapular rash, severe pruritus, induration at the injection site after 12-24 hours after administration (Figures 1,2). It persisted for a few hours, followed by improvement, but recurring after his next injection. Patient accused erythema and agitation after glargine administration. Due to the worsening of erythema, the patient was sent to allergy consult.



Fig 1. Local reaction to human regular insulin (Humulin R®).



Fig 2. Granuloma at the injection site of human regular insulin (Humulin R®).

The screening for the presence of atopy as an aggravating factor was performed, but the skin prick tests to common aero and trof-allergens were negative.

In the evaluation, the allergologist performed skin prick and intradermal tests for Lantus SoloStar[®], Humulin R[®] and, NPH[®], Actrapid[®] and Levemir[®]. This tests was positive. At that time, allergist concluded that the patient has hypersensitivity to substances tested and contraindicated for use. Until December 2011, when antiviral therapy with Interferon alfa-2b

and ribavirin was initiated, the patient had controlled blood sugar levels only by specific diet. Later, due to high blood glucose values, the opportunity of treatment with oral antidiabetic drugs was considered. Consequently, the tolerance to gimepiride by oral challenge test was performed (after prior written informed consent was obtained).

Also then, the skin tests have been performed again for Lantus[®], Humulin R[®], Humulin N[®], Actrapid[®] and Levemir[®] (Table 1, Figures 3,4).

Table 1. The results of skin tests to insulin.

Drug	Prick 1/10	Prick 1/1	ID 1/1000	ID 1/100	ID 1/10
Humulin R [®] 100U/ml - human insulin	negative	negative	Positive at 15 min wheal 15 mm persists up to 48 h	Positive at 15 min wheal 6 mm persists up to 48 h	Not performed
Actrapid [®] 100U/ml - human insulin	Not performed	negative	Rash after administration	Positive, wheal 6 mm persits up to 24 h	Not performed
Levemir [®] 100U/ml - insulin detemir	Not performed	Negative at 30 min positive after 24 h	Negative at 30 min positive after 24 h, wheal 8 mm	Negative at 30 min positive after 24 h, wheal 8 mm	Negative at 30 min positive after 24 h, wheal 8 mm
Lantus [®] 100U/ml - insulin glargine	negative	negative	Positive, wheal 6 mm persits up to 24 h	Positive, wheal 6 mm persits up to 24 h	Not performed

Humulin R[®] – regular insulin, Eli Lilly; Actrapid[®] - regular insulin, Novo Nordisk; Levemir[®] - insulin detemir, Novo Nordisk; Lantus[®] – insulin glargine, Sanofi; Humulin N[®] – NPH insulin, Eli Lilly



Fig. 3. Positive intradermic tests to Levemir[®] 1/1000, 1/100 and Humulin N[®] 1/1000, 1/100



Fig. 4. Positive intradermic tests to Levemir[®] 1/1000, 1/100 and Humulin N[®] 1/1000, 1/100

Because the presence of recurrent urticaria, we decided to put on antihistaminic medication for one month.

Given the high likelihood of metabolic decompensation with concomitant use of antiviral treatment, we considered the possibility of insulin treatment reintroduction. As a consequence, we discussed with the patient the possibility of performing a human insulin desensitization, especially for Actrapid® (human regular insulin) in the case of patient's need for emergency treatment with insulin.

Prior this protocol we need the results of *in vitro* tests basophils degranulation (BDT) and lymphoblastic transformation (LTT) to Actrapid®.

BDT is a test that can identify sensitization of type I, IgE mediated or a "pseudoallergy" (direct mast cell degranulation) to the antigen test (in our case Actrapid®), while the LTT is a test that can detect a possible sensitization in the sense of a type IV immune reaction to the tested antigen.

Both tests, along with IgE specific to human insulin were negative.

After a month of antihistamine treatment the patient stopped accusing recurrent urticarial eruptions and we decided to conduct a challenge test with Actrapid®,

The initiation test was performed 7 days after stopping the antihistaminic medication, not before obtaining the patient's written informed consent on how the test will be conducted, risks and adverse reactions including potential immediate type hypersensitivity reactions. The test was performed in the intensive care unit, under strict surveillance of allergist and diabetologist, therefore prepared for a rapid intervention by intensive care physicians. Initially the skin prick test was performed to Actrapid® versus negative control (0.9% saline solution) as shown in [Table 2](#).

Table 2. Skin prick test to Actrapid.

	15 min	30 min
Actrapid® 100U/ml human insulin	negative	negative
Normal saline	negative	negative
Histamine positive control	Positive, wheal 5 mm	Positive, wheal 5 mm

Doses were gradually increased at a dosing interval of 30 minutes ([Table 3](#)) in two consecutive days, in order to identify possible delayed local reactions.

Table 3. Actrapid® subcutaneous challenge test.

Day 1	Hour	Dose	Results
Actrapid® 100U/ml human insulin	10:16	0.01U	Without immediate-type hypersensitivity reactions
Actrapid® 100U/ml human insulin	11:16	0.1U	Without immediate-type hypersensitivity reactions
Actrapid® 100U/ml human insulin	11:16	1U	Without immediate-type hypersensitivity reactions
Actrapid® 100U/ml human insulin	12:16	2U	Without immediate-type hypersensitivity reactions
Actrapid® 100U/ml human insulin	12:16	3U	Without immediate-type hypersensitivity reactions
Day 2	Hour	Dose	Results
Actrapid® 100U/ml human insulin	10:00	3U	Without immediate-type hypersensitivity reactions
Actrapid® 100U/ml human insulin	10:30	4U	Without immediate-type hypersensitivity reactions
Actrapid® 100U/ml human insulin	11:00	6U	Without immediate-type hypersensitivity reactions

The patient was continuously monitored for vital functions, blood glucose values and

urticaria activity score. Throughout the test there were no significant changes in clinical status and laboratory tests and the patient tolerates a total dose of 19 U subcutaneous Actrapid.

Currently, several months after the challenge test, the patient tolerates daily doses of Actrapid, no hypersensitivity reactions. Small amount of Actrapid at meals it was sufficient for a good metabolic control (HbA1c around 7%).

Discussions

The presence of an insulin sensitization can be proven by skin prick test and determination of specific IgE [10]. The aim is to offer alternatives to the patient allergic to human insulin, by using alternative insulin analogs such as lispro, aspart and glargine.

Although these medications represent options for patients with allergy to human insulin [11], they have also been known to provoke hypersensitivity reactions including type 1 allergy in clinical practice [12-15].

Patients suspected of insulin hypersensitivity should be evaluated by an allergologist in order to obtain a correct diagnosis and to identify other possible causes for the insulin intolerance. Many prick skin tests could be falsely interpreted as positive reactions (either by using inappropriate concentrations or due to other mast cell degranulation causes).

Desensitization should be undertaken only in real insulin hypersensitivity cases in patients who need it. A method to induce tolerance is the

administration of insulin as continuous subcutaneous insulin infusion (CSII). Several case reports described the beneficial effect of this form of administration in allergic diabetic patients [16-20]. Furthermore, the use of desensitization for the treatment of insulin allergy has been reported previously and was successful in many cases [21]. The initial dose used for desensitization depends on the grade of sensitization and the duration is usually of 2 days.

In our patient's case, the initial positive tests could be explained by autoreactive chronic urticaria (anterior positive autologous skin prick test), which affected skin reactivity, leading to a false-positive result in the *in-vivo* tests.

The current insulin regimen used in our patient, including only rapid insulin, is unusual and could be a solution only on the short term. In the future, patient will need also basal insulin to be added for a proper glycemic control.

Conclusions

Insulin allergy is a rare condition that calls for a quick allergological work-up. It can be managed successfully with a good cooperation between the diabetologist and the allergologist. Patients need also a good metabolic control in order to avoid chronic complication and a safe treatment alternative. Specific desensitization should be considered if a type 1 allergy to insulin is diagnosed and may lead to a complete resolution of symptoms.

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