Case Report

Rapid Desensitization for Insulin Allergy in Type 1 Diabetes Using an Insulin Pump: A Case Report and Literature Review

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Objective: Insulin allergy, although uncommon, poses a significant challenge in those with type 1 diabetes mellitus (T1D) as insulin replacement is a necessity. Our objective is to describe a patient in whom rapid desensitization to insulin aspart was achieved using an insulin pump.

Methods: A 40-year-old woman with newly diagnosed T1D developed pruritic wheals over the abdomen after being injected with insulin glargine U-300 (Toujeo) and insulin aspart. Type 1 insulin hypersensitivity was confirmed through intradermal testing and positive insulin-specific immunoglobulin E levels.

Result: The patient underwent rapid desensitization with an insulin pump. Half the anticipated daily basal requirement was initially subcutaneously administered before initiating low-dose insulin via the pump (0.000025 units/h) and increasing the dose every 30 minutes to reach her basal requirements within 5 hours. Subsequent larger bolus insulin doses did not produce any local or anaphylactic reactions. No pretreatment with corticosteroids or antihistamines was provided.

Conclusion: Previous protocols for insulin desensitization span over days and often involve routine premedication. The case we presented suggests that insulin desensitization can be achieved over several hours using an insulin pump. A subcutaneous basal insulin cover should be provided prior to desensitization to avoid hyperglycemia necessitating an insulin bolus. Routine premedication may not always be necessary depending on reaction severity.

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Introduction

Insulin allergy affects 0.1% to 3% of insulin-treated diabetes, with symptoms ranging from a localized rash to life-threatening anaphylaxis.1 Recombinant human insulin analogs have decreased immunogenicity compared with animal insulin preparations.2 However, allergies to these insulins have been described. Short-acting insulin preparations are the least immunogenic because rapid absorption is believed to decrease immune exposure.3

We describe a case of a woman with a recent-onset type 1 diabetes mellitus (T1D) who developed insulin allergy and underwent insulin desensitization using an insulin pump. Our experience with this patient supports the feasibility of rapid up-titration over several hours without premedication with antihistamines or corticosteroids.

Case Report

A 40-year-old woman presented with a recently diagnosed T1D (1-month history; HbA1c, 15.5% [146 mmol/mol]), having had a 4-month history of polyuria, weight loss, and lethargy. She had no family history of diabetes mellitus and was lean (body mass index, 18.4 kg/m²). The results of glutamic acid decarboxylase and islet cell antibodies tests were positive, and the level of C-peptide was low (0.59 μg/L; glucose, 4.9 mmol/L). She was on multiple daily...
injections of insulin glargine U-300 (Toujeo) and insulin aspart; the total daily dose (TDD) was 17 units (0.35 units/kg/d), and glycemic control improved after 2 months (HbA1c, 8.4% [68 mmol/mol]).

Three months into insulin initiation, she developed pruritic wheals with either insulin, which appeared within seconds after injection and lasted beyond a day. Insulin glargine U-300 and insulin aspart were switched to insulin glargine U-100 (Lantus) and insulin glulisine, respectively; however, the reactions persisted.

She underwent an evaluation for type 1 hypersensitivity to insulin. The skin prick test was negative; however, the results of intradermal injections at 1:10 dilution of insulins, including aspart, glargine U-100, glulisine, detemir, soluble, isophane, and lispro, yielded positive reactions to all insulins following intradermal injections (Fig. A). The elevated level of immunoglobulin E (IgE) (1.78 kU/L [positive range, 0.7-3.49 kU/L]) specific to human insulin confirmed the insulin allergy.

Our patient was troubled by her symptoms and reduced carbohydrate intake to minimize insulin requirements. Furthermore, we were concerned about serious systemic reactions that may occur with the continuation of insulin. Therefore, she was admitted for rapid insulin desensitization via an insulin pump.

An insulin pump cannula was inserted, and saline was initially delivered to ascertain the absence of skin reactions to the pump cannula or adhesive. Half of her estimated daily basal dose (6 units insulin glargine U-100) was administered at 5 AM, followed by diluted insulin aspart via the insulin pump at 9 AM. Insulin aspart was diluted to a final concentration of 1:1000, and the initial insulin infusion rate of 0.000025 units/h (basal rate on pump = 0.025 units/h) was used. This was increased every 30 minutes, with close monitoring for adverse reactions and hourly capillary blood glucose checks (Table 1). She was kept fasted to avoid the need for bolus insulin, although later required small amounts of top-up long-acting carbohydrates to avoid hypoglycemia.

Her TDD on multiple daily injections was 17 units; we anticipated a 30% reduction in TDD on the insulin pump (11.9 units). Half the dose (6 units) would be required as basal insulin over 24 hours (0.25 units/h). We projected that this basal dose would be delivered within 5 hours. Throughout this period, no skin reactions were noted. After 5 hours, 1.75 units insulin bolus was administered for 35 g carbohydrates (insulin-to-carbohydrate ratio, 1:20 g) with no adverse reaction noted. Insulin pump therapy with insulin aspart was continued with no further skin reactions observed (Fig. B).

Discussion

Three types of allergic reactions to human insulin have been described. Type I immediate hypersensitivity is the most common, which is an IgE-dependent reaction mediated by the release of vasoactive substances from basophils and mast cells. Symptoms start at the injection site with swelling, erythema, and itching shortly after allergen exposure and may progress to a generalized reaction, ranging from simple urticaria to anaphylaxis.

Skin prick tests have lower sensitivity compared with intradermal testing. The appearance of a wheal >3 mm within 60 minutes indicates an immediate hypersensitivity, whereas delayed hypersensitivity induces a response between 2 hours and 24 hours. The measurement of specific IgE is another cornerstone of diagnosis, although it has limitations mainly because of poor clinical correlations. The positive intradermal test and IgE level in this patient support the diagnosis of a type 1 hypersensitivity reaction to insulin. Management typically involves switching to noninsulin agents or other insulin formulations. However, this was not feasible in our patient with T1D and allergies to all formulations.

Different treatments for insulin allergy have been described with the use of antihistamines or systemic corticosteroids, addition of glucocorticoids to insulin, tolerance induction with increasing doses of insulin, and continuous subcutaneous insulin infusion (CSII). As most desensitization protocols involve the frequent administration of small incremental doses of insulin to obtain low constant blood levels that gradually increase to therapeutic levels, CSII is an ideal method of desensitization to avoid repeated injections and has been reported successful in desensitizing patients with T1D with insulin allergy.

Fewer than 20 cases of insulin desensitization in T1D have been reported (Table 2). In our case, rapid insulin desensitization was conducted over 5 hours compared with previous reports (8 hours to 16 days). A very low dose of basal insulin was required to effect desensitization; however, this low basal rate would be insufficient to fulfill her insulin requirements, potentially leading to hyperglycemia. We, therefore, administered half the dose of her basal

Fig. A. Wheals to all insulins following intradermal injections. B. Upon insulin pump cannula removal, following insulin desensitization.
insulin desensitization. In most cases, the insulin used for desensitization could permit the safe use of alternative insulin preparations. In some cases, the successful use of other insulins has been observed following desensitization with soluble insulin or lispro, suggesting that desensitization was continued to be used for therapy. In some patients, the insulin used for desensitization was low, we omitted antihistamines or glucocorticoids. The successful desensitization suggests that premedication may not always be necessary.

Although it is unclear how CSII induces insulin desensitization, the mechanism might involve the depletion of chemical mediators of hypersensitivity at the site of continuous injection and blockade of immunoglobulin G antibodies. The significant reduction in rate and rapidity of insulin absorption minimize the time for local reactions to develop. Moreover, continuous basal infusion may induce tolerance to additional doses of prandial insulin.

Apart from insulin aspart, lispro has also been successfully used in insulin desensitization. In most cases, the insulin used for desensitization was continued to be used for therapy. In some cases, the successful use of other insulins has been observed following desensitization with soluble insulin or lispro, suggesting that desensitization to 1 insulin preparation could permit the safe use of alternative insulin preparations.

**Conclusion**

Allergies to insulin are rare and, in T1D, necessitate insulin desensitization. This may be achieved with rapid desensitization over several hours with an insulin pump and does not always require premedication. Administering subcutaneous basal insulin prior to desensitization in T1D should be considered to avoid hyperglycemia during the rapid up-titration period.

**Disclosure**

The authors have no multiplicity of interest to disclose.

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