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Case Report

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

Kristy Tian, MBBS, MRCP, MMed [1,*], Haur Yueh Lee, MBBS, MRCP, MMed [2], Huee Boon Lim, BHSN [1], Yoke Ling Chan, BHSN, MSN [1], Ai Heong Chong, BSND [1], Suresh Rama Chandran, MBBS, MD, MRCP [1], Daphne Su-Lyn Gardner, BA, BM BCh, MRCP [1]

[1] Department of Endocrinology, Singapore General Hospital, Singapore
[2] Department of Dermatology, Singapore General Hospital, Singapore

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ABSTRACT

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.

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/m^2). 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

Abbreviations: CSII, continuous subcutaneous insulin infusion; IgE, immunoglobulin E; T1D, type 1 diabetes mellitus; TDD, total daily dose.

* Address correspondence and reprint requests to Dr Kristy Tian, Department of Endocrinology, Singapore General Hospital, Outram Road, Singapore 169608.
E-mail address: kristy.tian@mohh.com.sg (K. Tian).

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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 protamine/lispro mix, were positive (wheal size, 11.0 × 8.0-26.0 × 16.0 mm) (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.

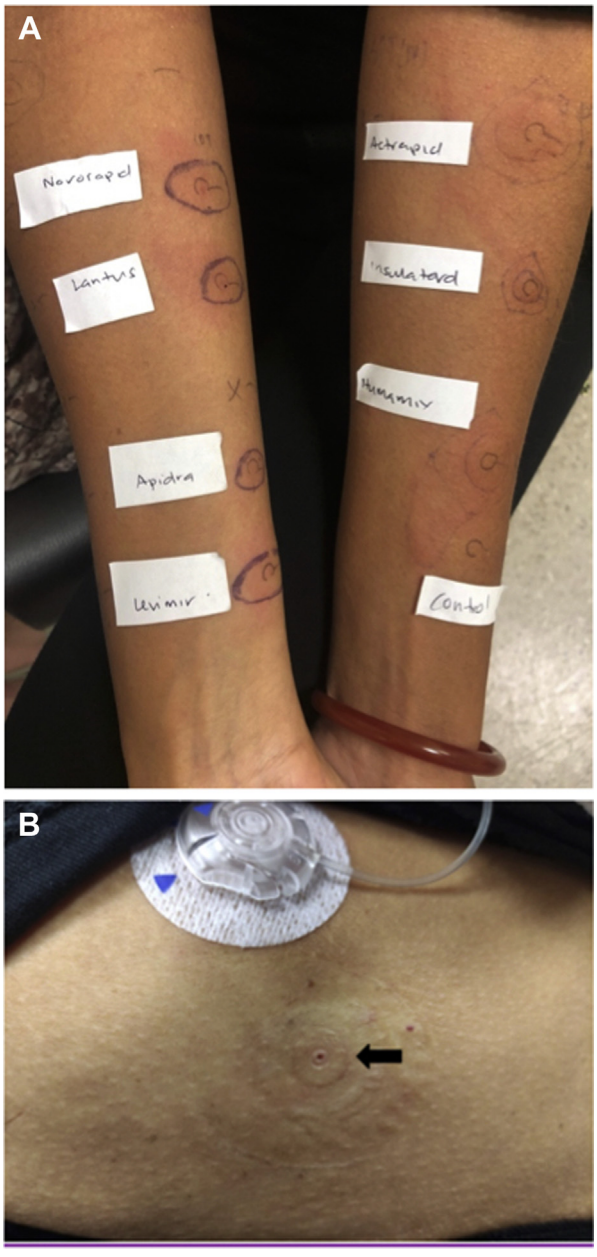

Fig. *A*, Wheals to all insulins following intradermal injections. *B*, Upon insulin pump cannula removal, following insulin desensitization.

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.[4] 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.[5] 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).[6] 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 reached 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.[7] 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.[8] 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.[8] 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.[9-11]

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.[12] We, therefore, administered half the dose of her basal

Table 1
Insulin Desensitization Protocol Using an Insulin Pump

Minutes	Basal rate on insulin pump	Dilution of insulin	Insulin rate (units/h)	Capillary blood glucose (mmol/L)	Comments
0	0.025	0.001	0.000025	5.8	
30	0.1	0.001	0.0001		
60	1	0.001	0.001	5.9	
90	2	0.001	0.002		
120	4	0.001	0.004	4.9	5 g carbohydrates
150	8	0.001	0.008		
180	16	0.001	0.016	5.4	
210	32	0.001	0.032		
240	0.05	1	0.05	6.3	
270	0.125	1	0.125		
300	0.25	1	0.25	4.9	2 g carbohydrates

Table 2
Literature Review of Case Reports on Insulin Desensitization in Patients With T1D

Report	Patient age	Duration of protocol	Insulin used	Premedications
Insulin allergy and resistance successfully treated by desensitization with Aspart insulin	25 years old	16 d	Aspart	Prednisolone
Insulin desensitization with insulin lispro and an insulin pump in a 5-year-old child	5 years old	8 h	Lispro	Cetirizine
Insulin allergy desensitization with simultaneous intravenous insulin and continuous subcutaneous insulin infusion	9 years old (2 cases)	192 h	Lispro	Fexofenadine
Successful treatment of insulin allergy in a type 1 diabetic patient by means of constant subcutaneous pump infusion of insulin	21 years old	Not reported	Lispro	Cetirizine
Continuous subcutaneous insulin infusion to resolve an allergy to human insulin	43 years old	22 h	Lispro	Not reported
Continuous subcutaneous insulin infusion allows tolerance induction and diabetes treatment in a type 1 diabetic child with insulin allergy	8 years old	36 h	Lispro	Not reported
Immediate-type human insulin allergy successfully treated by continuous subcutaneous insulin infusion	63 years old	4 d	Novolin R	Not reported
Primary systemic allergy to human insulin: recurrence of generalized urticaria after successful desensitization	22 years old	12 d	Humulin R	Not reported
Prolonged desensitization required for treatment of generalized allergy to human insulin	30 years old	9 d	Actrapid	Not reported
Successful management of insulin allergy and autoimmune polyendocrine syndrome type 4 with desensitization therapy and glucocorticoid treatment	17 years old	5 d	Glargine	Ebastine, prednisolone

insulin requirements in an alternative insulin formulation 4 hours prior to prevent unacceptable hyperglycemia that would require a larger insulin bolus for correction, thereby negating the desensitization. As she experienced only local reactions and the initial dose for insulin desensitization was low, we omitted antihistamines or corticosteroids. 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.[9,13] 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.[14]

Apart from insulin aspart, lispro has also been successfully used in insulin desensitization. [10] 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.[13,15]

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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