Case Report
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Immediate and Late Onset Forms of Insulin Hypersensitivity Presenting with Glucose Dysregulation

Glukoz Disregülasyonu ile Ortaya Çıkan Erken ve Geç Başlangıçlı İnsulin Aşırı Duyarlılığı

Ceyda Tunakan Dalgıç, Fatma Düşünür Günsen, Ilgın Yıldırım Şimşir*, Gökten Bulut, Aytül Zerrin Sin

Ege University Faculty of Medicine, Department of Allergy and Clinic Immunology, İzmir, Turkey
*Ege University Faculty of Medicine, Department of Endocrinology and Metabolism, İzmir, Turkey

Abstract

We report the case of a 35-year-old woman allergic to detemir, neutral protamine Hagedorn, and glargine. Initially, local reactions to the insulin preparations occurred, which continued even after the types of insulin and the application areas were changed. When the use of insulin therapy was continued, the local reactions developed into systemic forms. Interestingly, blood glucose levels kept increasing to uncontrolled levels every time the cutaneous reactions occurred. The patient was referred to our clinic for further investigation. The results of the skin prick tests with insulin preparations were negative; however, the intradermal test results were positive with the following dilutions of the insulin preparations: 1/100 detemir, 1/100 glargine, 1/1.000 neutral protamine Hagedorn, and 1/1.000 regular insulin. The intradermal skin test results for glulisine, aspart, and lispro were negative. The levels of immunglobulin E specific to human insulin were high (194 kU/L; N 0-87 kU/L); whereas, the specific immunglobulin G4 levels were normal (35 mg/dL; N 0-125 mg/dL). We attempted to treat the patient with glulisine and aspart; however, similar reactions were observed with these insulin preparations as well. As we considered the levels of the anti-insulin antibodies and the late-onset local reactions, the insulin allergy in our patient was reckoned to be mediated by Type 1 and Type 4 hypersensitivity. The only insulin preparation that had never been used with this patient before was lispro, which also demonstrated negative intradermal skin test results. Therefore, we suggested the use of a continuous subcutaneous insulin infusion pump with lispro. Finally, the insulin hypersensitivity was successfully treated, and glycemic control was achieved.

Keywords: Insulin allergy; continuous subcutaneous insulin infusion

Özet

Bu çalışmada, detemir, glarjin ve nötral protein Hagedorn insüline karşı alerjik 35 yaşındaki kadın olgu sunulmaktadır. İlk kez insülin preparatlarına karşı lokal reaksiyonlar oluşmuş ve devamında insülin çeşitleri ve uygulama alanları değişmesine rağmen lokal reaksiyonlar devam etmiştir. İnsülin tedavisi devam ettikçe lokal reaksiyonlar sistemik forma dönüşmüşlerdir. İlginç olarak, lokal deri reaksiyonları devam ettiği sürece, kan glukoz seviyesinde kontrolsüz seviyelere yükselmeler de devam etmiştir. Hasta, ileri tetkik için kliniğimize yönlendirildi. İnsülin preparatları ile yapılan deri prik testleri negatif saptandı, ancak intradermal deri testi sonuçları ise 1/100 dilüsyonda detemir, 1/100 dilusyonda glarjin, 1/1000 dilüsyonda nötral protein Hagedorn ve 1/1000 dilüsyonda regular insülin ile pozitif bulundu. Glulisin, aspart ve lispro insülin ile intradermal deri testleri negatif saptandı. İnsan insülinine karşı spesifik immünglobulin E seviyesi kanda yüksek (194 kU/L; N 0-87 kU/L) iken; insan insülinine karşı spesifik immünglobulin G4 ise normal (35 mg/dL; N 0-125 mg/dL) bulundu. Hastayı aspart ve glulisin ile tedavi etmeye çalışıldı, ancak bu insülinler ile de benzer reaksiyonlar gözlendi. Anti-insülin antikorları ve geç başlangıçlı lokal reaksiyonları göz önüne aldığımızda, hastamızda gözlenen insülin alerjisi Tip 1 ve Tip 4 aşırı duyarlılık reaksiyonları olarak değerlendirildi. Daha önce hastanın tedavisinde hiç kullanılmamış olan ve deri testleri negatif saptanan insülin lispro idi. Bu nedenle, hastaya lispro insülin ile sürekli subkutan insulin infüzyon pompası önerdik. Sürekli subkutan insülin infüzyon pompası ile hastanın insulin aşırı duyarlılığı başarılı bir şekilde tedavi edildi ve glisemik kontrol sağlandı.

Anahtar kelimeler: İnsülin alerjisi; sürekli subkütan insülin infüzyonu

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Address for Correspondence: Ceyda Tunakan Dalgıç, Ege University Faculty of Medicine, Department of Allergy and Clinic Immunology, İzmir, Turkey
Phone: +90 232 444 13 43 **E-mail:** dr_ceydat@yahoo.com **Received:** 01/02/2017 **Accepted:** 02/11/2017

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Introduction

Patients with poor glycemic control in type 2 diabetes, who are already receiving the maximum dose in the oral hypoglycemic therapy, invariably require insulin therapy (1). Allergic reactions to insulin are rare, with a frequency of less than 1% in the patients with diabetes, especially when recombinant human insulin is used. Management of this condition may be difficult. As a high-molecular-weight protein, insulin mainly induces the type I hypersensitivity reactions, which may range from local erythema to anaphylaxis. Desensitization is one of the treatment choices for systemic reactions in the patients who require insulin, and symptomatic treatment is recommended for the local reactions by several authors. Local forms of insulin allergy may, however, progress to systemic forms sometimes (2). Here, we report the case of a patient with type 2 DM and insulin allergy, who was successfully managed with continuous subcutaneous insulin infusion (CSII), in which desensitization was performed using an insulin pump with lispro (3).

Case Description

A 35-year-old woman with type 2 diabetes was referred to our clinic by a diabetologist. Five years ago, she had been diagnosed with gestational diabetes; however, after the delivery, she had no problems regarding the blood glucose levels. The diabetologist preferred using oral antidiabetics for her treatment. Diet, physical exercise, and metformin (2.000 mg) were prescribed to her; however, satisfactory glucose control was not achieved. Although she used a combination of oral antidiabetics in maximal doses (metformin, gliptin, and sulfonylurea), the patient was symptomatic with polyuria, tiredness, and depression. In order to control the deterioration caused by diabetes, insulin therapy was initiated in addition to metformin (2.000 mg per day). Past medical history included autoimmune thyroiditis, for which the patient had been using L-thyroxine tablets. Physical examination was normal, with a controlled blood pressure (125/80 mmHg); however, she had a high body mass index (BMI) (32 kg/m^2). The laboratory tests revealed high levels of HbA1c (10.5%; glucose level= 13.4 mmol/L), with normal renal and liver functions. She used detemir insulin initially, together with metformin. On the third day of detemir therapy, 12 h after the dose, a pruriginous papule (2 cm) occurred at the site of injection area. The local reaction occurred along with an uncomfortable feeling that persisted for several days. On the seventh day, detemir was changed to NPH insulin. The NPH therapy was continued along with antihistamines; however, a local reaction (papule size= 1.5-2 cm) occurred with the very first dose of NPH. All of these local reactions were the late-onset types. They began almost 12 h after the insulin therapy. Therapy was then changed to glargine insulin. One hour after the first dose of glargine, local reaction and generalized pruritus occurred. The patient was then referred to an allergologist. All the insulin types were terminated, and four weeks later, skin prick tests were performed with insulin preparations, the results of which were negative. The intradermal test results were positive with the following dilutions of the insulin preparations: 1/100 detemir, 1/100 glargine, 1/1000 NPH, and 1/1000 regular insulin. Intradermal test results with glulisine, aspart, and lispro were negative (Table 1, Figure 1).

The levels of the insulin-specific IgE antibody (ImmunoCap, Phadia) (194 kU/L; N 0-87 kU/L) and the anti-insulin IgG antibody (DIAsource ImmunoAssays S.A.) (47.8%; N<8.2%) were high; the levels of specific IgG4 (ImmunoCap, Phadia) were normal (35 mg/dL; N 0-125 mg/dL) (Table 2).

The therapy began with glulisine, and there was no allergic reaction initially. However, since the blood glucose levels and the serum glycated-hemoglobin A1c levels (10%) remained high, NPH (as a long-acting insulin) had to be added to the therapy, together with antihistamines. No allergic reaction was observed with NPH. On the 20th day of glulisine, late-onset local reactions were observed. Glulisine was then changed to aspart insulin. Similar reactions were observed with these two insulin preparations. Finally, the only insulin which had never been used earlier in this patient, i.e., lispro, was used. Desensitization with dilution techniques was considered; however, the patient was unwilling to follow this protocol. Hence, a review of the literature on the insulin desensitization using insulin pump was conducted, in which, we discovered several articles mentioning the use of short-acting insulin preparations, especially lispro due to its minimum allergic configuration. Therefore, we suggested the use of a CSII pump with lispro for the treatment of our patient. Insulin desensitization with lispro was performed using an insulin pump (Medtronic MiniMed Paradigm), beginning with a daily dose of 0.1 U/h, which was gradually increased to 1.4 U/h by Day 15 (Table 3).

Table 1. Prick tests were negative with all insulin types.

Drug	PRICK (mm) (wheal/erythema)	ID 1/100 concentration (mm) (wheal/erythema)	ID 1/1000 concentration (mm) (wheal/erythema)
Detemir	-	9/30	-
Glargine	-	9/25	-
Aspart	-	-	-
Glulisin	-	-	-
Lispro	-	-	-
NPH	-	-	9/25
Regular	-	-	10/30
Negative control	-	-	-
Positive control	8/35	10/40	

Intradermal tests were positive with the dilutions of 1/100 detemir, 1/100 glargine, 1/1000 NPH, 1/1000 regular insulin. But glulisine, lispro, and aspart were negative.

In the course of treatment with the insulin-pump therapy, local reactions were observed at the infusion site. As a result, we advised antihistaminic tablets (a combination of ketotifen, cetirizine, and fexofenadine, three times a day). After two weeks, the patient continued to use lispro as an insulin injection with a titration algorithm (an increase of 2 to 4 units in the dose of the insulin preparation, if the fasting glycemia exceeded the value of 140 mg/dL). HbA1c levels decreased to 8% (glucose level= 10.1 mmol/L) in the next six months, with the total lispro insulin dose of almost 60-70 U/day, and the additional metformin therapy of 2,000 mg per day. The patient has been receiving the CSII pump therapy since then, and this treatment method is going to be continued in the future. After six months of the CSII pump therapy, the patient's fasting blood glucose levels were in the range of 100-140 mg/dL, and the postprandial blood glucose levels were in the range of 140-200 mg/dL. Using this method, the insulin hypersensitivity was successfully treated within six months. Also, in addition to glycemic control, the allergic symptoms experienced by the patient, such as generalized and local pruritus, were controlled.

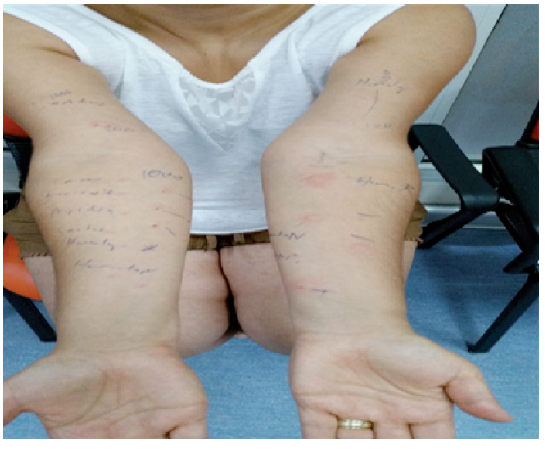

Figure 1: Photo of skin prick and intradermal tests on the patient.

Table 2. Insulin specific IgE [194 Ku/L (0-87)] and anti-insulin antibody 47.8% (reference <8.2%) were high and specific IgG4 was normal [35 mg/dL (0–125)].

	Result	Reference
Insulin specific IgE (Ku/L)	194	0-87
Anti-insulin antibody (%)	47.8	<8.2
Insulin specific IgG4 (mg/dL)	35	0-125

Discussion

Several studies have described the allergic reactions to insulin and its components. The development of novel technologies for the production and purification of insulin, and the new era of insulin analogues have decreased the prevalence of such allergic reactions during the insulin treatment, with less than one-third of the reported events of allergies being related to insulin therapy. The prevalence of suspected insulin allergy has been reported to range from 0.5% to 2.0% (1-3). One of the treatment options available for the patients with these allergies is to switch to the insulin analogues, which significantly decreases the number of allergic episodes. Substitutions by other types of insulin have been reported to decrease the allergic reactions (4-6). This is due to the fact that the allergenicity of insulin, caused by the beta-chain terminals, has been weakened in the substitutes of insulin,

Table 3. Insulin desensitization protocol is seen in the table. Maximum basal infusion rate is 1.4 U/h.

Number of days during desensitization	Insulin infusion rate (U/hr)	Total insulin dosage (U/day)
1–3	0.1	2.4
4–6	0.2	4.8
7–9	0.4	9.6
10–12	0.8	19.2
13–15	1	24
16–18	1.2	28.28
19–21	1.4	33.6

which have modified structures (6). Lispro, in particular, has the amino acid lysine instead of proline at position 28 of the beta chain, and proline instead of lysine at position 29 (7). Nevertheless, insulin analogues are able to cause allergic reactions as well (6-8). However, these modified structures might contribute to the attenuation of the allergic reactions to lispro during a CSII. In fact, allergic reactions to these types of insulin were observed even before the beginning of the treatment with CSII in case. In this case, switching to other insulin preparations proved unsuccessful, and therefore, we attempted to decipher the condition with different desensitization protocols. Further, certain previous studies had demonstrated the use of an insulin pump for a gradual desensitization protocol (9), which was found to be useful and within the tolerance limits for treating the patients experiencing allergic reactions to insulin. Most of the studies (10) demonstrated successful desensitization in patients with type 2 diabetes, when an insulin pump was used with a short-acting insulin analogue. In 2005, an interesting case report by Moyes et al. (1) demonstrated the successful management of insulin allergy in type 2 diabetes by using CSII. In that case the patient was commenced on an insulin pump therapy, in addition to his oral hypoglycemics, and achieved control with lispro, with little or no skin or systemic reactions. In 2012, Eguíluz-Gracia et al. (2) published another report about a patient with local reactions to insulin analogues. In that case, the 62-year-old male patient, who had developed a pruritic, erythematous nodule, tolerated the SCII treatment satisfactorily. Using a desensitization protocol described in that report improved the patient's comfort, and reduced the risk of chronic skin lesions. It appears to be well-established that a previous local reaction is the main risk factor for systemic reactions occurring in the future. Desensitization not only improves the patient's comfort, it might also aid in preventing the future episodes of anaphylaxis. In another report by Matheu (7), a 25-year-old patient with type I Diabetes Mellitus, who had previously received a diagnosis of protamine allergy (however, not to human insulin), began noticing allergic reactions immediately after receiving insulin. Gradual desensitization with aspart insulin, by using a subcutaneous insulin pump, was successful in this case. In another case report, a severe systemic allergy subsided after the initiation of lispro insulin therapy, using continuous subcutaneous insulin infusion (CSII) (11). Although the mechanism through which CSII induces insulin desensitization remains unclear, it might involve the depletion of chemical mediators of hypersensitivity from the mast cells and basophils present at the site of continuous injections (12). Moreover, several reports have discussed the possibility that desensitization proceeds by inducing a blockade of IgG antibodies (1, 13, 14) and the generation of suppressor T cells (15).

In conclusion, allergic reactions to insulin analogs are rare and require early diagnosis, which is a major therapeutic challenge. In the case of our patient, the local reactions continued even when the types of insulin preparations and the application areas were changed. Another interesting observation was that the blood glucose levels were increased to uncontrolled levels every time the cutaneous reactions occurred. It is possible that the insulin antibodies which affected our patient were mainly IgG and IgE. As we considered the anti-insulin antibodies and the late-onset local reactions, the insulin allergy, in this case, was reckoned to be mediated by type 1 (the immediate-type) and type 4 (the delayed-type) hypersensitivity reactions. In conclusion, we suggest that CSII could serve as an ideal treatment for insulin allergies, and it may also broaden the possible successive treatment options for such allergies.

Informed Consent: Consent form was filled out by the patient.

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Author Contributions

Concept: Ceyda Tunakan Dalgıç, Aytül Zerrin Sin; Design: Ceyda Tunakan Dalgıç, Aytül Zerrin Sin; Data Collection or Processing: Ceyda Tunakan Dalgıç, Aytül Zerrin Sin; Analysis or Interpretation: Ceyda Tunakan Dalgıç, Aytül Zerrin Sin, Ilgın Yıldırım Şimşir; Literature Search: Ceyda Tunakan Dalgıç, Aytül Zerrin Sin; Writing: Ceyda Tunakan Dalgıç, Ilgın Yıldırım Şimşir, Aytül Zerrin Sin

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