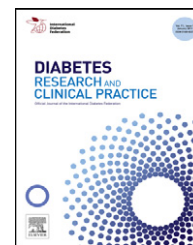


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Brief report

Severe insulin allergy successfully treated with continuous subcutaneous insulin infusion

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ARTICLE INFO

Article history:

Received 12 April 2012

Accepted 30 April 2012

Keywords:

Insulin allergy

Continuous subcutaneous insulin
infusion

Type 2 diabetes

ABSTRACT

Insulin allergy is a rare complication of insulin therapy. Proper management, though difficult, is critical. Here, we report the case of a patient with type 2 diabetes and insulin allergy, successfully treated with continuous subcutaneous insulin infusion (CSII).

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1. Introduction

Allergic reaction to insulin is rare, especially when using recombinant human insulin, with a frequency of less than 1% in patients with diabetes [1]. Here, we describe a case in which a severe systemic allergy subsided after the initiation of insulin lispro therapy by continuous subcutaneous insulin infusion (CSII). Subsequently, the long-acting insulin analogue glargine was also administered with no adverse effects.

2. Case report

A 50-year-old man was admitted with uncontrolled diabetes, and wheals and itching around the site of subcutaneous injections. He had suffered from type 2 diabetes and hyperuricemia for 6 years, and had no history of any allergy. Eight months prior to admission, the patient initiated subcutaneous insulin administration with the biphasic insulin

analogue aspart after secondary failure of sulfonylurea therapy [HbA1c 10.5% (91 mmol/mol)]. Glycemic control was initially improved [HbA1c 6.9% (52 mmol/mol), insulin 0.38 U/kg] and aspart administration caused no allergic symptoms. However, 8 months after the initiation of this regimen, itching and systemic wheals, especially distinct at the injection site, appeared. Wheals appeared within 10 min of injection and lasted several hours. The levels of fasting blood glucose and HbA1c deteriorated to 350 mg/dl and 12.2% (110 mmol/mol), respectively.

Aspart was then substituted for other preparations: neutral protamine Hagedorn (NPH) insulin, Humacart N, the fast-acting insulin analogue lispro, and regular human insulin. However, none of these preparations were suitable due to cutaneous reactions and attenuated effects of insulin. An allergy to insulin was then suspected. Intradermal skin testing was positive for all types of insulin, including the human insulin analogues lispro, aspart, glargine, and detemir; the regular human insulins Novolin R, Humulin R; NPH insulin, Humulin N, Humacart N, Novolin N, and Humalog N; and the

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<http://dx.doi.org/10.1016/j.diabres.2012.04.027>

Table 1 – Laboratory and clinical data.

	Before initiation of CSII	6 months after initiation of CSII	3 months after completion of CSII
HbA1c [% (mmol/mol)]	12.2 (110)	9.3 (78)	8.1 (65)
Insulin-specific IgE (UA/ml)	3.75	0.78	0.43
Insulin antibody (%)	94	57	65
Insulin dosage (U/kg)	0.81	0.69	0.65

biphasic insulin analogue humacart-3/7. Radioallergosorbent testing revealed a high level of human insulin-specific IgE (3.75 UA/ml; normal <0.34 UA/ml) and insulin-binding antibodies in the patient (^{125} I-insulin binding rate, 94%; normal <0.4%). Treatment with an anti-allergy drug did not provide relief from wheals and itching, and conventional desensitization with human insulin [2] was ineffective (Table 1).

Even when desensitization by conventional insulin treatment fails, CSII has been reported to be successful in desensitizing insulin allergy in patients with type 2 diabetes [3]. Although glycemic control deteriorated, subcutaneous insulin injections were suspended for several days with concomitant improvement in the skin condition. We then decided to initiate CSII with insulin lispro. The skin condition showed no deterioration after the initiation of CSII, and consequently both itching and wheals disappeared and glycemic control was gradually restored [HbA1c 9.3% (78 mmol/mol), insulin 0.69 U/kg]. One year later, after confirmation of lowered insulin-specific IgE (0.44 UA/ml) and significantly improved intradermal test results, particularly for lispro and glargine, we decided to withdraw CSII. Subcutaneous injections of lispro and glargine were initiated in place of CSII, and to date (i.e. more than 3 years later) no further allergic symptoms such as wheals and itching have occurred. Glycemic control is also adequately maintained [HbA1c 6.8% (51 mmol/mol), insulin 0.61 U/kg].

3. Discussion

Type I allergic reaction is the most common type of insulin allergy characterized by rapid onset reactions [3,4]. The insulin-IgE complex binds to IgE receptors on the surface of basophils and mast cells, causing release of inflammatory mediators such as histamine, resulting in the allergic reaction [5]. Our patient presented with a typical type I allergic reaction according to the Gell and Coombs classification [6].

HLA characteristics such as HLA B7, DR2, and DR4 may promote insulin allergy [7]. However, the allergy of this patient was different from HLA-mediated allergy, since the patient's HLA typing was HLA A3, A26, B40, B44, DR9, and DR13.

There are few reports of desensitization to insulin after treatment with CSII and the subsequent withdrawal of CSII [5,8,9]. In particular, no case has been reported of desensitization to insulin using CSII with good control afterwards. We report a case of desensitization to not only a fast-acting insulin analogue but also to a long-acting insulin analogue after treatment with the fast-acting insulin analogue by CSII and the subsequent withdrawal of CSII.

Although it is unclear how CSII induces insulin desensitization, the mechanism might involve depletion of the chemical mediators of hypersensitivity from mast cells and

basophils [10] at the site of continuous injection. In addition, several reports have discussed the possibility that desensitization proceeds by inducing blockade of IgG antibodies [3,11,12], and the generation of suppressive T cells [7].

It is possible that the insulin antibodies affected in our patient were mainly IgG or IgM, not IgE, since we did not analyse the composition of insulin antibodies. However, the decreased insulin antibody titer still remained high after insulin desensitization by CSII, and the type III allergic reaction induced by IgG- or IgM-mediated immune complexes [6] was not observed in our case. Hence, IgE is more likely to be involved in these allergic reactions than is IgG or IgM.

Substitutions by other types of insulin have been reported to decrease allergic reactions [13,14]. This is due to the fact that the allergenicity of insulin in the B chain terminal has been weakened in substituted insulins which have modified structures [15]. Specifically, lispro has the amino acid lysine instead of proline at position 28 of the beta chain and proline instead of lysine at position 29 [16]. Nevertheless, insulin analogues are still able to cause allergic reactions [15,17]. In fact, allergic reactions to these types of insulin were observed before treatment with CSII in our case. However, these modified structures might also contribute to attenuation of allergic reactions to lispro with CSII.

In conclusion, CSII could be an ideal treatment for insulin allergy and can broaden possible treatment options afterward.

Author contributions

T.F. wrote manuscript, researched data, contributed to discussion. H.I. researched data, contributed to discussion. M.D. contributed to discussion. Y.G. contributed to discussion. H.K. researched data, contributed to discussion, reviewed/edited manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

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