



Short Report

Continuous subcutaneous insulin infusion allows tolerance induction and diabetes treatment in a type 1 diabetic child with insulin allergy

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Received 24 May 2012; received in revised form 10 October 2012; accepted 10 October 2012

Abstract

Aim. – Insulin allergy is a rare but serious and challenging condition in patients with type 1 diabetes (T1D). This is a case report of an 8-year-old boy with T1D and an allergy to insulin.

Case report. – Three months after being diagnosed with T1D, the patient developed progressive skin reactions to insulin, characterized by small 1.5-cm pruritic wheals at injection sites that persisted for several days. Seven months after diagnosis, he experienced two episodes of generalized urticaria with systemic symptoms that were seen within a few seconds of insulin injection. Examination revealed lipoatrophy of the thighs. Intradermal skin tests were positive for protamine, glargine and lispro. The patient was started on a continuous subcutaneous insulin infusion (CSII) tolerance induction protocol, consisting of a very low basal rate that was progressively increased, with the first bolus given under medical supervision, and was well tolerated for 4 months. After this period of time, the skin wheals reappeared, localized to the infusion sites, but without urticaria or any other generalized reactions. Intradermal skin tests were repeated and were again positive. Serum insulin-specific IgE measured 30 months after the first allergic reactions were positive. After 3 years, pump therapy is ongoing and blood glucose control has remained relatively good (HbA_{1c} 7.6%).

Conclusion. – In T1D children with insulin allergy, CSII can successfully be used to both induce insulin tolerance and allow diabetes insulin therapy, although insulin desensitization cannot always be fully achieved. The induction protocol was easily manageable partly due to the “honeymoon” period that the patient was still in, but it should nonetheless be used even when the patient has higher insulin requirements.

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Keywords: Insulin allergy; Tolerance induction; Children; CSII; Type 1 diabetes

Résumé

Allergie à l'insuline chez un enfant diabétique : traitement du diabète et induction de tolérance par pompe à insuline.

But. – L'allergie à l'insuline est une pathologie rare mais dont la prise en charge est délicate chez les patients diabétiques de type 1 (DT1). Nous rapportons le cas d'un garçon de huit ans ayant un DT1 et une allergie à l'insuline.

Cas clinique. – Trois mois après un diagnostic de DT1, le patient développe progressivement des papules érythémateuses et prurigineuses de 1,5 cm de diamètre, persistant plusieurs jours aux sites d'injection de l'insuline. Sept mois après la découverte du DT1, deux épisodes d'urticaire généralisée avec symptômes systémiques ont lieu quelques secondes après une injection. L'examen clinique révélait des lipoatrophies sur les cuisses. Les intradermo-réactions (IDR) étaient positives pour protamine, glargine et lispro. Un protocole d'induction de tolérance a été débuté par perfusion continue d'insuline par pompe sous-cutanée (débit basal faible, augmenté rapidement, bolus réalisés initialement sous supervision médicale). Le traitement a été parfaitement toléré pendant quatre mois. Après cette période, les papules cutanées sont réapparues, localisées aux sites d'insertion des cathéters, sans urticaire ou autre réaction généralisée. Les IDR étaient à nouveau positives pour les mêmes substances. Les IgE spécifiques pour l'insuline mesurées 30 mois après la première réaction allergique étaient positives. Le traitement par pompe à insuline est poursuivi depuis 36 mois et le contrôle métabolique est assez satisfaisant (7,6 %).

Abbreviations: CSII, Continuous subcutaneous insulin infusion; IgE, Immunoglobulin E; NPH, Neutral protamine Hagedorn; IV, intravenous; T1D, type 1 diabetes.

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Conclusion. – Chez un enfant diabétique de type 1 avec une allergie à l'insuline, une insulinothérapie par pompe peut permettre d'induire une tolérance et de traiter efficacement le diabète, mais la désensibilisation peut ne pas être parfaitement atteinte. L'utilisation de ce protocole a été facilitée par la période de « lune de miel » que traversait le patient, mais il devrait être réalisé même chez un patient ayant des besoins en insuline plus élevés.

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Mots clés : Allergie à l'insuline ; Induction de tolérance ; Enfant ; Pompe à insuline ; Diabète de type 1

1. Introduction

Insulin allergy is a rare but serious phenomenon, as symptoms can range from localized wheals at injection sites to severe anaphylactic reactions [1–4]. Immunoglobulin E (IgE)-mediated symptoms are seen immediately after insulin injection. The incidence is not precisely known for the paediatric population. As insulin is a vital drug for insulin-dependent patients, a quick diagnostic workup and adequate management is critical. This report is of an 8-year-old type 1 diabetes (T1D) patient who presented with allergy to insulin and lipoatrophy of the thighs. His insulin regimen was switched from multiple daily insulin injections to continuous subcutaneous insulin infusion (CSII), which allowed relief of his allergic symptoms and a reduction in lipoatrophy while still maintaining good metabolic control.

2. Case report

This 8-year-old Caucasian boy was diagnosed with T1D at 7 years of age. Treatment with Umuline NPH® and lispro (Humalog®, Eli Lilly, Indianapolis, IN, USA) was initially well tolerated.

However, at 3 months after diagnosis, he started developing localized reactions at NPH injection sites, characterized by 1.5- to 3-cm areas of slightly swollen erythema, appearing within 30 min of injection and visible for 48 h.

Seven months after diagnosis and following an injection, a generalized urticarial reaction was seen in association with general symptoms (paleness, blurred vision, abdominal pain, vomiting and pruritus). The symptoms disappeared within a few hours while the patient was being taken care of by an emergency team. No drug was needed for treatment. His insulin regimen was switched to Insulatard® and insulin aspart (NovoRapid®, Novo Nordisk, Bagsværd, Denmark), and the patient was discharged home. Seven days later, the same phenomenon occurred again. After management of the acute reaction, the patient was transferred to our ward for investigation and treatment.

Examination on admission was normal apart from discrete areas of lipoatrophy on the upper thighs. There was no dermatological evidence of mastocytosis. The insulin regimen was switched to glargine (Lantus®, Sanofi, France) and lispro. The same localized reaction was seen with both insulins whereas there was no reaction with an equivalent volume of saline injected subcutaneously with the same brand of syringe. As a temporal relationship between the insulin injections and allergic signs had been established, it was necessary to document the presence of insulin-specific IgE antibodies with skin tests.

Intradermal tests consisted of injecting 0.03 mL of 10^{-3} diluted glargine, lispro and protamine, and measuring the mean diameter of the wheal after 20 min. All were positive. Only these three insulins were tested because of the high risk of hypoglycaemia in a young child. The latex test remained negative, excluding false-positive reactions. It was concluded that the boy had an allergy to insulin molecule and protamine. The clinical presentation and results of the skin tests suggested IgE-mediated allergy against human insulin, although specific anti-insulin IgE was not measured at this time.

After the diagnosis was made, the patient was started on an antihistamine drug (cetirizine). Tolerance induction with repeated, but increasing the doses of insulin was not appropriate because of the patient's strict insulin requirements, so CSII was chosen instead, using the following protocol: a catheter was put in place 24 h before CSII was started, while the patient still received insulin injections to check for localized reactions. A Silhouette® infusion set (Medtronic MiniMed, Northridge, CA, USA) was used, as it allows the injection site to be directly seen. An insulin lispro infusion was started at a rate of 0.02 U/h (10 IU/mL diluted insulin), and was gradually increased during the first 24 h up to the therapeutic basal level. Blood sugar levels were checked hourly as were the patient's vital signs. No bolus was given for the first 24 h; meals were based on low glycaemic index (GI) foods to prevent major hyperglycaemia and ketosis. The first bolus was given under physician supervision with resuscitation drugs readily to hand in the room. The therapeutic insulin dose was completely reintroduced over a 36-h period.

The use of insulin-pump CSII was well tolerated and no allergic reaction was noted either during the hospital stay or within the first months after discharge, even when the antihistamine drug treatment was stopped. The boy's parents were told to restart the antihistamine in case of urticarial relapse. Following tolerance induction carried out under hospital supervision, the patient was discharged with a prescription for an epinephrine injection kit in case of a severe acute allergic event.

After 4 months of CSII, the skin wheals reappeared at infusion sites, but without urticaria. CSII was continued and the sites of lipoatrophy disappeared after a few months. Intradermal skin tests were repeated and again were positive. CSII has been ongoing now for more than 3 years, and neither the patient nor his parents report any problems with supervision or compliance. The patient's current blood glucose control is also relatively good (HbA_{1c} 7.6%). Serum tryptase has been recently measured and has definitely ruled out any suspicion of mastocytosis. Human insulin-specific IgE (ImmunoCAP,

Phadia, Uppsala, Sweden) was positive (0.88 kUI/L) 30 months after the diagnosis of insulin allergy.

3. Discussion

Injecting insulin into the subcutaneous tissues can lead to various reactions by the immune system. Insulin antigenicity may be due to self-aggregation of insulin molecules into high-molecular-weight aggregates, thereby promoting the formation of anti-insulin antibodies in the subcutaneous tissue [5,6]. Insulin analogues are less likely to form aggregates than the earlier insulins used [7–9] and are also absorbed more rapidly and, thus, are exposed to subcutaneous mast cells for a shorter period of time. This might explain why analogues induce less immunogenicity.

Several cases of insulin allergy have already been published but, to our knowledge, only four paediatric cases have been described so far [1,3,4,10], three of which were desensitized using CSII. Different treatments for insulin allergy have been described in the literature: antihistamine drugs; addition of glucocorticoid to insulin [5,11,12]; use of general corticosteroids; use of human analogues instead of animal insulin; tolerance induction with increasing doses of insulin (ultra-rush desensitization) [7,9], or with increasing doses of insulin glargine [1,4,10], and with CSII using human analogues [4,11–13].

In a child with T1D, it is impossible to avoid the use of insulin or even to dramatically lower the doses, thereby eliminating the possible use of the ultra-rush protocol. However, continuous delivery avoids repeated injections, making CSII an ideal method of desensitization in cases where repeated injections are only accepted with difficulty.

The protocol used in our present case was adapted from a protocol previously used to treat adult patients with insulin allergy [13]. The process was made more comfortable because our patient was still in his “honeymoon” period, therefore requiring only small doses of insulin. No episode of ketosis was seen during the protocol. Nevertheless, cases of successful tolerance induction have been reported in adult patients who were not in their honeymoon period [11,13] and in a child [1]. Indeed, this protocol should be attempted even when the patient requires higher doses of insulin, as there are only limited options for a child with T1D and insulin allergy.

Recurrences of local allergic reactions after desensitization have been described in several case reports [1,4], but most of them were said to be easily manageable by the patient. As our patient was experiencing flare reactions and urticarial wheals at injection sites, the use of the method of desensitization described by Neville et al. [4] and Asai et al. [14], using intravenous (IV) insulin infusion, was questionable. In three patients treated with IV insulin, the systemic and local symptoms stopped while on IV insulin infusion, but came back when insulin was subcutaneously injected again. In two of the patients (two 9-year-old boys), the symptoms were mild and allowed CSII treatment whereas, in the third patient, a central venous catheter, a subcutaneously embedded reservoir and a portable infusion pump were needed to provide continuous IV insulin infusion, as severe allergic reactions recurred with CSII. For this reason, it was highly

likely that IV insulin would not have cured our patient of insulin allergy, but it would allow the treatment of his T1D should CSII become no longer possible.

Along with the local and systemic allergy symptoms, our patient had also developed lipoatrophy on both thighs. Insulin allergy with lipoatrophy in T1D patients has been reported, but the mechanisms are not well documented. An immune basis has been suggested by the immunohistochemical demonstration of deposits of both insulin and immunoglobulin G in subcutaneous tissue biopsies from lipoatrophic areas [6,15].

4. Conclusion

In children, insulin allergy remains a rare and challenging clinical situation. In our patient with T1D and allergy to insulin, the best therapeutic choice was tolerance induction by means of CSII with an insulin analogue, which allowed good control of both blood glucose and allergic symptoms. CSII may be proposed as a first-line treatment in the management of insulin allergy in children, even after the honeymoon period. Described here is a detailed protocol that can easily be used in such cases even by teams that have had little experience in managing insulin allergy.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References

- [1] Eapen SS, Connor EL, Gern JE. Insulin desensitization with insulin lispro and an insulin pump in a 5-year-old child. *Ann Allergy Asthma Immunol* 2000;85:395–7.
- [2] Kaya A, Gungor K, Karakose S. Severe anaphylactic reaction to human insulin in a diabetic patient. *J Diabetes Complicat* 2007;21:124–7.
- [3] Hermoso F, Vazquez M, Chaves G, Revigerio J, Andión R. Generalized allergy to human insulin treated with insulin lispro (abstract). *Diabetologia* 1997;40:A349.
- [4] Neville KA, Verge CF, Wainstein BK, Woodhead HJ, Ziegler JB, Walker JL. Insulin allergy desensitization with simultaneous intravenous insulin and continuous subcutaneous insulin infusion. *Pediatric Diabetes* 2008;9:420–2.
- [5] Grammer LC, Chen PY, Patterson R. Evaluation and management of insulin allergy. *J Allergy Clin Immunol* 1983;71:250–4.
- [6] Ratner RE, Phillips TM, Steiner M. Persistent cutaneous insulin allergy resulting from high-molecular-weight insulin aggregates. *Diabetes* 1990;39:728–33.
- [7] Pföhler C, Müller CS, Hasselmann DO, Tilgen W. Successful desensitization with human insulin in a patient with an insulin allergy and hypersensitivity to protamine: a case report. *J Med Case Reports* 2008;2:283.
- [8] Maislos M, Mead PM, Gaynor DH, Robbins DC. The source of the circulating aggregate of insulin in type I diabetic patients is therapeutic insulin. *J Clin Invest* 1986;77:717–23.
- [9] Heinzerling L, Raile K, Rochlitz H, Zuberbier T, Worm M. Insulin allergy: clinical manifestations and management strategies. *Allergy* 2008;63:148–55.
- [10] Hara M, Izumida Y, Sato N, Ohashi K, Osuga J-I, Tobe K, et al. Successful desensitization by glargine administration in a patient with insulin allergy: a case report. *Diabetes Res Clin Pract* 2009;84:e48–9.

- [11] Näf S, Esmatjes E, Recasens M, Valero A, Halperin I, Levy I, et al. Continuous subcutaneous insulin infusion to resolve an allergy to human insulin. *Diabetes Care* 2002;25:634–5.
- [12] Pratt EJ, Miles P, Kerr D. Localized insulin allergy treated with continuous subcutaneous insulin. *Diabet Med* 2001;18:515–6.
- [13] Sola-Gazagnes A, Pecquet C, Radermecker RP, Piétri L, Elgrably F, Slama G, et al. Successful treatment of insulin allergy in a type 1 diabetic patient by means of constant subcutaneous pump infusion of insulin. *Diabetes Care* 2003;26:2961–2.
- [14] Asai M, Yoshida M, Miura Y. Immunologic tolerance to intravenously injected insulin. *N Engl J Med* 2006;354:307–9.
- [15] Reeves WG, Allen BR, Tattersall RB. Insulin-induced lipoatrophy: evidence for an immune pathogenesis. *Br Med J* 1980;280:1500–3.