Clinical case

Desensitization of allergy to human insulin and its analogs by administering insulin aspart and insulin glargine

Désensibilisation à l’insuline humaine et ses analogues par l’administration de l’insuline asparte et de l’insuline glargine

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Abstract

Insulin allergy is a rare clinical situation. We report a 51-year-old patient with type 2 diabetes who required multiple daily insulin injections. The patient developed allergy to human regular insulin and insulin analogs (insulin aspart and insulin glargine), which was resolved by subcutaneous insulin desensitization.

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Résumé

L’allergie à l’insuline est une situation clinique rare. Nous rapportons le cas d’un patient de 51 ans ayant un diabète de type 2 pour lequel plusieurs injections quotidiennes d’insuline s’avéraient nécessaires. Le patient a développé une allergie à l’insuline humaine et aux analogues asparte et glargine. Une désensibilisation par injections sous-cutanées était réalisée.

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Allergic reaction to insulin is occasionally reported in medical literature. However, it is very rare to encounter patients allergic to human insulin and its analogs, particularly insulin glargine. Insulin allergy usually occurs within 1–4 weeks after starting insulin therapy. Here, we describe a patient with type 2 diabetes who required basal–bolus insulin injections because of deficient pancreatic activity. The patient experienced allergic reactions to human insulin (Novolin 50R and Scilin M30) and insulin analogs (Novomix 30, NovoRapid, and insulin glargine). These allergic reactions were resolved following progressive desensitization with subcutaneous insulin aspart and insulin glargine. To our knowledge, this is one of the first cases in China in which allergy to insulin was successfully treated by frequent subcutaneous injections of small, increasing doses of insulin aspart and insulin glargine.

1. Case report

A 51-year-old man was referred to our hospital for the management of uncontrolled diabetes. His HbA1c on presentation was 10.7%. He was diagnosed with type 2 diabetes 7 years previously, and he was treated with isophane protamine biosynthetic human insulin (Novolin 50R). However, upon starting this treatment, local pruritus developed at the injection sites within a few seconds of injection and would last for several hours. One month later, he referred to rhabdion in the site, so his therapy was switched to insulin aspart 30 (Novomix 30). Despite switching insulin formulation, the local pruritus persisted. Therefore, the patient was switched to oral agents, including metformin and gliclazide, which he used until referral to our hospital.

On presentation at our hospital, his HbA1c was 10.7%, fasting and postprandial C-peptide levels were 376.90 and 737.90 pmol/L, respectively, and fasting and postprandial insulin levels were 2.39 and 11.01 μIU/mL, respectively.

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0003-4266/$ – see front matter © 2012 Elsevier Masson SAS. All rights reserved.
http://dx.doi.org/10.1016/j.ando.2012.11.005

Based on the patient’s poor pancreatic function, basal–bolus insulin therapy was considered necessary to control his blood glucose levels. First, we prescribed insulin aspart to be administered before each meal. After 10 days of therapy, the patient reported having a skin rash and pruritus at the injection site, even though he correctly followed clinical advice to change the needle and injection site after each injection. Both events developed within 1 second after injection and lasted for a few hours or to the next day. Based on these events, the insulin was switched to Scilin M30. However, the patient reported the same symptoms 2 days later, which included skin rash, pruritus, and rhabdomy.

In patients that require multiple daily insulin injections, rapid desensitization should be considered using the dilutions of insulin summarized in Table 1. After obtaining informed consent from the patient, desensitization was started by administering 0.1, 0.2, 0.4, and 0.8 mL of 0.01 U/mL insulin aspart subcutaneously at 30-minutes intervals. Upon completion of this step, we administered a higher concentration of insulin aspart (i.e., 0.1 U/mL), in the same volumes. Finally, we sequentially administered 2, 4 and 6 U of undiluted insulin aspart (i.e., 100 U/mL) at 30-minutes intervals, until reaching the desired therapeutic dose, throughout desensitization, fingertip blood glucose levels were measured every 30 minutes to avoid hypoglycemia. And it took one day to finish the whole insulin desensitization course.

After this desensitization procedure, rhabdomy in the injection site had shrunk, but there was still evidence of pruritus. When we repeated this process with insulin glargine, the same allergic symptoms occurred. Therefore, the entire desensitization procedure with insulin aspart and insulin glargine was repeated.

In this repeated procedure, when we injected 0.4 mL of insulin aspart solution of (0.4 uU/mL), the injection site developed a red wheal and mild pruritus, so desensitization with insulin aspart was stopped and switched to insulin glargine. In this cycle, no allergic reactions occurred in response to insulin glargine administration at any dose.

During the desensitization procedure, insulin was administered in combination with triamcinolone acetonide in the first round, an antihistamine, to suppress local allergic reactions. Upon completing the desensitization procedure, the patient started a basal–bolus regimen with insulin glargine as basal insulin and insulin aspart before meals. The patient developed mild pruritus immediately after insulin injection, but it disappeared within 1 hour.

The patient was discharged and continued treatment with insulin aspart and insulin glargine. Nine months later, the patient has achieved good glycemic control. Mild pruritus sometimes occurs immediately after insulin injection but generally disappears within 1 hour, and was tolerated by the patient. No other adverse reactions have been reported.

### 2. Discussion

Insulin allergy occurs in about 2% of insulin-treated patients with diabetes. However, less than one-third of these cases are thought to involve reactions to insulin itself; most reactions are considered related to excipients present in the insulin preparations, such as zinc, protamine, and meta-cresol [1]. Reactions to insulin preparations range from local injection site reactions to severe generalized anaphylactic reactions. The type of allergic reactions include type I IgE-mediated reactions, type III immune complex-type, and type IV delayed-type hypersensitivity reactions, but most involve type I hypersensitivity [2].

Our patient was allergic to insulin preparations produced by several different manufacturers and contained different additives. Based on the clinical symptoms and patient’s history, we consider that the allergic reactions were induced by insulin itself and were probably type 1 reactions, because he has used and was allergic to several different types of insulin as a result of cross-reactivity.

Desensitization techniques can be beneficial for people who are allergic to different types of insulin and for who insulin therapy is essential. In case of failure, more prolonged protocols or repeated desensitization may be necessary. Although the mechanism of action is not yet fully understood, depletion of allergic mediators from mast cells or the production of anti-insulin IgG-blocking antibodies have been proposed as possible mechanisms. The technique combines two important parameters in the induction of tolerance: continuous/regular administration of small, increasing doses, and the use of potentially less immunogenic molecules. It can be performed either by continuous subcutaneous insulin infusion (CSII) or by successive subcutaneous injections [3].

Recent reports have described successful desensitization by CSII with rapid-acting insulin analogs, which seems particularly suited for desensitization, especially since this approach avoids repeated injections [4]. In particular, rapid-acting analogs, such as insulin lispro and insulin aspart, were reported to decrease antigenicity because of their rapid absorption and degradation at the injection site, and hence reduced presentation to mast cells [5]. Several case reports have described the successful use of insulin lispro or insulin aspart for the management of insulin allergy [6,7]. Our patient showed less severe allergic reactions to insulin aspart than to other insulins. Therefore, we administered insulin aspart subcutaneously for desensitization therapy.

In previous reports, it was described that long-acting insulins do not often cause allergic reactions in diabetic patients, although some case reports to describe allergic symptoms in patients treated with these insulins [8]. The relatively low immunogenicity of insulin glargine may be explained by two reasons [9]. First, insulin glargine forms a precipitate after injection, and these precipitates dissolve at a slow and constant rate, resembling the antigen presentation pattern after CSII. Second, the amino acid composition of insulin glargine could inhibit immune reactions. Until now, only Hara et al. [9] have reported

### Table 1

<table>
<thead>
<tr>
<th>Solution number</th>
<th>Insulin dose (mL)</th>
<th>0.9% NaCl dose (mL)</th>
<th>Concentration (0.1 mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>0.1 mL (10 U)</td>
<td>100 mL</td>
<td>0.01 U</td>
</tr>
<tr>
<td>3</td>
<td>0.1 mL (10 U)</td>
<td>9.9 mL</td>
<td>0.1 U</td>
</tr>
<tr>
<td>4</td>
<td>Original insulin solution</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>
a case of insulin allergy in which successful desensitization was achieved using insulin glargine administration. Their patient safely restarted pre-meal insulin aspart administration following desensitization, similar to our case.

In conclusion, this is an unusual case of allergy to human insulin and its analogs, including rapid-acting and long-acting insulins. Our method of desensitization was relatively easy, offering an alternative to CSII-based desensitization. The method might be particularly suitable for patients who require basal–bolus insulin therapy, but are immunogenic to many insulin preparations.

Disclosure of interest

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

Financial support: This work was supported by the Changzhou Program for Cultivation of Innovative Health talents.

Acknowledgments

Ping Wu was supported by a grant by the Changzhou Program for cultivation of innovative health talents. The authors thank the staff at the department of endocrinology, Nanjing Drum Tower Hospital, affiliated to Nanjing university medical school, for their assistance.

References