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Human insulin allergy-immEDIATE and late type III reactions in a long-standing IDDM patient

Maria E.R. Silva *, Maria J.M. Mendes, Mileni J.M. Ursich, Dalva M. Rocha, Alberto H.M. Brito, Rosa T. Fukui, Gláucia B. Ruggeri, Marcia Nery, Bernardo L. Wajchenberg

*Laboratory of Medical Investigation (LIM 18) and Endocrine Service,
Hospital das Clínicas of University of São Paulo Medical School, São Paulo, Brazil*

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Abstract

Human insulin allergy—immediate or late type III reaction—is a rare event. We report the case of a 33-year-old female patient with insulin-dependent diabetes mellitus for 25 years who presented, in the last 8 years, mild but generalized urticaria partially controlled with oral antihistamines. There was no improvement after changing from mixed beef-pork to human insulin. In the last 3 years another allergic manifestation began: small, localized, subdermal and painful non-erythematous nodules with central hematomas at injection sites, occurring 6–8 h after the insulin injection and lasting for 48 h. The following maneuvers had no benefit: (1) Human insulin (NPH or Lente) administered with dexametasone or xylocain locally. (2) Short acting human insulin with or without previous boiling. (3) Anti-histamine cetirizine dihydrochloride—10 mg/day. The allergic symptoms disappeared only after treatment with short acting human insulin (up to 100 U/day) associated to prednisone—40 mg/day and cetirizine dihydrochloride for 4 months. However, after stopping prednisone the urticaria reappeared and it was relieved with insulin desensitization. The pain at the site of injections persisted. Conclusion: This long-standing IDDM patient presented two types of reactions to human insulin: the immediate type (systemic urticaria), treated with antihistamines and desensitization, and the Arthus' type III reaction (nodules and hematomas occurring 6–8 h after the insulin injection) that required glucocorticoid therapy for more than 4 months. © 1997 Elsevier Science Ireland Ltd.

Keywords: Insulin; Allergy; Insulin-dependent diabetes mellitus

* Corresponding author. Endocrine Service, Hospital das Clínicas da Faculdade de Medicina da USP, Av. Dr. Eneas de Carvalho Aguiar 255. CEP 05403-000. São Paulo, SP, Brazil. Tel.: +55 11 2828554; fax: +55 11 2828554.

1. Introduction

Although the frequency of insulin allergy has been reduced with the present availability of high

purification technology and with the use of human insulin, reactions varying in severity from mild discomfort to life-threatening still occur in 2.4% of patients receiving human insulin [1].

2. Materials and methods

We report a case of a 33-year-old non-obese (BMI: 20.6 kg/m²) female patient with insulin-dependent diabetes mellitus since she was 8 years old, who in the last 8 years developed mild but generalized urticaria while using mixed pork-beef insulin. She did not report shortness of breath, hypotension or tachycardia. The symptoms were partially controlled with oral antihistamines. There was no improvement after changing to human insulin. In the last 3 years another allergic manifestation, typical of Arthus' type III reaction began: small, localized, subdermal, tenderness and painful non-erythematous nodules with central hematomas at injections sites, occurring 6–8 h after the insulin injection and lasting for 48 h.

When the patient was first seen she was on twice-daily Lente human insulin—44 U in the morning and 14 U in the evening, plus 5–7 U of short acting insulin before meals. The reactions did not depend if the insulin was administered isolated or mixed in the same syringe. The glycohemoglobin level was 12.1% (normal values: 5.5–8.5%) [2]. There were no retinal or renal complications but the neurological examination revealed a decreased sensitivity and paresthesia of lower extremities. Lypohypertrophy was already present at the site of insulin injections. The anti-insulin antibody level (11199 nU/ml) was in the usual range of our diabetic population using mixed insulin therapy (normal values < 98 nU/ml) [3]. The IgE level was elevated (510 IU/ml—normal values up to 170 IU/ml) and the IgG level was normal (1440 mg/dl—normal values: 952–1538 mg/dl).

The following sequence of maneuvers were tried in another service to treat this disorder:

1. Local factors were ruled out as: poor injection technique, use of impure alcohol for cleansing, exposure to other offending antigens or drugs. The insulin injector, that sometimes abrades or hurt the skin, was changed to plastic syringes with ultra-fine needles without relief of the complaints.
2. Human insulin (NPH or Lente) was administered in a solution containing either dexamethasone, based on the knowledge that glucocorticoids can prevent allergic reaction by inhibiting cellular lymphokine production [4,5] or xylocain to relief the local pain. The association of an anti-histamine with insulin in the same syringe was not tried since it may cause insulin precipitation [1,4].

The next step would have been the use of insulin kits for detecting which component of the injection was triggering the reactions: the vehicle, the pH of the solution, the presence and concentration of zinc or protamine, the insulin polymers or insulin fragments. As kits testing these specific isolated components were not available in Brazil, the skin-prick test was performed. The results were negative for all the insulin tested—human, pork and mixture beef-pork—in the short acting, Lente and NPH preparations. However, this does not exclude an allergic reaction as a negative result can depend on too little an amount of the antigen or the need of an antigen associated with some patient's protein. Therefore all the NPH or Lente human insulin commercially available in our country were tried in order to exclude the vehicle's allergy without however reverting the process. To exclude protamine or a great amount of zinc as potential offending allergenic agents, the patient was switched to short acting human insulin exclusively given four or more times a day (66 U/day). Short acting human insulin (with or without previous boiling for 30 min—the boiling changes spatial structure of the insulin molecule and can decrease immunological response) [6] did not change the clinical picture.

After concluding that it is possible that the immediate and type III allergic reactions were against an epitope on the insulin molecule, a new generation antihistamine with an anti-inflammatory effect (cetirizine dihydrochloride-10 mg bid) was started. After a month both kind of reactions still persisted; the urticaria even worsened and sometimes shortness of breath was reported. As delayed allergic reactions have been seen to be

refractory to insulin desensitization procedures [4], prednisone (40 mg/day) was associated to the regimen of short acting human insulin and oral antihistamine to treat both reactions. After 4 months of treatment the urticaria and the nodules disappeared. During this period her daily short acting insulin dose was increased from 66 to 100 U/day. She gained 3 kg and required Enalapril 30 mg/day to control her hypertension. The glycohemoglobin was kept in the normal range as well as serum cholesterol and triglyceride levels. There was no microalbuminuria or eye changes on ophthalmoscopy. After 4 months without allergic manifestations the prednisone dose was reduced slowly and the short acting insulin was switched to NPH. The nodules did not relapse but the urticaria reappeared after stopping prednisone, although as a mild and less frequent manifestation, despite the introduction of the short-acting antihistamine clorfeniramine chloridrate—8 mg/day. Then the patient was admitted to the Hospital, the antihistamine being withdrawn 2 days before. The skin-prick test was once again negative for all the insulin tested—human, pork and mixture beef-pork—in the short acting, Lente and NPH preparations. All these insulin types diluted 1:10 000 (0.01 U insulin/ml) in saline were administered intradermally, 0.1 ml (0.001 U/dose). At 30 min intervals increasing doses of insulin were administered at the dilutions 1:1000, 1:500, 1:250, 1:100—0.1 ml of the solution (0.01, 0.02, 0.04 and 0.1 U insulin/dose respectively) and a local reaction was noted only at 1:50 dilution (0.2 U/dose). The induction of tolerance was started on the next day with short acting human insulin (1:100 dilution) administered intradermally from 0.1 to 1 ml (0.1, 0.2, 0.4, 0.8 and 1 U) without local or systemic reaction. Then the same insulin dilutions were administered subcutaneously from 0.1 to 1 ml. The glucose control was maintained with NPH 30 U/day. On the following day she was given short acting human insulin (1:10 dilution) subcutaneously, 0.1 to 1 ml (1, 2, 4, 8, and 10 U) without reactions. The NPH dose was not administered because it was expected that she would have received a sufficient amount of short acting insulin (25 U in the morning). No nodules developed after 6 h of each procedure.

3. Results

After this induction of tolerance she stayed free of allergic reactions. Her insulin requirements decreased to 42 U of human insulin/daily (28 U of Lente insulin plus 14 U of short acting insulin) as her anti-insulin antibody level decreased to 4297 nU/ml. The IgE level was still high (decreasing from 510 to 461 IU/ml) and the IgG increased from 1440 to 1749 mg/dl as expected [6]. The complement C3 and C4 levels were normal. No circulating immunocomplexes were found. Lipohypertrophy and pain at the site of insulin injection continued to be present.

4. Discussion

Some patients with systemic allergy to insulin from animal sources also have reactivity to human insulin. The IgE and IgG antibodies appear to be directed against a determinant that is present in all insulins. However, insulin allergy is a rare event with human insulin and usually occurs within 1–4 weeks after initiation of insulin therapy and, more frequently, when it is resumed after a delay [5]. This was not the case in our patient since she had a long-standing IDDM. One possibility could have been the starting of intensive insulin therapy with multiple daily doses which could have enhanced an already present immune response to insulin in the last few years.

We presented an algorithm for treating insulin allergy. It is well known that systemic insulin allergy is mediated by IgE directed against the insulin molecule. The complex insulin-IgE acting on basophils and mast cells stimulate the release of mediators which elicit the type I generalized allergic reactions [1]. It can be treated with antihistamines, preventing local IgE mediated histamine release, or desensitization. On the other hand, the Arthus' type III reaction represents local insulin-antibody (IgG) complexes that cause basophil degranulation and local release of histamine and other mediators of hypersensitivity [1]; in addition, glucocorticoids are usually needed for 4 or more months for its control. Although a skin biopsy was not performed, the small, localized,

subdermal, tenderness and painful non-erythematous nodules with central hematomas at injection sites, occurring 6–8 h after the insulin injection and lasting for 48 h are typical of this extremely rare form of immunoallergic reaction. The nodules could also be distinguished from those of delayed hypersensitivity reactions which occur usually 24 h or more after the insulin injection lasting for 4–7 days [1,7].

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