

Multi Insulin Sensitization with Tolerante to New Therapeutic Option: Degludec

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Abstract

Introduction: Insulin has been used for the treatment of diabetes mellitus (DM) since 1920. At first, the animal insulins were available for human use having frequent allergic reactions due to the differences in amino acid sequences with human insulin. Currently, with the use of human insulin, the prevalence of these reactions is around 2% and less than a third of these events were associated with insulin itself. These cases are associated with their additives or preservatives. The most commonly hypersensitivity reaction found is type I. In these cases, the use of a rapid-acting insulin is the best therapeutic alternative. We report the case of a multi-sensitized patient to insulin presenting tolerance to the ultralong-acting: Degludec insulin.

Case report: Female patient, 74, referring use of NPH (Neutral Protamine Hagedorn) human insulin for 5 years, with papule at the site of application of the insulin minutes after application. She visited the Allergy and Immunology Clinic of the State Public Servant Hospital of Sao Paulo referring anaphylaxis few minutes after application of human insulin (NPH). Also reported extensive local reaction due the use of detemir, and local reaction to lispro insulin. We conducted immediate skin test reading with insulins: Regular, Lispro, NPH, Detemir and Degludeca at a concentration of 1:1; addition of the additive (Protamine 10 mg/ml) and latex. Presented positive test for all insulins, except Degludeca and presented negative test for protamine and latex.

Conclusion: we found no common additive to all insulins, which is not present in degludeca insulin (Tresiba®), enhancing insulin allergy hypothesis. Patient currently tolerates the use of long-acting insulin (Degludeca) and has adequate control of their blood sugar. In this case the patient had no insulin reaction prolonged action and this may be a new therapeutic option to be tested in patients with allergic reactions to insulin.

Keywords: Diagnosis; Drug hypersensitivity insulin; Insulin degludec; Insulin; Ultralente; Skin tests

Introduction

In January 1922, the first patient with diabetes mellitus (DM) received injection of bovine insulin pancreas, starting the "Insulin Age" and the success of therapy that immortalized its discoverers: Frederick Banting and Charles Best. Collip, chemist, worked in the extract preparation for clinical application. In 1923, Banting and Macleod won the Nobel Prize for Medicine and Physiology for the discovery of insulin [1].

Through crystallization, determining the structure of the amino acid sequence, long-acting insulins were made possible by the addition of zinc and protamine. In 1946, Kravaybuhl and Rosenberg developed the NPH (Neutral Protamine Hagedorn), with next action for 24 hours. But only in the 70s it is that insulins have undergone purification methods that led to the isolation of insulins practically free of other proteins, named as pro-insulin and peptide-C¹.

In 1973 it was launched on the market an insulin preparation Porcine free of immunogenic peptides, called single component insulin [2]. With the advent of molecular biology and recombinant DNA, began the era of human biosynthetic insulins, used by many patients to the present day. Compared to animal insulin, human insulin has a different pharmacodynamics and pharmacokinetics. Human insulin tends to be more rapidly absorbed and to have a shorter period of action, but with a peak action that occur totally unpredictable way [3].

Previously, animal insulins were available for human use causing frequent allergic reactions due to amino acid sequence differences with human insulin. Currently, with the use of human insulin, the

prevalence of these reactions is around 2% and less than a third of these events were associated with insulin itself. These cases are associated with their additives or preservatives including zinc, protamine, solvents (metacresol, glycerol, phenol, sodium phosphate etc.) [4,5].

Allergy may trigger from local symptoms to severe generalized allergic reactions. When IgE-mediated symptoms occur immediately after insulin administration (may present with redness and swelling at the injection site, to generalized reactions such as urticaria and angioedema). In rare severe cases, anaphylaxis with dyspnea and hypotension was observed [6].

The presence of insulin sensitization can be determined by skin tests and serum IgE specific levels [7]. We present the case of a patient who developed immediate hypersensitivity reaction to short and medium action insulin, but not with the prolonged. Similar cases have been reported previously in Japanese, Americans and Indians [8-10].

Case Report

ASM patient, female, 74 years old, physician, born and raised in

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São Paulo-SP, diagnosed with hypertension and type 2 diabetes, was treated at the Allergy and Immunology clinic of the State Public Servant Hospital of São Paulo-SP.

Reported using NPH human insulin for 5 years, with wheal at the site of insulin injections minutes after application. 15 days ago, a few minutes after application of human insulin (NPH), she presented glottis edema, labial angioedema and urticaria disseminated. Once symptoms started, she used hydroxyzine, dexchlorfeniramin and prednisolone at his residence and obtained improvement in symptoms, approximately 10 minutes after medication.

She also reported local reaction with lispro insulin (similar short-acting) and extensive local reaction due to the use of detemir insulin (similar long-acting), in an attempt to replace NPH insulin (they were prescribed after anaphylaxis event).

We conducted immediate skin test reading (Figure 1) with analogous human rapid-acting insulin (Regular Insulin and Lispro), NPH insulin and long-acting (Detemir and Degludeca) at a concentration of 1:1; addition of the additive (Protamine 10 mg/ml)

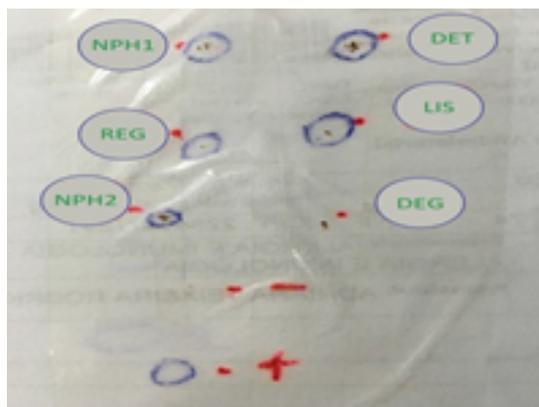


Figure 1: Decal prick test with insulins. NPH 1: Humulin N® (Lilly); REG: Novolin ® R (Novo Nordisk); NPH 2: Novolin N ® (Novo Nordisk); DET: Levemir ® (Novo Nordisk); LIS: Humalog ® (Lilly); DEG: Tresiba ® (Novo Nordisk); (-): Negative control (saline); (+): Positive control (histamine).

and latex. Presented positive test for all insulins, except Degludeca and presented negative test for protamine and latex [11].

The specific IgE to search for human insulin by CAP- fluorescein-enzyme immunoassay method was 0.89 kU/L.

Discussion

The allergy to insulin can be explained by the presence of a large amount of Langerhans cells in the epidermis, which act as antigen-presenting, performing transportation of foreign antigens and presenting to T cells in the regional lymph nodes, therefore increasing the antigenic components presentation of antigenic components of human insulin and mediate a localized immune response [12].

Human insulin is less immunogenic than animal insulin (porcine insulin is less immunogenic than bovine insulin). Bovine insulin differs from human insulin by three amino acids (two in the chain) and porcine insulin into one. When sensitization is limited to an origin of insulin or an additive, the allergen can be avoided by choosing a different preparation suitable for the patient [13].

The newly available degludec insulin is ultra-long acting basal insulin (Tresiba®), composed of a desB30 human insulin acylated at Lys B29 residue with a hexadecandioyl-γ-L-Glu side chain (Figure 2) [14].

Insulin has a high molecular weight, composed of multi-hexamers soluble and stable at the injection site, which upon subcutaneous injection occurs gradual diffusion of zinc from the ends of the multi-hexamers. As increasing zinc concentration in the depot injection, it will spread slowly, causing the uncoupling of the slow hexamer and gradually releasing monomers, which are then absorbed from the tank to the bloodstream, and thus a ultra-long term [14].

We analyzed the characteristics of the insulin used by the patient, but all had in common additives, including degludec (Table 1). With the result of the positive skin tests for insulin short and long action and the result of positive specific IgE sensitization to human insulin is proven.

The literature describes two allergy subtypes IgE mediated human insulin, i.e., a type showing the lack of responsiveness to insulin

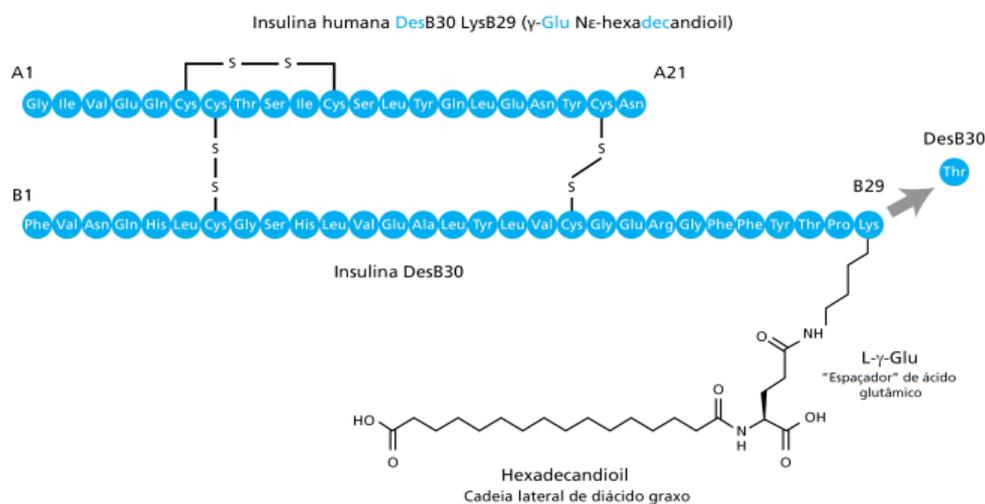


Figure 2: Structure of insulin degludeca [14].

	Regular	Lispro	Detemir	NPH 1	NPH 2	Degludec
Zinc chloride	X		X		X	x
Glycerol/Glycerin	X	X	X	X	X	X
Metacresol	X	X	X	X	X	X
Zinc oxide		X		X		X
Dibasic sodium phosphate		X		X		
Disodium phosphate dihydrate			X		X	
Phenol			X	X	X	X
Sodium hydroxide	X	X	X	X	X	X
Hydrochloric acid	X	X	X	X	X	X
Protamine sulfate				X	X	
Water for injection	X	X	X	X	X	X
Sodium chloride			X			

Table 1: Additives used in insulin.

analogues, including aspart and lispro insulin, and another type that responds to these insulin analogues, but not insulin long-acting insulin [8].

It can be assumed that the conformation and three dimensional structure of ultra-long-acting insulin molecule may mask its antigenicity, as after subcutaneous injection, a considerable amount of dimers are released from hexamers, divided into monomers (which is the active form of insulin). These dimers can be responsible for IgE-mediated reactions. The long-acting insulin can release very slowly insulin monomers and may have less antigenicity [15].

Other insulin allergy patients can safely use insulin analogues, as is the case of ultra-rapid insulins. Insulin lispro was designed by implementing B-28 amino acid residues and B-29, and aspart is produced by substituting the proline at position 28 in the insulin β chain [15,16]. Since these chemical modifications involve dimerization site of the insulin molecule, are markedly reduced immunogenicity events. Since these analogues of human insulin have been used safely for some patients with allergy to human insulin [16,17].

Even with the reduction of cases of allergy to insulin, there are reports in the literature. It is important that a good anamnesis be made, listing all the possible triggers so then we can make the best conduct, performing specific skin tests, specific IgE evaluation and looking to seek an alternative to the patient.

In this case, we can prove the multi-sensitization to human insulin and through specific tests could find a safe alternative to treatment, which was degludec insulin, which becomes a new alternative in the case of insulin sensitization.

Conclusion

Additives found in degludec insulin (Tresiba®), are also present in other insulins tested (short and long-acting) insulins such as: regular, NPH, lispro and detemir, which enhances insulin allergy hypothesis. Patient has currently tolerating insulin ultra long-acting (Degludec-Tresiba®) with adequate glycemic control.

We note that this insulin can be evaluated in other cases of allergic reactions to insulin and may be a new therapeutic option.

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