ISSN: 2584-0355
DOI: doi.org/10.51219/MCCRJ/Rauno-J-Harvima/181

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Medical & Clinical Case Reports Journal

https://urfpublishers.com/journal/case-reports

Vol: 3 & Iss: 1

Case Report

Case of Protamine-Containing Insulin Allergy of a Woman with LADA Diabetes

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Citation: Harvima RJ, Harvima IT. Case of Protamine-Containing Insulin Allergy of a Woman with LADA Diabetes. *Medi Clin Case Rep J* 2025;3(1):691-690. DOI: doi.org/10.51219/MCCRJ/Rauno-J-Harvima/181

Received: 28 January, 2025; **Accepted:** 29 January, 2025; **Published:** 31 January, 2025

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ABSTRACT

A case of 45-year-old woman is described where protamine, a constituent in insulin preparation, caused an urticarial adverse event, confirmed by lymphocyte stimulation test and basophil histamine liberation test. Thus, these tests could be used as additional tools to confirm the diagnosis. Protamine in intracutaneous skin test resulted in a supportive result.

Keywords: Insulin, Allergy; Protamine; Skin tests; Lymphocyte stimulation test; Histamine liberation test; LADA diabetes

Introduction

Insulin reactions are rare but are of high clinical importance. The first injection site reaction was reported in 1922 by insufficiently purified bovine insulin. Porcine insulin was less allergenic than bovine insulin[1]. The production of recombinant insulin with the same amino acid sequence as that in human insulin reduced adverse reactions. The prevalence of allergic reactions to insulin products are about 2% and less than 30% of these events are related to the insulin itself. Other reactions occur due to the preservatives added to insulin, including zinc, protamine and metacresol. Allergic reactions can include Type I IgE-mediated, Type III Arthus and Type IV delayed-type hypersensitivity reactions. Type I reactions are the most common and rarely may cause anaphylaxis. Type IV reactions can occur after several days. Skin prick testing, patch testing, intradermal testing and occasionally, skin biopsy is used for investigations[1].

Here we describe a case where protamine, a constituent in insulin preparation caused an urticarial adverse event, confirmed by basophil histamine liberation test and lymphocyte stimulation test.

Materials and Methods

Commercial Novo Insulin Test Set and patient's own insulin preparations, Humulin NPH and Humalog were used as well as those used by the patient previously.

Lymphocyte Stimulation Test (LST)

A heparinized blood sample was taken from the antecubital fossa and peripheral blood mononuclear cells (PBMCs) were isolated as described[2]. The LST test was performed in triplicate using a 3-day or 6-day incubation, ^{3}H-labeled thymidine incorporation technique, various concentrations of the test compound (final concentrations usually 0.1-50 µg/ml) and liquid scintillation counter with quench correction. The LST index is defined as the ratio of Disintegrations Per Minute (DPM, antigen) to DPM (control) and the index of over 2.5 is considered positive[3].

Whole Blood Histamine Liberation Test

Whole blood histamine liberation test was performed using heparinized blood as described[4] in quadruplicates: 950 µl of fresh whole blood was mixed with 50 µl of the test solution and incubated for 30 min and the liberated histamine from plasma was analyzed by radio enzyme assay using histamine-N-methyltransferase and ^{3}H-labeled S-adenosylmethionine as the methyl donor[5] by liquid scintillation detection with quench correction.

Skin Tests

Standard skin prick-test and intracutaneous (i.c.) test were performed on antebrachial dorsal skin area of the patient.

Case

A 45-yearl-old female patient had neither atopy background nor known allergies but been suffering from occasional alopecia areata lesions since the age of 18. There were also iritis episodes, once reactive arthritis, hypothyroidism without autoimmune etiology, dermographism and neurodermatitis. At the age of 45 years (174 cm, 61 kg), she was diagnosed with a Latent Autoimmune Diabetes in Adults (LADA) classified into Type I diabetes group. After about 2 years of use of detemir-insulin (Levemir) medication, serum antibodies against glutamate decarboxylase were highly elevated (5,300 kU/L, ref. <4 kU/L), like did so antibodies against serum Langerhans islet antibodies (320 JDF-Units, ref. <5 JDF-Units). Also, serum insulin antibodies were positive (21%, ref. <5%). Thereafter, human rDNA-insulin (Protaphane) was used, but later was changed to Humulin NPH-Humalog (lispro-insulin) combination. At the injection sites of Humulin NPH on thighs, she experienced daily redness and urticaria. However, at in other injection sites by Humalog, like at abdominal area, reactions occurred seldom.

Specific serum IgE for protamine was 0.0 kU/L and for human insulin 0.0 kU/L, both were negative (Ref. <0.3 kU/L). Total serum IgE was 10.9 kU/L (ref <87 kU/L).

Protaphan, Actrapid and Humutard insulins were tested with negative results in prick and i.c. tests. Protamine sulfate solution (1,400 IU/ml) in prick test was negative, but in i.c. test the result was uncertain positive.

Novo Insulin Test Set and patient's own insulins, Humulin NPH and Humalog, each tested as is where negative in prick tests. However, she daily experienced redness spots at the injection sites.

Histamine liberation test with patient's whole blood and Actrapid, Humalog or Humulin NPH were all negative. However, protamine sulfate (at final concentration of 72 IU/ml in the test conditions) caused a slight 12 nM increase in histamine liberation test.

Lymphocyte stimulation tests done in quadruplicate were negative for Actrapid and Humalog, but clearly positive for protamine sulfate (index 9.4 - 11.8) and protamine-containing Humulin NPH (index 8.6 - 9.5). Positive control indexes for phytohemagglutinin were 79 - 124.

By avoiding protamine-containing insulin products the patient has been without injection-related reactions as followed up to 23 years.

Discussion

The patient's urticarial reactions were related to protamine, which also has been described to cause reactions[1]. By avoiding only protamine-containing insulin, she has managed well with her LADA diabetes for over 20 years. Interestingly, prick test for protamine was negative, but uncertain positive in i.c. test, but positive in histamine liberation test[4] as well as in lymphocyte stimulation test[2,3]. Thus, these tests could be used as additional tools to confirm the diagnosis.

It may be possible that the weak histamine release in histamine liberation test is related to the stimulation of peripheral blood mononuclear cells, because there was no specific serum IgE against protamine[5].

Lymphocyte stimulation test has been shown to be a safe and valuable tool used for severe hypersensitivity immunologic reactions (i.e., Stevens-Johnson and Lyell syndromes, severe erythema multiforme) when drugs exposed in vivo are not possible to conduct[6,7].

Ethical Approval

Patient consent is obtained to publish this case report.

Conflict of Interests

The authors declare no conflicts of interests.

Acknowledgements

Ms. Katja Dufva is acknowledged for expert technical assistance.

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