Allergic Reaction to Exenatide and Lixisenatide but Not to Liraglutide: Unveiling Anaphylaxis to Glucagon-Like Peptide 1 Receptor Agonists

Oded Shamriz,[1] Adeeb NaserEddin,[1,2] Ofri Mosenzon,[3] Sigal Sviri,[4] and Yuval Tal[1]

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A 61-year-old man was admitted to our center following anaphylactic shock. His history includes type 2 diabetes, hypertension, and dyslipidemia. He was treated with extended-release (ER) exenatide (2 mg/week), which was later replaced with liraglutide (18 mg/day), and well tolerated both glucagon-like peptide 1 receptor agonists (GLP-1RA). After 2 years of liraglutide treatment he was prescribed a fixed-ratio combination (FRC) of insulin glargine and lixisenatide (300 units and 100 μg, respectively).

The morning of his admission, he was vaccinated for influenza and afterward received his first glargine/lixisenatide injection. Minutes later, he developed generalized urticaria, itching, dyspnea, and hoarseness. His systolic blood pressure was 70 mmHg. He was intubated, treated with adrenaline, and transferred to the emergency room. Upon arrival, his blood pressure was 103/57 mmHg. Adrenaline, antihistamines, and corticosteroids were commenced and the patient was transferred to the intensive care unit. The following day he was extubated, and he was discharged on the fifth day of admission.

Three months following admission, his blood count demonstrated no eosinophilia (absolute eosinophil count, 0.3; normal range, 0–1.3 cells $\times$ 10^9/L). Total immunoglobulin (Ig)E and tryptase levels were within normal ranges (values [normal ranges] 40.9 [0–87] IU/mL and 7.22 [0–11] μg/L, respectively).

An allergic workup was initiated. First, we tested for allergy to insulin glargine. Skin prick test (SPT) and intradermal skin test (IDT) were negative.

As the patient had previously well tolerated ER exenatide, we thought it would be safer to complete an IDT for this specific drug. Therefore, we continued with an SPT of 0.2 mg ER exenatide, which was remarkably positive. This was followed by an IDT, which demonstrated wheal and flare in dilutions of 1/1,000, 1/100, and 1/10 (Fig. 1*A*) (10.7/28.2, 14.3/39.6, and 14.3/28.6 mm, respectively).

We further evaluated lixisenatide. SPT and IDT of 1/1,000 were negative. However, IDT was positive in 1/100 dilution (19/49.8 mm) (Fig. 1*B*). Because of the anaphylactic shock the patient had, we decided not to proceed to 1/10 concentration.

Finally, SPT and IDT to liraglutide were negative. The patient is currently being treated with an FRC of insulin degludec and liraglutide injections (100 units and 3.6 mg, respectively) and has no allergic symptoms.

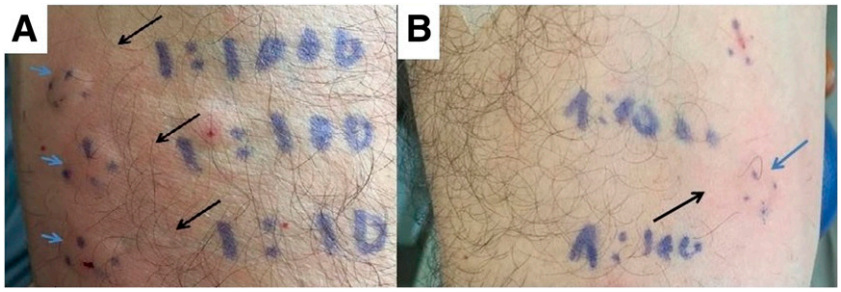

Figure 1—Skin tests for exenatide and insulin glargine and lixisenatide. *A*: Intradermal skin test for exenatide. Wheal (blue arrows) and flare (black arrows) are seen in dilutions of 1/10, 1/100, and 1/1,000. *B*: Intradermal skin test for an FRC of insulin glargine and lixisenatide. Wheal (blue arrows) and flare (black arrows) are demonstrated in dilution of 1/100 but not in 1/1,000.

[1]*Allergy and Clinical Immunology Unit, Hadassah Medical Center, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel*
[2]*Department of Bone Marrow Transplantation and Cancer Immunotherapy, Hadassah Medical Center, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel*
[3]*Diabetes Unit, Department of Endocrinology and Metabolism, Hadassah Medical Center, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel*
[4]*Medical Intensive Care Unit, Hadassah Medical Center, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel*

Corresponding author: Yuval Tal, yuvalt@hadassah.org.il

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GLP-1RA reduce HbA_{1c} and weight in patients with type 2 diabetes without increasing the risk for hypoglycemia. Exenatide and lixisenatide are 39- and 44-amino acid–long GLP-1RA based on exendin-4, which was originally isolated from lizard venom.

Lixisenatide is reported to have an anaphylaxis rate of 0.1% (1). A literature review of allergy to GLP-1RA has yielded five reports, all concerning exenatide. Two such reports were published by Pérez et al. (2) and Ornelas et al. (3). Reactions consisted mainly of urticaria, pruritus, and dyspnea. Unlike in our patient, hemodynamic instability was noted in none of the patients. Interestingly, all patients were previously exposed to a GLP-1RA for several months prior to developing allergy to exenatide.

The mechanism of allergy to exenatide was described as IgE mediated (2). This immune response was demonstrated by basophil activation tests (3) and related to exenatide's nonhuman origin (2).

Guidelines for drug allergy have recently been updated (4). Our patient is allergic to exenatide and lixisenatide. This can be explained by their homology, except for the N-terminals, in which lixisenatide has six lysines as compared with serine and proline in exenatide. Interestingly, our patient was previously treated with exenatide with no allergic reactions. Continuous exposure to exenatide probably sensitized the patient's mast cells but did not result in degranulation. Exenatide's discontinuation and recent exposure to lixisenatide resulted in cross-linking of IgE receptors, histamine release, and allergic response. This prior exposure to exenatide and mast cell sensitization can also account for the skin test being more reactive to exenatide than lixisenatide. However, reaction to drug skin testing is not always in correlation with the clinical response.

The patient was not allergic to liraglutide, as he had tolerated this treatment for 2 years, had negative SPT and IDT, and had no reaction to liraglutide renewal. Liraglutide appears to be less immunogenic than the exendin-4–based GLP-1RA. This was demonstrated in the Liraglutide Effect and Action in Diabetes (LEAD-6) trial, which found fewer skin reactions to liraglutide than exenatide, including eczema, urticaria, and pruritus (5). Lack of allergy is attributed to liraglutide's analogy to human GLP-1RA. There is a 53% homology between human-analog and exendin-4–based GLP1-RA. Therefore, our patient is probably allergic to the nonshared epitope.

In conclusion, understanding allergic mechanisms requires a differentiation between human-analog and exendin-4–based GLP-1RA. As exenatide and lixisenatide can induce allergy, we recommend testing for both drugs when allergy to one is suspected. In these patients, liraglutide treatment should be considered.

Duality of Interest. O.M. has served on advisory boards and speakers' bureaus for Novo Nordisk, Eli Lilly, Sanofi, Merck Sharp & Dohme, Boehringer Ingelheim, and AstraZeneca. She has served as a study physician for AstraZeneca, for which grants were paid to her institution, and received research grant support from Novo Nordisk through Hadassah Hebrew University Hospital. No other potential conflicts of interest relevant to this article were reported.

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