

Clinical Communications

A case report of allergy to exenatide

Eva Pérez, MD, Juan Martínez-Tadeo, MD,
Ariel Callero, MD, Guacimara Hernández, MD,
Elena Rodríguez-Plata, MD, and
José Carlos García-Robaina, MD, PhD

Clinical Implication

- This report shows that exenatide, a new glucagon-like-protein-1 analogue used for treatment of diabetes, was able to elicit immediate hypersensitivity reactions. Discontinuous treatments may be a risk factor for sensitization. Skin prick testing is useful to diagnose exenatide sensitization.

TO THE EDITOR:

Glucagon-like-protein-1 (GLP-1) analogues are a new class of antidiabetic agents. There are 2 molecules of this kind on the market: exenatide and liraglutide. Human GLP-1 is a gastrointestinal hormone, with 30 amino acids, released by the intestinal cells in response to food intake and stimulates insulin secretion, while suppressing glucagon production, delaying gastric emptying, and decreasing appetite, so it reduces plasma glucose levels. Exenatide improves glycemic control and induces weight loss in patients with type 2 diabetes. It is administered subcutaneously twice daily. A new longer-lasting formulation for weekly administration is currently in clinical trials.¹ Exenatide (exendin-4) was originally isolated from the salivary glands of the *Heloderma suspectum* lizard (Gila monster) and nowadays is obtained synthetically. It has 39 amino acids and shares a 53% sequence homology with human GLP-1. Exendin-4 is resistant to cleavage by dipeptidyl peptidase IV, whereas the first 2 *N*-terminal amino acids of GLP-1 are rapidly cleaved. As with insulin and other subcutaneously administered peptides, exenatide is able to induce antibody formation,² although there have been no reports of anaphylactic reactions to this drug so far.

Here we present a case report of an IgE-mediated reaction to exenatide. A 34-year-old woman with personal history of morbid obesity, type 2 diabetes treated with insulin and oral antidiabetics, hypercholesterolemia, allergic rhinitis, and asthma was prescribed exenatide as additional therapy because of poor glycemic control. She took exenatide, with good clinical response, for 6 months and stopped when she became pregnant. Four months after delivery, she was prescribed exenatide again. Ten minutes after the first administration, she developed itching, generalized urticaria, and difficulty swallowing. She went to an emergency facility and received treatment with antihistamines and corticosteroids, which achieved total recovery. Later her family physician, with the patient's consent, decided to carry out a second administration in the physician's office, where she developed an identical clinical picture, which was treated and recorded by her physician. She was then referred to our unit for study.

Skin prick testing (SPT) with exenatide 0.25 mg/mL (Byetta; Lilly, Giessen, Germany) was positive (12-mm papule and 41-mm erythema), with a positive histamine control of an 11-mm wheal and a 25-mm erythema. End point titration was positive at 1/10 (0.025 mg/mL) and negative at 1/100. SPT was negative in 6 healthy control individuals with no previous exposure to the drug. A controlled challenge was not performed because there was a documented re-exposure with the same symptoms, and the positive SPTs were congruent with her clinical history. A diagnosis of exenatide allergy was established, and we recommended avoiding the drug. Neither SPT nor challenge with liraglutide was performed because the patient had been proposed for bariatric surgery and does not need this medication at present.

Exenatide's most common adverse effect is nausea (up to 55% of patients in clinical trials), but the nausea usually is mild and transitory. Other common adverse effects are vomiting and diarrhea.¹ There also have been some reports of acute pancreatitis¹ and renal failure.³ Analysis of experimental data indicates that exenatide is able to induce pancreatic damage in mice.⁴ Only 1 report analyzed the immunologic effects of exenatide.⁵ Fifty-eight subjects from a previous clinical trial with this molecule were recruited. Treatment by using exenatide was restarted, and levels of antibodies against exenatide were assessed at several points in time during the 24 weeks of follow-up. An increase in the number of patients with positive antibodies during the study period was reported, but antibody formation was not linked to a higher incidence of adverse events. Glycemic control was better in the group with no antibody response, although the investigators attributed this to limitations of the study. Immune adverse effects were reported by 5 patients (2 developed localized itching; 1, a localized rash; 1, an eye allergy, and 1, a generalized rash). Interestingly, all these patients were in the positive-antibody group. Only 2 patients decided to abandon the study, but the investigators did not specify whether they were among the patients who presented immune-related adverse events. Postdose antibodies were determined by a screening assay relative to pre-dose control samples and later titration of positive samples. This technique does not seem to be reliable for detecting IgE; these antibodies were probably IgG or IgM. In addition, clinical data about the latency period of the reactions or continuity of treatment are lacking, and none of the patients were referred for allergologic study.

Exenatide has been on the market since late 2009, and hypersensitivity reactions have not appeared as a frequent problem to date. In any case, these reactions may be potentially severe and justify an interruption of the treatment so clinicians should be aware of them. As a protein of nonhuman origin, exenatide has the ability to elicit an immune response. Besides this, subcutaneous administration may increase its immunogenicity. Intermittent treatment could be a risk factor in developing an allergy to these molecules. We report the first case of anaphylaxis to exenatide so far, with complementary tests that support an IgE-mediated mechanism.

Acknowledgments

We thank John Amador Bedford and Rita Lourdes Martínez Santana for reviewing the English version of this manuscript.

Service of Allergy, Hospital Universitario Nuestra Señora de la Candelaria, Santa Cruz de Tenerife, Spain

No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication April 25, 2014; revised May 13, 2014; accepted for publication May 23, 2014.

Corresponding author: Eva Pérez, MD, Service of Allergy, Hospital Universitario Nuestra Señora de la Candelaria, Santa Cruz de Tenerife, Spain CP 38010. E-mail: evaprod@hotmail.com; evperrod@gobiernodecanarias.org.

2213-2198/\$36.00

© 2014 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaip.2014.05.011>

REFERENCES

1. Waugh N, Cummins E, Royle P, Clar C, Marien M, Richter B, et al. Newer agents for blood glucose control in type 2 diabetes: systematic review and economic evaluation. *Health Technol Assess* 2010;14:1-248.
2. Pérez E, González R, Martínez J, Iglesias J, Matheu V. Detemir insulin-induced anaphylaxis. *Ann Allergy Asthma Immunol* 2009;102:174-5.
3. Dubois-Laforgue D, Boutboul D, Lévy DJ, Joly D, Timsit J. Severe acute renal failure in patients treated with glucagons like peptide 1 receptor agonist. *Diabetes Res Clin Pract* 2014;104:e53-5.
4. Rouse R, Xu L, Stewart S, Zhang J. High fat diet and GLP 1 drugs induces pancreatic injury in mice. *Toxicol Appl Pharmacol* 2014;276:104-14.
5. Faludi P, Brodows R, Burger J, Ivanyi T, Braun DK. The effect of exenatide re-exposure on safety and efficacy. *Peptides* 2009;30:1771-4.