## Anaphylaxis to Long-Acting Release Exenatide

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Human glucagon-like peptide 1 (GLP-1) is an incretin hormone that was initially described in the 1980s as a proglucagon cleavage product, produced by intestinal cells in response to food intake [1]. Its main actions are stimulation of insulin secretion, suppression of glucagon production, delay in gastric emptying, induction of satiety in the central nervous system, and reduction of postprandial triglyceride and free fatty acid concentrations [2]. Given its main hypoglycemic properties, GLP-1 has become an important therapeutic target in type 2 diabetes. However, a major limitation of its use was its very short half-life [2]. This was overcome by the development of synthetic GLP-1 receptor agonists, which can be divided into short-acting GLP-1 receptor agonists (exenatide and lixisenatide) and long-acting GLP-1 receptor agonists (long-acting release [LAR] exenatide, liraglutide, albiglutide, and dulaglutide).

Exenatide, which has been approved in Europe since 2006, is a short-acting GLP-1 receptor agonist with a half-life of 2.4 hours that is administered subcutaneously twice daily. Its main action is lowering postprandial glucose levels by delaying gastric emptying. LAR exenatide was approved in Europe in 2011 and enables a constant drug plasma level with once-weekly subcutaneous administration. This is possible due to its composition (microspheres of biodegradable polymeric matrix containing exenatide), which enables slow release of exenatide as a result of breakdown of the microspheres. LAR exenatide has a more marked insulinotropic effect than exenatide, with more pronounced lowering of fasting glucose plasma levels, thus providing better glycemic control. Another advantage is its convenient weekly administration.

We report the case of a 66-year-old woman with a 10-year personal history of type 2 diabetes and no target organ lesions who was treated with oral antidiabetic drugs

(metformin, dapagliflozin) and insulin. She also had arterial hypertension, hypercholesterolemia, hypothyroidism, and depressive disorder, which were treated with carvedilol, amlodipine, simvastatin, levothyroxine, and fluoxetine. Given her poor glycemic control, she was prescribed subcutaneous LAR exenatide (AstraZeneca AB) at 2 mg once-weekly as additional therapy. She took the drug for 10 months with good glycemic control, until she developed sudden onset of urticaria, dysphonia, dysphagia, throat tightness, abdominal pain, and vomiting 15 minutes after administration. She denied concomitant consumption of other medications, an association with food intake, and infectious symptoms. The patient was admitted to the emergency department, where generalized urticaria and uvular edema were observed. She was hemodynamically stable and eupneic, with normal oxygen saturation. She received immediate treatment with intravenous corticosteroids and antihistamines, and the clinical response was good. After 12 hours she had fully recovered and was discharged, with a recommendation to attend the allergy department for further investigation.

We performed skin prick and intradermal tests with LAR exenatide 3 mg/mL (BYDUREON injectable suspension, 2 mg/0.65 mL) at 3 dilutions: 1/1000, 1/100, and 1/10 (oral and written informed consent were previously obtained). Skin prick tests were negative for all the tested dilutions. Intradermal tests were positive for the 1/100 dilution (0.03 mg/mL), with a wheal 4 mm wider than that obtained with the negative control and ipsilateral palmar pruritus. Skin prick and intradermal test results were negative for all the dilutions in 5 healthy controls with no previous exposure to the drug.

To further support an IgE-mediated mechanism, the basophil activation test (BAT) was performed in whole blood with LAR exenatide at 3 concentrations (0.075 mg/mL, 0.03 mg/mL, and 0.019 mg/mL). Basophils were identified in the lymphocyte-monocyte gate as $CD123^{+}HLA\text{-}DR^{-}CD203c^{+}$ cells. Basophil activation was expressed as a proportion of $CD63^{+}$ basophils, corrected for the negative control, and as a ratio of the mean fluorescence intensity of CD203c of stimulated to unstimulated basophils. The BAT result was considered positive if the stimulation index (SI) was ≥2 [3-5]. We observed positive results for all the dilutions tested, with a percentage of CD63 expression between 3.94% and 6.88% and an SI between 2.1 and 5.04. For CD203c, we observed upregulation of mean fluorescence intensity at all concentrations (0.075 mg/mL - 672; 0.03 mg/mL - 665; 0.019 mg/mL - 669) compared with the negative controls (218), with an SI of 3.08, 3.05, and 3.06, respectively (Figure).

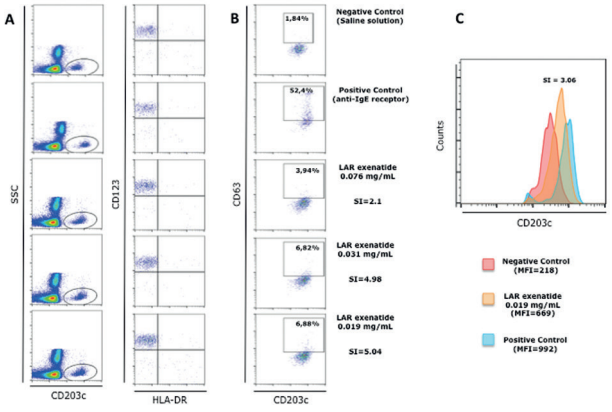


**Figure.** Basophil activation test performed in whole blood. A, Identification of basophils in the lymphocyte-monocyte area as SSC/$CD123^{+}$/$HLA\text{-}DR^{-}$/$CD203c^{+}$. B, Flow cytometry dot plots of the expression of CD63 and CD203c on unstimulated basophils (negative control), basophils stimulated with anti-FcεRI (positive control), and 3 concentrations of LAR exenatide. C, Histogram showing the expression of CD203c mean fluorescence intensity (MFI). Negative control, positive control, and cells stimulated with LAR exenatide (0.019 mg/mL) are represented. SI indicates stimulation index.

The patient was advised to avoid exenatide. A drug challenge test was not performed owing to previous anaphylactic reaction and positivity in intradermal tests and a BAT result that was consistent with the patient's clinical history. Skin and challenge testing with other GLP-1 agonist receptors were not performed because the endocrinologist decided to adjust the insulin dose and add sitagliptin to the patient's previous medication. Glycemic control is currently stable.

The most common reported adverse effects of LAR exenatide are gastrointestinal events, mainly nausea, vomiting (less pronounced than with short-acting GLP1 receptor agonists), and diarrhea. These symptoms are usually mild and transitory, disappearing completely after 4-6 weeks of treatment [6,7]. Injection site reactions, such as subcutaneous nodules, erythema, and pruritus, were reported in up to 20% of patients taking LAR exenatide [7]. An association between these drugs and pancreatitis, renal failure, and pancreatic and thyroid neoplasms has been reported, although evidence to date is lacking [6,7]. LAR exenatide, a peptide therapy, has the potential to elicit antibody formation. This was verified in 56.7% of patients treated with this drug, most of whom had low antibody titers (<125), with a progressive decrease over time and with no clinical significance regarding the efficacy of LAR exenatide [8]. Antibody-positive patients were reported to be more likely to have injection site reactions (all mild and transient), with no associations with systemic hypersensitivity reactions, which are considered extremely rare [8]. To our knowledge, there have only been 2 reports of systemic hypersensitivity reactions to exenatide, namely, one of generalized urticaria and dysphagia with exenatide [9] and another of generalized urticaria and dyspnea with LAR exenatide, both of which were immediate [10]. In both cases, skin tests were positive for the drug involved, and a BAT performed in the second case yielded a negative result.

We report a rare case of systemic hypersensitivity reaction to LAR exenatide, with positive results in skin tests and BAT that strongly support an IgE-mediated mechanism. We stress the need to be aware of these reactions owing to the increasing use of these drugs, self-administration by patients, and the long-acting release formulations, which have a longer duration of circulating drug levels in blood.

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*Conflicts of Interest*

The authors declare that they have no conflicts of interest.

*Previous Presentations*

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