

Delayed hypersensitivity reaction to liraglutide: a case report

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Glucagon-like peptide-1 receptor agonists (GLP-1RA) are a class of drugs used in the treatment of type 2 diabetes, and liraglutide is currently the only GLP-1RA approved by the FDA and EMA for obesity treatment [1]. Allergic reactions have been reported with the exendin-4-based subtype of GLP-1RA, but no cases with new human GLP-1 analogues, such as liraglutide and semaglutide, have so far been confirmed by allergy tests [2-5].

We present the case of a 42-year-old female diagnosed with obesity, for which she started treatment with liraglutide at an initial dose of 0.6 mg/day, with weekly increments of 0.6 mg until achieving a maximum dose of 3 mg/day. One week after starting with the daily 3 mg subcutaneous dose, she presented with pruriginous erythematous macules on the injection site, which appeared 24 hours after the liraglutide injection. This pattern repeated itself for four days, after which she was referred by her endocrinologist to our allergy department. At the physical examination, she had two 35x20 mm macules in the lower left abdomen and a smaller one in the

lower right abdomen, corresponding to the injection sites. A skin prick test (SPT) performed with liraglutide (6 mg/ml) was negative. This was followed with an intradermal skin test (IDT) which was negative at the 1/100 (0.06 mg/ml) and 1/10 (0.6 mg/ml) dilutions; the 1/1 (6 mg/ml) dilution was initially negative, but clearly positive at the 24-hour reading (22x17mm, Figure). The positive dilution was tested in five healthy control individuals with no previous exposure to the drug, with negative results at the immediate and delayed readings. The patient was diagnosed of delayed allergy to liraglutide and this drug was discontinued. She received topical steroid treatment, with remission of the lesions without reoccurrence at the two-week follow-up. The patient had no previous history of atopy. She had normal blood eosinophil count and liver function tests. She had never taken any GLP-1RA before. The study was completed with a skin patch test to liraglutide (6 mg/ml, as is) which was negative at the 48-hour and 96-hour readings. As a means of providing an alternative to liraglutide, SPT to semaglutide was performed (1.34 mg/ml), with negative results. IDT to this drug at 1/100, 1/10 and 1/1 dilutions (0.01 mg/ml, 0.13 mg/ml and 1.34 mg/ml, respectively) was also negative.

Allergic reactions to the exendin-4-based subtype of GLP-1RA have been described in the literature. Shamriz et al reported a case of anaphylaxis after a first dose of lixisenatide, with positive immediate IDT to this drug and to exenatide, which he had received in the past [2]. However, skin tests to liraglutide, which he had also received, were negative. He later tolerated this drug. The authors attributed this to the molecular differences between the two exendin-4-based drugs –exenatide and lixisenatide- and the human GLP-1 analogue, liraglutide. Homology between exendin-4-based GLP-1RA and the human GLP-1 is about 53%, which might explain the observed tolerance to liraglutide in this case, which has 97% homology with the human GLP-1 [6].

Regarding human GLP-1 analogues, Neel et al reported a case of an injection site reaction after two weeks of receiving a daily 3 mg dose of liraglutide, which resolved after discontinuing this drug; however, no allergy study was performed on this patient [3]. Cogen et al described a case of an exanthematous pustulosis in photoexposed areas after two days of liraglutide treatment, with resolution after several weeks of drug discontinuation and topical steroid treatment; no skin tests or photopatch tests were performed [4]. More recently, Bovijn et al reported a case of generalized erythematous plaques and nodules in a patient that had started liraglutide treatment two weeks before, with peripheral blood eosinophilia [5]. The lesions took five months to resolve after discontinuing the drug and receiving topical steroids; no allergy study was conducted. To the best of our knowledge, there have been no reported cases of a confirmed hypersensitivity reaction to liraglutide with positive skin testing in the literature so far.

Our patient's symptoms –pruriginous macules associated with the puncture areas- were compatible with a delayed hypersensitivity reaction to liraglutide, and they resolved in two weeks after discontinuing this drug without leaving residual skin lesions. In contrast with previously reported cases, no other associated skin lesions, such as pustules or nodules, were present. The diagnosis was confirmed with the positive IDT. In order to rule out this result as an irritant reaction due to the used concentration, we tested the same dilution in five healthy controls with negative results. In relation to the negative patch testing, the sensitivity of this method in the diagnosis of systemic drug reactions appears to be dependent on the drug type, which would explain the observed results [7].

It is worth noting that skin tests to semaglutide were negative in our patient despite it being a molecule derived from liraglutide, and both being analogues of human GLP-1. Differences between semaglutide and its precursor molecule include substitution of alanine with an alpha-aminoisobutyric acid at position 8, substitution of lysine with

arginine at position 34 and acylation of lysine at position 26 with a stearic diacid [8]. The fact that IDT was negative to semaglutide could suggest that our patient's sensitization was dependent on one or more of these changed molecular components. This could open up the possibility of using semaglutide as an alternative in patients allergic to liraglutide, despite their similarity. In the present case, the tolerance to semaglutide has not been assessed.

We report a case of a delayed hypersensitivity reaction with positive skin testing to liraglutide. The negative results with semaglutide suggest that this drug could be used as an alternative in patients with allergy to liraglutide. Further studies are needed to establish a clear pattern of cross-reactivity between these two human GLP-1 analogues.

Disclosures

The authors have no financial sources or conflicts of interests to disclose.

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FIGURE**Figure legend**

Intradermal skin test to liraglutide, showing the positive 1/1 (6 mg/ml) dilution at the delayed 24-hour reading.