

Allergy Workup in Immediate-Type Local Reactions to Glatiramer Acetate

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■ Abstract

Local reactions to glatiramer acetate are common, but few cases of hypersensitivity reaction have been reported.

We present 3 patients with multiple sclerosis who suffered immediate-type local reactions after subcutaneous injection of glatiramer acetate. Skin prick test (SPT), intradermal test (IDT), and determination of immunoglobulin (Ig) E to glatiramer acetate were performed in patients and controls (enzyme-linked immunosorbent assay).

The results of SPT were all negative. Those of IDT in controls were negative at concentrations below 200 µg/mL, but positive for patients 1, 2, and 3 at 2, 20, and 200 µg/mL, respectively. Serum IgE to glatiramer acetate in patient 1 was 2.1 times higher than in the controls, whereas no differences were found between controls and patients 2 and 3. Glatiramer acetate was safely reintroduced in patients 2 and 3. The results obtained for patient 1 suggest that an IgE-mediated mechanism was probably involved. In conclusion, IDT and serum IgE determination to glatiramer acetate seem useful for identifying allergic reactions among the common local reactions induced by this drug.

Key words: Glatiramer. Adverse drug reaction. Allergy. Hypersensitivity.

■ Resumen

Las reacciones locales por acetato de glatiramer (GA) (Copaxone®) son comunes, pero hay pocos casos publicados de reacciones de hipersensibilidad.

Presentamos 3 pacientes con esclerosis múltiple que presentaron reacciones locales inmediatas tras la inyección subcutánea de Copaxone. Se realizaron pruebas cutáneas en prick (SPT) e intradermorreacción (IDT) y ELISA IgE frente a Copaxone en las pacientes y controles.

Las SPT fueron todas negativas. Las IDT en controles fueron negativas a concentraciones de GA inferiores a 200 µg/ml, pero positivas en las pacientes 1, 2 y 3 a 2, 20 y 200 µg/ml respectivamente. La IgE sérica a Copaxone en la paciente 1 fue 2,1 veces mayor que en controles, mientras que en las pacientes 2 y 3 no se detectaron diferencias con los controles. En las pacientes 2 y 3 se readministró de nuevo el Copaxone con buena tolerancia. Los resultados de la paciente 1 sugieren la implicación de un mecanismo mediado por IgE. En conclusión, las IDT y la determinación de IgE sérica a GA parecen útiles para diferenciar las reacciones alérgicas del resto de reacciones locales inducidas por este fármaco.

Palabras clave: Glatiramer. Reacción adversa medicamentosa. Alergia. Hipersensibilidad.

Introduction

Glatiramer acetate (GA) is used to alleviate exacerbations in patients with relapsing-remitting multiple sclerosis (RRMS). GA is composed of the acetate salts of synthetic polypeptides containing 4 naturally occurring amino acids—L-glutamic acid, L-alanine, L-tyrosine, and L-lysine—with an average molar fraction of 0.14, 0.43, 0.09, and 0.34,

respectively. The average molecular weight of glatiramer acetate is 5-9 kDa. Injection site reactions due to GA are very common, and about 10% of patients have experienced at least 1 immediate-type systemic reaction [1]. In contrast, only a few cases of hypersensitivity to GA have been reported to date [2,3]. We present 3 patients who suffered immediate-type local reactions after subcutaneous injection of GA and illustrate our diagnostic approach.

Case Description

Patients

Patient 1 was a 26-year-old woman diagnosed with RRMS and treated with GA daily for 1 year with no reaction. Two weeks before her first visit to our allergy department, she presented a local inflammatory reaction immediately after an injection of GA on her left arm. The reaction lasted a few hours and resolved spontaneously. GA was later administered daily for 6 days with good tolerance. However, on day 7 of treatment, 5 minutes after administration of the drug on her abdomen, a pruritic wheal measuring 10 × 8 cm appeared at the injection site, with associated tachycardia. The patient recovered spontaneously on the same day. She continued to receive GA on the following 2 days, with good tolerance. Her neurologist recommended her to discontinue GA and referred her to our department. The second patient was a 45-year-old woman with a 13-year history of RRMS who presented erythema and itchy hives measuring 5 × 5 cm at the injection site immediately after administration of GA. These disappeared progressively after 30 minutes. No other symptoms were observed. She had been treated with GA daily for the previous 3.5 years with no reactions. The third patient was a 41-year-old woman who had experienced a pruritic wheal measuring 10 × 10 cm since she first started self-injecting GA. She also reported generalized pruritus and dermatographism, which subsided after stopping GA.

Skin Tests

Skin prick tests (SPT) with GA were performed on the volar side of the forearm at concentrations ranging from 0.2 µg/mL to 20 mg/mL. Reactions were considered positive when a wheal greater than 3 mm in diameter was present 15 minutes later. An intradermal test (IDT) with GA was performed at the same concentrations as SPT if the skin prick test was negative. Readings were taken 20 minutes after puncture. Results were considered positive if the size of the initial wheal increased by at least 3 mm in diameter and was surrounded by erythema [4]. Histamine (10 mg/mL) and saline were used as positive and negative controls, respectively. The control group comprised healthy subjects who had never received the drug (n=5) and a group of patients with RRMS who tolerated GA (n=5).

SPT results were negative in all the controls, although they all presented a positive IDT result (wheal >10 mm) at concentrations ≥200 µg/mL. SPT was negative in the 3 patients as well, but IDT was positive at a concentration of 2 µg/mL in patient 1 (8 × 15 mm), at 20 µg/mL in patient 2 (10 × 19 mm), and at 200 µg/mL in patient 3 (9 × 12 mm). As the formulation of GA we administered contains mannitol, which has previously been involved in IgE-mediated adverse reactions [5], SPT (at 100 mg/mL) and IDT (at 10 mg/mL) were carried out with mannitol in the 3 patients. The results were negative in all 3 cases.

In Vitro Tests

Serum specific IgE to GA was determined by enzyme-linked immunoassay (ELISA) in the 3 patients, in 5 controls with RRMS

who were taking GA with good tolerance, and in 4 healthy controls who had never received the drug. Briefly, 5 µg of GA (100 µL/well) in phosphate-buffered saline (PBS) was added to a polystyrene microtiter plate and incubated overnight at 4°C. Wells were washed 3 times with 100 µL/well of PBS with 0.05% Tween-20 (PBS-T). Blocking (200 µL/well) was performed using 2% bovine serum albumin in PBS-T at room temperature. Patients and control sera (diluted 1:10, 100 µL/well) were tested in duplicate. The bound complexes were detected with horseradish peroxidase-conjugated goat antihuman IgE (Fc) antibodies (Nordic Immunology, Tilburg, The Netherlands) diluted 1:2500 in blocking solution. Peroxidase activity was measured by adding 100 µL/well of tetramethylbenzidine ultrasensitive substrate (Chemicon, Temecula, California, USA) and reading absorbance at 650 nm.

Patient 1 had an IgE level to GA that was 4.3 times higher than that of the healthy nonexposed controls, and 2.1 times higher than the GA-treated controls. In contrast, no differences were observed between controls and patients 2 and 3 (Table). Inhibition of IgE to GA (ELISA) was not observed with mannitol tested at different concentrations (1.6 mg/mL to 200 mg/mL; results not shown).

Table. Detection of Specific Immunoglobulin E to Glatiramer Acetate Using Enzyme-Linked Immunosorbent Assay

	Immunoglobulin E ^a
Patient 1	0.652
Patient 2	0.044
Patient 3	0.165
Healthy controls (n=4)	0.153
GA-treated controls (n=5)	0.309

Abbreviation: GA, glatiramer acetate

^aTested in duplicate; mean value given after subtracting the blank

Glatiramer Challenge

In the light of the skin test and ELISA results, we readministered GA to patients 2 and 3 in our allergy department, and the drug was well tolerated. These patients have since continued to self-administer the drug daily at home and, at the time of writing, tolerated the drug well.

Patient 1 had a positive IDT result with GA at a concentration 100 times lower than the controls and specific IgE titers by ELISA higher than controls or patients 2 and 3. These results suggest that an IgE-mediated mechanism is probably involved in this patient's immediate-type local reaction, and the reintroduction of the drug was therefore considered hazardous and ruled out. After discontinuation of GA, patient 1 started treatment with interferon β-1a (Avonex, Biogen Idec Iberia SL, Madrid, Spain), with no further relapses in more than 18 months follow-up.

Discussion

Local adverse events with GA are frequent [1], and it is easy to overlook an IgE-mediated reaction. This possibility

should be taken into account, especially because of the risk of anaphylaxis in patients with anti-GA IgE [2]. In our experience, a positive IDT result at a concentration of ≥ 200 $\mu\text{g}/\text{mL}$ seems irritant, although a positive IDT result below that concentration should be regarded as positive.

We used ELISA to determine serum specific IgE to GA in our 3 patients. The levels of patients 2 and 3 were negative or similar to those of controls, and GA was reintroduced with good tolerance. However, patient 1 exhibited a higher IgE titer to GA than patients 2 and 3 or controls, and she had a positive response in the IDT to a GA concentration 100 times lower than patients 2, 3, or the controls. A challenge in this patient would have been of interest to assess the diagnostic value of the IDT and IgE-ELISA, but it was considered hazardous and therefore ruled out. Furthermore, alternative treatment with interferon β -1a was effective, with no need to reintroduce GA.

In conclusion, skin tests and specific IgE determination to GA can help to detect if there is an underlying IgE-mediated immunological mechanism, as seen in patient 1. These tests can also guide assessment of the risk of reintroducing the drug, as shown in patients 2 and 3, in whom the study result was negative and the drug was subsequently well tolerated.

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- *Manuscript received October 13, 2009; accepted for publication January 18, 2010.*
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