CASE REPORT

Urticaria Due to Antihistamines

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Abstract

H1-antihistamines are probably the most frequently used drugs in allergic diseases, with widely established efficacy, tolerance, and safety. We report a patient with urticaria due to ingestion of ebastine and fexofenadine. Skin prick tests, patch tests, and basophil activation tests with the implicated drugs and antihistamines from other families were negative. The oral challenges with the implicated antihistamines and other antihistamines tested were positive, but the patient tolerated an oral challenge with cetirizine. We present a patient with urticaria induced by different antihistamines in whom the diagnosis was established by oral challenge. The mechanism of sensitization remains unclear.

Key words: Adverse drug reaction. Antihistamines. Cross-reactivity. Urticaria.

Resumen

Los antihistamínicos son probablemente los fármacos más usados en la patología alérgica. Su eficacia, tolerancia y seguridad ha sido bien establecida en humanos. Presentamos un paciente con urticaria tras la administración de ebastina y fexofenadina. Realizamos pruebas cutáneas en prick, pruebas epicutáneas y test de activación de basófilos con los fármacos implicados y con otros antihistamínicos de otras familias, todos con resultado negativo. La prueba de provocación oral fue positiva con los antihistamínicos implicados y con otros testados. Finalmente la paciente toleró la toma de cetirizina. Presentamos una paciente con urticaria inducida por diferentes antihistamínicos. El diagnóstico fue establecido mediante prueba de provocación oral. El mecanismo de sensibilización no está demostrado.

Palabras clave: Reacciones adversas a medicamentos. Antihistamínicos. Reactividad cruzada. Urticaria

Introduction

H_1-antihistamines are probably the most frequently used drugs in allergic diseases, with widely established efficacy, tolerance, and safety [1].

Second-generation antihistamines are considered to be safe and are only rarely associated with mild and possible dose-dependent side effects such as somnolence, dry mouth, and fatigue [2]. The topical application of antihistamines commonly leads to sensitization, but skin reactions due to systemic use are less frequent [3].

Case Description

We report a case of urticaria induced by ebastine, fexofenadine, dexchlorpheniramine, and loratadine with confirmation of findings by single-blind oral challenge tests. Interestingly, the patient tolerated cetirizine.

The patient was a 45-year-old woman with a history of allergic rhinoconjunctivitis from January to June. Three years earlier, she had been treated with Ebastel Forte tablets (ebastine 20 mg; Almirall, Madrid, Spain) for allergic symptoms and 4 days after starting treatment, had developed generalized urticaria. The treatment was discontinued and the skin lesions resolved completely in 2 days without treatment. She also reported an identical reaction after the intake of a fexofenadine 180 mg tablet (Aventis Pharma, Madrid, Spain).

Skin prick tests were performed with a series of commercially available common inhalants (grass, weeds and tree pollens, house dust mites, molds, and cat and dog dander) (ALK-Abelló, Horlsholm, Denmark) with positive results for *Cupressus arizonica*, olive tree, and grass pollen. Isotonic glycerol saline was used as a negative control, and 10 mg/mL histamine hydrochloride as a positive control.

We carried out skin prick tests with loratadine 1 mg/mL, cetirizine 1 mg/mL, ebastine 1 mg/mL, fexofenadine 18 mg/mL, and dexchlorpheniramine 5 mg/mL, all with negative results. The patient described the injuries as hives that appeared after several days of treatment. We therefore performed patch tests with loratadine 0.1%, cetirizine 0.1%, ebastine 0.1%, fexofenadine 1.8%, and dexchlorpheniramine 0.5%, all in petrolatum. Results were read at 48 and 96 hours and were negative for all the antihistamines tested. Ten controls (5 atopic and 5 nonatopic) tested negative to the same prick and patch tests.

Flow cytometric analysis of CD63 expression by basophils was performed after in vitro allergen-specific stimulation with ebastine and dexchlorpheniramine (final concentrations of 0.25 and 0.025 mg/mL in both cases), cetirizine and loratadine (0.5 and 0.05 mg/mL), and hydroxyline (2.5 and 0.25 mg/mL), all with negative results. Ten individuals without antihistamine allergy were also tested as negative controls.

After obtaining informed consent, we performed a single-blind oral challenge with ebastine, with a positive result (Figure). Two hours after the last dose (cumulative dose, 35 mg), the patient developed urticaria on the trunk, neck, and arms. To investigate possible cross-reactivity between antihistamines, we performed an oral challenge with dexchlorpheniramine, fexofenadine, and loratadine. The patient developed generalized urticaria after the oral challenge with each of the 3 drugs. Finally, the patient tolerated an oral challenge with cetirizine and is currently tolerating this drug.

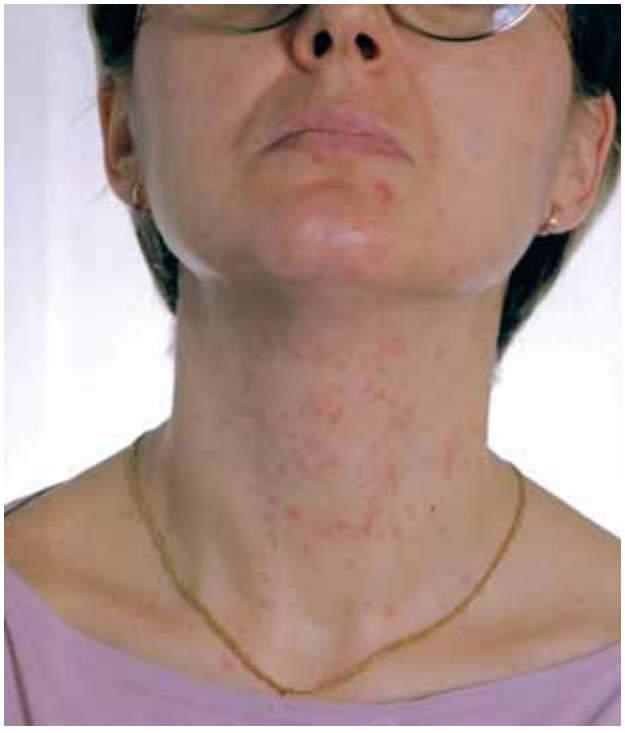

Figure. Hives on neck after a single-blind oral challenge with ebastine.

Discussion

Adverse drug reactions to histamine H1-antagonists are rare [4] and include urticaria, maculopapular rash, fixed drug eruption, photosensitivity, and Stevens-Johnson syndrome [5].

Cutaneous adverse reactions to orally administered antihistamines usually appear within 4 to 12 hours. These eruptions can be generalized and the lesions quite variable. Experience suggests that skin tests are less useful in evaluating these reactions. Oral challenge tests are necessary in many cases to reach a diagnosis [3,5].

In our case, we performed skin prick tests, patch tests, and basophil activation tests with different types of antihistamine agents (alkylamines, piperazines, and piperidines). The results in all cases were negative. However, the patient developed generalized urticaria after the oral challenge with ebastine, fexofenadine, dexchlorpheniramine, and loratadine. In other words, she presented urticaria with different groups of antihistamines: piperidines and alkylamines. She nonetheless tolerated cetirizine, a piperazine antihistamine.

González de Olano et al [6] described a patient with urticaria induced by different families of antihistamines. While skin tests with the implicated antihistamines were negative, they were positive for several other types of antihistamines. Inomata et al [7] reported a patient with urticaria due to different antihistamines who also had negative prick test results.

In our patient, the mechanism of H1-antihistamine-induced urticaria has not yet been elucidated. The negative prick test and basophil activation test results for a range of antihistamines strongly suggest a non-immunoglobulin E–dependent mechanism and consequently a non-type I hypersensitivity reaction. There is no shortage of theories: metabolite haptenization, abnormal metabolization routes, or many other mechanisms that cause skin injury.

No precise mechanism has been established in most of the cases published to date, and reactions have been classified as type I or IV on the basis of the clinical history and time between intake and reaction [7].

We have reported the case of a patient with several episodes of urticaria induced by different families of antihistamines. The diagnosis was established by oral challenge.

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