

Urticaria Caused by Antihistamines: Report of 5 Cases

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■ Abstract

Antihistamines are widely used drugs. Hypersensitivity reactions with these drugs are rare and a challenge for the physician. We describe 5 outpatients who experienced urticaria after taking antihistamines. All 5 were treated at our outpatient clinic over a period of 15 years. The allergy workup included a clinical history, skin prick testing, patch testing with antihistamines, and single-blind placebo-controlled oral challenge tests. Biopsy samples were taken and serum tryptase levels were determined in 1 patient.

The results of the skin prick tests and patch tests were negative in all patients but 1, in whom the prick test result was positive to some antihistamines. We confirmed all diagnoses using a single-blind challenge test. The biopsy obtained from 1 patient strongly supported urticaria. We present 5 cases of antihistamine-induced urticaria where the immunologic mechanism remains unclear. Hypersensitivity reactions should be taken into account in patients receiving antihistamines, especially in those who experience urticaria.

Key words: Antihistamines. Drug allergy. Ebastine. Hypersensitivity. Levocetirizine.

■ Resumen

Los antihistamínicos son fármacos ampliamente empleados. Las reacciones de hipersensibilidad son raras y su diagnóstico supone un reto para el facultativo. El objetivo de este estudio es describir 5 pacientes reclutados a lo largo de 15 años en nuestras consultas externas con cuadro de urticaria tras la toma de antihistamínicos y se les realizó historia clínica, prick test y pruebas epicutáneas con antihistamínicos junto con pruebas de provocación oral a simple ciego. En uno de ellos se realizó determinación de triptasa y biopsia cutánea.

Los prick tests y las pruebas epicutáneas fueron negativas en todos ellos salvo en un paciente que presentó positividad en el prick test para algunos de los antihistamínicos. Se confirmaron los diagnósticos mediante provocaciones orales a simple ciego en todos los casos. Los hallazgos histológicos en la biopsia obtenida en la paciente 1 respaldaron el diagnóstico de urticaria.

Presentamos 5 pacientes con urticaria por antihistamínicos en los que no se ha podido dilucidar el mecanismo inmunológico. El diagnóstico de hipersensibilidad a antihistamínicos debe ser tenido en cuenta en nuestros pacientes, sobre todo en aquellos con urticaria.

Palabras clave: Antihistamínicos. Alergia a medicamentos. Ebastina. Hipersensibilidad. Levocetiricina.

Introduction

Antihistamines are a widely used group of drugs. Since 1940 [1], when Daniel Bovet developed the first commercially available antihistamine (Antergan), their effectiveness and safety profile have been improved to provide us with second-generation antihistamines, which are based on active molecules.

The adverse effects of first-generation antihistamines are well known and are mainly caused by their action against

different receptors (central nervous system H₁ receptors, and muscarinic, α -adrenergic, and serotonin receptors) and on cardiac ion channels [2]. Second-generation antihistamines have a much-reduced sedative effect and their lipophobicity and relatively high molecular weight mean that they are less able to cross the blood-brain barrier. Cardiac toxicity is independent of antihistamine class. Although widely used, antihistamines rarely produce hypersensitivity reactions and few cases have been reported.

Case Description

We present 5 cases of hypersensitivity to antihistamines collected in our outpatient clinic over the last 15 years (Table).

Patient 1 attended our department because he had experienced 3 exacerbations of his recurrent acute urticaria 2-3 hours after taking hydroxyzine to treat it.

Patient 2 experienced 2 different episodes of itchy hives on the lower extremities 3 hours after taking 10 mg of loratadine and cetirizine at two different time points for rhinoconjunctivitis.

Patient 3 began treatment with dexchlorpheniramine at 5 mg for acute urticaria and, 2 hours after intake, her urticarial symptoms worsened. She stopped dexchlorpheniramine and initiated treatment with hydroxyzine at 25 mg. However, the same reaction occurred. She stopped taking hydroxyzine and the lesions resolved without rescue medication in about 3-4 hours.

Patient 4 experienced itchy erythematous lesions on her neck, angioedema on her hands, and generalized pruritus 24 hours after taking 10 mg of mequitazine and ebastine on 2 different occasions when she took them to treat acute urticaria.

Patient 5 is the most recent and complex case. She has had pollen-induced rhinoconjunctivitis and asthma since the age of 6 years, and has been using antihistamines since then on a regular basis. Two years ago she suffered an episode of acute urticaria 2 hours after taking 10 mg of mizolastine for seasonal allergic rhinitis. The episode resolved without rescue medication or medical care after a few hours. She also had these symptoms with chlorphenamine when she took it to treat a cold.

The first approach to diagnosis in all patients involved skin prick tests, which were prepared with a complete daily dose of antihistamine diluted in 1 mL of white petrolatum, and patch tests, which were performed at 5% in white petrolatum. Both were carried out following our department's protocol, which complies with the guidelines of the European Network for Drug Allergy [3]. The results of skin tests with the culprit drugs in 5 healthy and 5 atopic controls were negative.

Single-blind, placebo-controlled oral challenges were performed. Increasing doses were administered at 20-minute intervals starting with 10% of the total dose. Administration was stopped if a reaction occurred or the maximum daily dose was reached.

The results of skin tests with antihistamines were all negative in patients 1 to 4. Oral challenges were positive with hydroxyzine in

Table. Patient and Study Data

Patient	Sex	Age, y	Prick Test	Patch Test	Positive Oral Challenge	Time Till Onset of Reaction	Reaction in Oral Challenge	Antihistamines Tolerated
1	Male	36	NP	Negative	Hydroxyzine 25 mg	2-3 hours	Generalized itch, micropapules (neck and arms)	Oxatomide, terfenadine, astemizole, clemizole
2	Female	20	Negative	NP	Cetirizine 10 mg and loratadine 10 mg	3 hours	Itchy wheals (extremities)	Dexchlorpheniramine
3	Female	30	Negative	NP	Dexchlorpheniramine 5 mg and hydroxyzine 25 mg	2 hours	Generalized urticaria	Loratadine
4	Male	57	Negative	NP	Ebastine 10 mg and mequitazine 10 mg	24 hours	Erythematous lesions (neck), angioedema (hands), and generalized pruritus	Dexchlorpheniramine, loratadine
5	Female	36	Positive with hydroxyzine, ebastine, and levocetirizine Negative for the remaining drugs	Negative	Dexchlorpheniramine 5 mg, hydroxyzine 25 mg, levocetirizine 5 mg, ebastine 10 mg, mizolastine 10 mg, desloratadine 5 mg, rupatadine 10 mg, azelastine 0.05%	2-3 hours	Generalized pruritus, papules (lower and upper extremities)	None

Abbreviations: NP, not performed.

patient 1, cetirizine in patient 2, dexchlorpheniramine and hydroxyzine in patient 3, and mequitazine and ebastine in patient 4. All the challenges elicited reactions similar to those described by the patients. The complete dose was necessary to elicit a reaction, and all 5 patients were treated with intramuscular corticosteroids in our allergy department. We later assessed tolerance to other antihistamines.

In patient 5, the prick test was positive for some of the antihistamines (hydroxyzine, ebastine, and levocetirizine), although it was negative for the others. Challenges with different antihistamines (dexchlorpheniramine, hydroxyzine, levocetirizine, ebastine, mizolastine, desloratadine, rupatadine, and azelastine) by different routes of administration (oral, intravenous, conjunctival, and cutaneous) were carried out, and the same reaction was triggered by all of them, with the exception of cutaneous dexchlorpheniramine, which was tolerated. Forty-eight hours after treatment with azelastine eyedrops twice daily, the patient experienced generalized pruritus and isolated hives, with no conjunctival symptoms. Reactions during challenges consisted of generalized itching and micropapules and hives on the upper and lower extremities that were successfully treated with intramuscular corticosteroids. The serum tryptase determination 2 hours after the oral challenge with dexchlorpheniramine was 3.68 ng/mL. A skin biopsy after the oral challenge with dexchlorpheniramine showed a pattern typical of acute urticarial inflammation. The result of an oral challenge with an H₂ antagonist (ranitidine) was negative. The general characteristics of the study are shown in the Table.

Patient 1 tolerated oxatomide, terfenadine, astemizole, and clemizole; patient 2 tolerated dexchlorpheniramine; patient 3 tolerated loratadine; and patient 4 tolerated dexchlorpheniramine and loratadine. However, no alternative antihistamine could be found for patient 5, although all antihistamines were tested using an oral challenge.

Discussion

We present 5 cases of urticaria induced by antihistamines over the last 15 years. This infrequent diagnosis has received little attention in the literature. Although these cases occurred over a long period of time, the same diagnostic procedure was applied to determine the pathophysiological and immunochemical mechanisms.

Few authors consider this drug family as an allergen causing immunoglobulin (Ig) E-mediated reactions. Reports of anaphylaxis to mizolastine [4,5] and diphenhydramine [6] provide the most representative examples of a clear type I hypersensitivity reaction in terms of time between intake and onset, although prick test results were negative in 2 out of these 3 cases.

In our series, all the patients except patient 5 experienced immediate urticaria after taking antihistamines. Similarly, the results of skin prick tests and patch tests were negative in all patients except patient 5. The mechanisms involved in these reactions remain unclear, although there is no shortage of

theories: metabolite haptening, abnormal metabolism routes, enzymatic deficiency leading to antibody production, complement activation leading to C5a production, or many other mechanisms causing skin injury. However, none of these can be proved.

In order to determine the underlying mechanism involved in these reactions, we checked the available literature and found that, in most cases, no precise mechanism had been established, and the classification of reactions as type I or IV was based on the clinical history and time elapsed between intake and reaction. On the other hand, some cases of type IV reactions are well documented. Michel et al [7] described 3 patients who experienced a maculopapular rash or exacerbation of urticaria after taking hydroxyzine and had negative patch test results with all antihistamines but hydroxyzine.

The most complex case in our series was patient 5, who was unable to tolerate any antihistamines, regardless of the route of administration. Oral challenges with dexchlorpheniramine, hydroxyzine, levocetirizine, ebastine, mizolastine, desloratadine, and rupatadine were positive, as was intramuscular administration of dexchlorpheniramine. Continuous conjunctival administration of azelastine induced urticaria after 48 hours. No reaction occurred when dexchlorpheniramine was applied topically, although this may be because systemic levels were insufficient to trigger a reaction. The nasal route was not investigated, but as the ocular and nasal mucosae are similar and conjunctival azelastine triggered symptoms, we could expect a challenge result to be positive.

The results of skin tests were positive to hydroxyzine, ebastine, and levocetirizine in this patient, and negative to others. We also performed these tests in controls and no positive prick test results were observed. Unfortunately, we found no explanation for these findings. Demoly et al [8] report a case of hypersensitivity to several antihistamines where a 57-year-old patient experienced generalized urticaria 3-4 hours after taking cetirizine, hydroxyzine, triprolidine, loratadine, fexofenadine, and mequitazine, but tolerated mizolastine and cimetidine. Gonzalez de Olano et al [9] describe a patient who was allergic to several antihistamines (similar to our patient 5), with positive oral challenge results to antihistamines and negative skin prick test results. However, in this patient it was impossible to determine whether antihistamines could be tolerated, because the patient refused to undergo further challenges.

We were unable to determine a precise mechanism in any of our patients, but we think a type I hypersensitivity reaction may have been involved in patients 1 to 3 because of the specificity of their reactions and the time till onset. The mechanism in patient 4 is unclear and its classification into type I or IV is not possible. However, it was specific to mequitazine and ebastine. The mechanism responsible for the reactions observed in patient number 5 could be due to a malfunction of the H₁ receptor or to nonimmunologic antihistamine intolerance, as suggested by other authors [10]. The possibility of hypersensitivity to antihistamines should be taken into consideration in patients with urticaria.

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