Case Report

Urticaria induced by antihistamines

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Abstract. H_1-antihistamines are commonly used drugs, and probably the most frequently used for allergic diseases. They are pharmacologic inverse agonists of histamine at H_1 receptor sites and try to shift the equilibrium of this receptor toward the inactive state, preventing H_1 response. A wide variety of adverse effects have been attributed to antihistamines, and they can exceptionally induce skin reactions.
We report the case of a patient with several episodes of urticaria induced by different families of antihistamines - piperazines and piperidines.
We performed skin prick tests (SPT), patch tests and oral challenges to different antihistamines. We found positive SPT to some antihistamines, and positive oral challenge in others with negative SPT. The route of sensitization remained unclear, and our patient could not finally tolerate any antihistamine after the oral challenges we performed.
We support the hypothesis that antihistamines may shift the H_1 histamine receptor to the active conformation instead of the inactive conformation, prompting adverse reactions after dosing.
This is the first report of urticaria induced by different antihistamines in the same patient with positive SPT to several others.

Key words: Antihistamines, H_1 inverse agonist, H_1 receptor, urticaria.

Resumen. Los antihistamínicos H_1 son un tipo de fármacos de uso generalizado, y probablemente los más utilizados en las enfermedades alérgicas. Son agonistas inversos farmacológicos de la histamina en los lugares receptores H_1, e intentan cambiar el equilibrio de este receptor al estado inactivo, evitando así la respuesta H_1. Se han atribuido una gran variedad de reacciones adversas a los antihistamínicos, los cuales pueden, de forma excepcional, producir reacciones cutáneas.
Se presenta el caso de un paciente con varios episodios de urticaria inducida por diferentes familias de antihistamínicos (piperazinas y piperidinas). Se realizaron pruebas de punción cutánea (PPC), pruebas de parche y pruebas de provocación oral con diferentes antihistamínicos. Se observaron PPC positivas a algunos antihistamínicos y pruebas de provocación oral positivas en otros con PPC negativas. La vía de sensibilización siguió siendo incierta, y el paciente no pudo tolerar definitivamente ningún antihistamínico tras las pruebas de provocación orales que se realizaron. Se sostiene la hipótesis de que los antihistamínicos pueden cambiar el receptor H_1 de la histamina a la conformación activa en lugar de inactiva, lo que desencadena reacciones adversas tras su dosis.
Ésta es la primera notificación de urticaria inducida por diferentes antihistamínicos en el mismo paciente con PPC positivas a muchos otros.

Palabras clave: Antihistamínicos, agonista inverso de H1, receptor H1, urticaria.

H_1-antihistamines are commonly used drugs, and probably the most frequently used in allergic diseases. Their efficacy, tolerance and safety in humans have been widely established [1]. The molecular basis for their action stands on shifting from the active to the inactive conformation of one of the histamine receptors - H_1 receptor. Histamine is a chemical mediator of inflammation, produced and stored in mast cells and basophils. It is composed of a heterocyclic aromatic ring connected to an ethylamine group. Antihistamines are pharmacologic inverse agonists of histamine at H_1 receptor sites, and act by combining and stabilizing the inactive conformation of the receptor to shift the equilibrium toward the inactive state, preventing H_1 response [2,3]. A broad variety of adverse effects have been attributed to antihistamines, mostly to the first-generation substances

Table 1. Tests performed with antihistamines (previous reactions reported, SPT, patch test and oral challenges).

Antihistamine classification	Previous reaction	SPT	Patch test	Oral challenge performed
ALKYLAMINES				
Dexclorpheniramine	NO	2 mm	Negative	NO
ETHANOLAMINES				
Diphenhydramine	NO	**8 mm**	Negative	NO
ETHYLENDIAMINES				
Mepiramine	NO	3 mm	Negative	NO
PIPERAZINES				
1st Generation				
Hidroxyzine	NO	2 mm	Negative	NO
2nd Generation				
Cetirizine	NO	3 mm	Negative	**YES (positive)**
Levocetirizine	NO	2 mm	Negative	NO
PIPERIDINES				
Azatadine				
1st Generation				
Ketotifen	NO	**7 mm**	Negative	NO
2nd Generation				
Loratadine	YES	2 mm	Negative	NO
Desloratadine	NO	**5 mm**	Negative	NO
Terfenadine				
2nd Generation				
Fexofenadine	NO	2 mm	Negative	**YES (positive)**
Ebastine	YES	3 mm	Negative	NO
Piperidine - benzimidazole				
2nd Generation				
Mizolastine	NO	2 mm	Negative	NO
Phtalazinone				
2nd Generation				
Azelastine	NO	**6 mm**	Negative	NO
Alkyl - piperidines				
Rupatadine	NO	2 mm	Negative	NO
Others				
2nd Generation				
Levocabastine	NO	**6 mm**	Negative	NO
		Saline: 2 mm		

SPT: skin prick test. Positive reactions are indicated in bold type according to criteria for positivity.

[4]: central nervous system disorders, cardiovascular and anticholinergic effects have been the main ones reported. For the sake of solving such problems, newer antihistamine molecules are being synthesized.

Though antihistamines are the most commonly used drugs in the treatment of urticaria, they can exceptionally induce skin reactions. We report a case of a patient with several episodes of urticaria induced by different classes of antihistamines – piperazines and piperidines.

E.B. is a 30-year-old woman with a history of rhinoconjunctivitis due to grass pollens and animal danders. After 50 minutes of taking one tablet of ebastine (10 mg), she developed itching, wheal and flares; first located on her forearms, but extended to the entire body surface within the next 10 hours. She also reported a previous identical reaction after taking a 10 mg loratadine tablet, so she was then referred to our Hospital. We performed skin prick tests (SPT) to different antihistamine extracts (Table 1). Negative results were obtained for ebastine and loratadine, but SPT were positive to other molecules according to criteria for positivity [5] (Table 1). After obtaining an informed consent, we performed the same prick tests in five atopic and non-atopic patients, with negative results in all of them. The same drug additives were present in antihistamines with positive SPT and with negative results, so we decided not to carry out any SPT with those additives. Skin patch tests to all the related antihistamines were also performed. No positive reaction was detected (Table 1). We then decided to carry out blinded oral challenges to antihistamines which had been SPT negative. A positive skin reaction was observed 40 minutes after 10 mg cetirizine administration; once again the patient developed wheals and flares on her forearms that later on extended to the whole body within 8 hours. An identical reaction was observed 45 minutes after a 60 mg dose of fexofenadine oral challange (Figure 1). A histamine release test to the four drugs involved –ebastine, loratadine, cetirizine and fexofenadine – was also performed, with negative results. A serum tryptase determination two hours after cetirizine oral

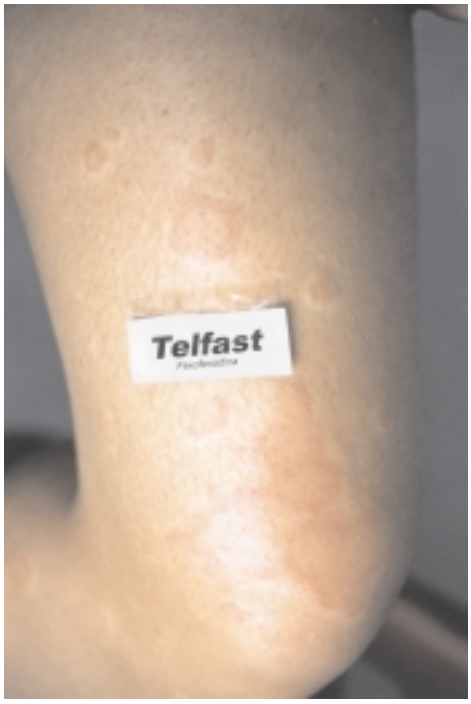

Figure 1. Skin reaction after 60 mg of Fexofenadine.

challenge was also negative. The patient refused to carry out any further oral challenges after these two – cetirizine and fexofenadine.

Cases of urticaria induced by antihistamines have been previously reported [6]. Some authors showed dependence of urticaria upon the cysteinyl leukotrienes [6]. Nevertheless, an immunological mechanism has been seldom demonstrated. In some cases, positive SPT - with mizolastine [7] and loratadine [8] - or intradermal test – cetirizine [9] and diphenhydramine [10]- suggested an IgE-induced mechanism. We have only found one report of urticaria induced by antihistamines in a single patient, involving different families of antihistamines [11]. Demonstration was carried out by oral challenge, but skin tests were all negative [12].

We report the case of a patient who developed urticaria after the intake of several antihistamines – ebastine, loratadine, cetirizine and fexofenadine – with negative skin tests to these drugs. We found five positive SPT with antihistamines which the patient had never taken before – dyphenydramine, ketotifen, desloratadine, azelastine, levocabastine. Thus, the route of sensitization remains unclear, and our patient could not finally tolerate any antihistamine after the oral challenges performed. We support the hypothesis that antihistamines may shift the H_1 histamine receptor to the active conformation instead of the inactive state, prompting adverse reactions after dosing. Antihistamines contain an ethylamine group and, in this sense, have same resemblance to histamine. In addition, because of the positive SPT obtained, an underlying immune mechanism cannot be ruled out either. The possibility that antihistamines themselves can be haptens or have chemically reactive metabolites to haptenate should be also taken into account.

To our knowledge, this is the first report of urticaria induced by different antihistamines in the same patient – ebastine, loratadine, cetirizine and fexofenadine – with positive SPT to several others. Physicians must be aware of the possibility that, occasionally, drugs used in the treatment of allergic reactions may act as the causal agent itself.

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