

## SHORT COMMUNICATION

## Management of Chronic Spontaneous Urticaria Exacerbated by Antihistamines: When Treatment Can Act as a Causal Agent Itself

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Although H1-antihistamines currently constitute the largest class of medications used in the treatment of allergic disorders, some cases of hypersensitivity reactions due to various antihistamine preparations, such as fixed drug eruptions, contact dermatitis, maculo-papular rash, and urticarial reactions, have been reported (1). We report here 2 cases of patients with chronic spontaneous urticaria (CSU) in which antihistamines were an exacerbating factor of the disease and alternative treatment was required. The underlying mechanism in these cases is not entirely clear, but a type-I (immediate) hypersensitivity reaction should be considered.

## CASE REPORTS

*Case 1.* A 35-year-old atopic woman presented with CSU of 3 years duration. She had an Urticaria Activity Score 7 (UAS7) of 32 (0–42) and a positive autologous serum skin test (ASST). She was treated with different oral H1-antihistamines, including dexchlorpheniramine, hydroxyzine, cetirizine, levocetirizine, cyproheptadine, ebastine, loratadine and rupatadine. The patient reported that antihistamines not only failed to control the disease, but induced severe urticaria exacerbation within 30 min to 3 h after its administration. Therefore, short courses of systemic steroids were needed, in spite of some adverse events. With the clinical suspicion of CSU exacerbated by H1-antihistamines, skin prick tests (SPT) were performed with 4 responsible drugs selected from 2 different families (piperazines and piperidines): ebastine, loratadine, cetirizine and cyproheptadine (dilution of 1%). An immediate positive reaction was observed for all tested drugs. Nevertheless, the flow cytometry-assisted basophil activation test (BAT) yielded negative results. The patient refused to carry out oral challenges.

*Case 2.* A 41-year-old Caucasian man suffered from CSU since his 30s. His past medical history was unremarkable. He had a UAS7 of 18 and a negative ASST. The patient was treated with multiple H1-antihistamine preparations throughout the course of the disease, including cetirizine, ebastine, rupatadine, loratadine and dexchlorpheniramine, with no clear-cut improvement.

Instead, he reported that each of these drugs had triggered a flare of wheals a few minutes after administration, including lip and eyelid angioedema on 2 occasions. For this reason, oral corticosteroids were usually needed, allowing partial relief of the disease. SPT (dilutions of 1%) and intradermal tests (dilutions of 1%, 0.1% and 0.01%) were carried out for rupatadine, ebastine and cetirizine. All of these showed positive results (reading time 15 and 30 min), confirming the hypersensitivity to antihistamines. A subsequent attempt to reintroduce the medication (loratadine and cetirizine) by the patient reproduced the urticarial exacerbation after a few minutes from drugs intake. BAT was also performed, and negative results were observed for all tested antihistamines.

## DISCUSSION

Exacerbation of CSU after treatment with oral H1-antihistamines seems to be a rare phenomenon that has received little attention in the literature. To our knowledge, only 5 cases of CSU exacerbated by antihistamines have been reported in the English literature (1–5) (Table I).

Shakouri & Bahna (1) conducted an exhaustive review of the literature of hypersensitivity reactions to H1 and H2-antihistamine preparations. They noticed that there is usually cross-reactivity between molecules within the same antihistamine class, so reactions to one preparation are likely to occur to other members of the same family. This issue makes it difficult to choose the maintenance treatment in patients who need these drugs for their underlying disease. In the described cases of CSU exacerbated by antihistamines, maintenance therapy with a different family of antihistamine (in cases of allergy to a single family) (2, 3) or with alternative agents, such as cyclosporine or corticosteroids (in cases of allergy to several families of antihistamines) (1, 4) was prescribed. Our 2 patients experienced exacerbation of CSU with any family of the prescribed H1-antihistamines; there-

Table I. Reports of chronic spontaneous urticaria exacerbated by H1-antihistamines

Reference	Age, years/ Sex	Causative drug	SPT	BAT	Oral provocation	Maintenance therapy
Schröter et al. (5)	36/F	Cetirizine	–	ND	+	No needed
Tella et al. (2)	32/F	Hydroxyzine, cetirizine	–	ND	+	H1-antihistamines
Kränke et al. (3)	33/F	Cetirizine, levocetirizine	–	ND	+	H1-antihistamines
Tedeschi (4)	23/M	Cetirizine, hydroxyzine, desloratadine, fexofenadine, ebastine	ND	ND	ND	Cyclosporine
Shakouri & Bahna (1)	44/F	Hydroxyzine, cyproheptadine, promethazine, diphenhydramine	ND	ND	+	Oral corticosteroids
Case 1	35/F	Cetirizine, ebastine, loratadine, cyproheptadine	+	–	ND	Omalizumab
Case 2	41/M	Cetirizine, rupatadine, ebastine	+	–	ND	Omalizumab

SPT: skin prick test; BAT: basophil activation test; F: female; M: male; ND: not done.

fore treatment with cyclosporine, 4–5 mg/kg/day, was established, being ineffective or unsafe to control CSU symptoms. Both subjects achieved complete remission after treatment with omalizumab, 300 mg monthly.

The underlying mechanism of antihistamine-induced urticaria remains controversial. Various theories have been proposed, including type-I hypersensitivity reaction, non-specific mast cell degranulation, activation of alternative pathway of the complement system, metabolite haptenization or malfunction of the H1-receptor (1, 5–7). In our patients, the clinical history, the time between intake and onset of the eruption and the positive skin tests could suggest a type-I hypersensitivity reaction. However, our first patient showed the same positive result for all the antihistamines previously tested when an additional SPT was performed being CSU symptom-free under treatment with omalizumab (therefore, with a blocked immunoglobulin-E; IgE). In addition, the BAT, which measures the basophil response to an allergen and currently considered a useful tool for diagnosis of immediate-type drug hypersensitivity (8), was negative in both cases. Specific IgE antibodies could not be detected in similar cases of antihistamine-induced urticaria or even in anaphylactic reactions (1, 5, 9). These facts support the hypothesis that the most likely mechanism involved in these cases is an IgE-independent reaction. A possible explanation could be, as suggested by other authors (7), a paradoxical effect in which antihistamines may shift the H1-histamine receptor to the active conformation instead of the inactive state due to their ethylamine group (which provides certain similarity to the molecular composition of histamine), causing the hypersensitivity reactions.

Regarding the diagnosis, it should be primarily suspected by clinical history, and then be appropriately verified by different types of allergy testing. Skin tests, such as SPT and intradermal tests, should be the first-line procedures (8). Despite the absence of a standardized protocol, it is recommended to perform these tests using the involved antihistamines, and also include other antihistamines from the same chemical class and different classes, in order to confirm sensitivity to a particular antihistamine or group of antihistamines and to look for therapeutic alternatives. Non-invasive *in vitro* tests, such as BAT or plasma histamine and leukotriene B4 levels (both reflect mast cell or basophil degranulation), may also provide useful information (1, 8). If these tests do not allow confirmation of the hypersensitivity reaction to antihistamines, an oral challenge test should be considered. This procedure is usually necessary to identify the culprit drug. However, it is potentially harmful, and thus the risk-benefit must be assessed carefully (10).

We report here 2 new cases of this unusual situation. Unlike the previously reported cases (Table I), the diagnosis of hypersensitivity reaction in our 2 patients was established by the positivity of skin tests in an appropriate

clinical context, thus oral provocation tests were not needed. The low reliability of skin allergy tests in cases of antihistamine-induced urticaria has been attributed to the lack of standardization of testing reagents, among other factors (1). Moreover, our cases describe the efficacy of omalizumab as a therapeutic option for CSU patients with hypersensitivity to multiple H1-antihistamines.

In summary, although adverse reaction to anti-allergic drugs, such as antihistamines, is a rare phenomenon, dermatologists should take them into account as a potential trigger or exacerbating factor in urticaria if suggested by the patient's clinical history. In these cases, different forms of allergy testing should be performed. Almost all H1-antihistamines can cause hypersensitivity reactions, with piperazines being the most commonly involved drugs. Change to another antihistamine class would be advisable if drug hypersensitivity is confirmed. Omalizumab may be an excellent therapeutic option for achieving disease control in cases of CSU with intolerance to different families of antihistamines.

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