Manuscript title: "Management of Chronic Spontaneous Urticaria exacerbated by antihistamines: when treatment can act as a causal agent itself"

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Short title: Chronic urticaria exacerbated by antihistamines

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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 herein two patients with chronic spontaneous urticaria (CSU) in which antihistamines acted as exacerbating factors of the disease and required an alternative treatment. The underlying mechanism in these particular cases is not entirely clear, but a type-I (immediate) hypersensitivity reaction should be considered.

CASE REPORTS

Case 1:

A 35-year-old atopic female with CSU of three-year duration required our assistance. Her Urticaria Activity Score 7 (UAS7) was 32 (0-42) and she showed a positive autologous serum skin test (ASST). She was treated with different oral H1-anithistamines, including dexchlorpheniramine, hydroxyzine, cetirizine, levocetirizine, cyproheptadine, ebastine, loratadine and rupatadine. The patient referred that antihistamines not only failed to control the disease, but induced severe urticaria exacerbation within 30 minutes to 3 hours 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 two 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:

Second case was a 41-year-old Caucasian male suffering of CSU since his 30s. Past medical history was unremarkable. He showed an 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, without a clear-cut improvement. Instead, he reported that each one of these drugs had triggered a flare of wheals few minutes after administration, including lip and eyelid angioedema in two 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 them showed positive results (reading time 15 and 30 minutes), confirming the hypersensitivity to antihistamines. A subsequent attempt to reintroduce the medication (loratadine and cetirizine) by the patient reproduced the urticarial exacerbation after 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 five cases of CSU exacerbated by antihistamines have been reported in the English literature (1-5) (Table I).

Shakouri and Bahna conducted an exhaustive review of the literature of hypersensitivity reactions to H1 and H2-antihistamine preparations (1). 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 two patients suffered CSU exacerbation with any family of the prescribed H1-antihistamines; therefore treatment with cyclosporine at a dose of 4-5 mg/kg/d was established, being ineffective or unsafe to control CSU symptoms. Both subjects have achieved complete remission after being treated with 300 mg monthly of omalizumab.

The underlying mechanism of antihistamine-induced urticaria has remained 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 suggested 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]). Additionally, the BAT, which measures the basophil response to an allergen and currently considered a useful tool for the diagnosis of immediate-type drug hypersensitivity (8), was negative in both cases. We also know that 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 provide 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, like 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 to confirm the hypersensitivity reaction to antihistamines, oral challenge test should be considered. This procedure is usually necessary to identify the culprit drug. However, it could be potentially harmful, and thus the risk-benefit needs to be carefully assessed (10).

Herein we report two new cases of this unusual situation. Unlike the previously reported cases (Table I), the diagnosis of hypersensitivity reaction in our two patients was established by the positivity of skin tests in an appropriate clinical context, so 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 like antihistamines is a rare phenomenon, dermatologists should take them into account as potential trigger or exacerbating factor of urticaria if suggested by clinical history. In these cases, different forms of allergy testing should be performed. Almost all H1-antihistamines can cause hypersensitivity reactions, with piperazines as 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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TABLES

Table I

Reference	Age/ Sex	Causative drug	SPT	BAT	Oral provocation	Maintenance therapy
Schröter *et al.* (2002)	36/ F	Cetirizine	-	ND	+	No needed
Tella *et al.* (2002)	32/ F	Hydroxyzine, cetirizine	-	ND	+	H1-antihistamines
Kränke *et al.* (2005)	33/ F	Cetirizine, levocetirizine	-	ND	+	H1-antihistamines
Tedeschi (2009)	23/ M	Cetirizine, hydroxyzine, desloratadine, fexofenadine, ebastine	ND	ND	ND	Cyclosporine
Shakouri *et al.* (2013)	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

TABLE LEGENDS

Table I:

Reports of chronic spontaneous urticaria exacerbated by H1-antihistamines.