

Cutaneous drug eruption induced by antihistamines

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Summary

Topical application of antihistamines commonly leads to sensitization for patients, but systemic administration of antihistamines rarely induces allergic hypersensitivity, which is mainly linked to phenothiazine-derived and piperazine-derived compounds. We report a 70-year-old woman whose medical history included lichen planus, and who was referred by the dermatology department of our hospital for suspected allergy to corticosteroids. The reason for referral was that on the fourth day of treatment with prednisone and hydroxyzine, the patient presented a bilateral highly pruritic palmar erythema that evolved to a generalized morbilliform rash with subsequent complete desquamation. At a later time, she took cetirizine for a cold, and developed palmar erythema and desquamation. Skin tests (prick and intradermal tests) were performed with steroids, and patch tests (read after 48 and 96 h) with corticosteroids and antihistamines. Controlled oral challenge tests were performed with prednisone and with an alternative antihistamine. Skin tests were negative for all corticosteroids. Patch tests were negative for all corticosteroids, but the antihistamine test was positive for hydroxyzine. Oral challenge with prednisone and dexchlorpheniramine was negative. The patient was diagnosed with cutaneous drug eruption from hydroxyzine and cetirizine. We consider it is important to assess every patient whose skin condition worsens after treatment with antihistamines, especially hydroxyzine, because it is known that antihistamines are often not recognised as the culprit in cases of cutaneous eruption.

Antihistamines are probably the most frequently used drugs in the treatment of allergic diseases, and they are generally considered safe. Topical application of antihistamines commonly leads to sensitization, but systemic administration of antihistamines can in rare cases induce allergic hypersensitivity. These reactions are mainly due to phenothiazine- and piperazine-derived compounds.¹ There are few cases reported of urticaria^{2–6} or skin reactions^{1,7} induced by antihistamines, as sometimes it is difficult to establish the causal relationship.

Report

A 70-year-old patient was referred for suspected allergy to corticosteroids. Her medical history included lichen planus. She had been on combined antihistamine treatments for years, usually hydroxyzine with a corticosteroid such as prednisone every 2–3 months. In June 2013, on the fourth day of treatment with prednisone and hydroxyzine, the patient developed highly pruritic, bilateral, palmar erythema that evolved to a generalized morbilliform rash with subsequent complete desquamation. Her referring dermatologist had stopped both treatments, and the episode resolved in about 15 days. There were no pictures of these lesions, and when the patient arrived at our unit, the symptoms were already resolved.

We suspected a possible allergy to corticosteroids. Skin prick test (SPT) and intradermal test were administered. Both the immediate reading after 15 min and the delayed reading after 24 h were negative. Saline

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(0.9% NaCl) was used as a negative control and histamine 10 mg/mL as a positive control. We did not have the equipment available to carry out lymphocyte stimulation tests or other laboratory tests. In addition, no tests for environmental or food allergy were performed because the patient had no respiratory symptoms and no discomfort with any food. We performed patch tests with a commercial corticosteroids battery (Marti Tor, Barcelona, Spain), which includes tixocortol pivalate, budesonide, desoximetasone, betamethasone valerate, hydrocortisone butyrate and prednisone; all readings at 48 and 96 h and at 10 days were negative.

Given these results, oral challenge to an alternative steroid was proposed, as the patient refused any re-challenge with the medication involved because of the seriousness of the reaction she had experienced.

On the day of the challenge, the patient informed us that a week earlier she had taken a 10 mg tablet of cetirizine to treat a common cold, and at 24 h she developed pruritic bilateral palmar erythema, which was self-limiting in about 12 h with posterior palmar desquamation. The corticosteroid oral challenge was performed with prednisone of 45 mg and it was completely negative.

At this point, given the patient's information about cetirizine, we performed tests to investigate allergy to antihistamines. Patch tests were performed (with readings at 48 and 96 h) with several antihistamines in petrolatum base (dexchlorpheniramine 0.5%, hydroxyzine 0.2%, loratadine 0.1%, cetirizine 0.1%, bilastine 2%, rupatadine 0.1%, ebastine 0.1%, desloratadine

0.5%, dimenhydrinate 5%, antazoline 0.5%, promethazine 0.1%, levocabastine 0.5% and azelastine 0.1%) and with petrolatum as a negative control. The only positive patch was hydroxyzine, which gave a reaction at both 48 and 96 h (Fig. 1). We also tested 10 healthy controls with the hydroxyzine patch, and all were negative. Because the patient's reaction was very uncomfortable and she declined oral challenge with hydroxyzine, we performed an oral challenge with dexchlorpheniramine at a cumulative dose of 8 mg to confirm whether this could be safely used as an alternative antihistamine. The patient was diagnosed with toxicoderma due to hydroxyzine and cetirizine intake.

Hydroxyzine is a first-generation antihistaminic derived from piperazine.^{5,7} and cetirizine is a chemically active oxidative metabolite of hydroxyzine.¹ For allergists, antihistamines are the mainstay of treatment in hypersensitivity reactions.⁵ Our patient developed toxicoderma after treatment with oral antihistamine. The mechanism is unlikely to be an IgE-mediated reaction, both because of the type of skin reaction and the time of latency to occurrence; in such cases SPT or patch test are not always reliable.⁵ According to Shaokouri and Bahna,⁵ nonspecific rashes are the main manifestations of adverse drug reactions in general, and among the antihistamines, piperazines are the most frequent causes of such reactions. In their review of the literature from 1949 to 2013, Shaokouri and Bahna compiled a total of 104 cases involving antihistamines, and the study showed clearly that the tests do not show optimum reliability in situations other than patch testing to diagnose



Figure 1 Skin test on the patient's back: (1) petrolatum, (2) dexchlorpheniramine, (3) hydroxyzine, (4) loratadine, (5) cetirizine, (6) bilastine, (7) rupatadine, (8) ebastine, (9) desloratadine, (10) dimenhydrinate, (11) antazoline, (12) promethazine, (13) levocabastine, (14) azelastine. Substance no. 3 (hydroxyzine; Atarax® 2 mg/mL) gave a positive reaction (++) at 48 and 96 h.

contact dermatitis or fixed pigmented erythema. Those authors also compiled 16 cases of fixed pigment erythema that appeared from a few hours to 2 days after drug ingestion, and in most cases was due to dimenhydrinate or cetirizine. They observed that there is crossreactivity between molecules of different generations of the same class of antihistamines, and in most cases where cetirizine was involved, hydroxyzine, levocetirizine patches, and oral challenge with hydroxyzine, cetirizine and levocetirizine were also positive. In contact dermatitis, the main antihistamine involved was doxepin cream. A review from 1994 to 2003⁵ revealed that there were 26 cases of contact dermatitis to doxepin, and 21 of these were positive patch tests. This exhaustive collection by Shaokouri and Bahna⁵ of reactions produced by antihistamines led to the conclusion that in most cases oral challenge is the only option to reach a conclusive diagnosis.

In our patient, the patch test to hydroxyzine was clearly positive, and thus we can safely say that the systemic skin reaction that led to the consultation can be attributed to hydroxyzine. However, the cetirizine patch was not positive, so we believe that this may be because the concentration we used was not correct. Another possibility is that observed by Gonzalez *et al.*³ who presented a case of a patient with urticaria induced by different families of antihistamines (including cetirizine) with negative cetirizine-specific skin and patch tests but positive oral challenge. In their cases, the sensitization mechanism was also uncertain, but the authors hypothesized that antihistamines can change the H1 histamine receptor from the inactive to the active conformation, triggering adverse reactions after ingestion. Because cetirizine is a derivative of hydroxyzine and it has been shown that there is cross-reactivity between antihistamines of the same family,⁵ and because our patient declined the oral challenge, we advised her to avoid cetirizine also.

This case report shows the importance of performing patch testing as a diagnostic measure to avoid oral challenge, especially in patients in whom the test could induce severe or very unpleasant effects, as has been described by Dalmau *et al.*⁷

Almost all antihistamines can cause any type of cutaneous reactions, but hydroxyzine and cetirizine are the most common oral preparations involved.⁵ Lew *et al.*¹ reported the first generalized morbilliform eruption induced by cetirizine and hydroxyzine, and they recommended that physicians should use caution with eruptions from antihistamines. We also

consider it is important to study every patient whose skin condition worsens after treatment with antihistamines,⁶ especially hydroxyzine and its derivatives because, as other authors have already proposed,^{1,5-7} it is known that the link between systemic exposure to antihistamines and cutaneous eruption is often not recognized, as the reaction may be similar to the original condition that is being treated with that antihistamine preparation.

Learning points

- Allergic reactions due to oral antihistamines are rare, and they can produce a wide range of manifestations, including urticaria, anaphylaxis and contact dermatitis.
- Hydroxyzine and cetirizine are the most common oral preparations involved.
- Physicians need to be alert for patients whose skin condition worsens after the ingestion of antihistamines.
- The link between systemic exposure to antihistamines and contact dermatitis is probably under-recognized.

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