

symptoms in the past two years. She also takes measure to avoid *Anisakis simplex*.

Wine is the alcoholic beverage most frequently involved in adverse reactions, most of them being due to the non-alcoholic components used as preservatives, such as sulphites.²

In asthmatic patients sulphite inhalation can cause bronchospasm depending on the amount of sulphur dioxide (SO₂) and the severity of the underlying asthma.^{1,7}

It is also important to know the type of wine, and the possibility of allergy to hymenoptera.⁸

We report a female patient with poorly controlled asthma who developed bronchospasm after drinking wine. Once her underlying asthma was properly controlled, with immunotherapy and dog avoidance, sulphite sensitivity subsided. The patient does not have allergy to hymenoptera, corroborated by clinical history and specific IgE antibodies.

Some previous studies suggest that sulphite sensitivity in asthmatics could be related with poor asthma control. These patients might be susceptible to cholinergic stimulation, such as sulphite inhalation, which could trigger bronchospasm.²

References

- Vally H, Thompson PJ. Role of Sulphite additive in wine induced asthma: single dose and cumulative dose studies. *Thorax*. 2001;56:763–9.
- Vally H, Thompson PJ. Allergic and asthmatic reactions to alcoholic drinks. *Addict Biol*. 2003 Mar;8:3–11.
- Yang HW, Purchase C.R.E. Adverse reactions to sulphites. *Can Med Assoc J*. Nov 1 1985;133.
- Bush RK. Sulphite and aspirin sensitivity: who is most susceptible? *Respir Dis*. 1987;8:23–32.
- Allen DH, Delohery J, Baker GJ. Monosodium L-glutamate induced asthma. *J Allergy. J Allergy Clin Immunol*. 1987;80:530–7.
- Lee RJ, Braman SS, Setippine GA. Reproducibility of metabisulfite challenge. *J Allergy Clin Immunol*. 1986;77:157 (abstract).
- Fine JM, Gordon T, Sheppard D. The roles of pH and ionic species sulphur Dioxides and sulphite-induced bronchoconstriction. *Am Rev Respir Dis*. 1987;136:1122–6.
- Armentia A, Pineda F, Fernández S. Wine-induced anaphylaxis and sensitization to hymenoptera venom. *N Engl J Med*. 2007 Aug 16;357:719–20.

V. Marenco Arellano*, M. Reaño Martos, M. Rodríguez Cabrerros, A. Bueso Fernández, J. García Loria, M. Rodríguez Mosquera

Allergy Department, Hospital Puerta de Hierro Majadahonda, (Madrid)

*Corresponding author.

E-mail address: vmarenco75@hotmail.com
(V. Marenco Arellano).

doi:10.1016/j.aller.2010.07.005

Antihistamines in chronic urticaria: threat or treat?

To the Editor:

Although antihistamines are the cornerstones for symptomatic treatment of urticaria,^{1,2} sensitivity reactions to antihistamines in systemic administration have been rarely reported. In this sense, antihistamines may cause fixed drug eruptions, urticaria and other hypersensitivity reactions. Other than these reactions, in a limited number of cases with chronic urticaria, antihistamines may exacerbate the underlying disease, which eventually lead to a difficulty in treatment. Here, we report two cases of chronic urticaria exacerbated with antihistamines and discuss the way of finding therapeutic options for these cases.

In both cases, patients first had skin prick and intradermal tests with antihistamines. If the skin prick tests (SPT) and intradermal tests (IDT) are negative, drug provocation tests were performed. All tests were performed under strict medical surveillance and written signed consents were obtained prior to tests.

Briefly, SPT were performed with dilutions of 1/100, 1/10, undiluted and IDT with dilutions of 1/1000 and 1/100 of the tested drugs. A wheal diameter of 3 mm greater than negative control and accompanied by erythema after 20 minutes was considered positive. Histamine and saline served as positive and negative controls, respectively. The

drug provocation tests were performed in a single-blinded, placebo-controlled design in which the patient was blinded. The doses of the drugs used for DPTs were ¼ and ¾ of the therapeutic doses. Tests were considered positive if any sign of hypersensitivity reactions such as urticaria; angio-oedema; laryngeal oedema; hypotension; dyspnoea; nasal symptoms; 20% fall in FEV₁ value; anaphylaxis; or other tests were observed during or after the test. The tests were considered negative if no adverse reaction occurred within 24 hours.

Case 1

The first patient was a 42-year-old woman who had chronic recurrent urticaria for three years. She experienced generalised urticarial lesions especially exacerbating with antihistamines like pheniramine maleate on several occasions. As she developed urticaria with the use of several other antihistamines of which she did not remember the names, there was a difficulty in treating the urticaria. On physical examination, she had generalised urticaria all around the trunk, arms and legs. No other pathological findings existed. Her routine blood and urine analysis were in normal range. Allergic work up with SPT with common aeroallergens and foods were negative. Other diagnostic work up such as thyroid autoantibodies, and immunological studies were in normal limits.

She was first skin tested with cetirizine. Prick and intra-dermal tests showed no reaction. However, she developed urticaria in oral challenge with a cumulative dose of 10 mg cetirizine. Therefore, she was tested with hydroxyzine, acrivastine, fexofenadine and desloratadine on consequent days in order to find safe alternatives. Although skin tests with these drugs were negative, oral challenges all resulted in urticarial reactions 3-4 hours after the administration of each drug. Finally, she tolerated levocetirizine and loratadine both in skin tests and oral challenges. Therefore, she was recommended to use these antihistamines. In the follow-up period, urticarial lesions showed good response to these antihistamines.

Case 2

The second patient was a 28-year-old-man suffering from chronic urticaria for seven years. His urticarial lesions were exacerbated by alcohol intake and use of some analgesic drugs. The patient also described generalised urticarial lesions one hour after intramuscular injection of pheniramine maleate. He was evaluated by a dermatologist and advised to take desloratadine tablets. However, he again had an urticarial reaction 3-4 hours after taking desloratadine tablets. He was also prescribed for ebastine and fexofenadine which also resulted with urticaria. SPT and IDT with the culprit drugs resulted negative. He developed urticarial lesions in oral challenge with cumulative dose of 10 mg tablet of ebastine 7 hours after taking the last dose and with cumulative dose of 180 mg tablet of fexofenadine 6 hours after taking the last dose. The patient refused to be submitted to oral challenge tests with alternative antihistamines.

In this report, we presented two cases in which chronic urticaria was triggered by several antihistamines. Regardless of underlying disease, chlorpheniramine maleate, and diphenhydramine were the most common antihistamines which cause hypersensitivity reactions. However, cetirizine is the most common antihistamine, reported to lead to hypersensitivity reactions in patients with chronic urticaria and allergic rhinitis.^{6,7} Both of our cases had hypersensitivity reactions to pheniramine maleate. But they also had challenge proven hypersensitivities to new generation antihistamines such as cetirizine, fexofenadine, ebastine, and desloratadine. So, one should be aware that even new generation antihistamines are capable of exacerbating urticaria in particular patients.

A relationship between certain drugs and exacerbation of urticarial lesions has been well documented for medications such as analgesics).⁹ However, such a relationship with drugs other than analgesics and urticaria is less defined. As the first line treatment of the underlying urticaria, antihistamines have been assumed as the drugs which least trigger urticaria. However, together with the literature data, although it is very rare, our cases suggested such a relationship for some patients. The underlying mechanism of such a relationship is not well understood. Metabolite haptens, enzyme deficiency resulting in some examples.⁸ Although the majority of the reactions are of an immediate nature, type I hypersensitivity is unlikely in the majority of the cases based on negative SPT but positive DPT results.^{7,8} Suggesting this, hypersensi-

tivity reactions to chemically different antihistamines in the same patient bring the possibility of a non-immune mediated reaction. Rarely, a possible type 1 IgE mediated hypersensitivity to some antihistamines such as diphenhydramine was reported.³ Anaphylactic shock due to antihistamines has been rarely reported.^{4,5} In terms of non-immediate reactions, a type IV hypersensitivity was diagnosed by a positive patch test in one case who had non-immediate reaction to antihistamines.¹⁰

The long term management of these cases carry some difficulties in drug selection as these patients might develop urticaria with use of chemically different antihistamines. However, these cases need some safe alternative antihistamines for the treatment of urticaria. Assuming the uncertainty of underlying mechanisms for immediate reactions, skin tests usually provide limited data about the tolerability of the antihistamines. Drug challenge tests are recommended as the best way to see whether the patient can tolerate a drug or not in such cases.^{1,2,7} Supporting this data, negative predictive value of SPT was poor and DPT provided safe alternatives in the first patient, however, such an option was not available for the second case as he refused further testing.

Interestingly, Case 1 had hypersensitivity reaction to desloratadine but loratadine and cetirizine but levocetirizine. This is somewhat unexpected as desloratadine and loratadine as well as levocetirizine and cetirizine share similar chemical structures. However, as these groups (ie: loratadine, desloratadine) revealed different drug challenge test results, drug challenge test is still worthy for trying to seek the tolerability of the other one in case of positive reaction to sister drugs, as these drugs are highly effective in treating urticaria.

In conclusion, although antihistamines rarely trigger urticaria, this possibility should be kept in mind when an exacerbation in symptoms after taking an antihistamine occurs. If such a relationship is demonstrated, drug challenge tests are the best way to find a safe alternative to these cases.

References

1. Nichols KM, Cook-Bolden FE. Allergic skin disease: major highlights and recent advances. *Med Clin North Am.* 2009;93:1211-24.
2. Zuberbier T, Asero R, Bindslev-Jensen C, Walter Canonica G, Church MK, Giménez-Arnau AM, Grattan CE, et al., Dermatology Section of the European Academy of Allergology and Clinical Immunology. Global Allergy and Asthma European Network; European Dermatology Forum; World Allergy Organization. EAACI/GA(2)LEN/EDF/WAO guideline: management of urticaria. *Allergy.* 2009;64:1427-43.
3. Lew BL, Haw CR, Lee MH. Cutaneous drug eruption from cetirizine and hydroxyzine. *J Am Acad Dermatol.* 2004;50:953-6.
4. Barranco P, Lopez-Serrano MC, Moreno-Ancillo A. Anaphylactic reaction due to diphenhydramine. *Allergy.* 1998;53:814.
5. Thurot-Guillou C, Bourrain JL, Jacquier JP, Beani JC. Anaphylactic reaction to ranitidine and dexchlorpheniramine. *Eur J Dermatol.* 2007;17:170-1.
6. Schröter S, Damveld B, Marsch WC. Urticarial intolerance reaction to cetirizine. *Clin Exp Dermatol.* 2002;27:185-7.

7. Chang YS, Kwon HS, Cho SH, Kim YY, Min KU. A case of urticaria induced by both hydroxyzine and cetirizine but not by levocetirizine. *Allergy*. 2007;62:819–21.
8. Pionetti CH, Kien MC, Alonso A. Fixed drug eruption due to loratadine. *Allergol et Immunopathol*. 2003;31:291–3.
9. Isik SR, Karakaya G, Celikel S, Demir AU, Kalyoncu AF. Association between asthma, rhinitis and NSAID hypersensitivity in chronic urticaria patients and prevalence rates. *Int Arch Allergy Immunol*. 2009;150:299–306.
10. Brown VL, Orton DI. Cutaneous adverse drug reaction to oral chlorphenamine detected with patch testing. *Contact dermatitis*. 2005;52:44–54.

Ömür Aydın*, Gülfem Çelik, Zeynep Misirligil

Ankara University School of Medicine Department of Chest Disease, Division of Immunology and Allergy

* Autor para correspondencia.

E-mail address: mdomuraydin@gmail.com (Ö. Aydın).

doi:10.1016/j.aller.2010.08.003

Delayed hypersensitivity challenged by subcutaneous Bemiparin

Bemiparin delayed type hypersensitivity

To the Editor:

Low-molecular-weight heparins (LMWHs) are now routinely used in protocols for the treatment of suspected myocardial infarction, unstable angina, deep vein thrombosis and pulmonary embolus.

A 65-year-old woman with contact dermatitis to nickel developed infiltrated itchy and big eczematous plaques at the subcutaneous injection sites on the lower abdomen, one week after beginning treatment with Bemiparin due to an orthopaedic surgery. This drug was changed for Enoxaparin, tolerated during her admission, but days later she complained of the same lesions.

In order to identify an alternative AU and once informed consent had been obtained, patch, intradermal, and subcutaneous tests were performed with a panel of unfractionated heparin (UFH), LMWHs and Fondaparinux.

Patch tests performed with Sodic Heparin, Bemiparin, Enoxaparin, Dalteparin, Nadroparin, Tinzaparin and Fondaparinux were negative, except for Bemiparin which was positive at 96 hours (eczematous plaque in application area) and less clear for Enoxaparin. Intradermal tests with Sodic Heparin, Enoxaparin, Dalteparin, Nadroparin, Tinzaparin and Fondaparinux were negative except for Enoxaparin which was positive at 24 hours.

Due to the necessity of anticoagulant treatment, subcutaneous challenge test was developed with Nadroparin, Dalteparin, Tinzaparin and Sodic Heparin, which were positive (itchy infiltrates and erythematous plaques hours later). However, subcutaneous challenge test with Fondaparinux was negative.

Heparins are complex mixtures of mucopolysaccharides produced from porcine or bovine intestines and lungs. Molecular weight differentiates UFHs (10–20 KDa) from LMWHs (4–6 KDa)¹.

Heparin eczema-like plaques result due to the binding of the heparin molecule to dermal protein, triggering a delayed-type hypersensitivity (DTH) reaction.²

The consulted bibliography shows the wide variability of heparin cross-reactivity, among LMWHs themselves and also between LMWHs and UFHs,^{1,3–6} so all heparins should be avoided in such individuals.

According to what Ludwig published⁷, a substance with a very low molecular weight is believed to reduce the frequency of DTH reactions to LMWH. Bemiparin (3.7 Kda) is supposed to be a suitable alternative when there is DTH reaction⁵. In our patient Bemiparin probably caused DTH reaction.

The study by Grims⁵ did not show a correlation between molecular weight and the frequency of cross-reactivity, and reported the first cases of cross-reactivity of Bemiparin with other LMWHs. In this study Fondaparinux was well tolerated, as happened to our patient.

Grims⁵ also found a particularly high cross-reactivity between Enoxaparin and Bemiparin. He explains this cross-reactivity because all patients had primarily been sensitized to Enoxaparin and cross-reactivity to Bemiparin was highest with Enoxaparin probably due to a similar chemical structure. We think our patient was sensitized first to Bemiparin and later, due to the cross-reactivity between them, she developed the eczematous plaques with Enoxaparin.

The use of a substance with an entirely different chemical structure such as recombinant hirudin (Lepidurin) or Fondaparinux (17 KDa) nearly excludes cross-reactivity with LMWHs,^{5,6} but they must be probed because there are described cases in the literature of type IV reaction to Fondaparinux^{2,8} and anaphylactic reactions to Lepidurin.⁹

We challenged with other LMWHs that had negative patch or intradermal tests to get an alternative and sure treatment and, with the exception of Fondaparinux, all proved positive. So patch and intradermal tests were partially useful to find an alternative drug, with subcutaneous challenge test being the best means of detecting the entire spectrum of sensitisation.^{4,5}

We have found in the literature some reports about the intravenous heparin tolerance in patients with DTH reaction.^{10,11,12} Gaigl et al.¹² published a prospective study in 2004 in which 28 patients with a proven delayed-type hypersensitivity to subcutaneous heparin were challenged with intravenous heparin, being well tolerated for all of them. So, in case of therapeutic necessity, the shift from subcutaneous to intravenous heparin would be justified¹². A possible reason for intravenous tolerance may be the difference in antigen processing and presentation of selectively sensitized lymphocytes in the dermis.^{11,12} Trautman and Seitz¹³ in their report, consider that, although there are some prospective studies supporting the use of intravenous administration of heparin in patients with DTH reaction, substantial doubt still