

Anaphylactic shock to H1 antihistamine drug bilastine: A case report

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Clinical Implications

- We report for the first time anaphylactic shock due to bilastine. We discuss antihistamine drug reactions, the rarity of the number of cases, and the possible mechanism of this reaction.

TO THE EDITOR:

Antihistamines are classified according to the histamine receptor that they act upon: H1 antihistamines, H2 antihistamines, H3 antihistamines, or H4 antihistamines. H1 Antihistamines are first-line treatment for chronic urticaria (CU), and are used to treat allergic reactions. However, antihistamines themselves may also cause allergic reactions, a fact that is often not known.¹ We present a case of anaphylactic reaction to H1 antihistamines to highlight the diagnostic and therapeutic pitfalls.

A 53-year-old woman with a 2-year history of CU presented for an allergic workup in 2009. The patient's presentation was consistent with the diagnosis of chronic spontaneous urticaria. Physical and other triggers were not identified. The thyroid function was normal and immunological screening was negative (no antinuclear and extractable nuclear antigen antibodies, no complement consumption, and no C1 inhibitor deficit). The basal tryptase level was in the normal range (5.8 µg/L, N < 11; ImmunoCAP, Thermo Fisher, Uppsala, Sweden). There were no other signs of cutaneous mastocytosis. Repeated stool and serologic tests for parasites were negative. Long-term treatment with cetirizine (up to 3-fold higher than standard dosage) and with hydroxyzine (once a day) was introduced.

Seven years later she presented again. She reported to have experienced repeated reactions following the intake of several H1 antihistamines with urticaria and angioedema (hydroxyzine, cetirizine) and urticaria, angioedema, and syncope (fexofenadine).

An alternative antihistamine therapy with a different molecular structure was warranted for her CU. A double-blind provocation test with bilastine versus placebo was performed. Bilastine was administered every 30 minutes (Table I). After a cumulative dose of 37 mg bilastine (90 minutes), the patient developed generalized urticaria. Prednisolone 100 mg was given orally. The patient felt uneasy and developed hypotension (84/54 mm Hg) and tachycardia (107/min) 360 minutes after the first intake of bilastine. The patient recovered after an intramuscular injection of 0.3 mg adrenaline. The tryptase level was elevated (36.7 µg/L, N < 11) 210 minutes after the development of urticaria, and 1 hour after onset of hypotension. Several days later, the tryptase normalized (5.8 µg/L, N < 11). The patient feared other reactions with other provocation tests and wished to have treatment as soon as possible. We refrained from further

provocation and diagnostic tests, which would have delayed a treatment. Her chronic spontaneous urticaria was subsequently treated with monthly subcutaneous injections of 300 mg omalizumab (Xolair) with good tolerance (follow-up 6 months), without any recurrence of urticaria after the first month of treatment.

Allergic reactions to H1 antihistamines are very rare and only 16 cases have been reported so far worldwide.¹⁻³ Two case reports describe patients who reacted to multiple H1 antihistamines.^{1,3}

In 7 cases, cetirizine, a second-generation antihistamine, was the culprit drug. The antigenic properties of cetirizine are speculative, but the piperazine ring might be involved.² However, prochlorperazine, an antiemetic drug containing the piperazine ring, was well tolerated in a provocation test after cetirizine-caused anaphylaxis.¹ Therefore, it is assumed that the allergenic structure of cetirizine resides on its side chain rather than in the piperazine ring. Interestingly, an intolerance reaction to cetirizine has also been reported with normal tryptase levels after provocation test and with negative *in vitro* tests (lymphocyte proliferation tests and IgE).³ Bilastine is a second-generation selective H1 antihistamine drug approved in the European Union for the symptomatic treatment of allergic rhinoconjunctivitis and urticaria, but not approved by the Food and Drug Administration. It shows similar efficacy and safety, but is considered to be less sedative as other second-generation H1 antihistamines.⁴ So far, through a PubMed search, we could not identify any report of anaphylactic reaction to bilastine. The delayed bilastine induced-hypotension might be an expression of a protracted anaphylaxis. Our patient did not experience an asymptomatic period after the onset of urticaria. Thus, a biphasic reaction has not been considered.

In this case, the concept of cross-reactivity between these different H1 antihistamines with different molecular structures is questionable. First, the reactions to hydroxyzine, cetirizine, and fexofenadine are based on the medical history. Therefore, we cannot prove a hypersensitivity to these antihistamines. We are not aware of the circumstances, respectively, and augmenting factors that may have contributed to the past reactions. Hydroxyzine and cetirizine are piperazine derivatives. Hydroxyzine is completely metabolized; the major metabolite is cetirizine, which is excreted mainly in the urine.^{5,6} However, bilastine and fexofenadine are benzimidazole-piperidine derivatives that are both excreted intact in the urine and feces.^{4,5,7} Considering the molecular structure and the metabolism of benzimidazole-piperidine and piperazine derivatives, the existence of a common epitope or a common antigenic metabolite is questionable. In view of the

TABLE I. Bilastine provocation test

Time	Dosing
0 min	2 mg
30 min	5 mg
60 min	10 mg
90 min	20 mg

observed reaction and the medical history, we assume that the patient developed multiple hypersensitivities to different molecular structures of antihistamines.

This is particularly challenging, because H1 antihistamines are used as first-line treatment for CU at up to 4-fold higher than the licensed doses⁸ and are also used to provide symptomatic relief in an anaphylactic reaction.

To our knowledge, this is the first report of an anaphylactic reaction to bilastine. Careful assessment of the risk/benefit ratio is necessary to avoid potentially harmful provocation tests. Omalizumab should be considered as first-choice treatment in patients with CU and H1 antihistamine hypersensitivity.

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REFERENCES

1. Rutkowski K, Wagner A. Cetirizine anaphylaxis. *Ann Allergy Asthma Immunol* 2014;113:247-9.
2. Afonso N, Shetgaonkar P, Dang A, Rataboli PV. Cetirizine-induced anaphylaxis: a rare adverse drug reaction. *Br J Clin Pharmacol* 2009;67:577-8.
3. Schröter S, Damveld B, Marsch WC. Urticarial intolerance reaction to cetirizine. *Clin Exp Dermatol* 2002;27:185-7.
4. Wang XY, Lim-Jurado M, Prepageran N, Tantilipikorn P, Wang de Y. Treatment of allergic rhinitis and urticaria: a review of the newest antihistamine drug bilastine. *Ther Clin Risk Manag* 2016;12:585-97.
5. Information obtained from summary of product characteristics for each individual compound. Available from: <http://www.medicines.org.uk/emc/>. Accessed July 28, 2017.
6. Simons FE, Simons KJ. Histamine and H1-antihistamines: celebrating a century of progress. *J Allergy Clin Immunol* 2011;128:1139-50.
7. Lucero ML, Gonzalo A, Mumford R, Betanzos M, Alejandro A. An overview of bilastine metabolism during preclinical investigations. *Drug Chem Toxicol* 2012; 35:18-24.
8. Zuberbier T, Aberer W, Asero R, Bindslev-Jensen C, Brzoza Z, Canonica GW, et al. The EAACI/GA(2) LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. *Allergy* 2014;69:868-87.

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