

The Paradox of Antihistamine Hypersensitivity



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In this issue, Coattrenec et al¹ report a case of anaphylactic shock during a double-blind drug provocation test (DPT) with bilastine that highlights the issue of rare, but potentially life-threatening, hypersensitivity reactions to antihistamines (AHs).

Histamine is a ubiquitous signaling molecule that targets mainly the histamine H1 and H2 G-protein–coupled receptors expressed in a wide variety of tissues. More recently, H3 and H4 receptors have been identified in the central nervous system and hematopoietic cells.² Most G-protein–coupled receptors exist in a dynamic equilibrium between inactive and active states. Mast cells, one of the most important effectors of allergic reactions, store and release histamine upon cross-linking of their high-affinity receptors for IgE (FcεRI) by allergens but also by autoantibodies as in a proportion of patients with chronic spontaneous urticaria (CSU).³ The H1 receptor is not only important in triggering the well-known clinical symptoms of allergy (including Gell and Coombs type I hypersensitivity/IgE-mediated reactions) but it is also present on mast cells, causing a positive feedback loop after activation.^{4,5}

H1 antihistamines act as inverse agonists by shifting the equilibrium of the H1 receptor to the inactive form. The first H1 AH was synthesized in 1940s and there are now 6 main chemical groups of AHs: alkylamines, ethanolamines, ethylenediamines, piperazines, piperidines, and phenothiazines.⁴ They are classified into either first-generation (sedating) or second-generation (non-sedating) AHs.⁵ Highly lipophilic first-generation AHs are less selective for the H1 receptor and easily cross the blood-brain barrier, resulting in undesirable drowsiness and impaired performance (sedation) and anticholinergic side effects. The lipophobic second-generation nonsedating AHs with a hydrophilic functional group (–COOH or –NH₂) reduced the incidence of sedation. The –COOH group creates “zwitterionic” compounds (dipolar ions with positive and negative charges in the same molecule), which explains poor brain-blood barrier penetration.⁴ AHs are the first-

line treatment for many common allergoimmunological conditions, including CSU and allergic rhinitis.^{6,7} They are also often used as second-line medication during anaphylaxis.

Despite being one of the most commonly sold drugs worldwide, adverse reactions are rare. Nevertheless, there has been an increasing number of reports on both immediate and non-immediate, as well as group-specific and nonspecific, adverse reactions.⁸ Immediate-type hypersensitivity reactions to both first-generation and second-generation AHs often involve acute cutaneous manifestations, such as urticaria and angioedema, but systemic reactions (anaphylaxis) have also been described. We previously reported on cetirizine anaphylaxis, including the role of skin testing and DPT, and reviewed published cases of AH anaphylaxis: 5 to first-generation AHs (diphenhydramine, dimenhydrinate, dexchlorpheniramine) and 5 to second-generation AHs (mizolastine and cetirizine).⁹ Although in some cases an IgE-mediated mechanism was suspected, results of skin prick tests and intradermal tests (when performed) were frequently negative. DPTs were needed to confirm the diagnosis of AH allergy. Shakouri and Bahna⁸ published a comprehensive review of the English language cases of AH allergy published between 1949 and May 2013. One hundred four cases were identified, which included urticaria, angioedema, anaphylaxis, fixed drug eruptions, allergic contact, and photosensitive dermatitis as well as generalized nonspecific rashes.⁸ However, many of those reports lacked a thorough allergy workup and some patients had active CSU at the time of a “positive” AH DPT result. Some experienced a DPT reaction suggestive more of a “spontaneous” flare-up of underlying CSU (rather than drug allergy); in some cases, DPT was not performed at all.

Coattrenec et al¹ describe the first case of anaphylaxis to bilastine, a new second-generation AH and a benzimidazole-piperidine derivative not structurally derived from any other currently available AHs.¹⁰ Interestingly, the patient was intolerant of multiple other AHs including hydroxyzine, a piperazine derivative. Unfortunately, no allergy workup was performed for other AHs. It is therefore difficult to comment on the potential group-specific cross-reactivity, which could hinder future treatment and patient counseling. For example, our group previously identified a patient with DPT-confirmed cetirizine (piperazine derivative) anaphylaxis who subsequently tolerated prochlorperazine (another piperazine derivative). This might suggest, contrary to previous reports, that a side chain rather than the piperazines moiety could be the allergenic epitope in cetirizine.⁹ This highlights the importance of further detailed epitope mapping in various AHs. Furthermore, it is of interest that many reports on multiple AH hypersensitivity have been in patients suffering from CSU. This may be due to selection bias because multiple AHs are most commonly prescribed in this cohort of patients. Moreover, the so-called multiple AH hypersensitivity, if

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not thoroughly investigated and critically appraised, could turn out to be nothing more than an (un)expected flare-up of CSU. However, one might propose a different underlying mechanism when instead of stabilizing the H1 receptor in its inactive form, the AH might shift the equilibrium to the active form.^{5,11} Indeed, phenotypic variations in the H1 receptor have been described.^{4,5} It is plausible that, at least in some patients with CSU, these variants might partially explain the underlying pathomechanism of the condition that prompts the patient to take the AH in the first place. All these questions await further research, which would enhance our understanding of the mechanism of CSU and the paradoxical response of some patients to the treatment with AHs. Finally, a recent report suggests that excipients such as gelatine can be, albeit very rarely, responsible for AH hypersensitivity reactions.¹²

The article by Coattre et al¹ is a welcome contribution to our understanding of AH hypersensitivity reactions. It encourages clinicians to be cognizant of the fact that even an AH, that is, an “antiallergic” medication, can trigger an allergic reaction. In such instance, a thorough allergy workup is crucial to avoid missing a potentially life-threatening diagnosis or making a false-positive diagnosis of antihistamine allergy.

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