

Clinical Pearl

Cetirizine anaphylaxis



Introduction

A 52-year-old woman with a 10-year history of chronic spontaneous urticaria usually managed with mizolastine attended a horse trial. She had eaten a homemade shepherd's pie at 9 PM. One hour 30 minutes later, she developed generalized pruritus, erythema, facial and peripheral angioedema, dyspnea, and diaphoresis with severe abdominal cramping pain and vomiting. Because of the abdominal symptoms, paramedics administered intravenous morphine followed by intravenous chlorphenamine and, only 3 hours later, oral prednisolone. The acute tryptase level was 16.9 ng/mL (upper limit 11.4 ng/mL).

Two months later, she was referred to the allergy department. Aero- and food allergy and hormonally induced exacerbation (perimenopause) of chronic urticaria were considered. An epinephrine auto-injector was provided. Specific IgE (sIgE) was undetectable to beef, horse, grass, cat, dog, rabbit, cow's milk, and gluten but positive to *Alternaria* species. sIgE to ω -5 gliadin was borderline positive (0.39 ng/mL) but the patient did not want to trial a wheat-free diet. On her way home, after the consultation, she developed severe abdominal pain, tachycardia, generalized urticaria, facial angioedema, erythema, and wheeze. She used her newly prescribed epinephrine auto-injector immediately. Paramedics administered intravenous chlorphenamine and hydrocortisone. This time, the acute tryptase level was 15.8 ng/mL.

Although wheat-dependent exercise-induced anaphylaxis was a possibility, the patient strongly believed cetirizine was the cause of her reactions. She had taken it, instead of mizolastine, 30 minutes before each episode. Therefore, a drug provocation test (DPT) was undertaken. Skin prick test with undiluted cetirizine oral solution (5 mg/5 mL of cetirizine hydrochloride; Pinewood Laboratories Ltd, Ballymacarbry, Clonmel, Ireland) was negative. However, within 20

minutes of taking 2 mg of the same liquid (20% of standard dose), she developed acute rhinitis; generalized pruritus; erythema; angioedema of the face, hands, and feet; tachycardia (129 beats/min); and bronchospasm with a decrease in peak expiratory flow rate from 450 to 290 L/min. The baseline tryptase level of 6.2 ng/mL increased to 11.7 ng/mL acutely. Oral chlorphenamine, prednisolone, and fluticasone propionate with salbutamol using a spacer were administered. She recovered within an hour. Epinephrine was not required.

Cetirizine belongs to a heterogeneous group of piperazine derivatives that includes many commonly used non-antihistamine (non-AH) drugs (Figs 1, 2).¹ Skin prick test and DPT with prochlorperazine, a commonly used piperazine antiemetic (prochlorperazine mesylate; Sanofi-Aventis, Guildford, United Kingdom), were both negative. DPT confirmed the patient's suspicion of cetirizine allergy but ruled out the allergy to a related piperazine drug, making an allergy to the core structure (piperazine ring) unlikely. She was advised to avoid cetirizine, its R enantiomer levocetirizine and hydroxyzine, whose active metabolite is cetirizine.¹ A medical alert bracelet was recommended. Six months later, her urticaria has remained controlled on mizolastine with no further episodes of anaphylaxis.

Discussion

The authors describe the first thoroughly investigated case of cetirizine (piperazine AH) anaphylaxis. Many features make it unique:

1. Confirmation by DPT with a severe reaction to 20% of the usual dose
2. Acute increase in serum tryptase level during DPT
3. DPT-confirmed tolerance of prochlorperazine, a chemically related piperazine derivative

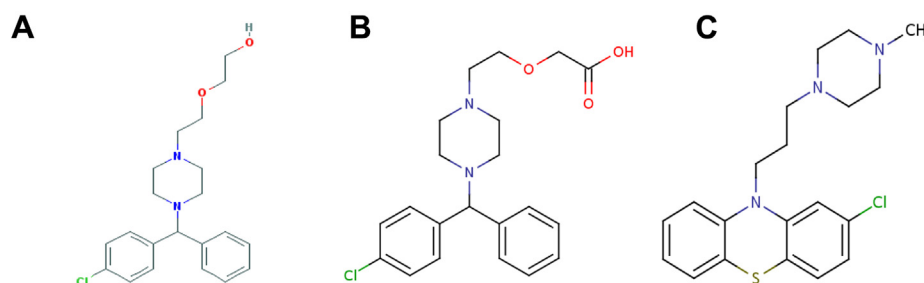


Figure 1. Chemical structure of some piperazine drugs: (A) hydroxyzine; (B) cetirizine; (C) prochlorperazine. (<http://www.ebi.ac.uk/chebi>).

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Disclosure: Authors have nothing to disclose.

<http://dx.doi.org/10.1016/j.anai.2014.06.030>

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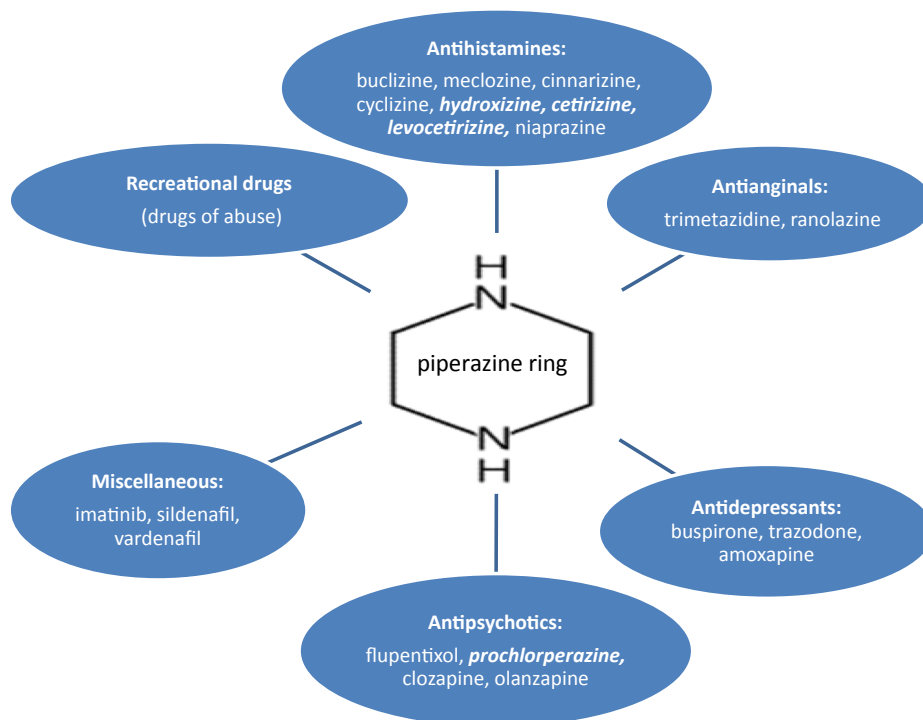


Figure 2. Piperazine derivate drugs (<http://www.rsc.org/merck-index>).

Antihistamines are divided into 6 major groups: alkylamines, piperazines, piperidines, ethanolamines, ethylenediamines, and phenothiazines.^{1,2} Hypersensitivity reactions to AH (ie, urticaria, fixed drug eruptions, contact dermatitis, or nonspecific rashes) are very rare. Most have been caused by first-generation AHs and very few by a second-generation AH preparation.³ Anaphylaxis to AH remains vanishingly rare. Over past 6 decades, only 10 cases have been reported: 5 to first-generation AHs (dexchlorpheniramine, dimenhydrinate, and diphenhydramine) and only 5 to second-generation AHs (cetirizine and 4 to mizolastine).^{3–7} Cetirizine belongs to a heterogeneous group of piperazine derivatives that includes non-AH drugs (Fig 1). Piperazine first-generation AHs (hydroxyzine) and second-generation AHs (cetirizine and levocetirizine) have been implicated in urticaria, fixed drug eruptions, and nonspecific rashes.³ However, only a single case of anaphylaxis has been described in a 30-year-old woman with chronic spontaneous urticaria who developed severe pruritus, urticaria, and loss of consciousness 15 minutes after 10 mg of cetirizine. She was resuscitated with epinephrine and crystalloids. Serum tryptase level was not measured and allergy workup not performed.⁷

The DPT was the only way to confirm the allergy in this patient. Skin prick test with low-molecular-weight drugs (all AHs) have unknown negative predictive value.^{3–6} No intravenous form of cetirizine is available and intradermal tests with viscous oral solutions are irritant. Moreover, cetirizine sIgE assays are not available. Serum tryptase is a valuable marker of mast cell degranulation and usually suggests an IgE-mediated mechanism. Baseline tryptase usually remains stable over time.⁷ In the present patient, it was 6.2 ng/mL (ImmunoCap Tryptase; ThermoFisher Scientific, Uppsala, Sweden). During the 2 episodes of anaphylaxis, its acute value exceeded the assay's cutoff point: 16.9 ng/mL (an increase of 272% from baseline) and 15.8 ng/mL (254%), respectively. During DPT with only 20% of the usual dose, the tryptase level increased acutely to 11.7 ng/mL (188% of baseline). Recent studies have suggested that an increase of as little as 135% from baseline or 2 mg/L during

suspected anaphylaxis indicates mast cell activation even below the tryptase assay's cutoff point.^{8–10}

Previously tolerated administration of cetirizine may have led to sensitization in this patient. Detailed analysis of cetirizine antigenicity is lacking and no epitope mapping has been undertaken. However, because cetirizine is a piperazine derivate, Afonso et al⁷ postulated that sIgE to the piperazine ring could be responsible for anaphylaxis. Based on the positive cetirizine but negative prochlorperazine DPT, this is unlikely in the present patient (Figs 1 and 2). It appears that the allergenicity of a cetirizine molecule resides in its side chain rather than in the piperazine moiety (Fig 1). Alternatively, cetirizine anaphylaxis may not be mediated by IgE.³

In conclusion, despite cetirizine's good safety record, it must be considered a rare but possible cause of anaphylaxis. Owing to the small number of cases of cetirizine hypersensitivity, the value of skin tests and other laboratory methods remains unknown. Therefore, the diagnosis can be confirmed only by DPT.

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