

Case report

Anaphylactic reaction to ranitidine (Zantac®)

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Ranitidine hydrochloride is an H₂-receptor antagonist widely used for the treatment of peptic ulcers, acute stress ulcers, and gastroesophageal reflux and is usually well tolerated. Because it is considered to be safe, ranitidine is available over the counter all over the world. It is a drug commonly administered in accidents and emergencies. This drug has been associated with urticaria,¹ anaphylactic reaction,² cutaneous delayed reaction,² toxic epidermal necrolysis,³ allergic contact dermatitis,⁴ lichenoid eruptions,⁵ ultraviolet B (UVB) photosensitivity,⁶ and exanthematous pustulosis.⁷ Cross-reactivity with other H₂-receptor antagonists is exceptional, and only one case has been published, involving a cross-reaction with nizatidine.⁸

Case Report

A 25-year-old man diagnosed with Achilles tendinitis took a medication composed of 75 mg ranitidine (Zantac®; GlaxoSmithKline, Inc., London, UK) and 100 mg aceclofenac (Airtal®; Daewoog Chemical Co. Ltd., Seoul, Korea) in an orthopedic clinic. At 15 minutes after the oral administration of the medication, the patient experienced itching, throat constriction, and dyspnea accompanied by marked erythema of the face. He was admitted to the emergency room (ER) for relief of his symptoms. The

doctor in the ER prescribed 125 mg methylprednisolone and 50 mg ranitidine (Zantac®) by IV infusion under the presumptive diagnosis that the patient was experiencing a drug reaction to aceclofenac (Airtal®). Ranitidine was administered for the prevention of peptic ulcers that may be caused by steroid injection. A few minutes after injection, the patient lost consciousness and developed a rash. His radial pulse was not palpable, and he stopped breathing. He required treatment with IM epinephrine injection and mask ventilation. His blood pressure subsequently

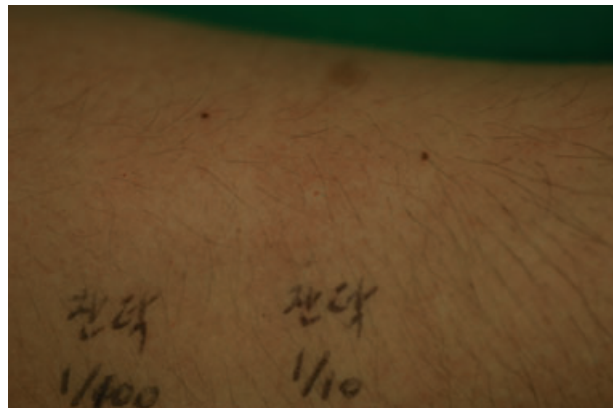


Figure 1 An erythematous wheal was observed after prick testing with ranitidine at a dilution of 1 : 10

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Figure 2 The patient's erythematous swollen left ear lobe after skin prick testing with ranitidine

returned to normal, and he regained consciousness. Three weeks later, the patient was referred to our outpatient unit for further evaluation. He had no other drug allergies and had no respiratory antecedents or previous episodes of asthma. An oral provocation test with aceclofenac was negative. A skin prick test with ranitidine was performed, with saline as a negative control. An intense reaction was observed after prick testing with ranitidine at a dilution of 1 : 10. The diameter of the resulting wheal was >3 cm (Fig. 1). Intradermal testing was prevented by the devel-

opment of erythematous swelling of both ear lobes (Fig. 2), headache, and dyspnea.

Discussion

Ranitidine is an H₂-receptor antagonist used in peptic ulcer disease therapy, acute stress ulcers, gastroesophageal reflux, Zollinger–Ellison syndrome, and related disorders. This drug is frequently given in combination with H₁ antihistamines and/or corticosteroids to prevent allergic or pseudoallergic reactions prior to the administration of anesthetics or contrast media. This drug has an excellent safety record, with fewer than 1% of patients receiving ranitidine developing gastrointestinal adverse effects, headache, or somnolence.⁹ Hypersensitivity reactions caused by ranitidine are not frequently encountered in everyday clinical practice. The use of this drug has rarely been associated with cutaneous adverse reactions (Table 1), such as toxic epidermal necrolysis,³ allergic contact dermatitis,⁴ lichenoid eruptions,⁵ UVB photosensitivity⁶, or exanthematous pustulosis.⁷ Two cases of angioedema and urticaria, with positive tests for immediate hypersensitivity, have been reported.² These reactions were observed in patients treated with either oral or IV ranitidine, including patients who underwent a premedication protocol containing ranitidine prior to chemotherapy or anesthesia. Interestingly, many ranitidine-induced anaphylactic/anaphylactoid reactions have occurred in obstetric patients.^{10–13} Some reports have documented positive skin test results to ranitidine,^{13–16} as in our case, suggesting that the drug can evoke hypersensitivity reactions through an immunoglobulin E (IgE)-mediated mechanism. Other indirect evidence of immediate hypersensitivity is the leukocyte histamine release test.⁸ Serum-specific IgE reactions to ranitidine have also been detected in a patient using an enzyme-linked immunosorbent assay.¹⁴ H₁-receptor antagonists can also induce an

Table 1 Reports of various ranitidine-induced adverse cutaneous reactions and anaphylaxis

No.	Published year	Author(s)	Patient age/sex	Clinical symptom	Provocation test	Prick test
1	1983	Picardo & Santucci ¹	62/F	Urticaria	+	+
2	1993	Lazaro <i>et al.</i> ²	22/F	Anaphylaxis	+	+
3	1996	Gonzalo-Garijo <i>et al.</i> ³	43/F	Itchy papules	+	–
4	1992	Juste <i>et al.</i> ⁴	79/M	Allergic contact dermatitis	NT	(Patch test) +
5	2003	Ryan <i>et al.</i> ⁵	8 patients	Allergic contact dermatitis	NT	(Patch test) +
6	2000	Kondo <i>et al.</i> ⁶	62/M	UVB photosensitivity	+	NT
7	2003	Martinez <i>et al.</i> ⁷	53/M	AGEP	NT	(Patch test) +
8	2007	Thurot-Guillou <i>et al.</i> ¹⁵	63/F	Anaphylaxis	NT	(Intradermal test) +
9	2007	Rethnam & Yesupalan ¹⁶	56/F	Anaphylaxis	NT	NT
10	2010	Our case	25/M	Anaphylaxis	NT	+

M, male; F, female; NT, not tested; UVB, ultraviolet B; AGEP, acute generalized exanthematous pustulosis.

urticarial eruption.¹⁷ The most frequent causative drug is reported to be cetirizine. Unlike ranitidine hypersensitivity, most cases of H₁ antihistamine-induced urticaria occur in the setting of a negative skin prick test. The causative drugs are instead confirmed by provocation tests, suggesting that urticarial reactions caused by H₁ antihistamines may not be IgE-mediated.¹⁷

Regarding the cross-reactivity between ranitidine and other H₂ antihistamines, available findings indicate a possible cross-reaction with nizatidine in the absence of cross-reactivity with cimetidine or famotidine.^{8,14,18} In such cases, it is possible that the patient has a ranitidine hypersensitivity and other H₂ antihistamines can be used. The frequency of anaphylactic reactions to H₂-receptor antagonists and proton pump inhibitors together has been estimated to be as high as 0.7%, with only two cases of anaphylaxis to ranitidine revealed among 8304 first referral patients over a 13-year period.¹³ Although ranitidine appears to rarely induce immediate hypersensitivity reactions, it seems to be the most frequent culprit for anaphylaxis among all H₂ antihistamines, with cimetidine and nizatidine involved in such reactions only under exceptional circumstances.^{18,19} In our case, the ER physician misattributed the patient's anaphylactic symptoms to a reaction to aceclofenac (Airtal®). Therefore, he administered an IV infusion of steroids and ranitidine, the latter for the prevention of peptic ulcer formation. The immediate response to the skin prick test suggests that ranitidine was the drug responsible for the clinical reaction, possibly produced by an immediate-type hypersensitivity reaction. This case report was prepared to highlight a rare and unusual adverse reaction to a widely used drug, ranitidine. Caution needs to be exercised in the IV administration of this drug as an adverse reaction can occur unexpectedly.

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