

Two Cases of H₂-Receptor Antagonist Hypersensitivity and Cross-Reactivity

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H₂-receptor antagonists, such as cimetidine, ranitidine and famotidine, are some of the most commonly prescribed medications for gastric acid-related disorders. These compounds are generally well-tolerated and anaphylactic reactions to them are rare. Here, we report two cases of H₂-receptor antagonist-induced anaphylactic reactions: the first presented with sudden dyspnea, sneezing, urticaria, and swelling of the eyelids after ranitidine intake. The second presented with sudden severe urticaria, facial swelling, chest discomfort, dizziness, and hypotension. Possible cross-reactivity with other H₂-receptor antagonists was assessed by oral challenge and skin tests. To date, only a few reports addressing cross-reactivity among H₂-receptor antagonists have been published. We review the literature and summarize the data available on drug cross-reactivity in H₂-receptor antagonist hypersensitivity.

Key Words: Histamine H₂ receptor antagonists; cross reactions; drug hypersensitivity; allergy

INTRODUCTION

H₂-receptor antagonists inhibit histamine action on gastric parietal cells, thus decreasing acid production. Such therapy is usually indicated for the treatment of peptic ulcers and gastro-esophageal reflux disease. These agents are typically well-tolerated, and severe hypersensitivity reactions are extremely rare.¹ Here, we report two cases of severe hypersensitivity reactions induced by H₂-receptor antagonists and possible cross-reactivities between drugs of this class.

CASE REPORT

Case 1

A 42-year-old female visited our clinic having recently suffered two episodes of angioedema. About 1 month earlier, she developed dyspnea, sneezing, and swelling of the eyelids 30 min after taking a single 150 mg ranitidine tablet (Zantac[®], GlaxoSmith-Kline, Brentford, UK). One week later she again took ranitidine (Zantac[®]) for dyspepsia, and once more developed the allergic

reactions immediately afterwards. She had dermatographism and a history of skin rash in response to penicillins and sulfonamides. Her father was also allergic to penicillins, and her son suffered from asthma.

Based on her clinical history and the timing of the reactions, ranitidine-induced hypersensitivity was suspected. Due to severe dermatographism, the patient was unable to undergo skin tests; a direct challenge was performed instead. No positive response was provoked to either placebo or 75 mg ranitidine (Curan[®], Il-Dong pharmaceuticals, Seoul, Korea) 30 min after oral challenge. However, the patient began to complain of rhinorrhea and generalized pruritus 30 min after administration of 150 mg ranitidine. On examination, urticaria was found in

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the axilla and ears. No significant change in FEV1 or blood pressure was observed. The test was stopped and the symptoms treated with methylprednisolone and chlorpheniramine.

One month later, another challenge was performed with famotidine (Gaster®, Astellas Pharma Inc., Tokyo, Japan). Thirty minutes after challenge with 10 mg, the patient reported itching and a hot sensation in the palms. Because we decided that these symptoms were non-specific, we proceeded with a challenge using 20 mg famotidine. Ten minutes after ingesting, she began to complain of not only itching of the palms, but also sudden sneezing and rhinorrhea. The test was immediately stopped, and symptoms subsided spontaneously without progression. As a result, we concluded that this patient was allergic to ranitidine and famotidine. Thus, we diagnosed this case as ranitidine-induced hypersensitivity reaction with possible cross-reactivity to famotidine.

Case 2

An 80-year-old male was transferred to the emergency room due to chest discomfort and dizziness. On arrival, his blood pressure was 60/40 mmHg and he was wheezing. He looked confused, and had a swollen face and severe generalized urticaria. He recovered after immediate administration of epinephrine, systemic corticosteroids, and chlorpheniramine. He was found to have taken chlorpheniramine, acetaminophen, and cimetidine 10 min before the onset of his symptoms because of mild urticaria, which allegedly developed after pork intake. Immediately after taking these medications, he developed severe generalized urticaria, facial swelling, chest discomfort, dyspnea, and dizziness.

He suffered from asthma and angina pectoris, and was taking inhaled budesonide/formoterol, nitrate, carvedilol, nicorandil and triflusal. He had no other medical history, known adverse drug reactions, or relevant family history. Initial tests, including cardiac enzymes and an electrocardiogram, revealed no remarkable abnormalities. Two weeks after recovery, a skin prick test was performed for common inhalant and food allergens, including pork. These revealed weak skin positivity to only willow, timothy and meadow, but no response to pork.

One month later, because this patient had suffered ischemic heart disease we performed skin instead of oral tests. Three commonly used H₂-receptor antagonists were prepared: cimetidine (100 mg/mL), ranitidine (25 mg/mL), and famotidine (10 mg/mL). The patient did not respond to any of the H₂-receptor antagonists. Subsequently, intradermal skin tests using cimetidine, ranitidine, and famotidine at 1:10,000, 1:1,000, and 1:100 dilutions in NaCl were performed. If no response was observed, the concentration was increased in ten-fold steps. Cimetidine began to provoke a response at a 1:100, and ranitidine and famotidine at a 1:10 dilution (Table 1). No systemic response was observed.

Later, we identified acetaminophen to be safe to take orally.

Table 1. Results of intradermal skin tests for cimetidine, famotidine, and ranitidine

Drug	1:10,000	1:1,000	1:100	1:10	1:1*
Cimetidine	0×0/0×0 [†]	0×0/0×0	6×6/28×34	7×7/30×35	8×8.5/40×40
Famotidine	-	-	0×0/0×0	5×8/22×22	6×8/25×35
Ranitidine	-	-	0×0/0×0	2×3/10×12	6×8.5/18×20
Saline	-	-	-	-	0×0/0×0

*Concentrations used were: cimetidine, 100 mg/mL; famotidine, 10 mg/mL; and ranitidine, 25 mg/mL.

[†]Data are expressed as increased wheal diameter (mm×mm)/flare diameter (mm×mm).

Chlorpheniramine was found to be safe after it was well-tolerated when accidentally injected in an emergency room. As a result, this case was diagnosed as cimetidine-induced anaphylaxis with possible cross-reactivity with famotidine and ranitidine.

DISCUSSION

The discovery of specific H₂-receptor antagonists in the 1970s revolutionized the management of gastric acid-related disorders. Cimetidine, the oldest and most used H₂-receptor antagonist, inhibits many isozymes of the cytochrome P450 enzyme system.² Thus, this agent has a higher risk of drug interactions than newer H₂-receptor antagonists. Ranitidine, introduced in 1981, was designed by replacing the imidazole ring of cimetidine with a furan ring. Ranitidine has only 10% of the affinity to CYP450 of cimetidine.³ Famotidine, developed in 1985, was structured by substituting the imidazole ring with a 2-guanidinothiazole ring. It does not bind to CYP450, and so has not been associated with significant interactions.⁴

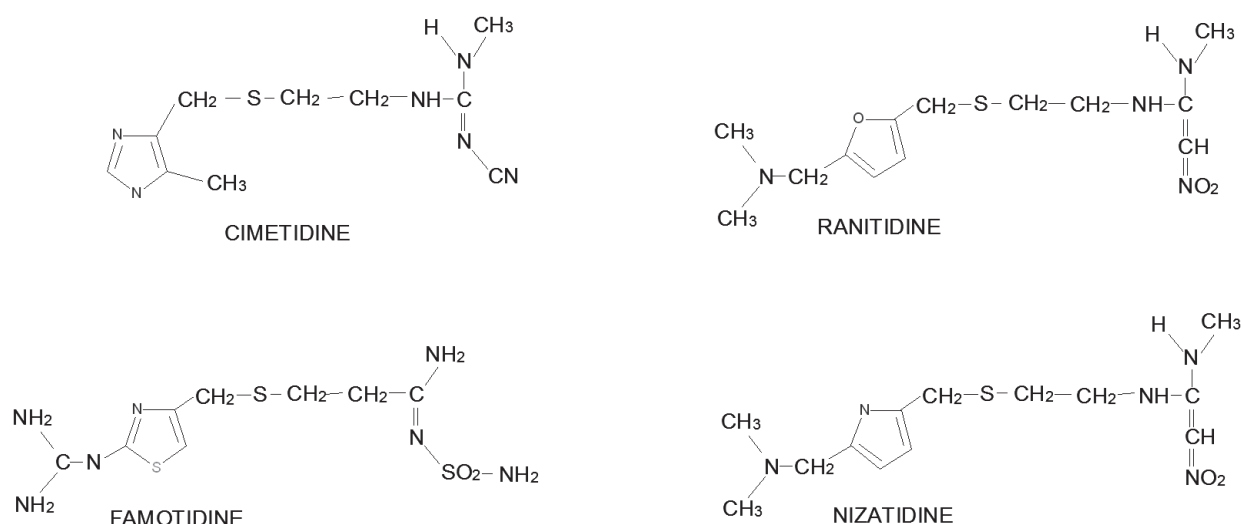
Apart from the known interactions of cimetidine, H₂-receptor antagonists are generally well-tolerated. Severe hypersensitivity reactions are rare.^{1,5-11} According to the Uppsala Monitoring Center database for May 1999, the incidence of anaphylaxis represented 0.2-0.7% of all the reported adverse reactions to both H₂-receptor antagonists and proton pump inhibitors.⁹

Direct challenge is considered the gold standard for diagnosis of drug allergies. However, performance of a direct challenge to a patient is often difficult, due to potential fatalities or unknown underlying diseases. In such cases, a skin or *in vitro* test can be helpful. In this report, we performed skin tests in the second case due to the risks arising from his cardiac conditions. It is sometimes problematic to distinguish true reactions from false positivity in intradermal tests. According to the literature, however, in normal controls skin irritation was not provoked at the most commonly used doses (20 mg/mL for famotidine, 75 mg/mL for ranitidine, and 150 mg/mL for cimetidine).¹ In this case, the minimum concentrations that provoked a response were: 1 mg/mL, 2.5 mg/mL and 1 mg/mL, respectively, indicating true positivity.

Interestingly, both cases showed cross-reactivity with other H₂-

Table 2. Summary of published reports on the cross-reactivity of hypersensitive reactions by H₂-receptor antagonists

Case	Causative drug	Reaction	Cross-reactivity between	Diagnostic method
Case 1	Ranitidine	Anaphylaxis	Ranitidine and famotidine	Oral challenge
Case 2	Cimetidine	Anaphylaxis	Cimetidine, ranitidine and famotidine	Intradermal test
Demirkan et al. ⁹ (2006)	Ranitidine, famotidine	Angioedema, anaphylaxis	Famotidine and ranitidine	Clinical diagnosis
Kim et al. ¹ (2010)	Famotidine	Anaphylaxis	Nizatidine, ranitidine and famotidine, but (-) cimetidine	Intradermal test
Bossi et al. ¹³ (1992)	Ranitidine, famotidine	Maculopapular eruption, pruritus	Nizatidine, ranitidine and famotidine, but (-) cimetidine, (-) roxatidine	Skin prick test, oral challenge
Morisset et al. ¹² (2000)	Ranitidine, nizatidine	Maculopapular eruption	Ranitidine and nizatidine, but (-) famotidine	Oral challenge

**Figure.** Chemical structures of H₂-receptor antagonists.

receptor antagonists. So far, only a few reports of this phenomenon have been published. We have summarized the literature published to date (Table 2). All of the cross-reactions were between famotidine and ranitidine or nizatidine, but none with cimetidine.^{1,9,12,13} This may be due to the differences between cimetidine and other H₂-receptor antagonists in terms of their side chain and ring structures. Ranitidine, nizatidine, and famotidine, but not cimetidine, share similar side chains on the ring structures (Figure).^{12,13} This may explain the rarity of cross-reactions of cimetidine with other H₂-receptor antagonists. To our knowledge, this is the first report of possible cross-reactivity of cimetidine with another H₂-receptor antagonist.

An IgE-dependent mechanism has been suggested for anaphylaxis induced by H₂-receptor antagonists, and ranitidine-specific IgE antibody has been isolated from one case.⁸

In summary, we report two cases of H₂-receptor antagonist hypersensitivity reactions, showing possible cross-reactivity within the class. The first case was ranitidine hypersensitivity showing cross-reactivity with famotidine, as determined by oral challenge tests. The second case was of cimetidine-induced anaphylaxis, together with possible cross-reactivity to ranitidine and famoti-

dine, as determined by skin tests.

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