CASE REPORT

A Case of Famotidine-Induced Anaphylaxis

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■ Abstract

Famotidine is considered to be safe, causing very few adverse events. We describe a case of famotidine-induced anaphylaxis in a 23-year-old man who presented with dyspnea, seizure-like activity, and comatose mental state immediately after an intravenous injection of cefazedone and famotidine for the preoperative preparation of left varicocele. He completely recovered with epinephrine, fluid replacement, and corticosteroids. Skin tests with cefazedone and other ß-lactam antibiotics were all negative but skin tests with famotidine showed a clear positive immediate reaction. Interestingly, we also observed clear positive skin reactions to other H_2-receptor antagonists such as nizatidine and ranitidine, which have similar side chains to the ring structures. Our case suggests that famotidine may induce immunoglobulin E–mediated anaphylaxis and have cross-reactivity with nizatidine and ranitidine. Clinicians should therefore be aware of possible life-threatening adverse reactions to commonly used H_2-receptor antagonists such as famotidine.

Key words: Famotidine. Anaphylaxis. Immunoglobulin E. Cross-reactivity. Skin test.

■ Resumen

La famotidina se considera un fármaco seguro, con muy pocos acontecimientos adversos. Se describe un caso de anafilaxia inducida por famotidina en un hombre de 23 años de edad que presentaba disnea, actividad convulsiva y estado comatoso inmediatamente después de una inyección intravenosa de cefazedona y famotidina para la preparación preoperatoria del varicocele izquierdo. El paciente se recuperó por completo con epinefrina, reposición de líquidos y corticoesteroides. Todas las pruebas cutáneas con cefazedona y otros antibióticos ß-lactámicos dieron negativo, pero las pruebas cutáneas con famotidina mostraron una reacción inmediata claramente positiva. Cabe destacar que también se observaron reacciones cutáneas claramente positivas a otros antagonistas de los receptores H_2, como la nizatidina y la ranitidina, que tienen cadenas laterales similares a las estructuras en anillo. Este caso indica que la famotidina puede producir anafilaxia mediada por inmunoglobulina (Ig) E y presentar reactividad cruzada con la nizatidina y la ranitidina. Por consiguiente, los médicos deben tener en cuenta las posibles reacciones adversas potencialmente mortales a los antagonistas de los receptores H_2 utilizados habitualmente, como la famotidina.

Palabras clave: Famotidina. Anafilaxia. Inmunoglobulina E. Reactividad cruzada. Prueba cutánea.

Introduction

Famotidine is a specific, long-acting H_2-receptor antagonist that is indicated for the treatment of peptic ulcer, gastroesophageal reflux disease, and Zollinger-Ellison syndrome. It is considered to have excellent safety profiles [1]. Extremely rare cases of famotidine-induced anaphylaxis have been documented, although we and others have reported cases of anaphylactic reactions to ranitidine [2-5] and nizatidine [5,6]. We herein describe a case of famotidine-induced anaphylaxis diagnosed on the basis of a typical anaphylactic episode and a positive skin reaction to famotidine.

Case Description

A 23-year-old man was admitted to the urology department of our hospital for operation of left varicocele. He had no past history of other medications, illnesses, or allergic diseases. On the operation day, cefazedone 1 g and famotidine 20 mg were administrated intravenously for preoperative preparation. Immediately after the injection of famotidine, the patient complained of dyspnea, showed seizure-like activities, and became comatose. Cardio-pulmonary-coronary resuscitation was performed immediately with epinephrine, fluid replacement, and corticosteroids because blood pressure

was not detected. Recovery was complete and there were no sequelae. Complete blood counts, liver functions, renal functions, and serum electrolytes were within normal limits. To exclude cardiac problems such as arrhythmias, we performed electrocardiography, 2D-echocardiography, and 24-hour Holter monitoring, but they showed no abnormal findings. The total serum immunoglobulin (Ig) E level was 93.8 IU/mL. Specific serum IgE levels to penicilloyl G, penicilloyl V, ampicilloyl, amoxicilloyl, and cefaclor were not detected with ImmunoCAP (Phadia AB, Uppsala, Sweden).

About 1 month later, skin prick tests with the following drugs were performed on the patient's back: cefazedone, ß-lactam antibiotics (penicillin G potassium crystal, ampicillin-sulbactam, and amoxicillin sodium), H_2-receptor antagonists (famotidine, nizatidine, ranitidine hydrochloride, and cimetidine), and proton pump inhibitors (pantoprazole and lansoprazole). The results were all negative. Intradermal skin tests with all the above drugs were subsequently performed on the back, with positive reactions to famotidine, nizatidine, and ranitidine and negative reactions to all the other drugs, including cefazedone and cimetidine. The maximal concentration of all the drugs used in the prick and intradermal skin tests was 3 mg/mL.

Additionally, we performed intradermal tests with famotidine, nizatidine, ranitidine, and cimetidine on the forearm of the patient and 6 male controls (mean [SD] age, 27.2 [1.0] years). Clear positive reactions to famotidine, nizatidine, and ranitidine were again observed in the patient (Figure 1 and Table), but not in the controls. The tests were performed with close monitoring of blood pressure and cardiac rhythm. There were no adverse cardiac events following the test dose of famotidine.

To determine famotidine-specific serum IgE, enzyme-linked immunoassay (ELISA) was performed. Unfortunately, however, we failed to detect famotidine-specific serum IgE. Famotidine-human serum albumin (HSA) conjugates were prepared according to a method described previously [7,8], and used to detect specific IgE in serum using ELISA. Thirteen healthy controls with negative skin prick tests to famotidine were included. The final absorbance value was determined by subtracting the HSA-coated value from that of the famotidine-HSA-coated value. The positive cutoff for specific IgE (0.04)

Figure 1. Intradermal skin tests with H_2-receptor antagonists on the forearm of the patient showed positive reactions to famotidine (A), nizatidine (B), and ranitidine (B), but not cimetidine (B). Each drug was diluted with saline to 1:10, 1:100, and 1:1000. The 1:1 concentrations were 20 mg/mL for famotidine, 150 mg/mL for nizatidine, 75 mg/mL for ranitidine, 150 mg/mL for cimetidine, and 0.1 mg/mL for histamine.

Table. Intradermal Skin Tests for Famotidine, Nizatidine, Ranitidine, and Cimetidine

Drug	10-Fold Dilutions of Each Drug			
	1:1000	1:100	1:10	1:1[b]
Famotidine	0 × 0/0 × 0	0 × 0/0 × 0	6 × 8/27 × 29	8 × 9/33 × 39
Nizatidine	0 × 0/0 × 0	5 × 6/23 × 25	6 × 7/37 × 38	7 × 7/35 × 37
Ranitidine	0 × 0/0 × 0	7 × 7/35 × 37	8 × 8/38 × 39	9 × 10/41 × 46
Cimetidine	0 × 0/0 × 0	0 × 0/0 × 0	0 × 0/0 × 0	0 × 0/0 × 0
Histamine	–	–	–	7 × 8/33 × 34
Saline	–	–	–	0 × 0/0 × 0

[a]Data are expressed as wheal diameters (mm × mm)/flare diameters (mm × mm).
[b]The concentrations used were 20 mg/mL for famotidine, 150 mg/mL for nizatidine, 75 mg/mL for ranitidine, 150 mg/mL for cimetidine, and 0.1 mg/mL for histamine.

was determined using the mean + 2 SD of the absorbance values observed in the controls. The patient had no detectable specific IgE level to famotidine-HSA conjugate (0.00).

To find safe alternatives to the H_2-receptor antagonists tested, which showed clear positive skin reactions, oral challenge tests with pantoprazole, lansoprazole, and cimetidine were performed after written informed consent was obtained. Oral challenge tests with ampicillin trihydrate and cefixime were also carried out. The patient tolerated those drugs well. However, he refused to undergo additional oral challenge tests with famotidine, nizatidine, or ranitidine due to fear of another severe anaphylactic episode. We also recommended that the patient underwent an intravenous challenge test with cefazedone due to the unavailability of oral forms of cefazedone but he also refused to undergo this test.

On the basis of the skin test and oral challenge test results, we recommended that the patient took proton pump inhibitors and cimetidine, but not famotidine, nizatidine, or ranitidine due to the risk of anaphylaxis.

The baseline level of total tryptase in serum was determined using ImmunoCAP due to the severe anaphylactic reaction. The result, however, 2.2l µg/L, was in the normal range (<11.4 µg/L).

Discussion

In the present case, famotidine-induced anaphylaxis was diagnosed on the basis of a typical history of an anaphylactic episode following the injection of famotidine and a positive skin reaction to this drug. A challenge test was not performed with famotidine. Because the patient clearly showed immediate reactivity to famotidine during skin testing, we assume that this drug induced anaphylaxis via an IgE-mediated pathway. However, we were unable to detect famotidine-specific IgE. This may be because the level was too low to be detected, a hypothesis supported by the fact that the immediate skin reaction to famotidine was observed in the intradermal but not in the prick tests in our case. Other mechanisms, however, might also be considered. Famotidine might, for example, induce an anaphylactoid reaction via a nonallergic mechanism such as direct mediator release from mast cells or basophils. There has been a case report of food-induced anaphylactic shock via direct histamine-releasing mechanisms [9]. However, based on the fact that the healthy controls showed no skin reactivity to famotidine, it is less likely that this drug caused the direct activation of mast cells.

Although a challenge test was not performed, it is unlikely that cefazedone caused the IgE-mediated anaphylaxis because the intradermal skin test to cefazedone was clearly negative and because this drug has been reported to be cross-reactive with penicillin derivatives or other ß-lactam antibiotics [10]. Our patient had negative skin tests to penicillin G, ampicillin, and amoxicillin, negative serum specific IgE tests to penicilloyl G, penicilloyl V, ampicilloyl, amoxycilloyl, and cefaclor, and negative drug challenge tests to ampicillin and cefixime.

There have been isolated reports that famotidine may be associated with acquired long QT syndrome [11] and complete atrioventricular block and cardiac arrest [12]. However,
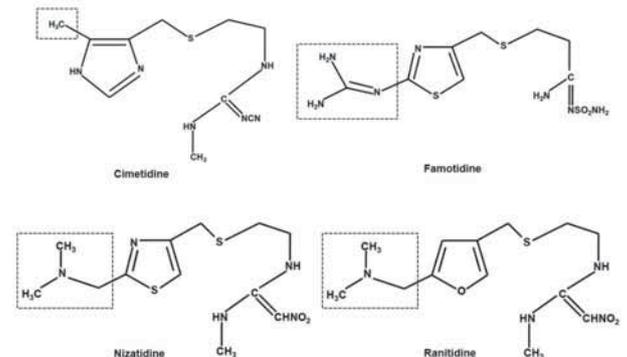

Figure 2. Structures of H_2-receptor antagonists. Famotidine, ranitidine, and nizatidine, but not cimetidine, have similar side chains to the ring structures (boxed area).

electrocardiography, 2D-echocardiography, and 24-hour Holter monitoring revealed no evidence of a prolonged QT interval or complete atrioventricular block in our patient.

Interestingly, our patient had positive skin reactions to ranitidine and nizatidine, but not to cimetidine, indicating possible cross-reactivity between famotidine, ranitidine, and nizatidine. There have been some reports of cross-reactivity between H_2-receptor antagonists [4,5,13]. Bossi et al [13] reported similar findings to ours in that they described maculopapular skin eruptions and positive skin prick tests with famotidine, ranitidine, and nizatidine but not cimetidine. Famotidine, ranitidine, and nizatidine, but not cimetidine, have similar side chains to the ring structures, possibly explaining the anaphylactic reaction experienced by our patient (Figure 2). Nevertheless, it has been reported that neither ranitidine nor nizatidine appear to cross-react with famotidine based on skin tests and oral challenge tests [2,5]. Further studies are needed to explore cross-reactivity between H_2-receptor antagonists.

In conclusion, we have reported a rare case of famotidine-induced anaphylaxis documented by drug skin tests, the results of which suggest that famotidine may induce IgE-mediated anaphylaxis with possible cross-reactivity with nizatidine and ranitidine.

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