

Anaphylactic Reaction to Drugs Commonly Used for Gastrointestinal System Diseases: 3 Case Reports and Review of the Literature

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Abstract. Proton pump inhibitors and H₂ receptor antagonists, which are commonly used to treat peptic ulcer and gastroesophageal reflux diseases, are associated with a low incidence of adverse reactions. We report 3 cases of anaphylactic reactions induced by lansoprazole or ranitidine diagnosed in a population of 8304 first-referral patients over a 13-year period. Cutaneous sensitivity to famotidine, ranitidine, omeprazole, pantoprazole, and lansoprazole was evaluated by skin prick tests with a concentration of 10 mg/mL (at 1:1000, 1:100, 1:10 and 1:1 dilutions), and if they were negative, intradermal skin tests were performed with the same dilutions of the extracts. Single-blind, placebo-controlled oral provocation tests were performed with lansoprazole, omeprazole, famotidine, and ranitidine in 2 cases. One case involved anaphylaxis during an oral provocation test with lansoprazole, and 2 cases were anaphylactic reactions to ranitidine. In both cases the skin test was positive for ranitidine and in 1 case an oral provocation test was also positive. The second patient refused that test. Cross reactivity to other H₂ receptor antagonists was not demonstrated and a safe alternative drug was found for all 3 patients. Although incidences of anaphylactic reactions induced by proton pump inhibitors or H₂ reactions are rare, they can be life threatening.

Key words: Anaphylactic reaction. Proton pump inhibitors. Histamine H₂ antagonists.

Resumen. Los inhibidores de la bomba de protones y los antagonistas de los receptores H₂, utilizados habitualmente en el tratamiento de la úlcera péptica y enfermedades por reflujo gastroesofágico, están asociados con una baja incidencia de reacciones adversas. Se describen 3 casos de reacciones anafiláticas, inducidas por fármacos (lansoprazol y ranitidina), que se produjeron en la Unidad de Alergia de adultos de nuestro hospital universitario de entre 8.304 pacientes de primera visita durante un período de 13 años. La sensibilidad cutánea a famotidina, ranitidina, omeprazol, pantoprazol y lansoprazol se evaluó mediante pruebas cutáneas (prick) con una concentración de 10 mg/ml (a diluciones 1:1000, 1:100, 1:10 y 1:1). En los casos en que las pruebas cutáneas (prick) fueron negativas, se realizaron pruebas cutáneas intradérmicas con las mismas diluciones de extractos utilizadas en el prick. En dos casos, se llevaron a cabo pruebas de provocación oral controladas con placebo y ciego simple con lansoprazol, omeprazol, famotidina y ranitidina. En un caso se desencadenó anafilaxia al realizar la prueba de provocación oral con lansoprazol. También hubo dos pacientes que experimentaron reacciones anafiláticas debido a la ranitidina. En uno de ellos, la prueba cutánea para la ranitidina fue positiva, pero puesto que el paciente rechazó la prueba de provocación oral, ésta no se realizó. No se ha demostrado reactividad cruzada con otros antagonistas de receptores H₂ en estos casos. Se recomendó al menos un fármaco alternativo seguro en los tres pacientes. Aunque las incidencias de reacciones anafiláticas inducidas por IBP y antagonistas de los receptores H₂ son raras, pueden ser responsables de riesgo vital.

Palabras clave: Reacción anafilática. Inhibidores de la bomba de protones. Antagonistas de los receptores H₂.

Introduction

Proton pump inhibitors and H₂ receptor antagonists, which are commonly used for the treatment of peptic ulcer and gastroesophageal reflux disease, are associated with a low incidence of adverse reactions [1, 2]. We report 3 cases in which 3 such drugs (lansoprazole, famotidine and ranitidine) induced anaphylactic reactions diagnosed in our university hospital adult allergy clinic. The diagnoses were made out of a case load of 8304 first-referral patients over a 13-year period (January 1991-December 2003). We also review other reported anaphylactic reactions induced by proton pump inhibitors and H₂ receptor antagonists in the literature.

Case Descriptions

Case 1

A 54-year-old woman with a 2-year history of multiple drug allergies, especially to antibiotics and drugs for treating gastrointestinal system disease, was admitted to our clinic to determine safe alternatives. The patient had a history of 3 anaphylactic reactions, 2 of which were most likely to lansoprazole or to another drug prescribed for gastrointestinal disease. It was not clear from the patient's medication records, however, which drugs had triggered the reactions: 5 months earlier, she was admitted to a city hospital with an anaphylactic reaction, but as she was taking several medications concurrently, the inducer drug could not be determined. The results of complete blood counts and blood biochemistry tests were within normal ranges during hospitalization. The patient reported various reactions due to different drugs. She had experienced faintness and unconsciousness with the use of opipramol, ramipril, amitriptyline, diltiazem, and estrogens; local allergy with etofenamate gel; and acute urticaria with ampicillin. She had a history of a partial gastrectomy (at age 34), cholecystectomy (at age 41), goiter (since age 39), and total abdominal hysterectomy and bilateral salpingo-oophorectomy (at age 51). Her family history was not remarkable.

Oral provocation tests were planned at our clinic for the medications (lansoprazole and famotidine) she had been taking before the anaphylactic reaction. Twenty minutes after taking 7.5 mg of lansoprazole, generalized flushing was observed over nearly the patient's entire body, and fatigue and nausea developed. Her blood pressure was 80/50 mmHg and pulse was 55 beats/min. Following intravenous (IV) infusion of 500 mL of normal saline, an IV push of 100 mg of prednisolone, and an IV push of 91 mg (2 ampoules) of pheniramine, her pulse and BP recovered to 100 beats/min and 90/60 mm Hg, 140/80 mm Hg, and 150/90 mm Hg after 30, 60, 90 minutes. She also received nasal oxygen therapy at a rate of 5 to 10 L/min. After 45 minutes, another IV push of 45.5 mg of pheniramine was administered because of tremors. Neurology consultation revealed no significant

findings. The patient was admitted to the intensive care unit (ICU) for monitoring and nasal oxygen therapy (4 L/min) was provided. An electrocardiogram was normal. After 24 hour in the ICU, she was discharged from the hospital with no further complications.

When the patient revisited our clinic to assess skin tests for allergy to omeprazole, pantoprazole, and lansoprazole, no reaction was seen with omeprazole or pantoprazole in skin tests. The epidermal tests with lansoprazole were positive with dilutions 1:10 and 1:1. Her total IgE level was 18 kU/L. No reaction developed after oral provocation tests with famotidine or omeprazole.

Case 2

A 49-year-old man with a history of allergic reactions to ranitidine and famotidine was referred to our clinic for further evaluation. He had experienced localized angioedema on his hands 15 to 20 minutes after taking a 150 mg tablet of ranitidine (Ulcuran[®]) when he was 42 years old. Approximately 6 to 7 months later, severe pruritus appeared 30 to 40 minutes after he took 150 mg of another brand of ranitidine (Ranitab[®]). The episode resolved within 2 to 3 hours without any intervention. Anaphylactic reaction (hypotension, shortness of breath, difficulty in swallowing, edema on hands, and generalized severe pruritus) developed within 5 minutes of taking a 20 mg famotidine tablet when he was 46 years old. As a result, he came to the emergency room.

He has had persistent rhinitis since he was 42 years old. He did not have familial history of atopy.

Intravenous ranitidine (Ulcuran[®]) had been administered (50 mg/8 h) for 3 days with no complications in a general surgery ICU during hospitalization after a motor vehicle accident when he was 41 years old. Thereafter he had received 150 mg/12 h oral ranitidine (Ranitab[®]) with no adverse reaction.

Skin tests with famotidine (Nevofam[®]), ranitidine (Ranitab[®]), omeprazole (Losec[®]), pantoprazole (Pantpas[®]), and lansoprazole were performed intradermally and epidermally. The patient had only reacted when 0.1 mL of intradermal ranitidine was administered at a dose of 0.01 mg/mL. All other skin test results were negative. His total IgE level was 620 kU/L. He refused an oral provocation test intended to find a safe alternative (eg pantoprazole).

Case 3

A 49-year-old woman was admitted to the hospital to receive thirteen intravenous immunoglobulin treatments for isolated eye vasculitis with uveitis. Prednisolone (25 mg), ranitidine (50 mg), and pheniramine (45.5 mg) were administered intravenously and a paracetamol tablet (500 mg) was administered orally as premedication 30 minutes before intravenous immunoglobulin treatment. She had symptoms of numbness all over the body, dyspnea,

dysphonia, and edema of the face, lips, throat and tongue right after the ranitidine injection, which had followed the pheniramine injection. There was no change in blood pressure. A 45.5-mg IV push of pheniramine and a 50 mg IV push of prednisolone were injected, in addition to 5 to 6 L/min nasal oxygen therapy. All of the symptoms resolved within 1 to 2 hours.

During the oral provocation test with 75 mg of ranitidine, the patient experienced difficulty in swallowing and breathing and throat edema. Physical examination revealed bilateral rhonchi. Also administered were 100 mg IV of prednisolone, 91 mg IV of pheniramine and nebulized salbutamol at a concentration of 2.5 mg/2.5 mL. Blood pressure was sustained within normal range.

Her past medical and surgical history included an appendectomy (at age 18 years), tonsillectomy (at age 21), coronary angiography (at age 43), lumbar disc hernia operation (at age 45), and isolated episodes of ocular vasculitis with uveitis. Skin prick tests were not performed, because the patient had been receiving oral corticosteroids and intravenous immunoglobulin therapy. Her family history was not remarkable.

The patient had received omeprazole during recent and earlier hospital admissions without adverse reactions. Furthermore oral famotidine was well-tolerated when she was readmitted to the hospital.

Discussion

For in vitro and in vivo tests, famotidine, ranitidine, omeprazole, pantoprazole, and lansoprazole were used at a concentration of 10 mg/mL. Drugs used in test preparations were obtained as pure products from dealers for the manufacturers. For this purpose, we used injectable famotidine (Nevofam[®]) 20 mg/mL, ranitidine (Ranitab[®]) 50 mg/mL, omeprazole (Losec[®]) 40 mg/mL, pantoprazole (Pantpas[®]) 40 mg/mL, and lansoprazole (Lansor) 30 mg/mL diluted in phosphate-buffered saline (PBS), pH 7.3.

For verifying cutaneous sensitivity to famotidine, ranitidine, omeprazole, pantoprazole, and lansoprazole was used in skin prick tests at a concentration of 10 mg/mL (at 1:1000, 1:100, 1:10 and 1:1 dilutions). Prick and intradermal tests were carried out as described by Österballe et al [3] by pricking the skin on the volar surface of the forearm with a special lancet. Histamine and saline were used as positive and negative controls, respectively. Resulting wheals were measured after 15 minutes. A positive reaction was defined as a wheal with a geometric mean diameter of at least 3 mm. If the skin prick tests were negative, intradermal skin tests were performed with the same dilutions of extracts used in the skin prick tests. Five normal subjects served as controls and all the skin tests performed in these controls were negative.

Total serum IgE was measured with an enzyme immune assay kit (Immulite 2000-TIE, Diagnostic Products Corporation, Los Angeles, California, USA) according to manufacturer's instructions.

Single-blind, placebo-controlled oral provocation tests were performed with lansoprazole, omeprazole, famotidine, and ranitidine at 30-minute intervals in fractionated dosages until the full therapeutic dose was reached or there was an adverse reaction (hypotension, shortness of breath, difficulty in swallowing, swollen hands, and generalized severe pruritus). The interval between the oral provocation test with each drug was at least 48 hours. Written informed consent was obtained from each patient before challenges. Tests were performed by an allergist in the outpatient clinic where the means to deal with an emergency were available. During the procedure blood pressures, peak expiratory flow values and possible allergic reactions were monitored every 15 minutes up to 3 hours and every hour thereafter for 4 hours [4].

Although H₂ receptor antagonists and proton pump inhibitors are widely used for gastrointestinal problems, anaphylactic reactions have rarely been described. According to the reports in the Uppsala Monitoring Center database [5] for May 1999, the frequency of anaphylactic reactions out of all reported adverse reactions for H₂ receptor antagonists (cimetidine and ranitidine) and proton pump inhibitors (lansoprazole, omeprazole and pantoprazole) were between 0.2% and 0.7%. However, these percentages are from a database of reports from all types of physicians, not only from allergy clinic physicians. The previously published cases summarized in Tables 1 and 2 and the 3 cases we have reported in this article (Table 3) were all well-documented life-threatening anaphylactic reactions.

Natsch et al [5] also reported a case of lansoprazole induced anaphylactic reaction during an oral provocation test that was similar to our Case 1. We also performed skin tests with lansoprazole, omeprazole, and pantoprazole, observing positive results only for lansoprazole. We have not demonstrated cross reactivity to other proton pump inhibitors.

We also report two patients who experienced anaphylactic reactions due to ranitidine and famotidine. In our Case 2, the skin test for ranitidine was positive, but since the patient refused the oral provocation test it was not performed. In our Case 3, the oral provocation test result was positive with ranitidine. We have not demonstrated cross reactivity to other H₂ antagonists in these cases, and we were able to provide at least one safe alternative drug for all three patients.

We searched the English language literature in relation to these 3 cases and summarized all reported anaphylactic reactions with proton pump inhibitors (10 patients) [5-13] and H₂ receptor antagonists (6 patients) [4, 14-18] in 2 tables (Tables 1 and 2). Ranitidine was the only H₂ receptor antagonist for which reactions were reported. According to the majority of cases given in Tables 1 and 2, skin prick tests and oral challenge tests were negative to other proton pump inhibitors and H₂ antagonists, suggesting a pharmacological mechanism was not implicated. A cross reaction was not present in the majority of those cases.

According to our literature review, rabeprazole and

Table 1. Reported Anaphylactic Reactions Induced by Proton Pump Inhibitors*

Reference	Anaphylactic Trigger	Reaction	Onset of Reaction	Previous Exposure	Reaction With Previous Exposure	Skin Test	Tolerance of H ₂ Receptor Antagonists	Cross Reaction	Other
5	LPZ, 30 mg PO	Pruritus, urticaria sweating, facial edema, loss of consciousness	Within 45 min	OPZ 40 mg PO	Periorbital edema, edema of the skin, pruritus, nausea, vomiting	NA	NA	OPZ	-
5	PPZ, 40 mg PO	Malaise, pruritus, urticaria, swollen tongue/eyes, sweating, hypotension	Within hours	PPZ 40 mg PO	No reaction	NA	NA	NA	-
6	OPZ, 40 mg IV	Angioedema, urticaria hypotension, unconsciousness	A few min	OPZ 20 mg, PO	Urticaria	Positive for OPZ	NA	NA	-
7	OPZ, 20 mg PO	Angioedema, urticaria, bronchospasm	2h	NA	NA	NA	Yes	NA	Capsule shell probably induced reaction
8	OPZ, 20 mg PO	Shortness of breath, mild angioedema, urticaria, pruritus, wheezing, cough	Within 2-3 h	NA	NA	NA	Yes	NA	Anaphylactic reaction with uncapsulated OPZ as well
9	OPZ, 40 mg IV	Sweating, paleness, abdominal pain, itching on legs, dyspnea, hypotension	Within a few min	OPZ	No reaction	Positive for LPZ	Yes	LPZ	-
10	OPZ, 40 mg PO	Urticaria, facial edema	30 min	LPZ	No reaction	Positive for OPZ, LPZ and PPZ	NA	LPZ	Urticaria, facial edema, vomiting and hypotension with LPZ intake
11	PPZ, 20 mg PO	Flushing, dyspnea conjunctivitis, hypertensive reaction	Whithin 2 h	NA	NA	Negative for PPZ	NA	NA	Non-allergic anaphylactoid reaction to PPZ
12	PPZ	Malaise, generalized pruritus, urticaria, diffuse sweating, hypotension	Within a few min	PPZ	Low SBP; tachycardia with syncope, mucosal hypersecretion conjunctival hyperemia, cutaneous erythema	NA	NA	NA	No reaction with LPZ intake
13	PPZ	Urticaria, angioedema, substernal chest discomfort, orthostasis, impaired consciousness	3 h	PPZ	Urticaria, angioedema, substernal chest discomfort, orthostasis, impaired consciousness	Positive	NA	NA	Positive intradermal test for PPZ

* OPZ indicates omeprazole; PPZ, pantoprazole, LPZ, lansoprazole, SBP, systolic blood pressure; IV, intravenous; PO, by mouth; NA, not available.

Table 2. Reported Anaphylactic Reactions Induced by H₂ Receptor Antagonists*

Reference	Anaphylactic Trigger	Reaction	Onset of Reaction	Previous Exposure	Reaction With Previous Exposure	Skin Prick Test	Intradermal Skin Test	Oral Provocation Test	Other
4	RTN, 150 mg PO	Itching, generalized urticaria, laryngeal edema	20 min	RTN 150 mg po	None	(+) for RTN, (-) for CTN, FTN, and NTN	(-) for CTN, FTN, and NTN	RTN 40 mg (10 min after; itching, generalized urticaria and dysphonia)	Oral provocation tests with CTN, FTN and were well tolerated
14	RTN, dosage NA	Erythematous rash with edema over the face, neck and hands with itching	2 d	NA	NA	Patch test (+) for RTN, (-) for CTN	NA	Not provided for RTN	Oral challenges with CTN gave no response
15	RTN, 150 mg PO	Edema of the face and lips, diffuse itching and laryngeal spasm	NA	NA	NA for RTN	Slightly (+) (-) for CTN	(+) for RTN, (lip edema,	RTN 40 mg response. No itching, urticaria of the face and dyspnoea in 2 hrs)	Oral CTN gave no response to additives. Patch test was (-) for RTN
16	RTN, 50 mg slow IV push	Difficulty breathing and speaking, facial and periorbital edema	Immediately	NA	NA	(+) for RTN only	NA	NA	No response to additives
17	RTN, 150 mg PO	Dyspnea, chest and loin pain, pruritus, facial and lingual edema	30 min	RTN 150 mg po and 50 mg iv	None	NA	NA	NA	-
18	RTN, 150 mg PO	Dyspnea, tachypnea, edema of the face, tongue and hands	20 min	No	NA	NA	NA	NA	-

* RTN, indicates ranitidine; CTN, cimetidine; NTN, nizatidine; FTN, famotidine; PO, by mouth; IV, intravenous; NA, not available.

Table 3. Summary of Our Cases of Anaphylactic Reaction Induced by Drugs Prescribed for Gastrointestinal Disease*.

Case	Anaphylactic Trigger	Reaction	Onset of Reaction	Previous Exposure	Reaction With Previous Exposure	Skin Prick Test	Oral Provocation Test	Other
1	LPZ, 7.5 mg PO	Generalized flushing, fatigue, nausea, hypotension	20 min	LPZ	Anaphylactic reaction most likely with LPZ but unclear	(+) for LPZ, (-) for OPZ and PTZ	Reaction during oral provocation test with LPZ	No reaction with oral OPZ and FTN
2	FTN, 20 mg PO	Hypotension, shortness of breath, difficulty in swallowing, swollen hands, severe pruritus	5 min	RTN, 150 mg PO	Angioedema, [†] severe pruritus [‡]	(+) for RTN, (-) for FTN, OPZ and PTZ	Patient refused oral provocation test	IV RTN ¹ and PO RTN ² well tolerated previously as well
3	RTN, 50 mg IV	Numbness all over the body, shortness of breath and edema of the face, lips, throat and tongue	Within a min	FTN	Well tolerated	No	RTN 75 mg: within 1 min, difficulty swallowing, throat edema, rhonchi	Skin test not performed because of routine use of immunoglobulin therapy and systemic corticosteroids

* LPZ indicates lansoprazole; OPZ, omeprazole; PTZ, pantoprazole; FTN, famotidine; RTN, ranitidine; IV, intravenous; PO, by mouth.

[†] Ulcuran, a brand name of ranitidine. [‡] Ramitab, a brand name of ranitidine.

esomeprazole are the only proton pump inhibitors without any anaphylactic reactions reported in the literature. However, rabeprazole and esomeprazole have only been recently marketed. No anaphylactic reaction has been reported with any H₂ receptor antagonist but ranitidine.

Proton pump inhibitors and H₂ receptor antagonists are extensively used in clinical practice and they are well tolerated by patients. However, these findings suggest that, although the incidences of anaphylactic reactions induced by these drugs are low, clinicians should be aware of this possibility of life threatening risk. Furthermore, the possibility of cross reactivity between drugs in the same group should be considered.

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