

Anaphylaxis to omeprazole

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Background: Omeprazole is a non-competitive inhibitor of the parietal cell enzyme H^+-K^+ -adenosine triphosphatase. To date, two cases of angioedema and urticaria and two cases of anaphylaxis from omeprazole have been published.

Objective: To report a new patient with omeprazole-induced anaphylaxis demonstrated by skin tests and increased serum tryptase levels.

Methods and results: Elevated serum tryptase levels (5.1 U/L) were detected 6 hours after the onset of the anaphylaxis. Skin intradermal tests were positive with omeprazole IV (4 mg/mL), omeprazole capsules diluted in saline serum (20 mg/mL), and lansoprazole (30 mg/mL). Serum specific IgE anti-omeprazole was negative.

Conclusions: According to the elevated serum tryptase levels and the positive skin test results, anaphylaxis was due to use of omeprazole. We think the adverse reaction to omeprazole was induced by an IgE-mediated hypersensitivity mechanism to omeprazole itself and not to a metabolite. We have also demonstrated crossreactivity, at least by skin tests, between omeprazole and lansoprazole.

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INTRODUCTION

Omeprazole is a substituted benzimidazole (Fig 1) and a non-competitive inhibitor of the parietal cell enzyme H^+-K^+ -adenosine triphosphatase. It is the first *proton pump inhibitor* commercially available. It reduces both basal and stimulated gastric acid secretion. It seems to be effective in the treatment of peptic ulcer disease, reflux esophagitis, and the Zollinger-Ellison syndrome.^{1,2} The incidence of adverse events is low and these are similar to those found with H_2 -receptor antagonists.³ A few cases of skin *rash* have been described, but the incidence is less than 0.5%.⁴ A case of *urticaria and angioedema* was triggered by constituents of omeprazole capsules, but he tolerated enteric coated omeprazole granules without the capsule shell.⁵ Bowlby et al⁶ reported a case of an-

gioedema and urticaria with bronchospasm associated with omeprazole confirmed by rechallenge. Ottervanger et al² reported a case of anaphylaxis after administering omeprazole intravenously.² Serrano et al⁷ described anaphylaxis occurring after taking a capsule of omeprazole. Here we report a new patient with omeprazole-induced anaphylaxis demonstrated by skin tests and increased serum tryptase levels.

CASE REPORT

The patient was a 35-year-old man with history of hepatitis and pancreatitis from ethanol abuse. He smoked 40 cigarettes per day. He had been hospitalized on several occasions for abdominal pain. At home he was taking ranitidine, vitamin K, and metamizole. He had taken omeprazole in other occasions. The patient was admitted to hospital because his pancreatitis was getting worse. Physical examination revealed normal hemodynamics and an abdominal pain without signs of peritonitis. The white cell count was $14.7 \times 10^9/L$ with normal differential. The erythrocyte sedimentation rate was 54 mm/h (elevated). Routine bio-

chemical data showed increased levels of GGT (143 IU/L, normal 10 to 50) and amylase (1,033 IU/L, normal 230 to 460). Urinalysis and coagulation tests were normal. Chest and abdominal x-ray and abdominal echography were normal. Therapy was started with 40 mg of omeprazole diluted in 100 mL of saline solution intravenously, twice per day (Losec, Schering-Plough), metamizole IV (*a pyrazole derivative analgesic not belonging to imidazoles derivatives compound*) and sucralfate by mouth. After two days of treatment and a few minutes after infusion of Losec was started, *the patient developed sweating, paleness, abdominal pain, itching on his legs, dyspnea, and hypotension (70/40 mm of Hg).* No skin abnormalities or wheezing were present. Treatment with methylprednisolone and chlorpheniramine IV and infusion of oxypolygelatin (Hemocce), *a fluid gelatin used as vascular filler in hypotension,* was started and the clinical picture resolved after 1 hour. Blood pressure returned to 120/70. *No other drugs had been administered during the previous 12 hours.*

Levels of tryptase in serum was determined by an radioimmunoassay (RIA), performed according to the manufacturer's instructions (Pharmacia Diagnostics, *Uppsala, Sweden*). Elevated levels (5.1 U/L, normal <2 U/L) were detected 6 hours after the onset of *anaphylaxis*, but they came below 2 U/L at 24 and 48 hours. Total serum IgE was 546 U/mL (normal <100). Specific IgE to echinococcus was negative by CAP-System (Pharmacia Diagnostics, *Uppsala, Sweden*).

Specific allergologic tests were performed 2 months later. Skin prick tests with common inhalant allergens, food, latex, and *anisakis simplex* (*a fish parasite that can produce anaphylaxis by ingestion of parasitized fish*),⁸ were negative.

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Prick and intradermal tests were performed with omeprazole and intradermal test was performed with lansoprazole. Losec IV was diluted in saline solution to 40 mg/mL and 4 mg/mL. The granules of a capsule of Losec (omeprazole with different excipients of Losec IV) and granules of a capsule of Opiren, Almirall laboratorios S.L. (lansoprazole), were mixed with 1 mL of saline solution (20 mg/mL and 30 mg/mL, respectively). Saline solution and histamine (0.1 mg/mL) were used, by intradermal test, as negative and positive controls. Skin tests were read after 15 minutes. The results of wheal in mm are shown in Table 1. Intradermal tests with all drugs mentioned previously were negative in six control subjects.

Serum specific IgE anti-omeprazole was measured by a RIA according to the method of Wide et al⁹ and modified by De Filippi et al.¹⁰ Solid-phase antigen was obtained by coupling the extract solution (Losec IV at 1 mg/mL of concentration of omeprazole) to cyanogen bromide-activated paper disks as described by Ceska and Lundqvist.¹¹ It was not detected.

The challenge test with omeprazole was not carried out for ethical reasons. The challenge tests with other imidazole derivatives were declined by the patient.

DISCUSSION

Anaphylaxis is an acute reaction that can involve the cardiovascular system (eg, hypotension), the respiratory system (eg, bronchospasm, laryngeal edema), the skin (eg, itch, urticaria), and the gastrointestinal system (eg, diarrhea, abdominal pain). The most fre-

quent causes of anaphylaxis are drugs, and especially penicillins and analgesics.¹² Omeprazole reduces acid gastric secretion and rarely induces urticaria, angioedema, or anaphylaxis.^{2,5-7} Here we present a patient suffering anaphylaxis (sweating, paleness, abdominal pain, itching on his legs, dyspnea, and hypotension) after intravenous administration of omeprazole.

According to the temporal relationship, the elevated serum tryptase levels and the positive skin test results, anaphylaxis was due to use of omeprazole. Although specific IgE to omeprazole was not detected, we think the adverse reaction was due to IgE-mediated hy-

persensitivity to omeprazole demonstrated by skin tests results. We used the same drug solutions in six control subjects without eliciting an irritative response. Additives present in omeprazole preparations are excluded as etiologic agents because commercial solutions we have tested (Losec capsules and Losec IV), have no excipients in common. Haeney MR et al⁵ described a 44-year-old man who developed angioedema and urticaria by omeprazole capsules but, tolerated the drug itself devoid of the capsule shell. This suggests that the patient was not truly reacting to omeprazole but rather to the capsule shell.

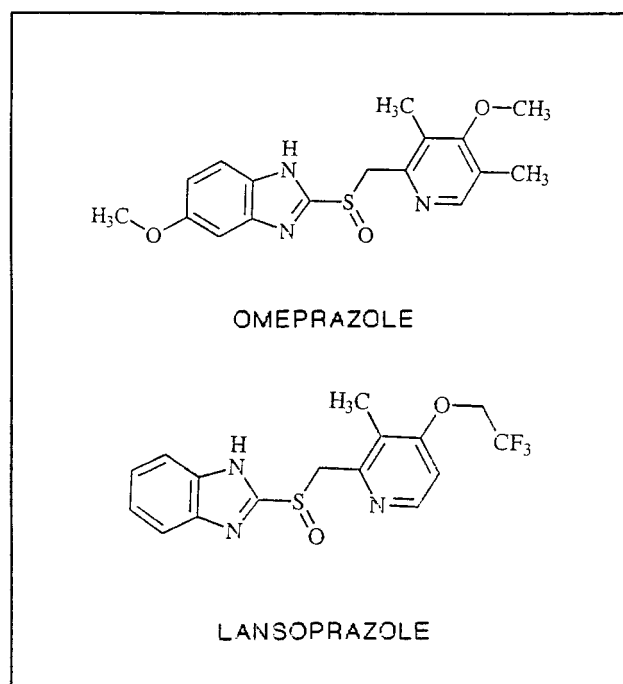


Figure 1. Chemical structure of omeprazole and lansoprazole.

Table 1. Results of Skin Tests*

Skin Tests	Omeprazole IV		Omeprazole Caps.	Lansoprazole Caps.	Histamine 0.1 mg/mL	Saline Solution
	4 mg/mL	40 mg/mL	20 mg/mL	30 mg/mL		
Prick†	—	—	NP	NP	NP	NP
Intradermal (0.02 mL)	9 × 5	NP	11 × 9	8 × 9	7 × 7	—

* Skin test results expressed in mm.

† — = Negative and NP = not performed.

Allergic reaction was probably due to sensitization to omeprazole itself, and not to a metabolite; this was supported by immediate onset of symptoms after intravenous administration and skin tests results.

To our knowledge, anaphylaxis to omeprazole has been described only in two cases. Ottervanger et al² reported a case of anaphylaxis after administering omeprazole intravenously. Skin prick test performed with omeprazole at 4 mg/mL was positive. Serum tryptase levels and specific IgE were not determined. Serrano et al⁷ described an anaphylaxis after taking a capsule of omeprazole. Skin prick tests were negative but intradermal tests with omeprazole IV and omeprazole capsules, both at 20 mg/mL were positive. Prick and intradermal tests with lansoprazole at 30 mg/mL were negative. Specific IgE anti-omeprazole was not detected. We have demonstrated cross reactivity, at least by skin tests, between omeprazole and lansoprazole, the second *proton pump inhibitor* commercially available. It is a benzimidazole derivative with chemical structure, activity, and clinical use very similar to omeprazole (Fig 1).

Elevation of serum tryptase levels has been described in anaphylaxis, presumably resulting from mast cell degranulation. Detection of serum tryptase levels may be critical for the differential diagnosis of anaphylaxis and other etiologies of shock. Tryptase levels increase 15 to 30 minutes after the onset of anaphylactic reactions and may remain elevated up to six hours. The most significant elevations occur 1 to 2 hours after anaphylaxis.¹³ In our case, we have detected high levels of serum tryptase 6 hours after the onset

of symptoms, which supported the diagnosis of anaphylaxis and excluded other causes of hypotension. We propose to perform *serial* determinations of serum tryptase levels if an anaphylactic reaction is suspected.

Cross-sensitization among imidazoles (metronidazole, tioconazole, bifonazole, econazole, miconazole, etc.) has been postulated, although it is neither constant nor complete between other imidazoles.^{14,15} We could not investigate cross-reactivity among imidazoles in our patients but this cross-reactivity is possible, and it must be determined, because cimetidine is an imidazole derivative with a clinical use similar to omeprazole. Imidazole derivatives should be avoided if cross-reactivity cannot be investigated.

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