
Anaphylaxis to omeprazole: diagnosis and desensitization protocol

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Background: Omeprazole is an inhibitor of the parietal cell enzyme H⁺/K⁺ adenosine triphosphatase. Immediate-type hypersensitivity reactions, such as urticaria, angioedema, and hypotension, induced by omeprazole and other proton pump inhibitors are rare.

Objectives: To confirm the immediate-type mechanism of recurrent anaphylactic reactions to the repeated administration of omeprazole using skin testing and to enable safe administration of the drug after successful oral desensitization.

Methods: Intradermal skin tests were performed with omeprazole (0.04 and 0.4 mg/mL) prepared from the oral and intravenous commercial preparations and with pantoprazole (0.02 and 0.2 mg/mL) prepared from the oral commercial preparation. Skin tests were repeated after completion of the desensitization. Oral desensitization was applied at a starting dose of 0.001 mg of omeprazole, and a full dose of 16 mg was achieved after 5.6 hours (cumulative dose of 32.6 mg).

Results: Intradermal skin test results were positive to omeprazole and pantoprazole at all tested concentrations. After successful desensitization, omeprazole was administered in the full dose uneventfully. The wheal size of the intradermal skin tests performed after completion of the desensitization was significantly reduced.

Conclusion: When indicated, this newly designed desensitization protocol may be used in patients with omeprazole-induced anaphylaxis.

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INTRODUCTION

Omeprazole is a noncompetitive inhibitor of the parietal cell enzyme H⁺/K⁺ adenosine triphosphatase. The major activities of proton pump inhibitors (PPIs) are related to increasing intragastric pH levels, which may enhance the effectiveness of the local immune response, reduce the washout of antibiotic agents from the mucosa, and lower the minimal inhibitory concentrations of pH-sensitive antibacterial agents. Since the introduction of omeprazole, the first PPI, this class of drugs has been widely used to treat dyspepsia. The PPIs have also been proved to be essential, along with antimicrobial agents, as part of the combination therapy for *Helicobacter pylori* infection.¹ Proton pump inhibitors have an excellent therapeutic index and a low incidence of adverse events. Anaphylactic reactions have rarely been described.^{2,3} We describe a patient who experienced recurrent anaphylaxis after the administration of omeprazole. Skin tests to different PPIs had positive results. Because PPIs were essential for the eradication of *H pylori* infection, desensitization to omeprazole was attempted and completed successfully.

MATERIALS AND METHODS

Patient

A 44-year-old man with a history of duodenal ulcer underwent gastroscopy as part of the workup for recurrent persistent heartburn classified as "ulcerlike." The procedure re-

vealed gastritis, with positive cultures for *H pylori*. During the next 3 years, he was treated twice with triple therapy that included clarithromycin (500 mg × 2), amoxicillin (1,000 mg × 2), and omeprazole (20 mg × 2) without success. Because the patient was still symptomatic and the breath test result was still positive, the same combination of drugs was administered for a third time. Forty minutes after taking the first 20-mg doses of omeprazole (Losec; AstraZeneca, Umea, Sweden), amoxicillin, and clarithromycin, the patient developed sweating, generalized itching, diffuse erythema, angioedema of the face and hands, and hypotension (blood pressure, 60/40 mm Hg). No wheezing or loss of consciousness was present. Treatment with subcutaneous epinephrine and intravenous promethazine hydrochloride and dexamethasone was started, as was rapid infusion of 0.9% sodium chloride. The clinical picture resolved after 40 minutes: blood pressure returned to normal (125/70 mm Hg), itching subsided, and angioedema and erythema disappeared.

Two weeks later, while at home, the patient, despite his physician's advice, took 1 capsule of omeprazole, 20 mg. Thirty minutes later he felt dizzy, and diffuse urticaria and itching appeared. He laid down and took loratadine, 10 mg. His symptoms resolved gradually within 1 hour. Because the patient was still symptomatic, gastroscopy and culture were performed. The culture was positive once again for *H pylori*, and the patient was offered a new treatment regimen consisting of levofloxacin, tetracycline (according to *H pylori* sensitivity), and omeprazole.

Skin Tests and Desensitization

Intradermal tests were performed using the commercial preparations of omeprazole (intravenous ampoules and capsules)

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Table 1. Skin Test Results Before and After Desensitization

	Skin test*	Concentration, mg/mL	Wheal/flare diameter, mm	Wheal ratio†
Ampoule omeprazole	Before	0.04	8 × 9/15 × 18	
		0.4	9 × 9/15 × 14	
Capsule omeprazole	Before	0.04	7 × 9/15 × 14	
		0.4	9 × 9/15 × 15	
	After	0.04	2 × 2/3 × 3	0.64
		0.4	5 × 5/6 × 5	
Tablet pantoprazole	Before	0.02	9 × 6/18 × 16	
		0.2	20 × 9/20 × 12	
	After	0.02	2 × 2/9 × 8	1.42
		0.2	4 × 2/5 × 7	
Histamine, 0.1 mg/mL	Before	0.1	18 × 10/25 × 32	0.22
	After	0.1	22 × 12/31 × 45	
Saline	Before	NA	4 × 2	
	After	NA	4 × 2	

Abbreviation: NA, not applicable.

* Before and after desensitization.

† Wheal produced by omeprazole or pantoprazole vs wheal produced by absolute histamine (histamine – saline).

and using pantoprazole (Contraloc tablet; Altana-Bayer, Konstanz, Germany). An ampoule of omeprazole was diluted in water for injection to 0.04 and 0.4 mg/mL. The granules of an omeprazole capsule and a finely crashed tablet of pantoprazole were dissolved in water for injection to concentrations of 0.04 and 0.4 mg/mL (omeprazole) and 0.02 and 0.2 mg/mL (pantoprazole). Saline solution and histamine (0.1 mg/mL) were used, intradermally, as negative and positive controls, respectively. Skin test reactions were positive to all PPIs tested (wheal produced by the drug – wheal produced by saline, ≥ 5 mm) (Table 1). Similar skin tests performed on 2 controls revealed negative results.

Because PPIs were essential for treatment, we offered the patient a desensitization procedure. The process was performed without premedication in an in-hospital allergy unit under the close supervision of nurses and physicians, with resuscitation equipment on standby.

The granules of omeprazole capsules were dissolved in bicarbonate to create serial 10-fold dilutions (the lowest was 0.002 mg/mL). Oral desensitization was administered in escalating doses, at 20-minute intervals, with a starting dose of 0.001 mg. A final dose of 16 mg was reached after 5.6 hours (Table 2). One hour later, the patient took 1 capsule of omeprazole, 20 mg. The patient tolerated the procedure uneventfully. Use of oral omeprazole, 20 mg twice daily, was reinstituted.

Skin tests to omeprazole and pantoprazole were repeated 24 hours after completion of the desensitization, and their reactions were significantly reduced (Table 1). One day later, levofloxacin and tetracycline were added to the patient's treatment and were well tolerated. The patient completed 14 days of treatment without any evidence of hypersensitivity.

DISCUSSION

Omeprazole is a PPI extensively used to treat peptic ulcer disease and reflux esophagitis, and it is part of the combina-

tion therapy used to eradicate *H pylori*. The therapeutic index of all PPIs is good, and the incidence of adverse events is low.¹ Although hypersensitivity reactions are rare, several anaphylactic reactions induced by these drugs have been reported.^{2–6} Haeney² described an anaphylactic reaction to the omeprazole capsule shell and not to the drug itself, as proved by readministration of the drug granules without the capsule. Bowlby and Dickens⁷ reported a case of urticaria and angioedema with bronchospasm associated with omeprazole and confirmed by rechallenge. We describe a patient with a clinical anaphylactic reaction induced, most likely, by omeprazole. Anaphylactic reactions are usually diagnosed on clinical grounds. In our patient, the clinical suspicion was confirmed by an unplanned challenge with the drug, which elicited similar immediate symptoms. Accurate identification of the agent that induced the anaphylactic reaction is important. Based on clinical observation, confirmation of the diagnosis using a challenge test is occasionally the only way to establish the diagnosis.⁸ However, the challenge should be performed only when other diagnostic alternatives have failed and establishing diagnosis is essential. In cases of suspected PPI hypersensitivity, challenge is not recommended because skin tests are available. Skin tests (prick and intradermal) were previously described^{4–6} and proved to be an effective diagnostic method for PPI hypersensitivity. In contrast, in vitro, specific serum IgE could not be measured by using radioimmunoassay⁶ or radioallergosorbent test.⁵ One case reported by Gamboa et al⁴ described the basophil activation test as a method for confirming the existence of specific IgE in a patient with a suggestive clinical history and a positive skin test result. In our patient, intradermal skin tests elicited positive reactions to omeprazole granules and to the intravenous preparation in a concentration 100-fold more diluted than previously reported.

Table 2. Desensitization Protocol*

Dose, mL	Dose, mg	Cumulative dose, mg
Omeprazole, 0.002 mg/mL		
0.5	0.001	0.001
1.0	0.002	0.003
2.0	0.004	0.007
4.0	0.008	0.015
Omeprazole, 0.02 mg/mL		
0.5	0.01	0.025
1.0	0.02	0.045
2.0	0.04	0.085
4.0	0.08	0.165
Omeprazole, 0.2 mg/mL		
0.5	0.1	0.265
1.0	0.2	0.465
2.0	0.4	0.865
4.0	0.8	1.665
Omeprazole, 2 mg/mL		
0.5	1	2.665
1.0	2	4.665
2.0	4	8.665
4.0	8	16.665
8.0	16	32.665

* Doses were increased at 20-minute intervals.

In looking for an alternate PPI, skin tests were also performed to pantoprazole, and the results were positive. Pantoprazole is a benzimidazole PPI widely used for the oral treatment of gastrointestinal diseases. There have been several case reports of anaphylactic reactions to pantoprazole,^{3,6,8–10} most of them suggesting cross-reactivity among the various PPIs. Natsch et al³ described a patient who experienced anaphylaxis 45 minutes after taking an omeprazole capsule and after oral lansoprazole. Galindo et al⁶ described a patient who experienced an anaphylactic reaction a couple of minutes after the intravenous infusion of omeprazole. Skin test reactions were positive to omeprazole and lansoprazole, suggesting cross-reactivity. Gonzalez et al⁵ reported a case of urticaria after oral omeprazole use and anaphylaxis after oral challenge with lansoprazole in the same patient. Skin test results were positive to omeprazole, lansoprazole, and pantoprazole. Only 1 study, by Fardet et al,⁹ described recurrent anaphylactic reactions specifically induced by pantoprazole but not by lansoprazole challenge. The patient we describe had positive skin test reactions to the offending PPI, omeprazole, and to the available alternative, pantoprazole. Based on previous reports of cross-reactivity, we decided not to challenge our patient with other PPIs but to offer him desensitization as part of triple eradication therapy for *H pylori*. Eradication of *H pylori* has a small but significant effect in *H pylori*-positive nonulcer dyspepsia.^{11,12} In patients, such as our patient, with a history of duodenal ulcer that is currently symptomatic, treatment is definitely recommended. The highest eradication rates are achieved with regimens that include PPIs. Furthermore, the H₂ receptor antagonists, such as ci-

metidine, that theoretically may replace PPIs are imidazole derivatives. Cross-sensitization among imidazoles has been suggested. Although it is not completely established, this suspected cross-reactivity with PPIs keep H₂ blockers from being an acceptable alternative in cases of PPIs hypersensitivity. Desensitization is limited to cases in which the offending drug is defined, no alternative medication is available, and the indication outweighs the risks of the procedure. It is typically applied to type I allergy in patients with a demonstrable IgE antibody response on skin tests or in vitro tests. Drug desensitization is usually accomplished within hours and is achieved by administering progressive doses of the drug every 20 to 30 minutes until a full therapeutic dose is clinically tolerated.¹³ The procedure may elicit acute allergic reactions, but under close supervision in hospitalized patients, the risk is acceptable.

In our patient, desensitization began, as recommended,¹⁴ with a dilution of 1:10,000 of the final required dose (starting dose of 0.001 mg), and the drug was administered in escalating doses at 20-minute intervals. A final dose of 16 mg was reached after 5.6 hours. Consequently, the patient tolerated 2 weeks of the full therapeutic dose uneventfully.

It has been demonstrated in penicillin allergy that successful clinical desensitization results in reduced wheal-and-flare skin test responses to the drug, whereas immediate skin responses to other allergens remains unchanged.¹⁵ In our case, in addition to the clinical tolerance induced by the desensitization, skin reactivity was also reduced. Table 1 demonstrates the differences in skin reactivity to omeprazole and pantoprazole before and after the desensitization. This observation further supports the assumption of an antigen specific IgE-mediated reaction.

In conclusion, to our knowledge, this is the first article describing a patient with an anaphylactic reaction to omeprazole who could tolerate the offending drug after desensitization. When indicated, this newly designed desensitization protocol may be used in patients with omeprazole-induced anaphylaxis. The desensitization protocol is brief and offers an effective method for inducing tolerance when no alternative treatment agent is available.

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