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Case Report

Unraveling a case of pantoprazole-induced-anaphylaxis requiring tracheostomy: a case report

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Abstract

***Background*:** Proton pump inhibitors (PPIs) are used by 50.85%, 42.16%, and 40.97% of doctors, nurses, and pharmacists, respectively. The reported incidence of anaphylaxis with PPIs is under 1%.

Case Presentation: We present the first-ever reported case of anaphylaxis to pantoprazole, which failed medical management with multiple attempts for endotracheal and nasotracheal intubation failed due to diffuse edema, necessitating the need for an urgent tracheostomy and mechanical ventilation. Famotidine replaced pantoprazole throughout the hospital course, and he had no further hypersensitivity reactions.

***Conclusion*:** PPIs are effective but not without severe complications. Unfortunately, anaphylaxis is often misdiagnosed, increasing the risk of mortality and morbidity. Although anaphylaxis is rare, these reactions can be life-threatening. Emergency medicine and primary care physicians must be aware of the potential side effects of PPIs and should carefully monitor patients in inpatient and outpatient clinical settings.

***Keywords*:** Anaphylaxis, Pantoprazole, Proton pump inhibitor, Tracheostomy

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Introduction

Proton pump inhibitors (PPIs) are among the most widely used medications, both in inpatient settings and over-the-counter use (1). According to Lou et al., usage rates of PPIs were 50.85%, 42.16%, and 40.97%, among doctors, nurses, and pharmacists, respectively (1). Despite their extensive use and good safety profile, there have been cases of anaphylactic reactions to this class of drugs, as reported in our case study and various other cases mentioned in the literature (2, 3).

PPIs are indicated for numerous conditions, including: gastroesophageal reflux disease (GERD) and

its complications, Helicobacter pylori infection, nonsteroidal anti-inflammatory drug (NSAID)-associated gastric ulcers, upper gastrointestinal bleeding, Zollinger-Ellison syndrome, and the prevention of stress ulcers. The widespread availability and use of PPIs present significant challenges for regulatory authorities. Two critical issues are the progressive and irreversible increase in therapy costs and the potential for patient harm (4). A study in China reported expenditures of ¥1.23 million on oral and ¥0.94 million on intravenous (IV) PPIs in December 2021 (5). In the United States, the combined cost of prescription and over-the-counter PPIs is approximately $10 billion per year (6).

Initially believed to be highly effective and well-tolerated, PPIs are now causing concerns due to various side effects. These include overuse, misuse, easy accessibility, long-term use, over-prescription, and anaphylaxis (4-6).

Our understanding and extensive literature review indicate this is the first reported case of severe anaphylaxis to pantoprazole. This case required urgent tracheostomy and hospitalization, complicated by bilateral cardiovascular accidents (CVAs), bilateral pulmonary emboli, and bilateral cavitary Pseudomonas aeruginosa pneumonia. We report this case to raise awareness about the need to educate patients on the safety and potential side effects of PPIs.

Case Presentation

A 63-year-old male with a past medical history of cerebrovascular accident presented with shortness of breath and edematous eyelids. The patient had recently been discharged from the hospital for melena, prompting an endoscopic evaluation, which revealed an erythematous duodenal bulb. He tested negative for Helicobacter pylori. A subsequent colonoscopy uncovered moderate diverticulosis. The gastroenterologist recommended an outpatient small bowel capsule study for further evaluation and discharged the patient on oral pantoprazole 40 mg once daily.

After taking the PPI for two days, the patient experienced worsening periorbital swelling in the last 24 hours, accompanied by breathing difficulty. There was no other change in medication. The patient had no known allergies to medications, the environment, or food besides a shellfish allergy. His vitals were notable for being afebrile, tachycardic (120 beats per minute), normotensive, and saturating at 95% on room air. His physical examination revealed periorbital and oral swelling, and a muffled voice with no skin rash observed.

The patient was immediately administered intramuscular epinephrine 1 mg thrice, dexamethasone 10 mg twice, and diphenhydramine with minimal effect. Multiple attempts for endotracheal and nasotracheal intubation failed due to diffuse laryngeal edema. The surgery team performed an urgent bedside tracheostomy, and the patient was placed on mechanical ventilation. Pertinent lab results included a tryptase level of 8.5 mcg/L and a C1 inhibitor level of 48 mg/dL with normal C3 and C4 levels. Other laboratory findings were unremarkable, including a complete blood count and comprehensive metabolic panel.

The hospitalization was complicated with cavitary Pseudomonas pneumonia and bacteremia, a new ischemic bilateral cerebrovascular accident, and bilateral pulmonary emboli. The patient was closely monitored in the intensive care unit. Famotidine 20 mg twice daily replaced pantoprazole during the hospital stay. The patient did not have any further hypersensitivity reactions. Following these interventions, the patient was discharged to a rehabilitation facility on famotidine, an oral antibiotic and anticoagulant, and a prescription for an outpatient capsule endoscopy.

Discussion

Pantoprazole is a membrane - permeable benzimidazole derivative that decreases gastric acid secretion by irreversibly inhibiting the H+/K+-ATPase within gastric parietal cells. Compared to other PPIs, it is less likely to activate in neutral to moderately acidic environments (pH 3 - 5). This characteristic restricts its

activity in the body and is believed to be the reason behind its limited adverse effects profile (7, 8).

Our literature review revealed nine cases of anaphylaxis to PPIs (Table 1), none of which required tracheal intubation. We reviewed case reports of PPIs with allergic reactions and anaphylaxis. Pantoprazole was the most common PPI prescribed in these cases, which is the PPI our patient received. The route of administration was IV (IV) in six cases and oral in the remaining three. Our patient took the oral route prior to presenting to the hospital. The most common regimen was 40 mg once daily.

Table 1. List of cases with anaphylactic reaction to pantoprazole administration.

No. and cases reported	Age	Sex	Route of drug	Symptoms	Treatment	Intubation required	Hospital complications
1. Faridaalaee G, Ahmadian Heris J. (15)	21	F	IV	Hives, Dyspnea, Cyanosis, hypotension	Normal Saline, Epinephrine, Hydrocortisone, Chlorpheniramine and Oxygen	No	None
2. Lai HC, et al (16)	50	M	IV	Hypotension, Tachycardia, Generalized erythema	Normal Saline, Epinephrine, Hydrocortisone, Antihistamine	Patient was already under anesthesia	None
3. Yadav A, Das I, Yadav D (17)	40	F	Oral	Spasmodic abdominal pain, Loose stools (Diarrhea), Vomiting, Hypotension, Urticaria.	Epinephrine, Oxygen (via oxygen mask), Normal Saline, Hydrocortisone, Pheniramine.	No	None
4. Alolabi R, Liem JJ (18)	39	F	Oral	Angioedema, Pruritus, Pyrexia, Vomiting, Diarrhea.	Patient did not report to the emergency ward and was confirmed on epicutaneous testing.	No	None
5. Bahuguna R, Joshi D, Rana M. (19)	64	F	IV	Urticaria, Pruritus, Pyrexia, Chills.	Immediate cessation of the infusion.	No	None
6. Yousefi H, et al (20)	45	M	IV	Urticaria, Pruritus, Angioedema, Hypotension, Cyanosis, Dyspnea.	Normal saline, Epinephrine, Hydrocortisone, Chlorpheniramine, Oxygen (via oxygen mask).	No	None
7. James J, et al (2)	75	F	IV	Urticaria, Pruritus, Angioedema, Hypotension, Cyanosis, Dyspnea.	Normal saline, Epinephrine, Hydrocortisone, Chlorpheniramine, Oxygen (via oxygen mask).	No	None
8. Telaku S, et al (3)	42	F	IV	Dyspnea, Pruritus, Angioedema	Chloropyramine Hydrochloride, Methylprednisolone	No	None
9. Telaku S, et al (3)	58	F	Oral	Angioedema, Urticaria, Pruritus, Bloating, Dizziness.	Calcium, Epinephrine, Hydrocortisone Chlorpheniramine and Oxygen (via oxygen mask)	No	None

The anaphylactic reaction is not limited by age or gender. For males and females, the age range was from the early 20s to 75 years (Table 1). Short- and long-term clinical trials indicate oral pantoprazole at 40 to 120 mg/day has a good safety profile (9). The incidence of adverse effects has been reported as low as 1-3% (9, 10), ranging from nonallergic common side effects including diarrhea (2%), headaches (2%), nausea (1%), constipation (1%) (11) to adverse allergic reactions. These reactions include anaphylaxis and various skin manifestations not limited to contact, photoallergic dermatitis, Steven Johnson Syndrome, Toxic Epidermal Necrolysis, drug rash with Eosinophilia, and Systemic Symptoms (DRESS). Some of these reactions can be life-threatening, requiring emergency care (3). Anaphylaxis does not always include hives or urticarial skin reactions, as seen in six cases. Our patient lacked any true skin rash manifestations.

The incidence of anaphylactic allergic reaction in response to H2 receptor antagonists and PPIs accounts for only 0.2%–0.7% of all anaphylaxis incidences reported by the Uppsala Monitoring Centre database (12). Anaphylactic reaction, an example of Type 1 hypersensitivity reaction, is a myriad of clinical symptoms that are often life-threatening and cause respiratory and cardiovascular problems. The mast cells and basophils release proinflammatory mediators on drug encounters, inciting an anaphylactic reaction leading to hypotension, angioedema, laryngeal edema, and bronchospasm with skin manifestations such as pruritus, urticaria, and erythema (12). Often, the only subtle sign would be worsening edema/angioedema or generalized pruritis. The latter was absent in our case, and the only early manifestation was periorbital edema. No single cause of anaphylaxis can be attributed to our case, as the pathophysiology is multifactorial (12, 13).

One theory proposed that PPIs lower stomach acid could have a double-edged effect. Gastric acid suppression allows more bacteria to flourish in the mouth and upper gut while disrupting the balance of bacteria by inhibiting H+/K+-ATPase found in fungal and bacterial cell membranes. Microbiome alteration, the effect on intestinal bacterial composition, and gastric pH suppression may explain why some people experience allergic reactions after taking pantoprazole (13). Another theory proposed that pantoprazole-induced anaphylaxis was an IgE-mediated reaction regulated by basophils and mast cells (12, 13).

The main contraindications of pantoprazole include patients with a known history of hypersensitivity to the drug itself, components of the formulation, and other benzimidazole PPIs, including omeprazole, lansoprazole, rabeprazole, esomeprazole, or dexlansoprazole. In case of a hypersensitivity reaction, following the administration of pantoprazole, the infusion should be stopped immediately (14).

Notice how most mild symptoms were treated conservatively with IV fluids, steroids, and antihistamines (Table 1). Nonetheless, emergency medicine providers and primary care physicians should carefully monitor patients in both inpatient and outpatient clinical settings. Of note, the physicians must document the allergy with specific PPI to avoid future prescriptions with similar drugs, as some still prescribe other agents in this drug class. In contrast, others avoid it as there is a concern for cross reactivity. Moreover, a comparison of PPI and histamine type 2 receptor antagonist (H2 blocker) can be drawn regarding safety profile in future studies.

Conclusion

Anaphylaxis is often misdiagnosed, increasing mortality and morbidity. Although anaphylaxis with PPI is rare, these reactions can be life-threatening. Therefore, emergency medicine providers and primary care physicians must be aware of this side effect of pantoprazole and should carefully monitor patients in both inpatient and outpatient clinical settings. This anaphylactic event also reemphasizes the importance of educating patients regarding the side effects of PPIs and when to seek timely emergency attention. No one can predict the severity of the anaphylaxis; however, the complications can be managed promptly if recognized earlier.

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Authors' Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Conflict of Interest

The authors declare that the study was conducted without commercial or financial relationships that could be interpreted as potential conflicts of interest.

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Ethical Statement

Patient details were omitted, and a de-identification process was implemented to ensure confidentiality and privacy. Written informed consent was obtained from the patient in this case report, and publication of the case did not require ethics from the institution; therefore, no further ethical review was needed.

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