

Immediate and Delayed Hypersensitivity Reactions to Proton Pump Inhibitors: Evaluation and Management

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Abstract PPIs are among the most commonly administered medications in the USA and are generally well tolerated. Immediate and delayed immune-mediated hypersensitivity reactions are rare but increasingly recognized adverse effects of proton pump inhibitors (PPIs). Immediate hypersensitivity reactions can occur due to IgE-mediated hypersensitivity to PPIs and can be evaluated by immediate hypersensitivity skin testing and oral provocation challenge testing. A desensitization protocol can be used when PPI use cannot be avoided in an allergic patient. Delayed hypersensitivity reactions to PPIs have also been reported. Occupational exposures causing cutaneous reactions to PPIs are the most commonly reported delayed hypersensitivity reaction, followed by drug-induced subacute cutaneous lupus erythematosus. This review presents a summary of the clinical presentation, diagnostic evaluation, and management of immune-mediated hypersensitivity reactions to PPIs.

Keywords Drug allergy · Hypersensitivity reaction · Adverse drug reaction · Proton pump inhibitor · PPI · Skin testing · Patch testing

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Introduction

PPIs are among the top 18 prescribed drugs in the USA [1]. They are pro-drugs that inhibit acid secretion and raise intragastric pH by noncompetitively antagonizing the enzyme H⁺/K⁺-adenosinetriphosphatase in gastric parietal cells and are most commonly used for treatment of gastroesophageal reflux disease, gastrointestinal ulcer treatment and prophylaxis, hypersecretory conditions, and *Helicobacter pylori* infections [2]. The first PPI (Omeprazole, or Prilosec) was approved by the US Food and Drug Administration for gastroesophageal reflux disease, active duodenal ulcer, severe erosive esophagitis, and pathologic hypersecretory conditions in 1990 [3]. There are now at least seven PPIs available [3].

Although PPIs are generally well tolerated, especially with short-term use, immune-mediated reactions to PPIs can occur [4•]. A prior review from our institution identified 39 English-language publications by performing a literature search in PubMed from June 1986 to September 2012 using a combination of keywords: *proton pump inhibitors*, *PPI*, *hypersensitivity*, *drug allergy*, and *adverse reactions* [4•]. A literature search from October 2012 to October 2015 with the same combination of keywords identified another 11 original English-language publications. In total, over 200 cases of immune-mediated reactions to PPIs have been reported in the literature [4•, 5•, 6•, 7–11, 12•, 13•, 14–16].

Immediate, IgE-Mediated Reactions

The USA is the world's largest PPI market, accounting for more than three quarters of all global sales in 2013 [17]. PPIs were prescribed for 7.8 % of the adult population in the USA between 2011 and 2012, and 31 % of 1959 adults

surveyed in 2011 reported using either over-the-counter or prescription PPIs [1, 18]. Immediate, IgE-mediated reactions account for the majority of hypersensitivity reactions to PPIs. In the literature to date, 199 IgE-mediated reactions to PPIs in 187 patients have been reported [4•, 5•, 6•]. Immediate hypersensitivity reactions to PPIs have been reported to occur across a wide range of ages (14 to 78 years of age) and predominantly in females (72 %) [4•, 5•, 6•].

The majority of immediate hypersensitivity reactions were due to lansoprazole ($n=77$) and omeprazole ($n=61$), followed by pantoprazole ($n=29$) and esomeprazole ($n=27$) [4•, 5•, 6•]. Ransoprazole was the least frequently implicated PPI ($n=5$) [4•, 5•]. There were no reported cases of immediate hypersensitivity reactions to dexlansoprazole.

The most commonly reported presenting symptoms were urticaria (65 %) and angioedema (42 %), followed by dyspnea (22 %), hypotension (22 %), and pruritus (33 %), with percentages obtained by combining data reported from Bose et al. and Ozdemir et al., [4•, 5•]. Nausea and vomiting (2 %), diarrhea (1 %), rhinitis (1 %), and syncope (1 %) have also been reported [5•]. Roughly half of the reactions were severe enough to be considered anaphylaxis by the reporting authors [5•, 6•].

Skin Testing

The validity of skin testing for the evaluation of immediate hypersensitivity to PPIs has been studied in a recent prospective study [5•]. This study performed standardized skin prick and intradermal testing for omeprazole (SPT: 20 mg/ml, 4 mg/ml, 0.4 mg/ml; IDT: 0.004 mg/ml, 0.04 mg/ml, 0.4 mg/ml), lansoprazole (SPT: 30 mg/ml), pantoprazole (SPT: 40 mg/ml, 4 mg/ml, 0.4 mg/ml; IDT: 0.004 mg/ml, 0.04 mg/ml, 0.4 mg/ml), rabeprazole (SPT: 20 mg/ml), and esomeprazole (SPT: 20 mg/ml, 8 mg/ml, 0.8 mg/ml; IDT: 0.008 mg/ml, 0.08 mg/ml, 0.8 mg/ml) in 65 patients with a history suggestive of PPI-induced immediate hypersensitivity and in 30 control subjects. Oral provocation tests with PPIs other than the suspected culprit PPI ($n=61$) and confirmatory oral provocation tests with the suspected culprit PPI ($n=12$) were also performed. Diagnostic values were calculated to be: sensitivity 58.8 %, specificity 100 %, negative predictive value 70.8 %, and positive predictive value 100 %.

Varying non-irritating concentrations for skin prick and intradermal testing have been reported [5•, 6•, 19–27]. Higher concentrations, provided they are non-irritating, are more likely to have higher sensitivity. Therefore, we recommend using the concentrations in Table 1 for skin testing. Care must be taken to use only injectable intravenous preparations of PPIs for the intradermal tests, as crushed tablets or oral solutions can be irritating.

Table 1 Recommended immediate hypersensitivity testing for PPIs

PPI	Skin prick test dilutions (mg/mL)	Intra-dermal tests dilutions (mg/mL) ^a	References
Omeprazole	40	0.04 0.4 4	Elfau et al. [19] Garrido et al. [20] Sanchez-Morillas et al. [6•]
Esomeprazole	40	0.04 0.4 4	Elfau et al. [19] Sanchez-Morillas et al. [6•]
Lansoprazole	30	0.03 0.3 3	Garrido et al. [20] Porcel et al. [21] Ozdemir et al. [5•]
Pantoprazole	40	0.04 0.4 4	Elfau et al. [19] Garrido et al. [20] Porcel et al. [21] Ozdemir et al. [5•]
Rabeprazole	20	0.02 0.2 2	Garrido et al. [20] Porcel et al. [21] Ozdemir et al. [5•] Sanchez-Morillas et al. [6•]

The first step of skin testing is to perform skin prick testing with the recommended dilution for skin prick testing. If the result of skin prick testing is negative, then three serial intra-dermal tests are performed using the three recommended dilutions for intra-dermal testing [28]. Concentrations are adapted from listed references [5•, 6•, 19–21]

^a Intradermal testing should only be performed using injectable intravenous preparations of PPIs, as crushed tablets and oral solutions can be irritating

Desensitization

A successful oral desensitization protocol has been reported [29]. Granules from an omeprazole capsule were dissolved into bicarbonate solution to create four tenfold serial dilutions (0.002 mg/ml, 0.02 mg/ml, 0.2 mg/ml, 2 mg/ml). The starting dose was 0.001 mg (0.5 ml of 0.002 mg/ml concentration). Escalating doses were administered at 20-min intervals. The protocol took 5.6 h to reach the final dose of 16 mg (cumulative dose 32.665 mg). After completion of the desensitization, the patient was able to tolerate one 20-mg omeprazole capsule and continued on omeprazole 20 mg twice daily for therapeutic purposes.

Cross-Reactivity

A review of reported cases found the following general cross-reactivity patterns:

1. There were three patterns of cross-reactivity among patients with hypersensitivity to omeprazole [5•, 6•, 19, 20, 27, 30]:
 - a. Hypersensitivity to omeprazole showed cross-reactivity with all other PPIs.

- b. Hypersensitivity to omeprazole showed cross-reactivity with pantoprazole.
 - c. Hypersensitivity to omeprazole showed cross-reactivity with pantoprazole and esomeprazole or rabeprazole, but not with lansoprazole.
2. Hypersensitivity to lansoprazole showed cross-reactivity with one other specific PPI (omeprazole, pantoprazole, rabeprazole, or esomeprazole) [5•, 19, 21, 23].

There was one exception to the described patterns, where a patient with hypersensitivity to omeprazole had cross-reactivity with lansoprazole, but not with pantoprazole [5•].

Skin testing positivity to one PPI does not eliminate possibility of positive hypersensitivity to another PPI based on cross-reactivity patterns alone. We recommend skin testing to the suspected culprit PPI and omeprazole and lansoprazole at a minimum and confirming negative skin testing with a graded challenge.

Other Immunologic Reactions

Delayed, Cell-Mediated Reactions

Delayed dermatologic reactions after occupational exposure to PPIs have been reported in the literature [7, 8, 12•, 31–34]. This is not surprising, as PPIs have been found to be among the most highly sensitizing benzimidazole derivative medications [35].

Pharmaceutical workers are the most frequently sensitized due to occupational exposure. Sensitization in pharmaceutical workers has been reported mostly in manufacturers involved in the preparation of PPIs, but has also been reported in a chemist, a supervisor, and an animal technician working at a pharmaceutical company [12•, 31, 32, 34]. Two cases of sensitization to omeprazole were reported in a horse trainer and horse racing “head lad” who had both been exposed to a veterinary preparation of omeprazole (GastroGard) [7, 8].

All cases were due to omeprazole sensitization, apart from one case of lansoprazole sensitization. The patient sensitized to lansoprazole was also positive on patch testing to omeprazole [33]. Limited patch testing results (two cases where patch testing was performed with more than one PPI) showed cross-reactivity between all the PPIs [7, 33, 36].

Ghatan et al. published the largest case series of occupational sensitization to omeprazole to date [12•]. These authors reported 96 cases of workers referred to the AstraZeneca Occupational Health Center between 1989 and 1999 for skin reactions on the face, hands, and neck. Evaluation with patch testing ($n=84$) and lymphocyte transformation test ($n=96$) identified 36 patients with evidence of omeprazole

sensitization on diagnostic testing (patch testing positive in 28 patients, lymphocyte transformation test positive in 31 patients).

Patch Testing

Patch testing was used to confirm suspected sensitization to PPI in all cases [7, 8, 12•, 31–34]. Dilutions and vehicles used for patch testing are summarized in Table 2. Skin testing is not helpful in evaluating delayed hypersensitivity reactions.

Severe, Life-Threatening Delayed Reactions

Isolated cases of severe, life-threatening, delayed hypersensitivity reactions to PPIs have been reported. Seven cases of DRESS syndrome, a potentially life-threatening syndrome characterized by cutaneous manifestations and multi-organ failure, have been reported to PPIs (three to esomeprazole, two to pantoprazole, one to lansoprazole, and one to omeprazole) [9, 16, 36]. One case of toxic epidermal necrolysis (TEN) attributed to lansoprazole [37] and one case of hypersensitivity vasculitis attributed to omeprazole [38] has also been reported. Although one case utilized patch testing with PPIs to confirm sensitization [36], re-exposure to a suspected culprit agent for testing purposes must be performed with caution in patients who have experienced life-threatening reactions.

Subacute Cutaneous Lupus Erythematosus

Drug-induced subacute cutaneous lupus erythematosus (SCLE) is an increasingly recognized adverse immunologic effect of PPIs. A total of 37 patients with PPI-induced SCLE have been reported in the literature [13•, 39–48]. The time of onset after initiation of culprit agent is highly variable, ranging from 1 week to 3–5 years, although most cases occur within 1 year [13•, 39–48]. PPI-induced SCLE occurred much more frequently in women ($n=33$, 89 %) than men ($n=4$, 11 %) [13•, 39–48]. Positivity to the following antibodies was seen in a systematic review of PPI-induced SCLE: antinuclear (61 %, 11/18 tested patients, most frequently with speckled pattern), anti-Ro/SSA (73 %, 11/15 tested patients), anti-La/SSB (33 %, 5/15 tested patients), anti-dsDNA (8 %, 1/12 tested patients), and antihistone (8 %, 1/13 tested patients) [13•].

The majority of drug-induced SCLE cases were due to lansoprazole ($n=18$) and omeprazole ($n=11$), followed by esomeprazole ($n=7$) and pantoprazole ($n=6$) [13•, 39–48]. Cross-reactivity between PPIs has been demonstrated with one case of esomeprazole- and pantoprazole-induced SCLE and two cases of lansoprazole- and omeprazole-induced SCLE [13•]. It has been suggested that patients with prior history of cutaneous lupus erythematosus are at risk for developing PPI-induced SCLE [13•].

Table 2 Summary of PPI patch testing in the literature [7, 8, 12•, 31–34]

PPI	Percent	Vehicle	Control (# subjects)	References
Omeprazole	0.1 %, 0.5 %, 1 %	Saline	6	Ghatan et al., Sanz-Gallen et al.
	0.1 %, 0.5 %, 1 %	Alcohol	22 ^a	Meding et al., Conde-Salazar et al.
	0.25 %, 0.5 %, 1 %	Petrolatum	10 ^b	Meding et al.
	1 %, 10 %	Petrolatum	5	Al Falah et al.
	10 %, 50 %	Petrolatum	50	Vilaplana et al.
Lansoprazole	1 %, 10 %	Petrolatum	5	Al Falah et al.
	10 %, 50 %	Petrolatum	50	Vilaplana et al.
Dexlansoprazole				
Rabeprazole				
Pantoprazole				
Esomeprazole	1 %, 10 %	Petrolatum	5	Al Falah et al.
GastroGard (37 % w/w omeprazolen)	25 %, 50 %, 75 %	Petrolatum	5	Al Falah et al.
	5 %	Water	20	Alwan et al.

Control (# subjects) is the number of reported subjects who had appropriately negative patch testing results

^a Highest dilution for patch testing in control subjects was 0.5 % alcohol

^b Patch testing for control subjects performed with 0.5% petrolatum only

Conclusions

In summary, PPIs are generally well tolerated, but can cause a variety of immune-mediated reactions. Reported immune-mediated reactions include (in order of decreasing frequency): immediate (IgE-mediated) hypersensitivity reactions, delayed cutaneous reactions due to occupational exposure, drug-induced cutaneous lupus erythematosus, DRESS, TEN, and hypersensitivity vasculitis.

- Skin testing and graded challenge are of diagnostic value when evaluating immediate hypersensitivity reactions to PPIs (Table 1) and have the following reported diagnostic values: sensitivity 58.8 %, specificity 100 %, negative predictive value 70.8 %, positive predictive value 100 %.
- For immediate hypersensitivity reactions, skin testing positivity to one PPI does not eliminate the possibility of sensitization to another PPI based on cross-reactivity patterns alone. We recommend skin testing to the suspected culprit PPI and omeprazole and lansoprazole at a minimum and confirming negative skin testing with graded challenge.
- In the majority of immediate hypersensitivity reaction cases, alternative tolerated PPIs can be identified. In cases where PPI therapy is essential and an alternative tolerated

PPI cannot be identified, a desensitization protocol can be used.

- Patch testing can be useful in the evaluation of delayed skin reactions due to sensitization to PPI through occupational exposure to PPIs.

Compliance with Ethical Standards

Conflict of Interest Drs. Otani and Banerji declare no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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