

Dermatologic adverse reactions to proton-pump inhibitors: A synthesized review

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Abstract

Background: Proton-pump inhibitors (PPIs) are one of the most prescribed drugs. Their dermatological adverse reactions are multiple and vary in severity.

Aims: This review discusses all reported cutaneous side effects of PPIs in order to help physicians understand them and provide appropriate management.

Methods: A thorough search of PubMed, Embase, and FDAQA8 drugs websites was conducted. 56 articles including case reports, case series, and review articles of PPI-induced cutaneous adverse reactions were selected. Data were recorded regarding patient age, gender, history, clinical manifestations, diagnostic tests, management, and clinical outcomes.

Results: PPI-induced adverse skin reactions are mostly immunological and include both immediate and delayed-type hypersensitivity reactions. These reactions are sometimes life-threatening. All PPIs can induce immediate IgE-mediated reactions. Most of previously published cases of delayed-type hypersensitivity reactions have involved esomeprazole, omeprazole, and lansoprazole. Skin tests are helpful in confirming PPI-induced hypersensitivity reactions and diagnosing potential cross-reactivities. PPIs should also be added to our list of usual suspects when considering possible culprits for a new presentation of drug-induced subacute lupus erythematosus. PPI-related occupational contact dermatitis has also been numerous reported.

Conclusion: PPIs should be considered in our list of culprits when considering a patient with a cutaneous drug reaction, taking into account that these drugs can cause severe immunological manifestations.

KEYWORDS

adverse reaction, allergy, hypersensitivity, proton-pump inhibitors, rash

1 | INTRODUCTION

Proton-pump inhibitors (PPIs) are the bread and butter in the treatment of gastroesophageal disease. Despite their overall safety profile, cutaneous adverse events are frequent and both immediate and delayed-type hypersensitivity reactions (HSR) have been reported.

The spectrum ranges from benign, localized dermatoses to generalized, life-threatening cutaneous toxicities.

All PPIs currently on the market are composed of a benzimidazole ring and a pyridine ring.¹ They differ by the nature of substituents located on both rings. Omeprazole, esomeprazole, and pantoprazole have changes in their benzimidazole rings, whereas

lansoprazole and rabeprazole have changes in their pyridine ring. Although the exact mechanism for PPI-induced hypersensitivity reactions is not yet fully understood, it is believed that the offending agent in some PPIs is the sulfur moiety located on the benzimidazole compound. Furthermore, PPIs are metabolized by the cytochrome P450 system, mainly the CYP2C19 and CYP3A4 isoenzymes.² Not all PPIs have the same affinities to these enzymes. More studies are needed to assess whether patients with PPI hypersensitivity reactions are associated with certain risk alleles.

Skin prick tests and patch tests have been validated for diagnosing PPI-related HSR and identifying potential cross-reactivities. To date, four general patterns have been identified: whole group hypersensitivity, omeprazole-esomeprazole-pantoprazole hypersensitivity, lansoprazole-rabeprazole hypersensitivity, and selective sensitization to a single PPI.³

In this paper, we aim to present an exhaustive and synthesized review of the dermatologic side effects associated with PPI use. We believe that it is important for all physicians to have an overview of all the skin manifestations caused by PPIs, as they are one of the most frequently prescribed drugs in the world.

2 | MATERIALS AND METHODS

This review included 59 articles (case presentations and case series or reviews) in which cutaneous adverse events of PPIs were represented. A meticulous electronic search was done using the following databases: PubMed, Embase, and the US FDA website.

The search aimed to retrieve all the articles reporting dermatologic side effects of the 5 most commonly studied and prescribed PPI molecules: omeprazole, rabeprazole, esomeprazole, lansoprazole, and pantoprazole. The advanced search strategies included key words such as: Proton Pump Inhibitors, Esomeprazole, Omeprazole, Rabeprazole, Lansoprazole, Pantoprazole, Hypersensitivity, Adverse reaction, Rash, Drug eruption with eosinophilia and systemic symptoms, Stevens-Johnson syndrome, Toxic epidermal necrolysis, Contact dermatitis, Fixed drug eruption, Allergy, Skin tests.

3 | PPI-INDUCED IMMEDIATE HYPERSENSITIVITY REACTIONS

Immediate, IgE-mediated reactions account for the majority of hypersensitivity reactions (HSR) to PPIs and all molecules have been implicated.⁴ In the study by Tourillon et al,⁵ the authors described 38 cases of immediate HSR to PPIs confirmed by skin tests or oral provocation tests. Urticaria and anaphylaxis were the most common clinical presentations. Omeprazole was the most commonly implicated molecule, followed by esomeprazole and pantoprazole.

However, lansoprazole was shown to be the main culprit in the series done by Özdemir and colleagues,⁶ which can be explained by the dissimilarities in prescription trends between the different countries. Isolated pruritus can be the only manifestation of a type I HSR to PPIs. Skin prick tests and intradermal tests have been validated for the confirmation of immediate hypersensitivity to PPIs and identification of potential cross-reactivity.⁷

4 | PPI-INDUCED STEVENS-JOHNSON SYNDROME/ TOXIC EPIDERMAL NECROLYSIS

Although maculopapular exanthem is the most frequent cutaneous presentation of PPI-associated delayed hypersensitivity reactions, other more severe immunological reactions are also known to occur (Table 1). The first case of toxic epidermal necrosis (TEN) caused by a PPI was reported in 1992 in a 72-year-old woman, 2 weeks after starting omeprazole for dyspeptic symptoms.⁸ Omeprazole and Lansoprazole were also the culprit drugs in another 5 and 6 published cases of TEN, respectively.⁹⁻¹³ In the European case-control surveillance of severe cutaneous adverse reactions (EuroSCAR) study published in 2008, pantoprazole was associated with a high univariate relative risk of Stevens-Johnson syndrome (SJS)/TEN; however, an accurate risk estimate could not be determined due to the low number of cases.¹⁴ Later, Frey et al¹⁵ observed an increased risk of SJS/TEN among new users of omeprazole, lansoprazole, and to a lesser extent rabeprazole. In a recent case series, both patch tests and lymphocyte activation tests measuring granulysin and INF- γ release were performed to confirm causality of the PPI.¹¹

5 | PPI-INDUCED DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a potentially life-threatening delayed-type hypersensitivity reaction that includes a maculopapular eruption, polyadenopathy, hematologic abnormalities (eosinophilia and hyperbasophilic lymphocytes), and possible internal organ involvement (mainly liver, kidneys, and lungs). To date, 20 cases of DRESS have been reported to PPIs, 11 cases to esomeprazole,¹⁶⁻¹⁸ 4 to pantoprazole,^{11,16} 2 to lansoprazole,^{11,16} and 3 to omeprazole.^{19,20} In most of these cases, the diagnosis was confirmed by a positive skin patch test and in one case, the patch test induced a transient flare of DRESS.¹⁶

6 | PPI-INDUCED FIXED DRUG ERUPTION

Fixed drug eruption (FDE) is a distinctive type of cutaneous drug reaction that is characterized by one or multiple erythematous and edematous plaques that recur in the same locations upon

TABLE 1 Severe delayed-type hypersensitivity cutaneous reactions caused by proton-pump inhibitors

Reference	Sex	Age	Offending drug (number of cases)	Mean duration of exposure in days (range)	Reaction	Diagnostic skin test	Treatment(s) received and clinical outcome
Descamps and Ranger-Rogez ²⁰	NA	NA	Omeprazole (2)	NA	DRESS	NP	NA
Barbaud et al ¹⁷	M; F F; F F	60; 64 31; 51 75	Esomeprazole (2) Pantoprazole (2) Lansoprazole (1)	>21 days	DRESS	Patch test	Improvement after PPI discontinuation without any systemic treatment
Zaiem et al ¹⁸	F	28	Esomeprazole (1)	NA	SJS/TEN	Patch test	
	F	84	Esomeprazole (1)	8	DRESS	NP	Gradual worsening of cutaneous signs, liver and kidney functions and systemic signs despite stopping esomeprazole. Death from multiorgan failure
Caboni et al ¹⁶	F	41	Esomeprazole (1)	20	DRESS	Patch test	Esomeprazole was suspected and stopped 1 month after onset of symptoms. After initial worsening of rash, hepatitis and hypereosinophilia. Gradual improvement with topical and systemic corticosteroids and remission at 4 months
Bourneau-Martin et al ¹⁹	F	88	Omeprazole (1)	45	DRESS	NP	Resolution 2 wk after discontinuation of PPI and treatment with topical corticosteroids
Fracaroli et al ¹²	F	23	Lansoprazole (1)	15	TEN	NP	Treatment with IVlg 2g/kg for 3 days and skin supportive care. Recovery after 15 days with postinflammatory hyperpigmentation
Thakor et al ⁹	F	43	Omeprazole (1)	21	TEN	NP	Improvement after administration of corticosteroids, IVlg and topical emollients
Heaton et al ¹³	M	72	Lansoprazole (1)	7	TEN or generalized fixed drug eruption	NP	Treatment with IVlg 0.5g/Kg/day for 5 days. Death on day 15 from multiorgan failure
Cockayne et al ¹⁰	M	83	Lansoprazole and Omeprazole (1)	63 and 49	Exfoliative erythrodermic dermatitis	NP	Resolution of symptoms after drug discontinuation and treatment with topical corticosteroids
	F	52	Omeprazole (1)	7	Erythema multiforme (erythrodermic)	NP	Resolution 2 wk after drug discontinuation and treatment with topical corticosteroids
	M	74	Omeprazole (1)	9	Toxic erythema progressing to erythroderma	NP	Resolution after 8 days with antihistamine oral treatment and emollients

Abbreviations: F, Female; IVlg, Intravenous immunoglobulin; LAT, lymphocyte activation test; M, Male; NA, not available; NP, not performed.

Revuz J Clin Exp Dermatol. 2006;33(1):148.⁶⁰

TABLE 2 Occupational contact dermatitis caused by proton-pump inhibitors confirmed with a positive patch test

Reference	Sex (number of cases)	Age (y)	History of atopy	Occupation	Duration of exposure before symptom onset	Offending drug	Reaction
Al-Falah et al ²⁹	F (1)	44	NA	Horse breeder	NA	Omeprazole	Pruritic dermatitis involving eyelids, face, neck, and forearms
Alwan et al ³¹	M (1)	49	(-)	Racehorse industry	NA	Omeprazole	Eczematous rash on left thumb spreading to scrotum, upper thigh, and eyelids
Bennett et al ³²	NA (3)	33, 43, 56	NA	Pharmaceutical process operators (2) Organic chemist (1)	NA	Omeprazole	Rash affecting the face and ears
Conde-Salazar et al ³³	M (1)	25	(+)	Pharmaceutical industry	5 y	Omeprazole	Eczematous eruption on eyelids, face, neck, and hands
	M (1)	35	NA	Pharmaceutical industry	NA	Omeprazole	Pruritic dermatitis affecting the eyelids, nose, and perioral area
Yu and Dekoven ³⁸	M (1)	58	(-)	Pharmaceutical industry	NA	Esomeprazole	Eczematous eruption involving the neck, posterior auricular areas, and extensor forearms
Ghatan et al ³⁰	NA (23)	NA	NA	Pharmaceutical industry	NA	Omeprazole	Diffuse pruritus, periorcular erythema, and edema
Neumark et al ³⁶	M (1)	33	(+)	Pharmaceutical industry	6 y	Pantoprazole	Eczematous rash involving face and eyelids
Vilaplana et al ³⁴	M (1)	58	(-)	Pharmaceutical industry	3.5 y	Lansoprazole	Erythematous and pruritic papular eruption on face, neck, upper arms, and forearms
Akan et al ³⁵	F (1)	41	(+)	Pharmacy technician	NA	Lansoprazole	Recurrent, pruritic perioral, and periorcular rash with eyelid edema
Alarcón et al ³⁷	M (1)	33	(-)	Pharmaceutical production worker	7 y	Pantoprazole	Rash involving face, neck, and hands
	M (1)	41	(-)	Pharmaceutical maintenance worker	7 y	Lansoprazole	Eyelid edema and facial rash
	M (1)	49	(-)	Pharmaceutical production worker	21 y	Lansoprazole and Pantoprazole	Rash involving face, neck, and hands

Abbreviations: F, Female; M, Male; NA, not available.

re-exposure to the offending drug. PPI-induced FDE is rare, and only 5 cases were reported so far: 3 cases associated with omeprazole²¹⁻²³ and 2 cases of diffuse FDE reported with esomeprazole,^{24,25} both confirmed with an oral provocation test.

7 | PPI-INDUCED ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS

Acute generalized exanthematous pustulosis (AGEP) is a T-cell mediated delayed-type HSR characterized by a rapid eruption of non-follicular sterile pustules on a background of edematous erythema caused by drugs, most often antibiotics, antifungals, diltiazem, and antimalarials. A case of profuse AGEP induced by lansoprazole was reported in a 66-year-old female patient, 48 hours after treatment initiation.²⁶ Another type IV hypersensitivity reaction with a diffuse pustular eruption was described with the use of pantoprazole, with a latency of 4 days. Skin biopsies were consistent with AGEP. The rash resolved 10 days after drug discontinuation.²⁷

8 | PPI-INDUCED LICHENOID DRUG ERUPTION

Lichenoid drug eruption, also known as drug-induced lichen planus, manifests as flat-topped, erythematous or violaceous papules symmetrically distributed on the trunk and extremities. 2 cases of lichen planus have been reported with lansoprazole, as well as 2 cases with omeprazole, one of which had cross-reactivity to lansoprazole and pantoprazole.²⁸

9 | PPI-INDUCED CONTACT DERMATITIS

There are 44 published cases of occupational contact dermatitis caused by PPIs in the setting of the pharmaceutical or horse industry. They presented with eczematous lesions mainly affecting the face, eyelids, neck, and arms. Cases were described as occurring after direct contact with the skin or with airborne exposure to omeprazole,²⁹⁻³³ lansoprazole,^{34,35} pantoprazole,^{36,37} and esomeprazole.³⁸ Duration of exposure before symptom development is usually long and can be up to 8 years in certain cases. Patch tests were performed to validate the suspected offending drugs (Table 2).

10 | PPI-INDUCED VASCULITIS

One case of an isolated cutaneous small cell vasculitis was reported 4 weeks after initiation of omeprazole.³⁹ The diagnosis was confirmed by histopathology, and the condition resolved shortly after discontinuation of the drug with no specific treatment. Jacobs-Kosmin also reported a case of pantoprazole-induced pANCA-positive vasculitis with skin involvement in a 65-year-old woman few weeks after drug initiation.⁴⁰ The

exact mechanism of these reactions is not yet understood. Later, a case of severe Henoch-Schoenlein purpura associated with pantoprazole was published, with rapidly progressing glomerulonephritis and ileitis.⁴¹

11 | PPI-INDUCED SUBACUTE CUTANEOUS LUPUS ERYTHEMATOSIS

Drug-induced subacute lupus erythematosus (DISCLE) presents clinically, histopathologically, and immunologically in a manner similar to that of idiopathic SCLE.⁴² It can be induced de novo or aggravated by culprit drugs. PPIs including lansoprazole, esomeprazole, omeprazole, and pantoprazole are becoming one of the most common drugs involved in DISCLE.⁴³ In the largest case series of PPI-induced DISCLE published to date, the authors observed that PPI-induced SCLE had a similar antibody profile to other DISCLE. Ro/SS-A autoantibodies were present in 73% of the cases, 61% of cases were positive for antinuclear antibodies, 36% had anti-La/SSB antibodies, and only 8% had anti-histone antibodies.⁴⁴ In a large case-control study of 234 patients with SCLE,⁴⁵ there was a significantly increased risk for SCLE following exposure to PPIs. Also, 2 cases of Rowell's syndrome, a morphological variant of SCLE with targetoid lesions, have been reported with esomeprazole and omeprazole.⁴⁶ The diagnosis is challenged by the variation in time from prescription of the culprit drug to the appearance of SCLE, as time intervals can range from 1 week-10 years. Patients with known Ro or La antibodies, previous CLE, or other autoimmune diseases may be particularly prone to PPI-induced or exacerbated SCLE. Cross-reactivity between different PPIs has also been demonstrated.⁴⁷

12 | MISCELLANEOUS

Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE, intertriginous drug eruption, and baboon syndrome) is an uncommon variant of exanthematous drug eruption that typically develops few hours to days after drug exposure, with a characteristic distribution and lack of systemic findings. Two cases occurred after administration of omeprazole with a latency of 9 and 17 days, respectively.⁴⁸

Erythema dyschromicum perstans (EDP), also called ashy dermatosis, is an uncommon, slowly progressive dermatosis characterized by ash gray hyperpigmented macules of variable size and shape symmetrically distributed over the neck, trunk and proximal arms. 6 cases of EDP have been described so far; 4 cases following the use of omeprazole,^{49,50} 1 case with esomeprazole⁵¹ and 1 case with lansoprazole.⁵² The latency between drug initiation and onset of the skin rash ranged between 2 to 12 months. The rash improved slowly after stopping the offending drugs.

Two cases of sticky palms were reported in individuals shortly after starting PPI treatment. In one patient treated with lansoprazole, symptoms showed 3 weeks after drug initiation, while in the second case where omeprazole was used, symptoms appeared earlier at 2 weeks. In both cases, symptoms resolved around 2 weeks following cessation of the PPI.⁵³

Sweet's syndrome, also known as acute febrile dermatosis, is characterized by the triad of fever, increased number of neutrophils, and sudden onset of tender erythematous plaques, nodules, or papules on the arms, legs, trunk, face, and neck. Some cases are idiopathic; however, others can be caused by drugs or myeloproliferative diseases.⁵⁴ Cohen described the case of an 86-year-old woman with a history of invasive lobular carcinoma who developed her first episode of Sweet's syndrome 8 days following treatment with omeprazole and her second episode 6 hours after esomeprazole was started.⁵⁵

One case of diffuse alopecia was attributed to the use of omeprazole. The onset of hair loss was 4 weeks after initiation of therapy; it was reversible soon after discontinuation of the drug and recurred when omeprazole was reintroduced.⁵⁶

13 | SUMMARY

This review discusses the portfolio of dermatological side effects observed with the use of PPIs. As shown, PPI immunological adverse skin reactions are common and include both immediate and delayed hypersensitivity reactions. Immediate reactions have been reported with all PPIs,⁵⁷ whereas omeprazole, esomeprazole, and lansoprazole were mostly implicated in delayed-type hypersensitivity reactions.¹⁶ Physicians should be aware of the possible severe and life-threatening skin reactions associated with these drugs; a high level of clinical suspicion and temporal relationship is crucial for early diagnosis and proper management. PPIs should also be added to our list of usual suspects when considering possible culprits for a new presentation of DISCLE.⁴² PPI-induced contact dermatitis from occupational exposure is also possible and should be prevented by wearing adequate protective equipment. Interestingly, rabeprazole seems to have the best skin tolerance and is associated with less than 1% of all PPI-associated dermatological adverse events.^{58,59} It is important to note that this review only includes case reports and case series; thus, no epidemiological conclusions can be drawn. Understanding the patterns of cross-reactivity between the different molecules is particularly important to find a safe alternative drug in a patient who requires PPI treatment, after sufficient allergy workup has been done.

CONFLICT OF INTEREST

None declared.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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