

Hypersensitivity reactions to proton-pump inhibitors: Clinical presentation, diagnosis, and management

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ABSTRACT

Background: Proton-pump inhibitors (PPI) are one of the most commonly prescribed drugs, and they are generally well tolerated. However, several immediate and delayed hypersensitivity reactions due to PPIs have been reported.

Objective: To review the clinical characteristics and management of immune-mediated immediate and delayed hypersensitivity reactions to PPIs.

Methods: We performed a search of a medical literature data base from January 1980 to October 2019 by using keywords that included “proton-pump inhibitors” and “hypersensitivity.”

Results: Anaphylaxis is the most-common clinical presentation in patients with immediate hypersensitivity reactions to PPIs, followed by urticaria and/or angioedema. Occupational contact dermatitis, maculopapular eruption, fixed drug eruption, symmetrical drug-related intertriginous and flexural exanthema, and severe cutaneous adverse reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms, and acute generalized exanthematous pustulosis have also been reported with PPIs.

Conclusion: The current knowledge and severity of the reported reactions indicated the importance of consideration of a causal relationship between hypersensitivity reactions and PPIs, and awareness of the existence of cross-reactivity among PPIs.

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The introduction of powerful acid-suppressive drugs, e.g., proton-pump inhibitors (PPI), has reformed the management of acid-related diseases and has minimized the role of surgery; we observed an almost continuous growth of their use in the past decade.¹ PPIs consist of a benzimidazole and a pyridine ring but vary in the specific side-ring substitution.² Omeprazole, esomeprazole, and pantoprazole are substituted on the benzimidazole ring, whereas rabeprazole and lansoprazole are not substituted.³ PPIs are the most potent inhibitors of gastric-acid secretion available,² and they are generally well tolerated, with a low incidence of adverse effects.⁴ However, several anaphylactic reactions due to PPIs have been reported^{5–16} and, in the past decade, there has been an increase in hypersensitivity reactions, possibly related to their increased consumption.¹⁷ It was observed that a significant portion of the patients with immediate hypersensitivity reactions to PPIs had more than one episode with the same drug; this is probably related to the fact

that these drugs are usually not thought by physicians to induce hypersensitivity reactions.¹⁷

Methods

This review focused on the clinical characteristics, diagnostic approach, and management of immune-mediated immediate and delayed hypersensitivity reactions to PPIs. We performed a literature search of PubMed from January 1980 to October 2019, with the keywords that included “proton-pump inhibitors” and “hypersensitivity.” We included English language studies that consisted of at least five patients suspected of previous immediate hypersensitivity reactions after administration of a PPI and all available case reports and studies suspected of previous delayed hypersensitivity reactions after administration of a PPI.

RESULTS

PPI-Induced Immediate Hypersensitivity Reactions

Clinical Presentation. Immediate immunoglobulin E (IgE) mediated reactions account for the majority of hypersensitivity reactions to PPIs.¹⁸ We identified 12 studies that evaluated a total of 395 patients with 416 immediate-type hypersensitivity reactions to PPIs (Table 1).^{5,6,9,10,12,14,15,17,19–22} The majority of immediate hypersensitivity reactions to PPIs were due to lansoprazole ($n = 169$ [40.6%]) and omeprazole ($n = 109$ [26.2%]), followed by pantoprazole ($n = 65$ [15.6%]), esomeprazole ($n = 60$ [14.4%]), and rabeprazole ($n = 13$ [3.1%]). The

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Table 1 Reports of immediate-type hypersensitivity reactions to proton pump inhibitors

Study, y	Patients, n	Culprit Drug	Anaphylaxis, n	Urticaria and/or angioedema, n	Diagnostic evaluation	ST sensitivity, %	Control Subjects, n	ST Positivity in Control Subjects	Cross-Reactivity
Lobera <i>et al.</i> , ⁹ 2009	9	O	2	7	ST, OPT	88.9	20	0	O-P, O-L
Sobrevia Elfau, <i>et al.</i> , ¹⁰ 2010	5	O	4	1	ST	100	14	0	All
Abdul Razzak <i>et al.</i> , ¹² 2012	8	O	4	4	ST, OPT	62.5	—	NP	O-P
Bonadonna <i>et al.</i> , ¹⁴ 2012	53	All	*	*	ST, OPT	61.3	—	NP	P-O, P-E
Kepil Özdemir <i>et al.</i> , ⁵ 2013	65	All [#]	33	32	ST, OPT	58.8	30	0	L-P, L-O, L-E, L-R, All
Sánchez-Morillas <i>et al.</i> , ¹⁹ 2014	11	O	4	7	ST, OPT	62.5	10	0	All, O-R-P
Mota <i>et al.</i> , ¹⁵ 2016	5	O, P, E	5	0	ST	100	—	NP	P-O, P-O-E
Kepil Özdemir <i>et al.</i> , ⁶ 2016	60	All [#]	40	17	ST, OPT	50	—	NP	L-P, L-O, P-E, All; L-P-E, O-P-R-E
Laguna <i>et al.</i> , ¹⁷ 2018	42	O	29	11	ST, OPT, BAT	66.7	22	0	—
Tourillon <i>et al.</i> , ²⁰ 2019	38	All	NA	NA	ST, OPT	NA	—	NP	O-P, O-E, E-P, O-L, O-E-P, O-P-R, P-L-R, O-R-P-E, All
Kepil Özdemir <i>et al.</i> , ²¹ 2019	88	All [#]	41	45	ST, OPT	55.8	—	NP	NA
Casciaro <i>et al.</i> , ²² 2019	11	O, L, P, E	1	10	OPT	NA	—	NP	—

O = Omeprazole; ST = immediate skin testing (prick and intradermal tests); OPT = oral provocation test; P = pantoprazole; L = lansoprazole; All = omeprazole, pantoprazole, lansoprazole, rabeprazole, esomeprazole; NP = not performed; E = esomeprazole; R = rabeprazole; BAT = basophil activation test; NA = not available.

*Grade 1–3 according to Ring-Messmer Scale, Ref 56.

[#]Mainly lansoprazole.

culprit PPIs involved in the reactions varied among countries, lansoprazole in studies from Turkey,^{5,6,21} esomeprazole and lansoprazole in a study from Italy,¹⁴ and omeprazole in studies from Spain.^{9,10,12,17} This is probably related to the prescription patterns because lansoprazole is the most commonly prescribed PPI in Turkey, and omeprazole was reported to be the most commonly

consumed PPI in Spain.¹⁷ Anaphylaxis was the most common clinical presentation in patients with immediate hypersensitivity reactions to PPIs (163 patients [53.6%]), followed by urticaria and/or angioedema (134 patients [44.1%]).^{5,6,9,10,12,14,15,17,19–22}

Immediate hypersensitivity reactions generally occur within a few hours after a dose. However, there are

Table 2 Recommended maximum skin test concentrations in immediate hypersensitivity reactions with proton-pump inhibitors

Proton-Pump Inhibitor	Skin-Prick Test Concentration, mg/mL	Intradermal Test Concentration, mg/mL	References
Omeprazole	40	4	10, 17
Lansoprazole	30	1.5	5, 19
Pantoprazole	40	4	5, 10
Rabeprazole	20	2	5, 19
Esomeprazole	40	4	10

case reports of delayed anaphylaxis to PPIs that begin up to 24 hours after drug intake.^{6,13,23,24} In such a patient, with a history of anaphylaxis after 7 hours of the last dose of pantoprazole, an intradermal test with pantoprazole was found to be positive, which suggests an immediate hypersensitivity mechanism.⁶ This may be explained by the enteric coating of the PPIs, which may cause a delay in the onset of the reaction.⁶ It was also hypothesized that polymorphisms in the cytochrome *P450 CYP2C19* gene (associated with a poor metabolizer phenotype) might be related to anaphylaxis timing.²³ Therefore, in patients with symptoms typical of immediate-type allergic reactions to PPIs with a delayed onset (up to 24 hours) an IgE-mediated mechanism may still be possible, and these patients should also be evaluated with immediate skin tests.

Diagnostic Approach. Skin tests are very important for the evaluation of drug hypersensitivity reactions.²⁵ However, drug skin tests are often not carried out because of a lack of concise information on specific test concentrations.²⁵ With regard to PPI-induced immediate-type hypersensitivity reactions, several large studies demonstrated that skin tests are useful for the diagnosis^{5,6,14,17} and that nonirritating concentrations for skin-prick tests, and intradermal tests were defined.⁵ As a general rule, skin tests should precede drug provocation tests with the culprit or the alternative PPIs in patients with PPI-induced immediate-type hypersensitivity reactions. Although different large studies obtained different sensitivity values (50.0–66.7%), complete specificity has been reported in all of these studies.^{5,14,17} A total of 96 healthy controls were included in previous studies to date (Table 1),^{5,9,10,17,19} and false skin test positivity to PPIs has not been reported so far. Recommended immediate skin test concentrations are shown in Table 2.

Only injectable intravenous preparations of PPIs should be used for the intradermal tests; crushed tablets or oral solutions can be irritating.¹⁸ We suggest that oral provocation tests should be performed only in cases of negative results in skin tests, to rule out the diagnosis or to find an alternative PPI for the patient,

in immediate-type PPI hypersensitivity reactions. A recent study evaluated the use of the basophil activation test to diagnose omeprazole hypersensitivity and found that the basophil activation test with omeprazole is useful for diagnosis, with a sensitivity of 73.8% and a complete specificity (100%).¹⁷ In this study, 57% of patients with a negative skin test result with omeprazole obtained positive results with the basophil activation test; by combining skin test and basophil activation test results, 86% of the patients could be diagnosed.¹⁷ Incubating cells with wortmannin, a potent inhibitor of the IgE signaling pathway, have significantly reduced basophil activation rate in 10 patients with initially positive basophil activation test results, which demonstrated the involvement of IgE in the stimulation of basophils by omeprazole.¹⁷ The basophil activation test may be a promising tool to diagnose omeprazole allergy, and further studies with other PPIs are needed to evaluate the role of basophil activation test in immediate-type PPI hypersensitivity.

Management. Cross-reactivity existed among the various PPIs; however, the patterns of cross-reactivity were quite variable and not consistent across the studies (Table 1).^{5,6,9,10,12,14,15,19,20} Cross-reactivity within the PPI family is likely related to the similar organic structure of these PPIs.²⁶ PPIs consist of a benzimidazole and a pyridine ring but vary in the specific side-ring substitution.¹⁶ Omeprazole and pantoprazole have a methoxy and a difluoromethoxy chain, respectively, in their benzimidazole ring, whereas lansoprazole and rabeprazole have no modifications in that ring, but their pyridine rings have a trifluoroethoxy and methoxypropoxy chain, respectively.⁹ Previous reports on reactions to PPIs describe the presence of cross-reactivity of the whole group, and there are case reports that demonstrated cross-reactivity between lansoprazole and rabeprazole.^{27,28}

Four general patterns of cross-reactivity have been identified, based on the published articles in a previous review²⁹: whole-group hypersensitivity, omeprazole-esomeprazole-pantoprazole hypersensitivity, lansoprazole-rabeprazole hypersensitivity, and selective sensitization to a single PPI. However, not all of the cross-

Table 3 Reports of delayed hypersensitivity reactions to proton-pump inhibitors

Study, y	Patients, n	Culprit Drug	Reaction, n	Diagnostic Evaluation	ST Sensitivity	Control Subjects, n	ST Positivity in Control Subjects	Cross-Reactivity
Lin <i>et al.</i> , ³² 2018	69	All*	29 MPE, 27 SJS and/or TEN, 10 DRESS, 2 FDE, 1 AGEP	PT, LAT	4/7 Patients (57%)	7 for LAT	NP	P-E, L-R, D-R, All, P-E-O
Fracaroli <i>et al.</i> , ³⁴ 2013	1	L	1 TEN	NP	—	—	NP	NP
Thakor <i>et al.</i> , ³⁵ 2009	1	O	1 TEN	NP	—	—	NP	NP
Heaton <i>et al.</i> , ³⁷ 2004	1	L	1 TEN	NP	—	—	NP	NP
Cockayne <i>et al.</i> , ³⁸ 1999	3	O, L	1 Severe exfoliative, dermatitis, 1 EM, 1 erythroderma	NP	—	—	NP	O-L
Cox, ³⁹ 1992	1	O	1 Acute disseminated epidermal necrosis	NP	—	—	NP	NP
Kardaun <i>et al.</i> , ⁴⁰ 2012	2	O	2 SDRIFE	PT	—	—	NP	NP
Vilaplana <i>et al.</i> , ⁴¹ 2001	1	L	1 OCD	PT	—	50	0	L-O
Neumark <i>et al.</i> , ⁴² 2011	1	P	1 OCD	PT	—	10	0	O-P
Sanz-Gallén <i>et al.</i> , ⁴³ 2011	1	O	1 OCD	PT	—	6	0	NP
Al-Falah <i>et al.</i> , ⁴⁴ 2014	1	O	1 OCD	PT	—	5	0	All
Alwan <i>et al.</i> , ⁴⁵ 2014	1	O	1 OCD	PT	—	—	NP	NP
Ghatan, <i>et al.</i> , ³³ 2014	96	O	36 OCD	PT, LTT	—	21 for LTT	NP	NP
Barbaud, <i>et al.</i> , ⁴⁶ 2013	6	E, P, L	5 DRESS, 1 SJS and/or TEN	PT	—	—	NP	NP
Bourneau-Martin, <i>et al.</i> , ⁴⁷ 2014	1	O	1 DRESS	NP	—	—	NP	NP
Zaïem <i>et al.</i> , ⁴⁸ 2015	1	E	1 DRESS	NP	—	—	NP	NP
Caboni <i>et al.</i> , ⁴⁹ 2007	1	E	1 DRESS	PT	—	—	NP	E, O, P
Kai <i>et al.</i> , ⁵¹ 2011	1	O	1 FDE	NP	—	—	NP	NP
Morais <i>et al.</i> , ⁵² 2010	1	E	1 FDE	PT, OPT	—	—	NP	NP
Sobrinho-García <i>et al.</i> , ⁵³ 2019	1	E	1 FDE	PT, OPT	—	—	NP	NP

ST = Skin test; All = omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, dexlansoprazole; MPE = maculopapular eruption; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis; DRESS = drug rash with eosinophilia and systemic symptoms; FDE = fixed drug eruption; AGEP = acute generalized exanthematous pustulosis; PT = patch test; LAT = lymphocyte activation test; NP = not performed; P = pantoprazole; E = esomeprazole; L = lansoprazole; R = rabeprazole; D = dexlansoprazole; O = omeprazole; EM = erythema multiforme; SDRIFE = symmetrical drug-related intertriginous and flexural exanthema; OCD = occupational contact dermatitis; LTT = lymphocyte transformation test; OPT = oral provocation test; 0 = no ST positivity in control subjects.

*Mainly esomeprazole.

reactivities observed in some previous studies can be explained by these patterns.^{5,6} In a previous study from Turkey, the drug most frequently involved was lansoprazole, and many different patterns of cross-reactivity were observed.⁵ Despite the molecular⁵ differences, the most common pattern was lansoprazole and pantoprazole cross-reactivity in that study. The different patterns of cross-reactivity shown in the previous studies^{5,6,9,10,12,14,15,19,20} (Table 1) suggest that several chemical characteristics (*e.g.*, substitutions, metabolites) may be involved. Although, general

conclusions cannot be drawn from an analysis of the data with regard to cross-reactivity among PPIs, a thorough drug allergy workup for finding safe alternatives and not assuming cross-reactivity of the whole group are important. Physicians should be aware of the possible cross-reactivity among PPIs; however, a safe, alternative PPI can usually be detected by a thorough drug allergy workup in immediate-type PPI hypersensitivity.⁶

A successful oral desensitization protocol has been reported in a single patient with omeprazole-induced

anaphylaxis and positive skin test results with omeprazole and pantoprazole.³⁰ 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. The patient tolerated the procedure uneventfully and completed 14 days of treatment without any evidence of hypersensitivity.³⁰ In cases in whom a PPI is necessary for treatment and a safe alternative PPI cannot be found, desensitization may be a rational approach.

PPI-Induced Delayed Hypersensitivity Reactions

Clinical Presentation. Drug-induced delayed hypersensitivity reactions may range from mild maculopapular eruption (MPE) and fixed drug eruption (FDE) to fatal, severe cutaneous adverse reactions, such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS).³¹ Data with regard to PPI-induced delayed hypersensitivity reactions are limited; we identified two large studies and several case reports that evaluated a total of 133 patients with delayed-type hypersensitivity reactions to PPIs (Table 3).^{32–53} The largest study of PPI-related delayed hypersensitivity reactions is a 14-year case series study from Taiwan, which reported 69 cases, including 29 patients with MPE, 27 patients with SJS and/or TEN, 2 patients with FDE, 1 patient with acute generalized exanthematous pustulosis (AGEP), and 10 patients with DRESS.³² The average latent periods of PPI exposure were 18.6, 20.8, 7.0, and 27.2 days for MPE, SJS and/or TEN, AGEP, and DRESS, respectively.³²

SJS, TEN, and DRESS are severe, life-threatening delayed hypersensitivity reactions that can result in disability or death.³² A total of 32 cases of SJS and/or TEN have been reported due to PPIs (14 to esomeprazole, 8 to omeprazole, 7 to lansoprazole, 2 to pantoprazole, and 1 to dexlansoprazole).^{32,34–37,46} Eighteen cases of patients with DRESS due to PPIs have also been reported (11 to esomeprazole, 4 to pantoprazole, 2 to lansoprazole, and 1 to omeprazole).^{32,46–49} Lin *et al.*³² reported 29 cases of MPE: 13 to esomeprazole, 7 to omeprazole, 7 to lansoprazole, 1 to pantoprazole, and 1 to dexlansoprazole. Six cases of patients with FDE due to PPIs have also been reported (three to esomeprazole, two to omeprazole, and one to pantoprazole).^{32,50–53} There were two cases of patients with SDRIFE (symmetrical drug-related intertriginous and flexural exanthema), and they were induced by omeprazole.⁴⁰ There is only one case of a patient with AGEP attributed to PPIs, and it was due to esomeprazole.³² If we evaluate the reported delayed hypersensitivity reactions with the exception of occupational contact dermatitis cases, then the majority of delayed hypersensitivity reactions to PPIs were due to

esomeprazole ($n = 42/92$ [45.6%]), followed by omeprazole ($n = 23/92$ [25.0%]), lansoprazole ($n = 17/92$ [18.5%]), pantoprazole ($n = 8/92$ [8.7%]), and dexlansoprazole ($n = 2/92$ [2.2%]) (Table 3). Mortality was reported in five of these 92 patients (5.4%), with delayed hypersensitivity reactions induced by PPIs (four patients due to TEN and one patient due to DRESS)^{32,37,48} Physicians should be aware of PPI-related delayed hypersensitivity reactions (DHR), because a delayed diagnosis and a delay in discontinuing the culprit drug may cause increased mortality.^{32,54}

PPIs have been shown to exhibit strong cutaneous contact sensitizing capacity, which suggests that these drugs have the potential to cause contact allergy in humans.^{33,55} Therefore, direct contact of PPI formulations with the skin should be avoided.²⁹ Direct PPI contact with skin would normally be avoided by using enteric-coated formulations. In the occupational setting, a number of cases of contact dermatitis on exposure to omeprazole during manufacture have been reported.³³ Ghatan *et al.*³³ reported the largest case series of occupational sensitization to omeprazole so far. This study evaluated 96 workers who reported potential allergic symptoms after occupational exposure to omeprazole. Patch testing and a lymphocyte transformation test confirmed contact hypersensitivity in 36 patients to omeprazole.³³

Pharmaceutical workers were the most commonly sensitized cases as a result of occupational exposure; however, allergic contact dermatitis in a horse breeder and in a head lad due to contact with a veterinary product containing omeprazole has also been reported.^{44,45} The vast majority of the occupational contact dermatitis cases were due to omeprazole; single cases induced by lansoprazole⁴¹ and pantoprazole⁴² have also been reported. Sanz-Gallen *et al.*⁴³ reported a pharmaceutical worker with a skin rash and facial edema recurring at work. This interesting case showed positivity both on skin-prick tests and patch tests with omeprazole, which suggests occupational sensitization, with both type I and type IV hypersensitivity being involved.⁴³

Diagnostic Approach. Data with regard to diagnostic role of the patch test in PPI-induced delayed hypersensitivity reactions are scanty. Lin *et al.*³² performed patch tests in seven patients with the causative PPIs and reported positivity in four of them (57%) (Table 3). Barbaud *et al.*⁴⁶ reported positivity with patch tests with PPIs in five patients with DRESS. Caboni *et al.*⁴⁹ also reported a positive patch test result with esomeprazole in a patient with DRESS; this patient had a flare up of DRESS 60 hours after skin patch testing, which suggests that caution should be taken in the allergological testing of severe adverse drug reactions. Reported patch test concentrations and vehicles used in delayed hypersensitivity reactions with PPIs are summarized in Table 4. A

Table 4 Reported patch test concentrations used in delayed hypersensitivity reactions with PPIs

PPI	Patch Test Concentration, %	Vehicle	Study
Omeprazole	0.1, 0.5, 1	Petrolatum	Sanz-Gallén <i>et al.</i> ^{43*}
	0.1, 0.5, 1	Saline solution	Ghatan <i>et al.</i> ³³
	1, 10	Petrolatum	Al-Falah <i>et al.</i> ^{44#}
	10	Petrolatum	Lin <i>et al.</i> ³²
	10, 50	Petrolatum	Vilaplana <i>et al.</i> ^{41§}
Lansoprazole	1, 10	Petrolatum	Al-Falah <i>et al.</i> ^{44#}
	10	Petrolatum	Lin <i>et al.</i> ³²
	10, 50	Petrolatum	Vilaplana <i>et al.</i> ^{41§}
	30	Petrolatum	Barbaud <i>et al.</i> ⁴⁶
Pantoprazole	1, 10	Petrolatum	Al-Falah <i>et al.</i> ^{44#}
	30	Petrolatum	Barbaud <i>et al.</i> ⁴⁶
Rabeprazole	1, 10	Petrolatum	Al-Falah <i>et al.</i> ^{44#}
Esomeprazole	1, 10	Petrolatum	Al-Falah <i>et al.</i> ^{44#}
	2	Petrolatum	Moraes <i>et al.</i> ⁵²
	10	Petrolatum	Lin <i>et al.</i> ³²
	30	Petrolatum	Barbaud <i>et al.</i> ⁴⁶
Dexlansoprazole	1, 10	Petrolatum	Al-Falah <i>et al.</i> ^{44#}

PPI = Proton-pump inhibitor.

*Patch test results with the same concentrations of omeprazole in six controls were negative.

#Patch test results were negative in five controls.

§Patch test results with the same preparations of lansoprazole and omeprazole in 50 controls were negative.

recent study evaluated the use of the lymphocyte activation test by measuring granulysin and interferon- γ to diagnose delayed hypersensitivity reactions to PPIs and found that the lymphocyte activation test by measuring granulysin showed a sensitivity of 59.3% and specificity of 96.4%.³²

Management. As reported in PPI-induced immediate-type hypersensitivity reactions, cross-reactivities have also been observed in delayed hypersensitivity reactions due to PPIs (Table 3). Re-challenging the culprit drugs in patients with severe delayed hypersensitivity reactions may cause fatal recurrence of the reaction and is not suggested.³² In cases with a necessity of PPI treatment, the choice of the alternative PPI can be based on the results of patch tests or lymphocyte activation tests.³² Desensitization does not seem to be an alternative approach with the current information about patients with delayed hypersensitivity reactions due to PPIs.

DISCUSSION

More than 400 immediate and approximately 140 delayed hypersensitivity reactions due to PPIs have been reported to date, and, in the past decade, there has been an increase in these reactions, probably parallel to

the increasing consumption of PPIs.^{5,6,14,17,32} With regard to immediate-type hypersensitivity reactions, several anaphylactic and urticarial reactions and delayed-type hypersensitivity reactions, occupational contact dermatitis, maculopapular eruption, FDE, SDRIFE, and severe cutaneous adverse reactions (*e.g.*, SJS, TEN, DRESS, AGEF) due to PPIs have been reported. Anaphylaxis was the most common clinical presentation in patients with immediate-type hypersensitivity reactions to PPIs and, with the exception of occupational contact dermatitis cases, the majority of the reported delayed-type hypersensitivity reactions to PPIs were SJS and/or TEN.

It was observed that some patients with immediate and delayed hypersensitivity reactions to PPIs had more than one episode with the same drug or another PPI, and this was probably related with the fact that these drugs are usually not thought by physicians to induce hypersensitivity reactions.¹⁷ In addition, PPIs are usually used together with multiple other drugs. The current knowledge and the severity of the reported hypersensitivity reactions indicate the importance of consideration of a causal relationship between hypersensitivity reactions and PPIs and of awareness of the existence of cross-reactivity among the PPI family.

Skin tests with the implicated PPIs have perfect specificity in the diagnosis of immediate-type hypersensitivity reactions,^{5,14} but, in case of negativity in skin tests, an oral provocation test is necessary to exclude PPI hypersensitivity. Several large studies demonstrated that skin tests are useful for the diagnosis of immediate-type hypersensitivity reactions due to PPIs, and nonirritating concentrations for skin-prick tests and intradermal tests are well defined.^{5,14,17} Therefore, skin tests should precede drug provocation tests with the culprit or the alternative PPI in patients with PPI-induced immediate-type hypersensitivity reactions.

An IgE-mediated mechanism may be possible in some patients with symptoms typical of immediate-type allergic reactions to PPIs with a delayed onset (up to 24 hours), and these patients should also be evaluated with immediate skin tests.^{6,13,24,25} The basophil activation test may be a promising tool to diagnose PPI-induced immediate hypersensitivity reactions and co-administration with immediate skin testing may lessen the need for provocation tests.¹⁷ A successful oral desensitization protocol has been reported in a single patient with omeprazole-induced anaphylaxis.³⁰ In patients in whom a PPI is essential for treatment, and a safe alternative PPI cannot be found, desensitization may be a rational approach in immediate-type hypersensitivity reactions.

Data with regard to PPI-induced delayed hypersensitivity reactions and the role of patch tests in the diagnosis of such cases are limited. However, positivity in patch tests and patch test concentrations and vehicles for PPI-induced delayed-type hypersensitivity reactions are mentioned in case reports.^{32,46,49} The lymphocyte activation test may be a promising tool in the diagnosis of delayed hypersensitivity reactions due to PPIs,³² and further studies are needed to evaluate the role of lymphocyte activation tests in these reactions. Cross-reactivity between PPIs is the case in both immediate and delayed hypersensitivity reactions. The data with regard to cross-reactivity among PPIs is not sufficient to be able to draw general conclusions. Physicians should be aware of the possible cross-reactivity among PPIs; however, with a thorough drug allergy workup, a safe alternative PPI can usually be found.

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