

ORIGINAL ARTICLE

EXPERIMENTAL ALLERGY AND IMMUNOLOGY

Immediate-type hypersensitivity reactions to proton pump inhibitors: usefulness of skin tests in the diagnosis and assessment of cross-reactivity

S. Kepil Özdemir¹, İ. Yılmaz¹, Ö. Aydın¹, S. Büyükoztürk², A. Gelincik², M. Demirtürk², D. Erdoğan², Ş. Cömert³, T. Erdoğan³, G. Karakaya³, A. F. Kalyoncu³, F. Öner Erkeköl⁴, A. B. Dursun⁴, Z. Mısırlıgil¹ & S. Bavbek¹

¹Department of Chest Diseases, Division of Allergy and Immunology, Ankara University School of Medicine, Ankara; ²Istanbul Faculty of Medicine, Department of Internal Medicine, Division of Allergy and Immunology, İstanbul University, İstanbul; ³Department of Chest Diseases, Division of Allergy and Immunology, Hacettepe University School of Medicine, Ankara; ⁴Department of Chest Diseases, Division of Allergy and Immunology, Atatürk Chest Disease and Thoracic Surgery Training and Research Hospital, Ankara, Turkey

To cite this article: Kepil Özdemir S, Yılmaz İ, Aydın Ö, Büyükoztürk S, Gelincik A, Demirtürk M, Erdoğan D, Cömert Ş, Erdoğan T, Karakaya G, Kalyoncu AF, Öner Erkeköl F, Dursun AB, Mısırlıgil Z, Bavbek S. Immediate-type hypersensitivity reactions to proton pump inhibitors: usefulness of skin tests in the diagnosis and assessment of cross-reactivity. *Allergy* 2013; DOI: 10.1111/all.12189.

Keywords

cross-reactivity; drug allergy; hypersensitivity; proton pump inhibitors; skin tests.

Correspondence

Prof. Sevim Bavbek, Department of Pulmonary Diseases, Division of Allergy and Clinical Immunology, Ankara University, School of Medicine, 06100, Ankara, Turkey.
Tel.: +90-312-595-65-81
Fax: +90-312-319-75-39
E-mail: bavbek@medicine.ankara.edu.tr

Accepted for publication 22 April 2013

DOI:10.1111/all.12189

Edited by: Pascal Demoly

Abstract

Background: Data are limited about the value of skin tests in the diagnosis of proton pump inhibitor (PPI)-induced hypersensitivity reactions and the cross-reactivity between PPIs. We aimed to assess the role of skin testing in the diagnosis of PPI-related immediate hypersensitivity reactions and the cross-reactivity patterns among PPIs.

Methods: The study was designed in a prospective, national, multicentre nature. Sixty-five patients with a suggestive history of a PPI-induced immediate hypersensitivity reaction and 30 control subjects were included. Standardized skin prick and intradermal tests were carried out with a panel of PPIs. Single-blind, placebo-controlled oral provocation tests (OPTs) with the PPIs other than the culprit PPI that displayed negative results in skin tests ($n = 61$) and diagnostic OPTs with the suspected PPI ($n = 12$) were performed.

Results: The suspected PPIs were lansoprazole ($n = 52$), esomeprazole ($n = 11$), pantoprazole ($n = 9$), rabeprazole ($n = 2$), and omeprazole ($n = 1$). The sensitivity, specificity, and negative and positive predictive values of the skin tests with PPIs were 58.8%, 100%, 70.8%, and 100%, respectively. Fifteen of the 31 patients with a hypersensitivity reaction to lansoprazole had a positive OPT or skin test result with at least one of the alternative PPIs (8/52 pantoprazole, 6/52 omeprazole, 5/52 esomeprazole, 3/52 rabeprazole).

Conclusion: Considering the high specificity, skin testing seems to be a useful method for the diagnosis of immediate-type hypersensitivity reactions to PPIs and for the evaluation of cross-reactivity among PPIs. However, OPT should be performed in case of negativity on skin tests.

Proton pump inhibitors (PPIs) consist of a benzimidazole and a pyridine ring, but vary in the specific side ring substitution (1). Omeprazole, esomeprazole, and pantoprazole are substituted on the benzimidazole ring, whereas rabeprazole and lansoprazole are not (2). PPIs are the most potent inhibitors of gastric acid secretion available (1) and are commonly used for the treatment of acid-related gastrointestinal diseases. They are generally well tolerated, with a low incidence of adverse effects (3).

Although hypersensitivity reactions due to PPIs are rare, several anaphylactic reactions have been reported (4–14). However, limited data are available about the value of skin tests in the diagnosis of PPI-induced hypersensitivity reactions and the cross-reactivity between PPIs (9, 13, 15). Therefore, in this prospective multicentre study, we aimed to assess the role of skin testing in the diagnosis of PPI-related immediate hypersensitivity reactions and the cross-reactivity patterns among PPIs.

Methods

Patients and controls

The study was designed in a prospective, multicentre manner. Patients who were referred to the allergy departments of four hospitals located in the two biggest cities, İstanbul and Ankara, in Turkey with a suggestive history of an immediate-type hypersensitivity reaction (urticaria, angioedema, wheezing, anaphylaxis) after administration of a PPI were included in the study. Cases were prospectively enrolled over a one-year period (2011–2012). Subjects with symptoms attributable to known side-effects or nonimmediate reactions were not included. Clinical data were recorded using a modified European Network of Drug Allergy questionnaire (16). The severities of the reactions were determined using the Ring–Messmer scale (17). The controls consisted of 30 subjects who did not have a history of a drug hypersensitivity reaction, either tolerated or unexposed to PPIs. The study was approved by the Local Ethics Committee of Ankara University, School of Medicine, and written informed consent was obtained from all subjects.

Skin tests

Skin prick tests (SPTs) were performed with the undiluted commercial oral preparations of omeprazole capsule (20 mg) (Omeprazid[®], Nobel, Turkey), lansoprazole capsule (30 mg) (Lansoprol[®], Nobel, Turkey), pantoprazole tablet (40 mg) (Panto[®], Sandoz, Turkey), rabeprazole tablet (20 mg) (Prabex[®], Sandoz, Turkey), esomeprazole tablet (20 mg) (Nexium[®], AstraZeneca, Turkey) by prick method and 1/10 and 1/1 dilutions of injectable preparations of omeprazole (4 mg/ml) (Losec[®], AstraZeneca, Turkey), pantoprazole (4 mg/ml) (Panto[®], Sandoz, Turkey) and esomeprazole (8 mg/ml) (Nexium[®], AstraZeneca, Turkey) along with positive (histamine 0.01%) and negative control (saline 0.9%). For prick testing, the tablets and micropellet capsules were smashed in a mortar and diluted with 1 ml of 0.9% NaCl according to the method described previously (18). SPTs were performed on the volar forearm and were read after 20 min. A wheal reaction with a mean diameter of 3 mm greater than the negative control was considered positive. For drugs that have both oral and injectable preparations available, SPTs were performed with both forms, and positivity with either of these was considered as a positive result. If SPTs were negative, intradermal tests (IDTs) were performed with the injectable preparations of omeprazole (4 mg/ml), pantoprazole (4 mg/ml), and esomeprazole (8 mg/ml) at 1/1000, 1/100, and 1/10 dilutions. An amount of 0.03 ml test solution was injected into the skin to produce a bleb. Readings were conducted after 15 min and considered positive if the size of the initial wheal had increased by at least 3 mm in diameter and was surrounded by erythema.

Drug provocation tests

After skin tests, to evaluate the cross-reactivity between the PPIs, single-blind, placebo-controlled oral provocation tests (OPT) with the PPIs that displayed negative results in skin

tests were performed in patients who gave their informed consent. During these tests, omeprazole capsule (5 mg, 10 mg, 20 mg), lansoprazole capsule (7.5 mg, 15 mg, 30 mg), pantoprazole tablet (5 mg, 10 mg, 20 mg), rabeprazole tablet (5 mg, 10 mg, 20 mg), and esomeprazole tablet (5 mg, 10 mg, 20 mg) were administered each on different days at 30-min intervals at increasing doses until the full dose was reached or symptoms of a drug reaction occurred. OPTs with the suspected PPIs were performed in a subgroup of patients who displayed negative results in diagnostic skin tests. During OPTs blood pressure, pulse and FEV1 were monitored before each drug dose and repeated according to the patient's symptoms. The test results were accepted positive if clinical signs (urticaria, angioedema, bronchospasm, or other objective signs of the original drug reaction) or 20% fall in FEV1 was observed.

Inclusion to the final analysis group and statistical analysis

As we were not able to perform diagnostic OPTs with the suspected PPIs in all patients, while evaluating the diagnostic accuracy of the skin tests and cross-reactivity among PPIs, patients in whom diagnostic OPTs were performed or the diagnosis of PPI hypersensitivity was supported with positive results in skin tests or OPTs with the alternative PPIs were included. Skin test sensitivity was calculated as the percentage of diagnostic skin test-positive subjects among these patients. Comparisons for quantitative variables were performed using the Student's t-test or the Mann–Whitney test and for qualitative variables by the chi-square test. *P*-values < 0.05 were considered statistically significant. The statistical analysis was performed using the SPSS program version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

Subject characteristics

Sixty-five patients with a suggestive history of a PPI-induced immediate hypersensitivity reaction were included to the study. Fifty-three were women (81.5%) and the median age was 43 years (min–max: 22–78 years). The culprit PPI was lansoprazole in 52 patients (80.0%), esomeprazole in 11 (16.9%), pantoprazole in 9 (13.8%), rabeprazole in two (3.1%), and omeprazole in one (1.5%). Eight patients had a history of distinct reactions to different PPIs in separate episodes. The clinical symptoms were urticaria and/or angioedema in 32 (49.2%) and anaphylaxis in 33 patients (50.8%). The severity of the reaction was grade 1 in 32 (49.2%), grade 2 in 22 (33.8%), and grade 3 in 11 patients (16.9%). The median interval between the reaction and the diagnostic tests was 3 months (min–max: 1–72 months). The time interval between the last administration of the drug and the reaction was ≤ 1 h in 49 (75.4%) patients and 1–24 h in 16 (24.6%) (median, min–max; 1, 0.1–24 h). The control group included 30 subjects of whom 17 (56.7%) were women and the median age was 33 years (min–max: 21–54 years).

Skin test results

The characteristics of the patients and results of the skin tests and OPTs for each PPI and for the individual cases are shown in Table 1. Five patients refused diagnostic skin tests with the culprit PPIs. Skin tests with the suspected PPI were positive in 20 patients (20/60, 33.3%) (Fig. 1, Table 2). Among 20 patients, 19 had positivity on SPT, and two on IDT. All skin test results in controls were negative. Diagnostic skin tests were positive in 17 of the 47 patients (36.2%) for lansoprazole, two of the 10 patients (20.0%) for esomeprazole, two of the nine patients (22.2%) for pantoprazole, and one of the two patients (50.0%) for rabeprazole. Diagnostic skin tests with omeprazole were performed in one patient and were negative. Time to onset of the reaction after last exposure was significantly lower in patients with positive skin test results than in patients with negative skin test results [median (min–max) 0.5 (0.1–3.0) vs 1.0 (0.1–24.0) h, respectively; $P = 0.028$]. The time interval between the reaction and the diagnostic tests [median (min–max) 3.75 (1.0–72.0) vs 3.0 (1.0–24.0) months], and severity of the reaction [55.0% grade 1, 32.5% grade 2, 12.5% grade 3 vs 45.0% grade 1, 25.0% grade 2, 30.0% grade 3] were not different statistically between patients with negative and positive skin test results ($P = 0.468, 0.255$, respectively).

Drug provocation test results

Diagnostic OPTs with the culprit PPIs were performed in 12 patients in whom diagnostic skin tests with the culprit drug were negative (Table 1). Eight of them were positive (66.7%). Of these eight patients with a positive diagnostic OPT, three had history of grade 1, three had grade 2, and two had grade 3 reactions. All of the four patients with negative OPTs with the suspect PPI had a history of grade 1 reaction. All provoked patients reacted to the culprit drug during the first hour of the OPTs. The severity of these reactions was grade 1 in three (37.5%), grade 2 in three (37.5%), and grade 3 in two patients (25%). All reactions showed full recovery shortly after treatment.

Oral provocation tests with the PPIs other than the culprit PPI in the clinical history which displayed negative results in skin tests were performed in 61 patients (61/65, 93.8%). Positivity rates were as follows: 3/49 (6.1%) for omeprazole, 0/12 for lansoprazole, 2/44 (4.5%) for pantoprazole, 3/47 (6.4%) for rabeprazole, and 1/42 (2.4%) for esomeprazole.

Diagnostic value of skin tests and cross-reactivity among proton pump inhibitors

The results of the diagnostic procedures are summarized in Fig. 1. Six of the 40 patients with negative skin test responses to the suspect PPI reacted to at least one PPI other than the culprit one during the OPTs. These reactions were assumed as cross-reactivity, and further OPTs with the culprit PPI were not performed. We were able to check negative skin test results by means of OPTs in 12 of the remaining 34 patients. Thus, a definitive diagnosis could not be provided for 22

(36.7%) patients. These 22 patients together with the five patients who refused diagnostic skin testing were excluded from the accuracy analysis of the diagnostic skin tests. Of the remaining 38 patients, four had a negative diagnostic OPT and 20 had positive diagnostic skin tests, other 14 patients with PPI hypersensitivity had negative diagnostic skin tests. Thus, the sensitivity, specificity, and negative and positive predictive values of the skin tests with PPIs were 58.8%, 100%, 70.8%, and 100%, respectively. Age, gender, interval between the reaction and diagnostic tests, time to onset of the reaction after last exposure, and severity of the reaction were not different statistically between the 38 patients with a definitive diagnosis and the 27 patients who were excluded from the accuracy analysis ($P > 0.05$).

Sixteen of the 34 patients (47.1%) with PPI hypersensitivity had at least one cross-reaction. Fifteen (48.4%) of the 31 patients with hypersensitivity reaction to lansoprazole showed positivity on skin tests or OPTs with the other PPIs (8/52 pantoprazole, 6/52 omeprazole, 5/52 esomeprazole, 3/52 rabeprazole). Among four patients with hypersensitivity to pantoprazole, one had positive skin test results with lansoprazole and esomeprazole (Table 1, patient-4), one had a positive skin test result with omeprazole (Table 1, patient-14), and one had a reaction history with esomeprazole (Table 1, patient-9). Cross-reactivity among all of the five PPIs was detected in only one patient (Table 1, patient-23).

Discussion

In this study, we analyzed the diagnostic value of skin tests and cross-reactivity patterns among PPIs in a group of 38 patients with PPI-induced immediate-type hypersensitivity reactions. The specificity and positive predictive value of our skin tests were both 100%, whereas the sensitivity and negative predictive value were 58.8% and 70.8%, respectively. There have been several reports of hypersensitivity reactions to PPIs (4–14), most being case reports with few patients. One large study (15) has compared the diagnostic performance of skin tests vs OPTs in 53 patients with immediate reactions to PPIs. They reported 100% specificity and 100% positive predictive value that were in agreement with our data, and 91.9% negative predictive value and 61.3% sensitivity that were higher than our results. In that study, patients with previous grade 1 and grade 2 reactions underwent OPT, and these tests ruled out PPI hypersensitivity in 85% of the subjects (15). However, we could perform confirmatory OPT in only a small part of patients with negative skin test results (12 patients), which is the limitation of our study. Despite the negative skin test results, the majority (8/12, 66.7%) of our patients reacted to provoked PPI which supported low rate of negative predictive value. Of the 12 patients, seven had a history of grade 1, three had grade 2, and two had grade 3 reactions. All patients with negative OPT results had previous grade 1 reaction. On the contrary, the great majority of patients challenged with implicated PPI by Bonadonna et al. (15) had previous grade 1 reaction. Therefore, this difference may be attributed to the fact that

Table 1 Clinical characteristics, skin test and oral provocation test (OPT) results of the patients (patients 1–20, patients with positive skin test results with the suspected PPI; patients 21–26, 6 patients who had negative skin test responses to the suspect PPI but positive OPTs with at least one of the alternative PPIs; patients 27–38, 12 patients in whom OPTs with the suspected drug were performed; patients 61–65, 5 patients who refused skin testing with the suspected PPI)

Patient	Age	Gender	Drug*	Reaction	Grade	Latency†	Time‡	Skin tests					OPT				
								O	L	P	R	E	O	L	P	R	E
1	47	F	R	U	1	3	2	–	–	–	+	–	–	–	–	np	–
2	51	F	L	U, A, D	2	0.25	8	–	+	+	–	–	–	np	np	–	–
3	59	F	L	U, A, D, V	3	0.5	1	–	+	–	–	–	–	np	–	–	–
4	78	M	L, P, E	U	1	1	8	–	+	–	–	+	–	np	np	–	np
5	30	F	L	U, A	1	0.5	3	+	+	–	–	–	np	np	–	–	–
6	55	F	L	A	1	0.5	24	–	+	–	–	+	+	np	–	–	np
7	41	M	L	U, A, D	2	0.5	2.5	–	+	–	–	–	–	np	–	–	–
8	53	F	L	U	1	0.25	3	–	+	+	–	–	–	np	np	–	–
9	32	M	P, E	H	2	0.25	2	–	–	+	–	–	–	–	np	–	np
10	52	F	L	U, V	3	0.25	12	–	+	–	–	–	–	np	–	–	–
11	22	F	L, E	U	1	1	2	–	+	–	–	+	–	np	–	–	np
12	49	M	L	A	1	0.4	15	–	+	–	–	–	–	np	–	–	–
13	52	F	L	U, R, D	2	0.25	3	–	+	–	–	–	–	np	–	–	–
14	29	F	L, P	P, V, S	3	2	3	+	–	+	–	–	np	np	np	–	–
15	52	F	L	U	1	0.3	2	–	+	–	–	–	–	np	+	–	–
16	51	F	L	A, V, H	3	0.5	5	–	+	–	–	–	–	np	–	–	–
17	37	M	L	U	1	1	2	–	+	+	–	–	–	np	np	–	–
18	37	F	L	P, D, H	2	0.5	12	–	+	–	–	–	–	np	–	–	–
19	41	F	L	U, A, V, Dia	3	0.5	18	–	+	–	–	–	–	np	–	–	–
20	36	F	L	U, D, V	3	0.1	1	–	+	–	np	–	–	np	–	np	–
21	75	F	L	U, A	1	1	12	–	–	–	–	–	–	np	–	–	+
22	41	F	L	U	1	0.5	1	–	–	–	–	–	–	np	–	+	–
23	30	F	L	U, V	3	0.15	3	+	–	+	–	+	np	np	np	+	np
24	51	F	L	U	1	0.5	2	–	–	–	–	–	–	np	+	–	–
25	40	F	L	U, A	1	2	30	–	–	–	–	–	+	np	–	–	–
26	32	F	L	U, N, H	2	1	10	–	–	+	–	–	+	np	np	+	–
27	52	F	L	A	1	24	48	–	–	–	–	–	–	–	–	–	–
28	35	F	L	U, A	1	7	12	–	–	np	np	np	np	–	np	np	np
29	56	F	L	U	1	1	Unknown	np	–	np	np	–	np	–	np	np	–
30	55	F	L	U, A	1	0.5	3	–	–	–	–	–	–	+	–	–	–
31	40	F	E	A	1	24	2	–	–	–	–	–	–	–	–	–	–
32	22	F	L	U, A	1	4	20	–	–	–	–	–	–	+	–	–	–
33	69	M	L	U, D	2	1	12	–	–	–	–	–	–	+	–	–	–
34	41	F	L	U, H	2	0.25	48	–	–	–	–	–	–	+	–	–	–
35	45	F	L	A, D, V	3	0.1	12	–	–	–	–	–	–	+	–	–	–
36	45	F	L	U, A	1	3	3	–	–	–	–	–	–	+	–	–	–
37	44	F	P	U, V	3	1	1	np	–	–	np	np	np	–	+	np	np
38	51	M	L	U, A, D	2	0.6	24	–	–	–	np	np	–	+	–	np	np
39	30	F	P	U, A, D, H	2	0.25	18	–	–	–	–	–	–	–	np	–	–
40	38	F	L	U, A	1	8	3	np	–	np	np	–	np	np	np	np	–
41	47	F	E	U, A	1	24	1	–	–	–	–	–	–	–	–	–	np
42	28	F	P	U	1	10	7	–	–	–	–	–	–	–	np	–	–
43	43	F	L	U, V, Dia	3	18	1	–	–	–	–	–	–	np	–	–	–
44	31	F	L, E	U, A, D	2	9	24	–	–	–	–	–	–	np	–	–	np
45	40	F	L	U, H	2	0.5	24	–	–	–	–	–	–	np	–	–	–
46	44	F	L	U	1	1	Unknown	–	–	–	np	np	–	np	–	np	np
47	35	F	E, P	U	1	1	4	–	–	–	np	np	np	np	np	np	np
48	53	F	L	U, A	1	1	2	–	–	–	np	np	np	np	np	np	np
49	26	F	P	U, A, H	2	0.5	72	–	–	–	–	–	–	–	np	np	–
50	49	M	P	U	1	0.5	12	–	–	–	–	–	–	–	np	–	–
51	43	F	L	U, A	1	0.1	2	–	–	–	–	–	–	np	–	–	–

Table 1 (continued)

Patient	Age	Gender	Drug*	Reaction	Grade	Latency†	Time‡	Skin tests					OPT				
								O	L	P	R	E	O	L	P	R	E
52	47	F	L	U, N	2	1	2	–	–	–	–	–	–	np	–	–	–
53	41	F	R, L, E	U	1	0.5	2	–	–	–	–	–	–	np	–	np	np
54	50	F	L	A, D	2	0.5	2	–	–	–	–	–	–	np	–	–	–
55	38	M	E	U	1	3	7	–	–	–	–	–	–	–	–	–	np
56	41	M	O, E	H, V	3	0.1	2	–	–	–	–	–	np	–	–	–	np
57	53	M	L	U, H	2	1.5	1	np	–	np	np	–	np	np	np	np	–
58	49	F	L	U, A, H	2	0.1	60	–	–	–	–	–	–	np	np	–	–
59	42	F	L	U, A, D	2	1	3.5	–	–	–	–	–	–	np	–	–	–
60	41	F	E	U, A	1	0.1	1.5	–	–	–	–	–	–	–	–	–	np
61	34	M	L	U	1	1	Unknown	np	np	–	np	np	np	np	–	np	np
62	69	F	L	A, D	2	1	4	np	np	–	np	np	np	np	–	np	np
63	44	F	L	U, A, D, H	2	1	1	np	np	–	np	np	np	np	–	np	np
64	52	F	L	U, D, H	2	2	1	–	np	–	np	np	np	np	np	np	np
65	29	F	L	U, D	2	1	2	np	np	–	np	np	np	np	–	np	np

O, omeprazole; L, lansoprazole; P, pantoprazole; R, rabeprazole; E, esomeprazole; F, female; M, male; U, urticaria; A, angioedema; D, dyspnea; Dia, diarrhea; H, hypotension; N, nausea; P, pruritus; R, rhinitis; S, syncope; V, vomiting; np, not performed.

*Suspected PPI.

†Time interval between the last administration of the drug and the reaction, hours.

‡Time interval between the PPI reaction and the diagnostic tests, months.

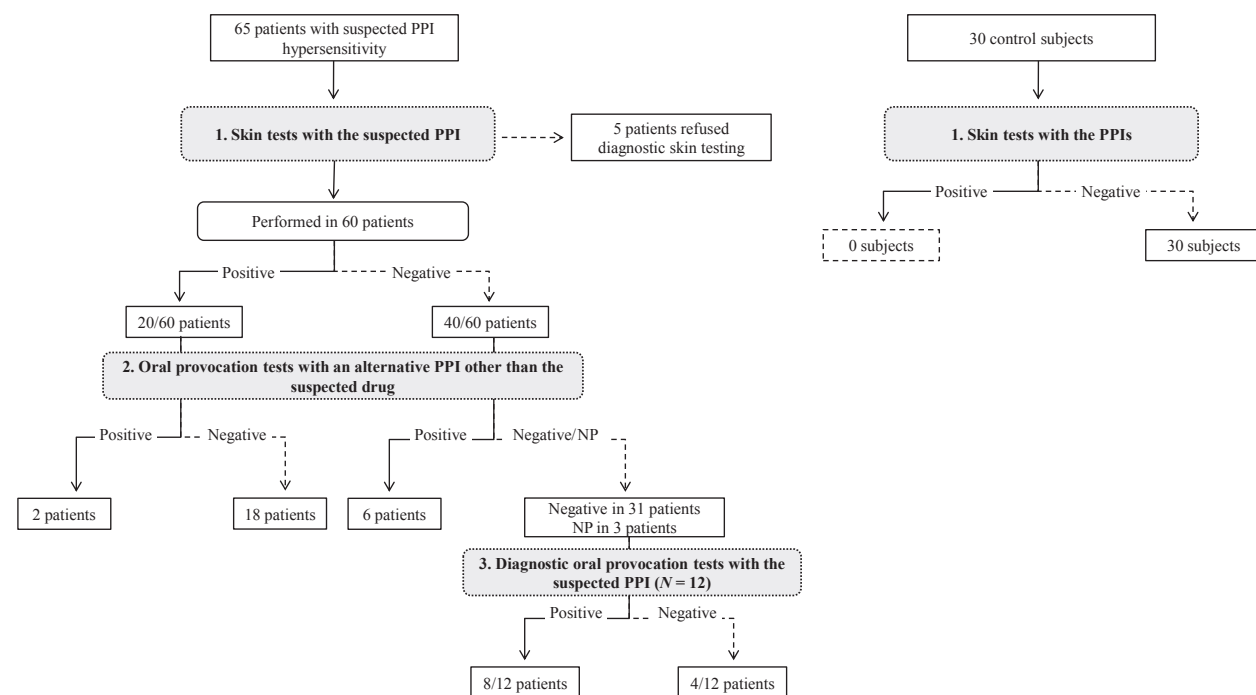


Figure 1 Steps and results of the allergologic work-up in 30 control subjects and in 65 patients with symptoms suggestive of

an immediate hypersensitivity reaction after administration of PPIs (NP, not performed).

severities of the reactions were different. We used skin test concentrations that were proved nonirritating in 30 control subjects because none of the controls showed positivity in skin tests. On the basis of literature data showing

confirmation of skin test positivity with OPT with PPIs (4–6, 9, 15), and considering the ethical aspect, we did not perform confirmatory OPT in patients with skin test positivity to the culprit or alternative PPI.

Table 2 Details of skin test results of the 20 patients who showed skin test positivity to the culprit PPI

Patient	Drug*	Skin tests				
		O	L	P	R	E
3	L	–	+ (30 mg/ml, prick)	–	–	–
7	L	–	+ (30 mg/ml, prick)	–	–	–
10	L	–	+ (30 mg/ml, prick)	–	–	–
12	L	–	+ (30 mg/ml, prick)	–	–	–
13	L	–	+ (30 mg/ml, prick)	–	–	–
15	L	–	+ (30 mg/ml, prick)	–	–	–
16	L	–	+ (30 mg/ml, prick)	–	–	–
18	L	–	+ (30 mg/ml, prick)	–	–	–
19	L	–	+ (30 mg/ml, prick)	–	–	–
20	L	–	+ (30 mg/ml, prick)	–	np	–
2	L	–	+ (30 mg/ml, prick)	+ (0.04 mg/ml, ID)	–	–
8	L	–	+ (30 mg/ml, prick)	+ (0.004 mg/ml, ID)	–	–
17	L	–	+ (30 mg/ml, prick)	+ (0.004 mg/ml, ID)	–	–
6	L	–	+ (30 mg/ml, prick)	–	–	+ (0.8 mg/ml, ID)
11	L, E	–	+ (30 mg/ml, prick)	–	–	+ (0.008 mg/ml, ID)
4	L, P, E	–	+ (30 mg/ml, prick)	–	–	+ (20 mg/ml, prick)
14	L, P	+ (4 mg/ml, prick)	–	+ (0.04 mg/ml, ID)	–	–
5	L	+ (0.04 mg/ml, ID)	+ (30 mg/ml, prick)	–	–	–
9	P, E	–	–	+ (0.4 mg/ml, 40 mg/ml prick)†	–	–
1	R	–	–	–	+ (20 mg/ml, prick)	–

O, omeprazole; L, lansoprazole; P, pantoprazole; R, rabeprazole; E, esomeprazole; ID, intradermal test; np, not performed.

*Culprit PPI.

†Patient-9 had positive skin prick test results with both oral (40 mg/ml) and injectable (0.4 mg/ml) preparations of pantoprazole.

Omeprazole and pantoprazole have, respectively, a methoxy and a difluoromethoxy chain in their benzimidazole ring, whereas lansoprazole and rabeprazole have no modifications in that ring, but their pyridine rings have, respectively, a trifluoroethoxy and methoxypropoxy chain (9). Previous reports on reactions to PPIs describe the presence of cross-reactivity of the whole group which could be explained by structural similarity (7, 10). In keeping with that, there are case reports demonstrating cross-reactivity between lansoprazole and rabeprazole (5, 19). In our trial, the drug most frequently involved was lansoprazole, and of the 31 patients with a lansoprazole-induced hypersensitivity reaction, 15 (48.4%) reacted to the other PPIs on skin tests or OPTs (8/52 pantoprazole, 6/52 omeprazole, 5/52 esomeprazole, 3/52 rabeprazole). These results do not agree with those obtained in another study, in which patients sensitized to lansoprazole and rabeprazole had negative test results with the other PPIs (15). In isolated cases, cross-reactivity between omeprazole and lansoprazole (9, 20) and between omeprazole, pantoprazole, and lansoprazole (4, 21) has been reported, previously. This was also the case in our study. However, we observed many different patterns of cross-reactivity. Despite the molecular differences, the most common pattern was lansoprazole and pantoprazole cross-reactivity. The different patterns of cross-reactivity shown in this and the previous studies suggest that several chemical characteristics (e.g. substitutions, metabolites) may be involved. The data point to the importance of a thorough drug allergy work-up for finding safe alternatives and of not assuming the cross-reactivity of the whole group.

In this study, the majority of the historical reactions had occurred in < 1 h, but in a small group, the interval between the last drug dose and the reaction was between one and 24 h. We did not exclude these cases with immediate-type symptoms for two reasons. Firstly, the enteric coating of the PPIs may cause a delay in the onset of the reaction. Secondly, it is problematic to separate drug hypersensitivities into immediate and nonimmediate reactions at an arbitrary cutoff of 1 hour only (22). Nevertheless, the interval between the last drug dose and the reaction was shorter in skin test-positive patients than skin test-negative patients.

In conclusion, this study reports that skin tests in PPI-induced immediate hypersensitivity reactions have perfect specificity and positive predictive value but low sensitivity. Considering that, skin testing seems to be a useful method for the diagnosis of immediate-type hypersensitivity reactions to PPIs and for the evaluation of cross-reactivity among PPIs. However, OPT should be performed in case of negativity on skin tests.

Author contributions

SB designed the study. All authors were involved in acquisition and interpretation of data and in revision of the content. SKO and SB wrote the manuscript.

Conflicts of interest

None of the authors has a conflict of interest pertaining to this study.

References

1. Savarino V, Di Mario F, Scarpignato C. Proton pump inhibitors in GORD: An overview of their pharmacology, efficacy and safety. *Pharmacol Res* 2009;**59**:135–153.
2. Gouraud A, Vochelle V, Descotes J, Vial T. Proton pump inhibitor-induced neutropenia: possible cross-reactivity between omeprazole and pantoprazole. *Clin Drug Investig* 2010;**30**:559–563.
3. Thomson AB, Sauve MD, Kassam N, Kamitakahara H. Safety of the long-term use of proton pump inhibitors. *World J Gastroenterol* 2010;**16**:2323–2330.
4. González P, Soriano V, López P, Niveiro E. Anaphylaxis to proton pump inhibitors. *Allergol Immunopathol (Madr)* 2002;**30**:342–343.
5. Pérez Pimiento AJ, Prieto Lastra L, Rodríguez Cabreros MI, González Sánchez LA, Mosquera MR, García Cubero A. Hypersensitivity to lansoprazole and rabeprazole with tolerance to other proton pump inhibitors. *J Allergy Clin Immunol* 2006;**117**:707–708.
6. Demirkan K, Bozkurt B, Karakaya G, Kalayoncu AF. Anaphylactic reaction to drugs commonly used for gastrointestinal system diseases: 3 case reports and review of the literature. *J Investig Allergol Clin Immunol* 2006;**16**:203–209.
7. Garrido S, Cumplido JA, Rábano A, Martínez D, Blanco C, Carrillo T. Allergy to proton pump inhibitors: diagnosis and assessment of cross-reactivity. *J Investig Allergol Clin Immunol* 2008;**18**:140–141.
8. Vovolis V, Koutsostathis N, Stefanaki E. IgE-mediated anaphylaxis to proton pump inhibitors – cross-reacting study. *Allergy* 2008;**63**:1251–1252.
9. Lobera T, Navarro B, Del Pozo MD, González I, Blasco A, Escudero R et al. Nine cases of omeprazole allergy: cross-reactivity between proton pump inhibitors. *J Investig Allergol Clin Immunol* 2009;**19**:57–60.
10. Sobrevia Elfau MT, Garcés Sotillos M, Ferrer Clavería L, Segura Arazuri N, Monzón Ballarín S, Colás Sanz C. Study of cross-reactivity between proton pump inhibitors. *J Investig Allergol Clin Immunol* 2010;**20**:157–161.
11. Pérez-Ezquerro PR, Morillas LS, Martínez JJ, Fernández DG, Gomez-Tebleque Mdel P, Alvarez AS et al. Anaphylaxis to omeprazole. Cross-reactivity with the other proton pump inhibitors. *Allergol Immunopathol (Madr)* 2011;**39**:54.
12. Vovolis V, Christogianni K, Koutsostathis N. Immunoglobulin E-mediated anaphylaxis to rabeprazole. *J Investig Allergol Clin Immunol* 2010;**20**:360–361.
13. Abdul Razzak E, Tomás M, Tornero P, Herrero T. Nine cases of allergy to omeprazole. *J Investig Allergol Clin Immunol* 2012;**22**:228–230.
14. Aksu K, Kurt E. Anaphylaxis to lansoprazole with tolerance to omeprazole. *Allergol Immunopathol (Madr)* 2012;**40**:393–394.
15. Bonadonna P, Lombardo C, Bortolami O, Bircher A, Scherer K, Barbaud A et al. Hypersensitivity to proton pump inhibitors: diagnostic accuracy of skin tests compared to oral provocation test. *J Allergy Clin Immunol* 2012;**130**:547–549.
16. Demoly P, Kropf R, Bircher A, Pichler WJ. Drug hypersensitivity: questionnaire. EAACI interest group on drug hypersensitivity. *Allergy* 1999;**54**:999–1003.
17. Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. *Lancet* 1977;**1**:466–469.
18. Brockow K, Romano A, Blanca M, Ring J, Picher W, Demoly P. General considerations for skin test procedure in the diagnosis of drug hypersensitivity. *Allergy* 2002;**57**:45–51.
19. Porcel S, Rodríguez A, Jiménez S, Alvarado M, Hernández J. Allergy to lansoprazole: study of cross-reactivity among proton pump inhibitors. *Allergy* 2005;**60**:1087–1088.
20. Tayman C, Mete E, Catal F, Tonbul A. Hypersensitivity reaction to omeprazole in a child. *J Investig Allergol Clin Immunol* 2009;**19**:64–79.
21. Garmendio Zallo M, Sánchez Azkarate A, Kraemer Mbula R, Liarte I, Nuñez Hernandez A, Cid de Rivera C. Cross reactivity among proton pump inhibitors: does it exist? *Allergol Immunopathol (Madr)* 2004;**32**:92–95.
22. Bircher AJ, Scherer Hofmeier K. Drug hypersensitivity reactions: Inconsistency in the use of the classification of immediate and nonimmediate reactions. *J Allergy Clin Immunol* 2012;**129**:263–264.