

Analysis of the factors associated with diagnostic skin test positivity in immediate-type hypersensitivity reactions due to proton pump inhibitors

To the Editor,

In the last decade, there has been an increase in hypersensitivity reactions due to proton pump inhibitors (PPIs), probably related to their increasing consumption.¹ Immediate-type reactions account for the majority of hypersensitivity reactions to PPIs, and roughly, half of all reactions are severe enough to be considered as anaphylaxis.² Our previous study showed that skin tests in PPI-induced immediate hypersensitivity reactions had perfect specificity and positive predictive values but low sensitivity.³ However, the factors associated with diagnostic skin test positivity in immediate-type hypersensitivity reactions due to PPIs have not been sufficiently investigated. This report describes the results of our secondary analysis of the data from our two previous studies,^{3,4} with the addition of new eligible patients who were referred to the study centers after the completion of these studies. The report aims to investigate the factors associated with skin test positivity in PPI-induced immediate-type hypersensitivity reactions.

The criteria used for the inclusion of patients to the current multicenter study were as follows: a definitive/highly probable diagnosis

of immediate-type PPI hypersensitivity and to have undergone diagnostic skin tests with the culprit PPI. A definitive/highly probable diagnosis of immediate-type PPI hypersensitivity was accepted as a suggestive history of a PPI-induced immediate hypersensitivity reaction and positive skin test or oral provocation test (OPT) results with the culprit and/or alternative PPIs. On the basis of these criteria, we included data from our previously published two studies performed in 2011-2012 and 2013-2016.^{3,4} Thirty-four and 14 patients, respectively, from these studies met the inclusion criteria.^{3,4} Additionally, we retrospectively reviewed charts of 88 new patients, who were referred in the period of 2016-2018, with a history suggestive of an immediate hypersensitivity reaction after administration of a PPI. We included the data of these new patients, who were eligible based on the same inclusion criteria. The study was approved by the Local Ethics Committee of Ankara University, School of Medicine. Details for methods are provided in this article's Data S1.

A total of 88 patients were referred to the study centers with a history suggestive of a PPI-induced immediate hypersensitivity

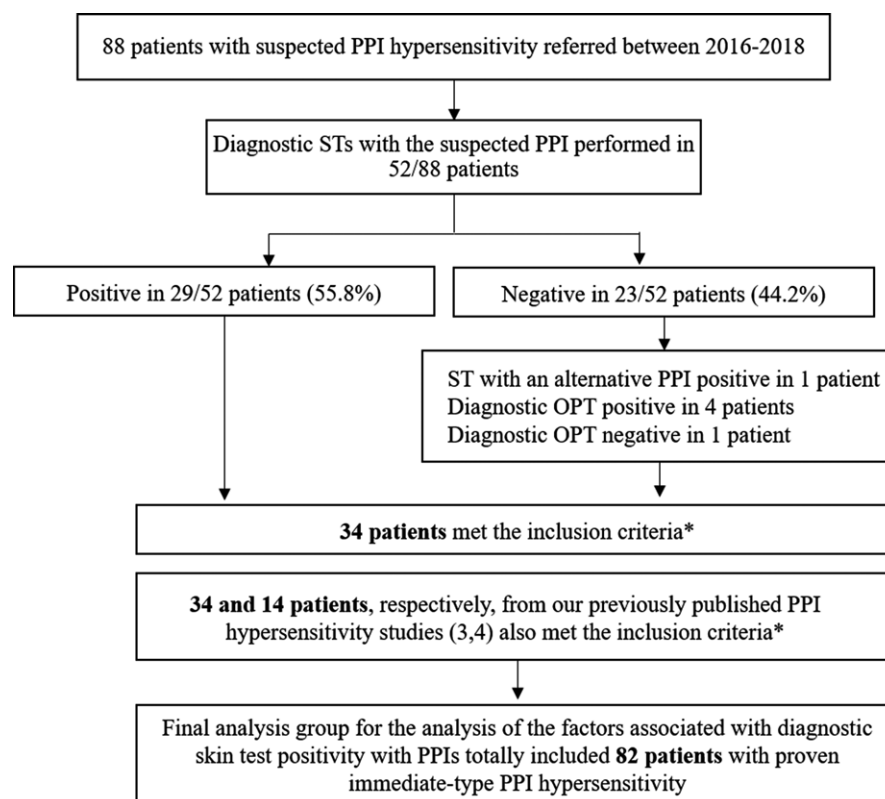


FIGURE 1 Inclusion of the patients to the final analysis group for the analysis of the factors associated with diagnostic skin test positivity (*a definitive diagnosis of proton pump inhibitor (PPI) hypersensitivity and having results of diagnostic skin tests with the culprit PPI; ST, skin test)

TABLE 1 Characteristics of the patients with positive and negative diagnostic skin test results with proton pump inhibitors (PPIs)

	Patients with positive diagnostic skin test results	Patients with negative diagnostic skin test results	P value
n	62 (75.6%)	20 (24.4%)	-
Gender (F/M)	53 (85.5%)/9 (14.5%)	18 (90.0%)/2 (10.0%)	0.606
Age, median (min-max)	46 (22-78)	42.5 (22-75)	0.749
Time to onset of the reaction after last exposure, median (min-max) hours	1.0 (0.1-8.0)	0.5 (0.1-4.0)	0.823
Interval between the reaction and the diagnostic tests, median (min-max) months	3 (0.5-36)	12 (1-60)	0.047
Severity of the reaction,			
Grade 1, n (%)	24 (38.7%)	10 (50.0%)	0.672
Grade 2, n (%)	19 (30.6%)	5 (25.0%)	
Grade 3, n (%)	19 (30.6%)	5 (25.0%)	
Prevalence of anaphylaxis, n (%)	38 (61.3%)	10 (50.0%)	0.373

Bold values indicates statistically significant.

reaction between 2016 and 2018. Of these, 85.2% (n = 75) were female, and the median age was 47.0 years (min-max: 19-77 years). Lansoprazole was the most commonly suspected drug in 56 (63.6%) patients, followed by pantoprazole in 16 (18.2%) patients, esomeprazole in 13 (14.8%) patients, omeprazole in 3 (3.4%) patients, and rabeprazole in 2 (2.3%) patients. The median time interval between the last reaction and diagnostic tests was 6 months (min-max: 0.5-60 months), and the median time interval between the last administration of the drug and the reaction was 1 hour (min-max: 0.1-12 hours). The clinical symptoms were urticaria and/or angioedema in 45 (51.1%) patients, anaphylaxis in 41 (46.6%) patients, and intense pruritus and erythema in 2 patients (2.3%). The severity of the reaction was grade 1 in 47 (53.4%) patients, grade 2 in 21 (23.9%) patients, grade 3 in 19 (21.6%) patients, and grade 4 in 1 (1.1%) patient. Additional data regarding the clinical characteristics of these 88 patients are provided in Data S1. Diagnostic skin tests with the suspected PPI were performed on 52/88 patients, which resulted as positive in 29/52 (55.8%) patients. Among these 29 patients, 27 (93.1%) had positivity on SPT, and two on IDT. A definitive diagnosis was obtained with skin testing and/or OPTs with the suspected and/or alternative PPI in 41 patients (positive in 40 patients and negative in one patient). Diagnostic skin testing with the suspected PPI was performed in 34 of these 40 patients with a positive definitive diagnosis; therefore, these 34 patients were included in the analysis of the factors associated with diagnostic skin test positivity (Figure 1, Table S1).

The population of the analysis of factors associated with diagnostic skin test positivity comprised 82 patients with proven PPI hypersensitivity: 34 and 14 patients from our previous PPI hypersensitivity studies, respectively,^{3,4} and the 34 new patients (Figure 1, Table S1). Time to reaction onset after the last exposure, reaction severity, and the prevalence of anaphylactic reactions were not statistically different between patients with negative and positive skin test results (Table 1). Age, sex, and prevalence of concomitant allergic diseases were also similar among patients with negative and positive skin test results ($P = 0.749$, $P = 0.606$, $P = 0.607$, respectively). The time interval between the reaction and the diagnostic tests was

shorter in patients with positive skin test results (median [min-max] 3.0 [0.5-36.0] vs 12.0 [1.0-60.0] months; $P = 0.047$). Patients with a duration of ≤ 6 months between the reactions and the diagnostic tests were found to have a higher positivity rate of diagnostic skin tests (43/51, 84.3% vs 16/27, 59.3%; $P = 0.014$).

In the current study, the only factor that showed a significant difference was the time interval between the reaction and the diagnostic tests. Similar results were obtained in other studies among patients with immediate hypersensitivity reactions to contrast media and beta-lactams.⁵⁻⁸ In a recent study in patients with omeprazole hypersensitivity, no correlation was observed between the time intervals between the last reaction and the performance of basophil activation test or skin test results.¹ However, the time interval between the reaction and diagnostic testing was shorter in that study.¹ Similarly, Bonadonna et al⁹ found no difference in the interval between the reaction and the diagnostic procedure between patients with positive and negative skin test results. Time intervals were not given in that study.⁹ The numbers of patients included in these two studies were lower (42 and 53 patients, respectively)^{1,9} than in the present study. Additionally, the culprit PPIs were different, and the frequencies of anaphylaxis were lower in the studies of Bonadonna et al and Laguna et al.^{1,9} These factors may contribute to this discrepancy.

In conclusion, performing diagnostic tests within 6 months of a reaction increases the likelihood of positivity in skin tests. Reaction severity, the presence of an anaphylactic reaction, age, sex, and the presence of concomitant allergic diseases do not seem to be associated with skin test positivity with culprit PPIs.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

1

2 **Table 1. Clinical characteristics of the 82 patients with a definitive diagnosis of PPI**
3 **hypersensitivity.**

Patient	Age	Gender	Drug	Reaction	Skin tests					OPT				
					O	L	P	R	E	O	L	P	R	E
1	24	F	L	anap	np	+	np	np	-	np	np	np	np	-
2	41	F	L	anap	np	+	-	np	np	np	np	-	np	np
3	51	M	L	anap	np	+	-	np	np	np	np	-	np	np
4	40	F	L	anap	np	-	-	np	np	np	+	-	np	np
5	x	F	L	anap	np	+	np	np	-	np	np	np	np	-
6	47	F	L	anap	-	+	-	-	-	-	np	-	-	-
7	61	F	E	pru	-	-	+§	-	+	+	-	np	-	np
8	36	F	P	urt	-	-	-	-	-	-	-	+	-	-
9	46	F	L	anap	np	+	-	-	np	np	np	np	-	np
10	49	F	L	anap	np	+	-	-	-	np	np	np	-	np
11	59	F	L	urt	np	+	-	-	-	np	np	-	np	np
12	36	F	L	anap	np	+	-	np	-	np	np	np	np	-
13	39	F	L	anap	np	+	-	-	np	np	np	np	-	np
14	52	F	L	urt	np	+	-	-	-	np	np	np	-	np
15	57	F	P	urt	np	-	+	np	-	np	np	np	np	-
16	51	F	L	urt	np	+	-	-	np	np	np	np	-	np
17	39	F	L	anap	np	+	-	-	np	np	np	+	-	np
18	56	F	L	anap	np	+	-	-	-	np	np	np	-	np
19	34	F	L	anap	np	+	-	-	-	np	np	-	+	np
20	61	M	L	anap	np	+	-	-	np	np	np	np	-	np
21	55	F	L	anap	np	+	-	np	-	np	np	-	np	np
22	69	F	E	urt	-	np	-	np	+§	np	np	-	np	np
23	32	F	L	urt	np	+	-	-	-	np	np	np	-	+
24	43	F	L	urt	np	+	-	-	np	np	np	-	np	np
25	65	F	L	urt	np	+	-	-	-	np	np	np	-	np
26	30	M	E	urt	np	-	-	-	+	np	np	-	np	np
27	37	F	L	urt	np	+	-	-	-	np	np	np	-	np
28	38	F	P	urt	np	-	+§	-	np	np	-	np	np	np
29	39	F	O	anap	-	-	-	np	np	+	-	-	np	np
30	51	F	O	urt	-	-	np	np	np	+	-	np	np	np
31	48	F	L	anap	np	+	-	np	-	np	np	np	-	-
32	44	F	L	anap	np	-	-	np	+§	np	np	-	np	np
33	30	F	L	anap	np	+	-	np	np	np	np	-	np	np
34	50	F	L	anap	np	+	np	np	np	np	np	np	np	np
35	47	F	R	urt	-	-	-	+	-	-	-	-	np	-
36	51	F	L	anap	-	+	+§	-	-	-	np	np	-	-
37	59	F	L	anap	-	+	-	-	-	-	np	-	-	-
38	78	M	L,P,E	urt	-	+	-	-	+	-	np	np	-	np
39	30	F	L	urt	+§	+	-	-	-	np	np	-	-	-
40	55	F	L	ang	-	+	-	-	+§	+	np	-	-	np

41	41	M	L	anap	-	+	*	-	-	-	-	np	-	-	-
42	53	F	L	urt	-	+	*	+	§	-	-	-	np	np	-
43	32	M	P,E	anap	-	-	+	*	-	-	-	-	np	-	np
44	52	F	L	anap	-	+	*	-	-	-	-	np	-	-	-
45	22	F	L,E	urt	-	+	*	-	-	+	§	-	np	-	np
46	49	M	L	ang	-	+	*	-	-	-	-	np	-	-	-
47	52	F	L	anap	-	+	*	-	-	-	-	np	-	-	-
48	29	F	L,P	anap	+	*	-	+	§	-	-	np	np	np	-
49	52	F	L	urt	-	+	*	-	-	-	-	np	+	-	-
50	51	F	L	anap	-	+	*	-	-	-	-	np	-	-	-
51	37	M	L	urt	-	+	*	+	§	-	-	-	np	np	-
52	37	F	L	anap	-	+	*	-	-	-	-	np	-	-	-
53	41	F	L	anap	-	+	*	-	-	-	-	np	-	-	-
54	36	F	L	anap	-	+	*	-	np	-	-	np	-	np	-
55	75	F	L	urt	-	-	-	-	-	-	-	np	-	-	+
56	41	F	L	urt	-	-	-	-	-	-	-	np	-	+	-
57	30	F	L	anap	+	*	-	+	*	-	+	np	np	np	+
58	51	F	L	urt	-	-	-	-	-	-	-	np	+	-	-
59	40	F	L	urt	-	-	-	-	-	-	+	np	-	-	-
60	32	F	L	anap	-	-	-	+	*	-	-	+	np	np	+
61	55	F	L	urt	-	-	-	-	-	-	-	+	-	-	-
62	22	F	L	urt	-	-	-	-	-	-	-	+	-	-	-
63	69	M	L	anap	-	-	-	-	-	-	-	+	-	-	-
64	41	F	L	anap	-	-	-	-	-	-	-	+	-	-	-
65	45	F	L	anap	-	-	-	-	-	-	-	+	-	-	-
66	45	F	L	urt	-	-	-	-	-	-	-	+	-	-	-
67	44	F	P	anap	np	-	-	-	np	np	np	-	+	np	np
68	51	M	L	anap	-	-	-	-	np	np	-	+	-	np	np
69	59	F	L	anap	np	+	*	np	np	-	np	np	np	np	np
70	29	F	P	anap	np	-	-	+	§	np	np	np	np	np	np
71	29	F	P	anap	+	§	-	+	*	+	§	np	+	np	np
72	25	F	P	anap	np	np	+	§	np	np	np	-	np	np	+
73	45	F	E,R,L	urt	np	-	-	+	*	np	+	*	np	np	np
74	60	F	L	anap	np	+	*	-	np	np	np	np	-	np	np
75	44	F	E	anap	-	-	np	+	*	np	+	§	-	-	np
76	43	F	L	anap	np	+	*	-	np	np	np	np	-	np	np
77	50	F	L	anap	np	+	*	-	np	np	np	np	-	np	np
78	69	F	L	anap	np	+	*	-	np	np	np	np	-	np	np
79	39	F	L	urt	-	+	*	-	np	-	-	np	-	np	-
80	38	F	L	urt	np	-	-	+	*	np	-	np	np	np	np
81	33	M	L	anap	np	+	*	np	-	-	-	np	np	np	np
82	44	F	L	pru	np	+	*	-	np	np	np	np	-	np	np

- 4 OPT, oral provocation test; O, omeprazole; L, lansoprazole; P, pantoprazole; R, rabeprazole;
- 5 E, esomeprazole; F, female; M, male; urt, urticaria; anap, anaphylaxis; pru, intense pruritus
- 6 and erythema; ang, angioedema; np, not performed; * positivity on skin prick test; § positivity
- 7 on intradermal test.

1 **Methods**

2 Demographics, clinical features, relevant medical history, and the results of skin tests and
3 OPTs with PPIs were analyzed. The severity of the reaction was assessed according to the
4 Ring-Messmer scale (1). For the diagnosis of anaphylaxis, we used the clinical criteria
5 proposed in the World Allergy Organization Anaphylaxis guidelines (2). We used skin test
6 concentrations previously proven as non-irritant in 30 healthy controls (3). Skin-prick tests
7 (SPTs) were performed with the undiluted commercial oral preparations of omeprazole
8 capsule (20 mg), lansoprazole capsule (30 mg), pantoprazole tablet (40 mg), rabeprazole
9 tablet (20 mg), and esomeprazole tablet (20 mg) and 1/10 and 1/1 dilutions of injectable
10 preparations of omeprazole (4 mg/mL), pantoprazole (4 mg/mL), and esomeprazole (8
11 mg/mL), along with positive (histamine 0.01%) and negative (saline 0.9%) controls. SPTs
12 were performed on the volar forearm, and were read after 20 minutes. A wheal reaction with a
13 mean diameter of 3 mm greater than the negative control was considered positive. If SPTs
14 were negative, intradermal tests (IDTs) were performed with the injectable preparations of
15 omeprazole (4 mg/mL), pantoprazole (4 mg/mL), and esomeprazole (8 mg/mL) at 1/1000,
16 1/100, and 1/10 dilutions. An amount of 0.03mL of test solution was injected into the skin to
17 produce a bleb. Readings were conducted after 15 minutes and were considered positive if the
18 size of the initial wheal had increased by at least 3 mm in diameter and was surrounded by
19 erythema.

20 Single-blind placebo-controlled OPTs with alternative PPIs after negative SPT results and/or
21 diagnostic OPTs with the culprit PPI were performed in patients with non-severe reactions
22 and gave consent. During these tests, an omeprazole capsule (5, 10, and 20 mg), a
23 lansoprazole capsule (7.5, 15, and 30 mg), a pantoprazole tablet (5, 10, and 20 mg), a
24 rabeprazole tablet (5, 10, and 20 mg), and an esomeprazole tablet (5, 10, and 20 mg) were
25 administered each on different days at 30-minintervals at increasing doses till reaching the full

dose or the symptoms of a drug reaction occurred. The test results were accepted as positive if objective clinical signs (urticaria, angioedema, bronchospasm, or other signs) were observed.

Statistical analysis

Comparisons for quantitative variables were performed using the Student's t-test or the Mann–Whitney U test and for qualitative variables by the chi-square test or the Fisher's exact test. P-values of < 0.05 were considered as statistically significant. The statistical analysis was performed using the SPSS program version 18.0 (SPSS Inc., Chicago, IL, USA).

Additional data regarding the clinical characteristics of the 88 patients with a suggestive history of a PPI-induced immediate hypersensitivity reaction:

Seventy five (85.2%) patients reported one and 13 patients (14.8%) reported more than one episode. Ten out of 13 patients reported more than one episode with the same PPI. SPT results with common inhalant allergens were available in 47 patients (53.4%), and 21 of these (44.7%) had positivity with common inhalant allergens. Majority of the patients (49 patients, 55.7%) had history of concomitant atopic diseases (22 patients (25.0%) had allergic rhinitis, 12 (13.6%) had asthma, 11 (12.5%) had chronic urticaria and/or angioedema, 2 (2.3%) had bee venom allergy, 1 (1.1%) had idiopathic anaphylaxis, and 1 (1.1%) had food hypersensitivity, 21 (23.9%) had other drug hypersensitivity – 12 cases with non-steroidal anti-inflammatory drugs, 5 with penicillins, 1 with a H2 receptor blocker, 1 with a muscle relaxant, 1 with a quinolone and 1 case with an unknown antibiotic).

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