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What is the place of empirical proton pump inhibitor testing in the diagnosis of gastroesophageal reflux disease? (Description, duration, and dosage)

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ABSTRACT

Empirical acid suppression tests that are performed with proton pump inhibitors (PPI) are used to detect both the presence of acid-related gastrointestinal symptoms and gastroesophageal reflux disease (GERD). In comparison to other diagnostic methods, it is non-invasive, easily applicable, and cost-effective in the diagnosis of GERD. In addition to typical reflux symptoms, it can also be used for diagnostic purposes in patients with non-cardiac chest pain (NCCP). If the symptom response is 50% and above when obtained using the PPI test in patients with NCCP, it can be considered as positive and the treatment should be continued sensitivity of the PPI test in patients with typical symptoms of GERD is 27%-89%, while its specificity is 35%-83%. Although there are differences related to the duration and dosage of the PPI test, a significant difference has not been found according to the type of PPI. When PPI test sensitivity and specificity were calculated by cumulatively evaluating the data regarding the PPI test in the literature, a sensitivity of 82.3% and specificity of 51.5% was obtained. It has been found that high doses of PPI were mostly used in studies, and the duration of the median test was 14 days. As a result, the sensitivity of PPI trial test is good, but the specificity is low in the diagnosis of GERD in patients with typical reflux symptoms.

Keywords: Empirical PPI test, GERD, PPI trial test

In routine clinical practice, empirical acid suppression tests that are performed with proton pump inhibitors (PPI) are used to detect the presence of acid-related upper gastrointestinal (GI) symptoms and GERD (1). Empirical PPI test is usually called as the "PPI test."" Its first diagnostic use in patients with GERD was in 1995 (2). In comparison to other diagnostic methods for the diagnosis of GERD, it is non-invasive, easily applicable, and cost-effective. It can also be used for diagnostic purposes in patients with NCCP in addition to typical reflux symptoms. Mostly, high doses were used in the studies performed as a PPI test using omeprazole, esomeprazole, lansoprazole, and rabeprazole (2-12). Questionnaires and symptom records were used in most studies for the assessment of PPI response; although the symptom response threshold varied according to the study, in comparison with the beginning of the test, a 50%-75% recovery in symptoms was acceptable. A significant difference was not detected among PPIs in terms of effectiveness (10-12).

Although the sensitivity of the PPI test is 27%-89% in patients with typical symptoms of GERD, its specificity is 35%-83% (2,4-8,13,14). Because of the use of different methods and populations in studies, it is quite difficult to make comparisons. Similarly, because different PPIs were used in the PPI test studies and the durations were also different, an optimal dose or duration could not be determined through meta-analyses or systematic reviews; however, the duration was determined as 7-14 days in most studies (3). Some of the PPI test studies were performed comparatively only with upper gastrointestinal endoscopy or 24h pH monitoring. The symptoms are associated with GERD in 60% of the NCCP cases, and the response to the treatment is fairly good (15-17). Although the sensitivity of the PPI test is 69%-95% in patients with GERD-related NCCP in different studies, its specificity is 67%-86% (3,9,10,18,19).

In the prospective study by Bytzer et al. (20) that consisted of 308 patients and was performed com-

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Table 1. The cumulative sensitivity and specificity values of the studies

	The number of patients	A	B	C	D
Fass et al. (3)	37	18	2	5	12
Pandak et al. (9)	38	11	16	5	6
Xia et al. (10)	36	11	8	1	16
Bautista et al. (11)	40	14	4	4	18
Pace et al. (23)	544	414	70	20	40
Dent et al. (27)	296	106	35	91	64
Cho et al. (28)	73	49	4	15	5
Kim et al. (25)	42	13	7	3	19
Aanen et al. (29)	67	41	17	5	4
Dekel et al. (30)	14	8	2	1	3
Bate et al. (7)	58	22	11	10	15
Fass et al. (31)	35	21	8	0	6
Juul-Hansen et al. (8)	56	29	11	5	11
Schenk et al. (2)	41	15	7	7	12
Juul-Hansen et al. (21)	52	34	17	0	1
Fass et al. (6)	42	28	3	7	4
Cumulative	1471	834	222	179	236

	Prevalance	68.9%							GERD +	GERD -
	Sensitivity	82.3%	PPV	79.0%	LR+	1.7	Odds Ratio	4.95%	PPI Response +	A	B
	Specificity	51.5%	NPV	56.9%	LR-	0.34	Probability	83.2%	PPI Response -	C	D

PPV: positive predictive value; NPV: negative predictive value; LR: likelihoodratio; PPI: proton pump inhibitors; GERD: gastroesophageal reflux disease

paratively in both upper gastrointestinal endoscopy or 24h pH monitoring with 40 mg/day esomeprazole for 2 weeks, the PPI test was found to be positive in 69% patients with GERD and 51% patients with non-GERD. Similarly, in the prospective study by Juul-Hansen et al. (21) that consisted of 52 patients and was performed comparatively in both upper gastrointestinal endoscopy or 24h pH monitoring with 30 mg/day lansoprazole for 1 week, the PPI test was found positive in 17 out of 18 patients whose PPI test was positive and 24h pH monitoring was normal among all the patients with pathological reflux; therefore, the specificity was found to be 6%. Although the specificity was found to be 36% in the prospective study of Johnsson et al. (22) that consisted of 440 patients and was performed comparatively in both upper gastrointestinal endoscopy or 24h pH monitoring with 40 mg/day esomeprazole for 2 weeks, it was indicated that the PPI test could be used for the diagnosis of GERD. The sensitivity of the PPI test that was performed for 5 days with 60 mg/day lansoprazole in patients who were endoscopically detected as GERD negative and in pH-metric-controlled patients was found to be 85% and the specificity was found to be 73% (8). In the PPI test that Schindlbeck et al. (4) performed in endoscopy-negative cases in 2 different omeprazole doses for 1 week (40 mg/day and 40 mg bid), they found that the sensitivity was 27% for the dose of 40 mg/day and 83% for the dose of 40 mg bid.

In the 14-week study that Pace et al. (23) conducted with omeprazole in terms of the determination of threshold dose and duration in the PPI test, it was emphasized that the optimal duration was 1 week and at least a 75% of response reduction was required to occur in the symptom scores. It is widely accepted in the literature that the PPI test can also be performed in patients who do not have alarm symptoms or GERD complications but have NCCP and typical reflux symptoms (1). Upper gastrointestinal endoscopy or 24h pH monitoring should be performed in cases with inadequate response to the treatment or negative PPI test results (24). The PPI test was indicated as an effective method for patients with GERD-related NCCP in the study that Kim et al. (25) performed for 2 weeks with a high dose of rabeprazole (20 mg bid). If the symptom response is 50% and above with the PPI test in patients with NCCP, the test can be accepted as positive and the treatment should be continued (26).

Table 2. The PPI dose and durations of the studies

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Active ingredient	Usage	Duration	The number of patients
Xia et al. (10)	91.7	47.1	37.9	94.1	Lansoprazol	30 mg AM	28 days	36
Pace et al. (23)	95.4	36.4	85.5	66.7	Omeprazol	20 mg AM and 20 mg PM	15 days	544
Pandak et al. (9)	68.8	27.3	40.7	54.5	Omeprazol	20 mg AM and 20 mg PM	14 days	38
Bate et al. (7)	68.8	57.7	66.7	60.0	Omeprazol	40 mg AM	14 days	58
Fass et al. (31)	100.0	42.9	72.4	100.0	Omeprazol	40 mg AM and 20 mg PM	14 days	35
Schenk et al. (2)	68.2	63.2	68.2	63.2	Omeprazol	40 mg AM	14 days	41
Cho et al. (28)	76.6	55.6	92.5	25.0	Lansoprazol	30 mg AM and 30 mg PM	14 days	73
Dent et al. (27)	53.8	64.6	75.2	41.3	Esomeprazol	40 mg AM	14 days	296
Kim et al. (25)	81.3	73.1	65.0	86.4	Rabeprazol	20 mg AM and 20 mg PM	14 days	42
Dekel et al. (30)	88.9	60.0	80.0	75.0	Rabeprazol	20 mg AM and 20 mg PM	14 days	14
Aanen et al. (29)	89.1	19.0	70.7	44.4	Esomeprazol	40 mg AM	13 days	67
Fass et al. (3)	78.3	85.7	90.0	70.6	Omeprazol	40 mg AM and 20 mg PM	7 days	37
Fass et al. (6)	80.0	57.1	90.3	36.4	Omeprazol	40 mg AM and 20 mg PM	7 days	42
Bautista et al. (11)	77.8	81.8	77.8	81.8	Lansoprazol	60 mg AM and 30 mg PM	7 days	40
Juul-Hansen et al. (21)	100.0	5.6	66.7	100.0	Lansoprazol	60 mg AM	7 days	52
Juul-Hansen et al. (8)	85.3	50.0	72.5	68.8	Lansoprazol	60 mg AM	5 days	56
Cumulative	82.3	51.5	79.0	56.9	7 Omeprazol 5 Lansoprazol 2 Esomeprazol 2 Rabeprazol	High doses in all: bid Median test for 14 days		

PPI: proton pump inhibitors; PPV: positive predictive value; NPV: negative predictive value; AM: ante meridiem; PM: post meridiem

By comprehensively examining the data of sensitivity and specificity of the PPI test in the literature, when the cumulative PPI test sensitivity and specificity were recalculated by means of the 2×2 cross tables along with the data of all the studies, the sensitivity was found to be 82.3% and the specificity was found to be 51.5% (Table 1) (2,3,6-11,21,23,25,27-31). Cumulative positive predictive value (PPV) is 79% and negative predictive value (NPV) is 56.9%. It was observed that high-dose PPI was mostly used in the studies, and the median test duration was 14 days (Table 2) (2,3,6-11,21,23,25,27-31). As a result, the sensitivity of the PPI trial test is good, but the specificity is low for the diagnosis of patients with GERD in with typical reflux symptoms.

RECOMMENDATIONS

- A PPI trial test can be performed in patients with NCCP or in patients whose diagnosis cannot be ensured. PPI trial test should be performed for 2 weeks at a dose of bid, similar to the use of PPI (Level of evidence: 1A).
- The sensitivity of the PPI trial test is good, but the specificity is low in the diagnosis of GERD in patients with typical reflux symptoms. A majority of patients with GERD respond to the PPI test; however, the absence of response does not exclude the diagnosis of GERD. On the other hand, non-GERD causes are found in about half the patients who respond to the PPI test (cumulative sensitivity: 82.3%; specificity: 51.5%; PPV: 79%; NPV: 56.9%). (Level of evidence: 1A)
- The sensitivity and specificity of the PPI trial therapy in patients with NCCP is at an acceptable level. (Level of evidence: 1A)
- PPI response in patients with erosive esophagitis and abnormal acid reflux is higher. (Level of evidence: 1A)
- PPI response should be considered as >50% recovery in typical reflux symptoms. (Level of evidence: 5)

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