ALIMENTARY TRACT

Limited Ability of the Proton-Pump Inhibitor Test to Identify Patients With Gastroesophageal Reflux Disease

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See editorial on page 1367.

BACKGROUND & AIMS: The efficacy of proton-pump inhibitor (PPI) therapy often is assessed to determine whether patients' symptoms are acid-related and if patients have gastroesophageal reflux disease (GERD), although the accuracy of this approach is questionable. We evaluated the diagnostic performance of the PPI test, in conjunction with other tests, for the diagnosis of GERD. **METHODS:** We analyzed data from the DIAMOND study, a multinational trial that compared the ability of the reflux disease questionnaire with that of symptom-based clinical diagnosis to identify GERD in primary care patients with frequent upper-gastrointestinal symptoms. Patients (n = 308) were given placebo and further evaluated by endoscopy, wireless esophageal pH-metry, and symptom association monitoring. Those with GERD (n = 197) were identified based on the presence of reflux esophagitis, esophageal pH level less than 4 for more than 5.5% of 24 hours, or positive results from symptom association monitoring (or a positive result from the PPI test in patients with borderline levels of esophageal acidity). All patients then were given single-blind therapy with esomeprazole (40 mg once daily) for 2 weeks and symptoms were recorded daily. **RESULTS:** A positive response to the PPI test was observed in 69% of patients with GERD and in 51% of those without GERD. Response to placebo did not influence the diagnostic ability of the subsequent PPI test. More patients with reflux esophagitis had a positive result from the PPI test than patients without GERD (57% vs 35%; $P = .002$) or patients with GERD but no esophagitis. A clinical diagnosis by the primary care physician of an acid-related disease was not associated with response to PPIs. **CONCLUSIONS: In a well-characterized population of primary care patients with frequent upper-gastrointestinal symptoms of any type, the PPI test has limited ability to identify patients with GERD, diagnosed by current standard tests. (ClinicalTrials.gov Number, NCT00291746.)**

Keywords: Dyspepsia; Acid Reflux; Esophagitis; Esomeprazole.

In routine clinical practice, empiric acid suppression in the form of the proton-pump inhibitor (PPI) test often is used to determine whether upper-gastrointestinal (GI) symptoms are acid-related and whether gastroesophageal reflux disease (GERD) is present.[1] However, its accuracy as a diagnostic tool has been questioned in some studies.[2,3] The PPI test was used in the large international DIAMOND study in conjunction with other tests and symptom analysis to determine whether GERD was present in patients consulting in primary care with upper-GI symptoms.[4] The DIAMOND study was unique in its study of a large population of primary care patients with frequent upper-GI symptoms. The main aim was to assess the accuracy of the Reflux Disease Questionnaire[5] (RDQ) as a diagnostic tool for GERD and to compare it with endoscopy, pH-metry, and, in cases of borderline high esophageal acid exposure, also a positive PPI test. The overall results of the DIAMOND study showed that the RDQ, primary care physicians (PCP), and gastroenterologists have moderate and similar accuracy for diagnosis of GERD in a primary care population with frequent upper-GI symptoms. It also showed that a 2-week course of acid suppression did not add to the diagnostic precision when based on the predefined analyses. In this study, we examined various definitions of the response to PPI and the responses obtained in various patient subgroups and compared this with investigation-based criteria for GERD. Our aim was to investigate the diagnostic performance of the PPI test for prediction of GERD in this large population of patients reporting in primary care with frequent upper-GI symptoms.

Methods

We analyzed data from the DIAMOND study, a multinational trial (Northwestern Europe, Canada) that tested the ability of the RDQ in diagnosing GERD among patients consulting for frequent upper-GI symptoms in primary care. Detailed information on recruitment, study design, and main results have been published elsewhere.[4]

In brief, a total of 73 PCP clinics screened 706 patients, who consulted with bothersome upper-GI symptoms. A total of 507

† Deceased.

Abbreviations used in this paper: GERD, gastroesophageal reflux disease; GI, gastrointestinal; LR, likelihood ratio; PCP, primary care physicians; PPI, proton-pump inhibitor; RDQ, Reflux Disease Questionnaire; SAP, symptom association monitoring.

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Table 1. Positive PPI Test Results in Patients With Typical Reflux Symptoms Diagnosed With GERD According to the Protocol, or by Excluding the PPI Test From the Diagnostic Criteria

	GERD diagnosis according to the protocol		GERD diagnosis excluding the PPI test[a]	
PPI test positive	Non-GERD (n = 102)	GERD (n = 197)	Non-GERD (n = 111)	GERD (n = 188)
Most/second-most bothersome symptoms				
Heartburn/central chest pain/regurgitation	51% (20/39)	69% (94/136)	60% (29/48)	67% (85/127)
Heartburn/central chest pain	61% (20/33)	72% (86/119)	68% (28/33)	70% (78/111)
Most bothersome symptom				
Heartburn/central chest pain/regurgitation	60% (14/26)	72% (70/97)	61% (19/31)	71% (65/92)
Heartburn/central chest pain	62% (13/21)	74% (60/81)	68% (17/25)	73% (56/77)

NOTE. A positive test was defined as the absence of the symptom during the last 3 days on PPI.
[a]Defined as a positive PPI test in patients with borderline abnormal esophageal acid exposure (pH < 4 for 3.5%–5.5% of the 24 hours).

patients were enrolled; of these, 308 patients were fully evaluable. All patients completed the RDQ at entry and the investigators were blinded to this response. The PCP and the study gastroenterologist acting independently selected a symptom-based diagnosis from a prespecified list. After this, the patient was asked to identify the most and second-most bothersome upper-GI symptom from a predetermined list of 19 symptoms. During treatment with placebo, identical in appearance to esomeprazole (patients were blinded as to when placebo or esomeprazole were administered), all patients had endoscopy with wireless 48-hour esophageal pH and symptom association monitoring (SAP). After investigation, patients received active esomeprazole 40 mg daily for 2 weeks (the PPI test) and the effect of treatment on their most and second-most bothersome symptoms (any type including symptoms typical for GERD, eg, heartburn) were recorded in daily diaries. Based on the outcome of investigation, all patients were classified as GERD or non-GERD according to predefined criteria. GERD was diagnosed when at least one of the following 4 criteria was present: (1) reflux esophagitis (any Los Angeles grade), (2) esophageal pH level less than 4 for more than 5.5% of the time, (3) positive SAP (≥95%) for association of symptoms with acid reflux, and (4) borderline high esophageal acid exposure (pH< 4 for 3.5%–5.5% of the time) and positive response of reflux-related symptoms to esomeprazole treatment (PPI test criteria).

Analyses

A total of 203 patients were diagnosed with GERD using the investigation-based criteria. In 9 of these 203 patients, a diagnosis of GERD was based exclusively on a positive PPI test in patients with borderline high esophageal acid exposure. For the original publication,[4] we performed exploratory analyses to examine the influence of excluding the PPI test criterion from the diagnosis of GERD and found only minimal change in the diagnostic yield of GERD. The possible influence of selecting different end points for a positive/negative PPI test on diagnostic yield also was explored because the DIAMOND study allowed patients to select their most bothersome and second-most bothersome upper-GI symptoms, regardless of whether they were typical for GERD or not. Absence of the most bothersome symptom in the last 3 days of active treatment (esomeprazole 40 mg daily for 2 weeks) was a priori defined to be a positive response to the PPI test. In our exploratory analyses, we examined different combinations of symptoms typical for GERD (heartburn, central chest pain, dysphagia, or regurgitation) as the most or second-most bothersome symptoms and also restricted the analysis to the most bothersome symptom, to evaluate strategies for assessing whether a PPI test is positive or negative for reflux disease.

The placebo period was introduced to allow the endoscopy and pH-metry to take place and to form a run-in period for the PPI test to quantify the proportion of placebo responders. We analyzed outcome of the PPI test in placebo responders (absence of most bothersome symptom during the last 2 days of the placebo period) and nonresponders.

The likelihood ratio (LR) indicates the usefulness of a test in making a diagnosis. Values greater than 1 are associated with increasing likelihood of the disease.[6] We analyzed positive (LR+) and negative (LR−) values for all patients and for subgroups.

All authors had full access to the study database.

Results

Prevalence of Investigation-Based Gastroesophageal Reflux Disease and Response to Proton Pump Inhibitor Based on Heartburn, Central Chest Pain, or Regurgitation as the Most or Second-Most Bothersome Symptoms

The outcome of the PPI test was available for 299 of the 308 patients. As illustrated in Table 1, excluding the positive PPI test in borderline pathologic pH criterion for GERD did not change the diagnostic precision, with 66% (197 of 299) of patients being diagnosed with GERD on investigation, compared with 63% (188 of 299) when the positive PPI test in borderline pathologic pH criterion was excluded from the diagnosis. This is not surprising because only 9 patients were defined as having GERD on the basis of this criterion alone, and we therefore decided not to classify these patients as GERD in most of our post hoc analyses.

More patients with GERD had a symptom typical for GERD (eg, heartburn, regurgitation) as their most or second-most bothersome symptom compared with patients without GERD on investigation (69% vs 38%; Table 1). Dysphagia was not included as a symptom typical for GERD in these analyses because of the low numbers of patients reporting this as their most or second-most bothersome symptom.