The Usefulness of a Structured Questionnaire in the Assessment of Symptomatic Gastroesophageal Reflux Disease

R. CARLSSON, J. DENT, E. BOLLING-STERNEVALD, F. JOHNSSON, O. JUNGHARD,
K. LAURITSEN, S. RILEY & L. LUNDELL

Dept. of Surgery, Sahlgren's University Hospital, Göteborg; Dept. of Surgery, Linköping University Hospital, Linköping; Dept. of Surgery, Lund University Hospital, Lund; and Astra Hässle AB, Mölndal; Sweden; Gastrointestinal Medicine, Royal Adelaide Hospital, Adelaide, South Australia, Australia; Dept. of Medical Gastroenterology, Odense University Hospital, Odense, Denmark; and Dept. of Gastroenterology, Northern General Hospital, Sheffield, England

Carlsson R, Dent J, Bolling-Sternevald E, Johnsson F, Junghard O, Lauritsen K, Riley S, Lundell L. The usefulness of a structured questionnaire in the assessment of symptomatic gastroesophageal reflux disease. Scand J Gastroenterol 1998;33:1023–1029.

Background: The diagnosis of gastroesophageal reflux disease (GERD) rests primarily on recognition of symptom patterns that are classical for reflux disease, but little attention has been paid to the use of a formal questionnaire for identifying such symptom patterns. *Methods:* A self-administered questionnaire was developed which has seven items that focus on the nature of the symptoms and the precipitating, exacerbating, and relieving factors. The diagnostic validity of the questionnaire was tested against endoscopy and 24-h pH monitoring. A further evaluation was undertaken in patients with symptoms suggestive of GERD and in patients with non-ulcer dyspepsia, to identify factors that might predict symptom relief during treatment with omeprazole. *Results:* When endoscopic esophageal mucosal breaks and 24-h pH data were used as criteria for the diagnosis of GERD, the questionnaire had a sensitivity of 92% but a very low specificity of 19%. Symptom relief during treatment with omeprazole was predicted by the presence of heartburn, described as 'a burning feeling rising from the stomach or lower chest up towards the neck' ($P = 0.004$), and 'relief from antacids' ($P = 0.02$). In non-ulcer dyspepsia a positive response to omeprazole was confined to the subgroup of patients who identified their main discomfort as heartburn as described above. *Conclusion:* The present questionnaire using descriptive language usefully identified heartburn in patients presenting with upper abdominal symptoms, and this symptom predicted symptom resolution during treatment with omeprazole.

Key words: Endoscopy; gastroesophageal reflux disease; heartburn; non-ulcer dyspepsia; omeprazole; pH-monitoring; questionnaire

Rolf Carlsson, Ph.D., GI Management & Strategies, Astra Hässle AB, S-431 83 Mölndal, Sweden (fax: +46 31 776 3801)

Heartburn and acid regurgitation are the commonest symptoms of gastroesophageal reflux disease (GERD). It is estimated that 20%–40% of the adult population experience heartburn and that 7% of adults experience this symptom daily (1–3). When present as the predominant symptom, heartburn has a high positive predictive value for the diagnosis of GERD, but its sensitivity is low (4, 5). Endoscopy is not a substitute for careful symptom evaluation, since most patients with troublesome reflux symptoms do not have any evidence of endoscopic esophagitis (6, 7). Esophageal pH monitoring provides strong supportive evidence when abnormally high levels of esophageal acid reflux are found, but a normal pH study does not exclude the diagnosis (8–11). Furthermore, this investigation is expensive, invasive, technically demanding, and not readily available.

Heartburn has been shown to correlate with abnormal esophageal acid exposure (12) and, when present as the predominant symptom, may be the sole basis for the diagnosis of GERD (3). Symptom evaluation, however, is complicated by the wide variety of symptoms in GERD, the imprecise definitions of these symptoms, and the overlap between reflux symptoms and other upper abdominal symptoms. In many patients, therefore, the diagnosis is missed because heartburn is neither identified nor recognized among other symptoms (13, 14).

To structure and simplify this evaluation, we have, therefore, developed a self-administered questionnaire that is focused on the nature of the sensations experienced by the patient and the provoking, exacerbating, and relieving factors. The diagnostic performance of this questionnaire has been evaluated against endoscopy and 24-h pH monitoring. A further evaluation was undertaken in patients with symptoms suggestive of GERD and in patients with non-ulcer dyspepsia, to identify items in the questionnaire that predicted symptom relief during short-term treatment with omeprazole.

MATERIALS AND METHODS

The questionnaire was developed by an advisory group of physicians, surgeons, and primary care physicians who have a

special interest in the management of gastroesophageal reflux disease. Seven items were devised to evaluate the nature of the sensations experienced by patients and the temporal relationship of symptom occurrence to factors that are known to provoke (meals, bending, stooping, lifting), exacerbate (fatty or spicy food), or relieve (antacids) gastroesophageal reflux (Table I). Each response was assigned a positive, neutral, or negative score, on the basis of knowledge of its pathophysiology and assumed diagnostic significance for GERD. The score for each item was weighted so that the highest positive values were assigned to factors considered strongly indicative of the diagnosis of GERD. Particular emphasis was placed on the predominance of heartburn, consistent provocation of symptoms by meals, and early relief by antacids. Atypical relationships with known provocative factors (foods and posture) were given negative values. A score ranging from −7 to +18 was calculated by adding the individual positive and negative scores from the questionnaire. The draft questionnaire was reviewed by a group of general practitioners in the UK and Sweden. Their comments on the items included in the questionnaire and comments about language and scoring were considered, and the questionnaire was revised accordingly. Before using the questionnaire in study 1, different scoring models were tested against a patient database in a computerized model by Dr. P. Bytzer and Dr. J. Møller Hansen, Dept. of Medical Gastroenterology S, Odense University Hospital. On the basis of this evaluation a cut-off score of 4 or higher was chosen.

Testing of the questionnaire

The questionnaire was tested in two studies. In the first study the aims were to i) evaluate the ability of the questionnaire to identify patients with reflux esophagitis and ii) determine the prevalence of heartburn defined as 'a burning feeling rising from the stomach or lower chest up towards the neck' and to compare this with the symptom term selected by the patients for their predominant symptom. In the second study the sensitivity and specificity of the questionnaire in identifying GERD were determined in patients in whom the disease was diagnosed by endoscopy and 24-h pH monitoring.

The first study was done in consecutive patients newly referred from primary care for endoscopic examination who had upper abdominal symptoms with or without heartburn and acid regurgitation. The patients were asked to complete the test questionnaire and a more general symptom questionnaire that enquired about heartburn, acid regurgitation, 'stomach' pain, 'stomach' discomfort, dysphagia, nausea, and vomiting. Patients were specifically asked to select the predominant symptom in the latter questionnaire. Both questionnaires were completed before endoscopy. At endoscopy the esophagus, stomach, and duodenum were inspected, and any abnormal findings were recorded. Esophagitis was graded in accordance with the classification by Savary & Miller (15).

In the second study patients with a history of heartburn alone or in combination with epigastric pain or discomfort

Table I. Patient questionnaire. The weighted scores within parentheses, which were added to obtain the diagnostic score, were not disclosed on the self-report form. Indigestion medicines were specified by giving the trade names of the most commonly used antacids/alginates in each country

---

Please answer the following questions by ticking <u>one</u> box only, except for question 3, where you must tick one box for each statement.

1. *Which one of these four statements BEST DESCRIBES the main discomfort you get in your stomach or chest?*
(5) ☐ A burning feeling rising from your stomach or lower chest up towards your neck
(0) ☐ Feelings of sickness or nausea
(2) ☐ Pain in the middle of your chest when you swallow
(0) ☐ None of the above, please describe below:

2. *Having chosen one of the above, please now choose which one of the next three statements BEST DESCRIBES the timing of your main discomfort?*
(−2) ☐ Any time, not made better or worse by taking food
(3) ☐ Most often within 2 hours of taking food
(0) ☐ Always at a particular time of day or night without any relationship to food

3. *How do the following affect your main discomfort?*

	Worsens	Improves	No effect/Unsure
Larger than usual meals	(1) ☐	(−1) ☐	(0) ☐
Food rich in fat	(1) ☐	(−1) ☐	(0) ☐
Strongly flavored or spicy food	(1) ☐	(−1) ☐	(0) ☐

4. *Which one of the following BEST DESCRIBES the effect of indigestion medicines on your main discomfort?*
(0) ☐ No benefit
(3) ☐ Definite relief within 15 minutes
(0) ☐ Definite relief after 15 minutes
(0) ☐ Not applicable (I don't take indigestion medicines)

5. *Which of the following BEST DESCRIBES the effect of lying flat, stooping, or bending on your main discomfort?*
(0) ☐ No effect
(1) ☐ Brings it on or makes it worse
(−1) ☐ Gives relief
(0) ☐ Don't know

6. *Which of the following BEST DESCRIBES the effect of lifting or straining (or any other activity that makes you breath heavily) on your main discomfort?*
(0) ☐ No effect
(1) ☐ Brings it on or makes it worse
(−1) ☐ Gives relief
(0) ☐ Don't know or this does not apply to me

7. *If food or acid-tasting liquid returns to your throat or mouth what effect does it have on your main discomfort?*
(0) ☐ No effect
(2) ☐ Brings it on or makes it worse
(0) ☐ Gives relief
(0) ☐ Don't know or this does not apply to me

---

during the last 6 months and with either a normal endoscopic appearance of the esophagus or grade-1 to -3 esophagitis in accordance with a modification of the classification by Savary & Miller (16) had an ambulatory 24-h esophageal pH-monitoring study. Patients with esophageal stricture and/or ulcer in the esophagus, stomach, or duodenum were excluded. Ambulatory pH monitoring was performed within 2 weeks of the endoscopy. After a 4-h fast the pH probe was introduced nasally and positioned 5 cm above the upper margin of the

Table II. Number of patients, mean diagnostic score, and 95% confidence interval (CI) by endoscopic diagnosis

	Normal	Reflux esophagitis	Gastric ulcer	Duodenal ulcer	Gastritis/duodenitis	Other
No. of patients	133	91	18	23	95	64
(% of total)	(31%)	(21%)	(4%)	(5%)	(22%)	(15%)
Mean diagnostic score	3.9	5.9	4.6	4.0	4.6	4.4
(95% CI)	(3.2, 4.6)	(5.0, 6.8)	(2.8, 6.4)	(1.8, 6.2)	(3.7, 5.4)	(3.3, 5.5)

lower esophageal sphincter, previously located by esophageal manometry. Acidic or sour drinks and foodstuff and alcohol were not allowed. A positive diagnosis of GERD was defined as reflux esophagitis of at least grade 2 (scattered erosions) and/or distal esophageal pH below 4 for more than 4% of the 24-h period. The questionnaire was completed before the patient was informed of the results from the investigational tests.

Evaluation of factors predicting response to omeprazole

Data from the studies by Carlsson et al. (17) and Lauritsen et al. (18) were used to identify factors in the test questionnaire which predicted symptom relief during short-term treatment with omeprazole. In the study by Carlsson et al. (17) patients attending primary care centers because of upper gastrointestinal symptoms were screened with the test questionnaire. Patients achieving a score of 4 or more underwent endoscopy if the following additional criteria were met: age, 18–80 years; history of upper GI symptoms for at least 3 months; and episodes of upper GI symptoms occurring on at least 2 days during the past 7 days. Endoscopic grading was recorded using the Savary & Miller (15) and the Los Angeles classification systems (19). Patients were grouped as endoscopy-negative if they had no endoscopic mucosal breaks and as endoscopy-positive if they had mucosal breaks of any

extent. The main exclusion criteria were esophageal ulcer or stricture, Barrett's esophagus, current peptic ulcer disease, history of esophagogastric surgery or gastrointestinal bleeding. Endoscopy-negative patients were randomized to double-blind treatment with 20 mg omeprazole, 10 mg omeprazole, or placebo, once daily for 4 weeks. Endoscopy-positive patients were randomized to double-blind treatment with either 20 mg or 10 mg omeprazole once daily for 4 weeks. Symptom assessment was performed after 2 and 4 weeks of treatment. For the analysis in this report, however, only the data from patients treated with 20 mg omeprazole was used, and a positive response was defined as those who answered 'yes' to the direct question of whether treatment had given sufficient control of their upper GI symptoms after 2 weeks.

The study by Lauritsen et al. (18) recruited patients with non-ulcer dyspepsia, with normal endoscopic findings, and with at least a 1-month history of epigastric pain and/or discomfort. Patients were excluded if they had peptic ulcer disease or gastroesophageal reflux disease or if their predominant symptom was heartburn or regurgitation. To be included, patients were required to have had dyspeptic symptoms on at least 3 days in the week before study entry. Eligible patients were randomized to double-blind treatment with either placebo or 20 mg omeprazole twice daily for 2 weeks. The test questionnaire was completed by the patients
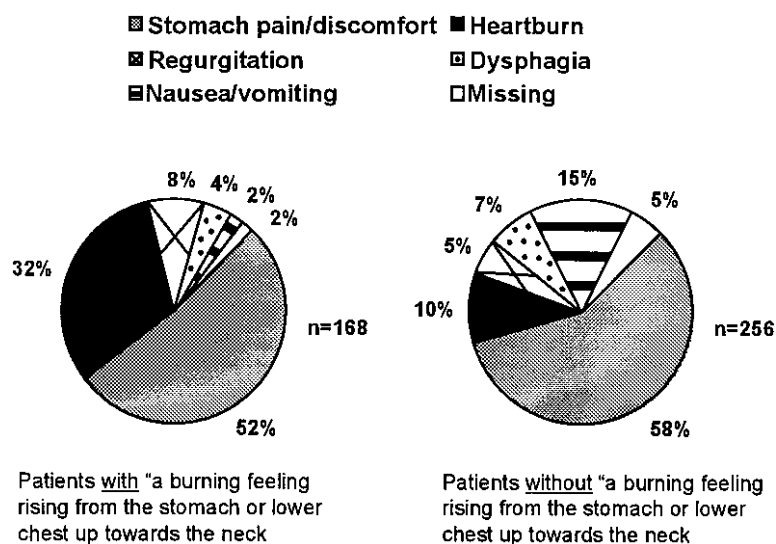

Fig. 1. Distribution of predominant symptom in accordance with the symptom term selected by the patients among those with (left) and without (right) a burning feeling rising from the stomach or lower chest up towards the neck.

before randomization but did not influence patient selection. A positive response to treatment was defined as no dyspeptic symptoms during the last 2 days of the treatment period.

Statistical analysis

Sensitivity was defined as the proportion of patients with a positive diagnosis of GERD who had a questionnaire score that reached or exceeded the threshold for reflux disease (see below). Specificity was defined as the proportion of patients without GERD who had a questionnaire score that was below the diagnostic threshold value.

An established diagnosis of GERD was defined as the presence of esophagitis of grade 2 or 3 or a pH below 4 for more than 4% of the 24-h period.

A total score of 4 or higher was chosen arbitrarily as the threshold score to be taken as indicative of GERD.

In the studies by Carlsson et al. (17) and Lauritsen et al. (18) a logistic regression model was applied to identify items in the questionnaire that predicted a positive response to omeprazole.

RESULTS

In the first study 439 patients (348 in Sweden and 91 in the UK) were included. The test questionnaire and the additional symptom questionnaire were completed by 424 patients. The mean test questionnaire score was 4.6 for all patients. Table II shows the mean score in accordance with the endoscopic diagnosis. The highest mean score, 5.9 (95% confidence interval, 5.0–6.8), was obtained in patients with reflux esophagitis, and the lowest, 3.9 (3.2–4.6), in those with normal endoscopic appearance (that is, no abnormalities noted on the endoscopy report).

The sensitivity of the test questionnaire in identifying patients with esophagitis was 70%, using a cut-off score of 4 or higher for a positive test. When the higher score of 6 or more was used, the sensitivity decreased to 54%. The specificity was 46% for the lower cut-off score and 60% for the higher.

The rate of recognition of heartburn differed substantially for the test questionnaire and the other symptom questionnaire. The test questionnaire defined heartburn as a burning feeling rising from the stomach or lower chest up towards the neck, and this was reported as the main discomfort by 168 of the 424 patients (40%). Notably, however, of these 168 patients who indicated that they had heartburn as defined above, only 32% responded positively to the question whether they experienced heartburn in the other symptom questionnaire. The symptom description chosen most commonly by patients with the burning feeling was 'pain or discomfort in the stomach', which was reported by 52%. Fig. 1 shows the distribution of the predominant symptom by presence or absence of a burning feeling rising from the stomach or lower chest up towards the neck.

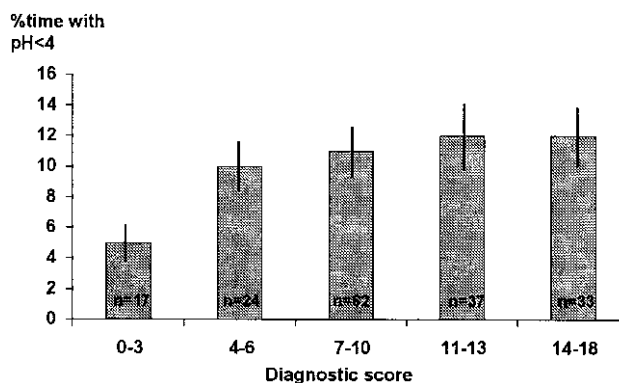In the second study the test questionnaire was completed by

Fig. 2. Level of esophageal acid exposure by diagnostic score. The bars represent the mean percentage of the 24-h period with pH below 4, and the standard error is also given.

176 of the 188 patients who had 24-h pH monitoring. Esophagitis of grade 2 or 3 was present in 102 patients (54%), and the diagnosis of GERD was confirmed by 24-h pH monitoring in a further 46 patients. The results of the pH-monitoring studies showed that the level of esophageal acid exposure was higher in the patients who scored 4 or higher than in those with lower scores (Fig. 2). When these criteria were applied, the sensitivity of the test questionnaire was 92%, and the specificity was 19%.

A burning feeling rising from the stomach or lower chest up towards the neck was the predominant symptom in 79% of the patients. This symptom had a sensitivity of 73% and a specificity of 43% for reflux disease as defined.

In the study by Carlsson et al. (17) 538 patients were included, of whom 261 had no esophageal mucosal breaks (endoscopy-negative), and 277 had esophageal mucosal breaks (endoscopy-positive). The mean test questionnaire score was 10.7 in the endoscopy-negative patients and 11.2 in the endoscopy-positive group. The difference was not statistically significant.

Two hundred and twenty-five of the 538 patients were randomized to 20 mg omeprazole. Of those, 138 patients had esophagitis at entry, and 87 were endoscopy-negative. Response to omeprazole was predicted by the presence of a burning feeling rising from the stomach or lower chest up towards the neck and relief from antacids. The odds for achieving symptom control were four times higher in those patients whose main discomfort was a burning feeling rising from the stomach or lower chest up towards the neck than in those without this symptom ($P = 0.004$). The corresponding odds ratio was 2.2 for 'relief from antacids'. Neither the total score nor any other item in the test questionnaire was found to predict symptom response to treatment with omeprazole. In the endoscopy-positive group the proportion of patients with adequate symptom control was high, regardless of the presence or absence of a burning feeling rising from the stomach or lower chest up towards the neck (82% and 78%). In the

endoscopy-negative group more patients, 58%, reported adequate symptom relief among those with this symptom, compared with 33% of those without. The response rate in the endoscopy-negative patients without a burning feeling rising from the stomach or lower chest up towards the neck was identical to the response in the placebo group (33%).

In the study by Lauritsen et al. (18), which was designed as a pilot study for the evaluation of omeprazole in non-ulcer dyspepsia, 188 of the 196 patients who were included in the study completed the test questionnaire. Of these 188 patients, 42% indicated on the test questionnaire that their main discomfort was a burning feeling rising from the stomach or lower chest up towards the neck. It should be noted that the study protocol excluded patients whose predominant symptom was heartburn. Complete resolution of abdominal symptoms during treatment with omeprazole, however, was confined to patients with a symptom pattern that is best described as heartburn, as shown in Fig. 3. Logistic regression analysis identified this symptom ($P = 0.02$) and relief from antacids ($P = 0.02$) as factors predicting a positive response to treatment with omeprazole. On the other hand, patients who reported that large meals improved their main discomfort ($P = 0.04$) or that food rich in fat worsened it ($P = 0.01$) were less likely to achieve symptom relief during treatment.
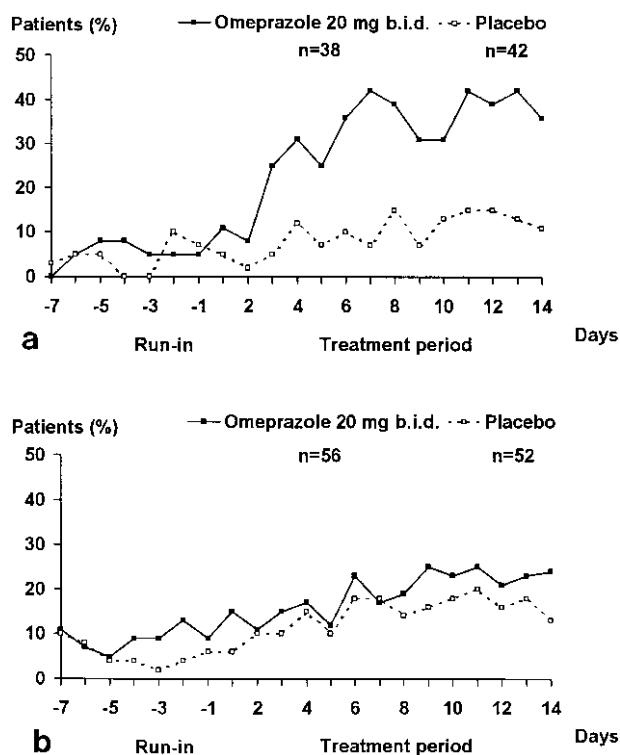

Fig. 3. Non-ulcer dyspepsia. Proportions of patients without dyspeptic symptoms as recorded each day in diary cards in those with (3a) and without (3b) 'a burning feeling rising from the stomach or lower chest up towards the neck' as their main discomfort at base line.

DISCUSSION

We have found that the test questionnaire, presumably by giving a word picture for the symptom of heartburn, identifies this symptom in substantially more patients who present with upper abdominal symptoms than if patients are merely asked if they have heartburn. Description of the symptom was of practical value, as it identified patients whose symptoms resolved during treatment with omeprazole. These results are clinically important, providing guidelines for the identification and more efficient management of patients with probable GERD as opposed to those who have true dyspepsia as defined by the Rome criteria, this definition being 'persistent or recurrent abdominal pain or discomfort centered in the upper abdomen' (20).

Our results suggest that it is important to give a word picture that describes heartburn with simple language; otherwise the limited understanding that patients have of the sensation of heartburn will give misleading responses. In our questionnaire heartburn was defined as a burning feeling rising from the stomach or lower chest up towards the neck. Our data show that this sensation was not recognized as heartburn by most patients who described this symptom as their most troublesome. More than 50% of the patients identified the burning feeling as pain or discomfort in the stomach, and only one-third of the patients reported it as heartburn. Locke et al. (21) also found that the term 'heartburn' was confusing to the patients, and that there was less agreement between patients and physicians in identifying the presence of heartburn when this term was used alone instead of describing the sensations. Surprisingly, according to our definition, heartburn was also not identified as a predominant reflux symptom by the clinical investigators in the study of non-ulcer dyspepsia. These observations indicate that history-taking needs to be carefully structured to maximize its potential for diagnosis of GERD. Johnsson et al. (22) have also used descriptive language to identify heartburn and found that GERD was predicted by an upward-moving, burning chest sensation that was relieved by antacids. Our own data and those of others referred to above support the suggestion that a self-administered patient questionnaire that describes the symptoms is clinically useful and may aid history-taking in identifying patients with GERD. Given the results of our study, such a questionnaire could be substantially simpler than the one we tested.

The selection of patients and the diagnostic approaches used in our studies did not enable a scientifically complete evaluation of the validity of the questionnaire for the diagnosis of GERD. Although the questionnaire had a high sensitivity, further information about the quality of the test is desirable. In particular, it would be important to determine how well the questionnaire would work in a broader group of patients with dyspeptic and upper abdominal symptoms. The high prevalence of reflux disease in the study population of the second study makes it unsuitable for determining the

predictive values of the test, since it would result in a high positive predictive value also when patients were classified at random. This problem was not encountered in the first study, in which the questionnaire was evaluated in consecutive patients with upper gastrointestinal symptoms. The diagnostic validity, however, could only be tested against the endoscopic diagnosis of GERD. Macroscopic evidence of esophagitis at endoscopy is, however, found in less than half of the patients with GERD (6, 7), which makes this test far from optimal for the diagnosis of this disease.

The specificity of the diagnostic score (<4) was poor, suggesting its limited value in excluding GERD. It must, however, be noted that the study included few patients who did not have GERD as defined and that 24-h pH-monitoring is a far from perfect test for diagnosis of GERD in patients with reflux symptoms without esophagitis (10). Furthermore, all patients included had heartburn alone or in combination with epigastric pain or discomfort, and it is likely that this selection also influenced the scoring based on the questionnaire in favor of a positive test result. Thus, further studies are required to fully assess the specificity of the test and to validate the diagnostic accuracy of the questionnaire in patients with dyspeptic symptoms with and without heartburn.

It should be noted that the test questionnaire was purely directed at symptom-based diagnosis and not at assessment of symptom severity or its impacts on patient well-being. In the clinical diagnosis and management of GERD it is important to distinguish the patients whose major concern is that their symptoms are due to serious disease (23) from those in whom symptoms have a major impact on health-related well-being (24).

It has been suggested that dyspeptic patients can be divided into subgroups such as ulcer-like, reflux-like, and dysmotility-like on the basis of their predominant symptoms (25). The clinical utility of this subgrouping has been widely questioned because of the large overlap between different subgroups, the common occurrence of alteration in patterns to those of other subgroups in individuals over time, and lack of evidence that response to specific therapy can be accurately predicted (26–28). Previous studies in non-ulcer dyspepsia have usually not excluded patients with reflux symptoms, and this may explain the benefits of acid inhibition in such studies (29). In our study of non-ulcer dyspepsia patients with predominantly heartburn or acid regurgitation were excluded. Despite this, 42% of the patients included described their main discomfort as heartburn in accordance with our definition. Symptom resolution during treatment with omeprazole was predicted by this symptom and by relief from antacids. This is consistent with the results in endoscopy-negative patients in the other study (17), although that study did not exclude patients with predominantly reflux symptoms.

In summary, the results of our studies show that the present questionnaire using descriptive language usefully identified heartburn in patients presenting with upper abdominal symptoms, and this symptom predicted symptom resolution during treatment with omeprazole. The questionnaire also had a high sensitivity for the GERD diagnosis when related to endoscopic esophagitis and abnormal acid reflux as assessed by 24-h pH monitoring. Further studies, however, are needed to determine the diagnostic accuracy of the test in terms of specificity and predictive values.

REFERENCES

1. Spechler S. Epidemiology and natural history of gastro-oesophageal reflux disease. Digestion 1992;51 Suppl 1:24–9.
2. Wienbeck M, Barnert J. Epidemiology of reflux disease and reflux esophagitis. Scand J Gastroenterol 1989;24 Suppl 156:7–13.
3. Heading RC. Epidemiology of oesophageal reflux disease. Scand J Gastroenterol 1989;24 Suppl 168:33–7.
4. Johnsson F, Joelsson B, Gudmundsson K, Greiff L. Symptoms and endoscopic findings in the diagnosis of gastro-oesophageal reflux disease. Scand J Gastroenterol 1987;22:714–8.
5. Klauser AG, Schindlbeck NE, Müller-Lissner SA. Symptoms in gastro-oesophageal reflux disease. Lancet 1990;335:205–8.
6. Venables TL, Newland RD, Patel AC, Hole J, Wilcock C, Turbitt ML. Omeprazole 10 milligrams once daily, omeprazole 20 milligrams once daily, or ranitidine 150 milligrams twice daily, evaluated as initial therapy for the relief of symptoms of gastro-oesophageal reflux disease in general practice. Scand J Gastroenterol 1997;32:965–73.
7. Jones RH, Hungin PAS, Phillips J, Mills JG. Gastro-oesophageal reflux diasease in primary care in Europe: clinical presentation and endoscopic findings. Eur J Gen Pract 1995;1:149–54.
8. Murphy DW, Yuan Y, Castell DO. Does the intraesophageal pH probe accurately detect acid reflux? Simulataneous recording with two pH probes in humans. Dig Dis Sci 1989;34:649–56.
9. Masclee AAM, de Best ACAM, de Graaf R, Cluysenaer OJJ, Jansen JBMJ. Ambulatory 24-hour pH-metry in the diagnosis of gastroesophageal reflux disease. Determination of criteria and relation to endoscopy. Scand J Gastroenterol 1990;25:225–30.
10. Ghillibert G, Demeyere AM, Janssens J, Vantrappen G. How well can quantitative 24-hour intraesophageal pH monitoring distinguish various degrees of reflux disease? Dig Dis Sci 1995;40:1317–24.
11. Shi G, Bruley des Varannes S, Scarpignato C, Le Ruhn M, Galmiche J-P. Reflux related symptoms in patients with normal oesophageal acid exposure to acid. Gut 1995;37:457–64.
12. Joelsson B, Johnsson F. Heartburn—the acid test. Gut 1989; 30:1523–5.
13. Jones RH, Lydeard SE, Hobbs FDR, Kenkre JE, Williams EI, Jones SJ, et al. Dyspepsia in England and Scotland. Gut 1990; 31:401–5.
14. Castell DO, Holtz A. Gastroesophageal reflux. Don't forget to ask about heartburn. Postgrad Med 1989;86:141–8.
15. Savary M, Miller G. L'oesophage. In: Savary M, Miller G, editors. Manuel et atlas d'endoscopie. Soleure: Gassmann AG; 1977. p. 135.
16. Sandmark S, Carlsson R, Fausa O, Lundell L. Omeprazole or ranitidine in the treatment of reflux esophagitis. Results from a double-blind, randomized, multicentre study. Scand J Gastroenterol 1988;23:625–32.
17. Carlsson R, Dent J, Watts R, Riley S, Sheikh R, Hatlebakk J, et al. Gastro-oesophageal reflux disease in primary care—an international study of different treatment strategies with omeprazole. Eur J Gastroenterol Hepatol 1998;10:119–24.
18. Lauritsen K, Aalycke C, Havelund T, Knudsen T, Glise H, Unge P, et al. Effect of omeprazole in functional dyspepsia: a

randomized, placebo-controlled study. Gastroenterology 1996; 110:A702.

19. Armstrong D, Bennett JR, Blum AL, Dent J, de Dombal FT, Galmiche J-P, et al. Endoscopic assessment of esophagitis: a progress report on observer agreement. Gastroenterology 1996; 111:85–92.

20. Talley NJ, Colin-Jones D, Koch KL, Koch M, Nyrén O, Stanghellini V. Functional dyspepsia: a classification with guidelines for diagnosis and management. Gastroenterol Int 1991;4:145–60.

21. Locke RG, Talley NJ, Weaver AL, Zinsmeister AR. A new questionnaire for gastroesophageal reflux disease. Mayo Clin Proc 1994;69:539–47.

22. Johnsson F, Roth Y, Damgaard Pedersen N-E, Joelsson B. Cimetidine improves GERD symptoms in patients selected by a validated GERD questionnaire. Aliment Pharmacol Ther 1993; 7:81–6.

23. Lydeard S, Jones R. Factors affecting the decision to consult with dyspepsia: comparison of consulters and non-consulters. J R Coll Gen Pract 1989;39:495–8.

24. Dimenäs E, Carlsson G, Glise H, Israelsson B, Wiklund I. Relevance of norm value as part of the documentation of quality of life instruments for use in upper gastrointestinal disease. Scand J Gastrenterol 1996;31 Suppl 221:8–13.

25. Colin-Jones DG, Bloom B, Bodemar G, Crean G, Freston J, Gugler R, et al. Management of dyspepsia: Report of a working party. Lancet 1988;1:576–9.

26. Talley NJ, Zinsmeister AR, Schleck CD, Melton JL. Dyspepsia and dyspepsia subgroups: A population-based study. Gastroenterology 1992;102:1259–68.

27. Veldhuyzen van Zanten SJO, Cleary C, Talley NJ, Peterson TC, Nyrén O, Bradley LA, et al. Drug treatment of functional dyspepsia: a systematic analysis of trial methodology with recommendations for design of future trials. Am J Gastroenterol 1996;91:660–73.

28. Klauser AG, Voderholzer WA, Knesewitsch PA, Schindlbeck NE, Müller-Lissner SA. What is behind dyspepsia? Dig Dis Sci 1993;38:147–54.

29. Johannesen T, Fjosne U, Kleveland PM, Halvorsen T, Kristensen P, Loge I, et al. Cimetidine responders in non-ulcer dyspepsia. Scand J Gastroenterol 1988;23:327–36.