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Diagnostic Value of Potent Acid Inhibition in Gastro-Oesophageal Reflux Disease

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Abstract

Gastro-oesophageal reflux disease (GORD) is defined as 'Chronic symptoms or mucosal damage produced by abnormal reflux of gastric contents into the esophagus'. The Genval Workshop Report defines that GORD exists when the frequency of heartburn is equal to or greater than 2 days/week and that it is one of the most common gastrointestinal conditions in the general population. Endoscopy is the most recommendable exploratory procedure in a patient with symptoms of GORD, fundamentally heartburn and regurgitation. However, 50–75% of the patients with symptoms compatible with GORD have normal endoscopy. Thus, endoscopy does not appear to be indispensable in a large group of patients with GORD. Endoscopy is therefore the gold standard for the diagnosis of reflux oesophagitis (histopathological changes in the oesophageal mucosa), but there is no gold standard for the diagnosis of non-erosive GORD.

Twenty-four-hour pH monitoring has come to be considered the most sensitive and specific test in the diagnosis of GORD, but a significant proportion of patients (about 25%) have symptoms compatible with GORD and have 24-h pH monitoring results that can be considered normal. Besides, demonstrating the presence of acid reflux alone does not prove that it is the cause of suspected GORD-related signs or symptoms. Therefore, despite 'positive' pH studies, there is a significant number of patients failing to respond to therapy, mainly ear, nose and throat complaints, supposed as manifestations of gastro-oesophageal reflux disease. Despite 24-h oesophageal pH testing being an excellent diagnostic tool, it has no utility in routine clinical settings and hence its availability should be limited to tertiary care settings.

With the demonstration that antisecretory treatment with high doses of proton pump inhibitors (PPIs) for 1 week or 2 weeks achieves significant improvement or even remission of the symptoms of GORD, it not surprising that it has been proposed as a diagnostic test for the disease. For patients with symptoms compatible with GORD without alarm symptoms or other suspected complications of GORD, a short course of empiric PPI therapy gives valuable information about the presence of GORD. The PPI test is a simple, sensitive and cost-effective tool, but it has insufficient specificity for use as an objective criterion alone. The use of PPIs both as a diagnostic test (1–2 weeks) and as a diagnostic–therapeutic test (1–4 months) has a moderate usefulness and may be used especially in those environments in which there are difficulties in performing the objective test.

1. Introduction

In the developed world, between 6 and 12% of all adult individuals experience heartburn daily, and about 30% experience it at least once monthly.[1,2] This symptom, which is quite specific for gastro-oesophageal reflux disease (GORD), is thus relatively frequent and therefore an almost daily cause for consultation in Primary Health Care clinics. Some of these patients, either of their own volition or referred by their family physician, are seen by the gastroenterologist.[3] Among the population of patients with symptoms of GORD, only about 20% have lesions in the oesophageal mucosa demonstrable on endoscopy (oesophagitis). There is but poor correlation between the severity of the symptoms and the presence or absence of oesophagitis, and there is also no clear-cut relationship between the degree of oesophagitis, the severity of the clinical manifestations and the results achieved through the administration of generic and specific quality-of-life questionnaires.[4,5]

As in all the other chapters in this monograph, the scientific evidence will be categorised according to the proposals of the Centre for Evidence-Based Medicine in Oxford (UK), which have been adopted by the Ibero-American Cochrane Centre (see the Introduction to this Supplement).

2. Endoscopy in the Diagnosis of GORD

All the medical literature endorses endoscopy as the most recommendable exploratory procedure in a patient with symptoms of GORD (fundamentally, heartburn and regurgitation). Nevertheless, a number of points should be considered.

1. **Is endoscopy the one exploration that must necessarily be performed in a patient with symptoms suggestive of GORD?**

   Endoscopy in the face of symptoms compatible with gastro-oesophageal reflux is better able to characterise the patient, and even allows a more accurate prognosis to be established; endoscopy data may also change therapeutic strategies.[6] In fact, when GORD is diagnosed in the absence of oesophagitis, it is recommended that, once a treatment cycle has been completed, any medication should be discontinued; in the presence of severe oesophagitis (grades C or D according to the Los Angeles classification), maintenance therapy is recommended, because relapse is common.[7] However, this strategy implies the requirement for a considerable number of endoscopy procedures, which in turn involve great cost, by no means negligible discomfort for the patient, and increased waiting lists in the digestive endoscopy units, causing delay to other endoscopies for which there are more urgent indications. This problem might be solved by increasing both human and material resources, and this should always be the aim; however, requests of this nature are often turned down, either because of investment difficulties or because there are other priorities at a given time.

2. **Is it clearly established when a person with heartburn should be considered to be a patient with GORD?**

   Put another way: individuals presenting what might be catalogued as occasional symptoms that fall within the range of what is considered 'physiological' or 'normal' should be clearly differentiated from those individuals who, because of the frequency or severity of their symptoms, or both, might be classed as patients with GORD. The Genval Workshop Report and the Trondheim Consensus statement define that GORD exists when the frequency of heartburn is equal to or greater than 2 days per week.[8] On the basis of these criteria for GORD, the proportion of endoscopies that reveal some degree of oesophagitis increases to 45%, as demonstrated in a European multicentre trial in which early endoscopy was performed in patients with heartburn, and from which those who had taken a proton pump inhibitor (PPI) in the previous days were excluded[9] (*degree of recommendation C*).

3. **Can a patient with symptoms compatible with GORD but without oesophagitis be considered to be free of disease?**

   It is obvious that endoscopic normality does not rule out GORD, as demonstrated by the fact that patients who are symptomatic yet have no oesophagitis experience a deterioration of their quality of life similar to that experienced by those in whom the presence of an oesophageal lesion is demonstrated, and who therefore require therapeutic intervention in order to benefit from improvement.[10] Thus endoscopy does not appear to be indispensable in a large group of patients with symptoms compatible with GORD (*level of evidence 1 b; degree of recommendation A*).

4. **Is endoscopy indicated as a screening procedure for Barrett's oesophagus in patients with heartburn?**

   It is fully accepted that oesophagogastroscopy is not warranted by this sole indication (*level of evidence 2 a; degree of recommendation B*).

5. **Is endoscopy indicated in the presence of the so-called 'alarm symptoms' (dysphagia, anaemia, digestive tract bleeding)?**

   When one or more of these signs or symptoms occurs in a patient with heartburn or regurgitation, or both, oesophagogastroscopy should be considered to be, not merely unavoidable, but indispensable, as it sometimes only confirms the presence of oesophagitis but may, on occasion, reveal the presence of a malignant lesion in the oesophagus (*level of evidence 1 a; degree of recommendation A*).

   In summary, and taking into consideration the above, oesophagogastroscopy is an excellent diagnostic exploratory procedure, but in GORD without alarm symptoms it has only a moderate diagnostic yield, particularly as regards cost-effectiveness.

3. 24 h pH Monitoring in the Diagnosis of GORD

Twenty-four-hour pH monitoring has come to be considered the most sensitive and specific test in the diagnosis of GORD. However, it does have some disadvantages.

1. **Can 24 h pH monitoring be considered the most sensitive and specific test in the diagnosis of GORD?**

   This exploratory procedure has some features that render it very attractive (it objectively measures acid gastro-oesophageal reflux, even at various levels within the oesophagus or with one sensor in the stomach and another or various others in the oesophagus). However, it must be admitted that, even though it is an excellent diagnostic tool, it has insufficient sensitivity to be considered the gold standard, as a significant proportion of the patients (according to some authors, up to 25%) have symptoms compatible with GORD and 24 h pH monitoring results that can be considered normal; furthermore, such normal results have also been observed in patients with endoscopically confirmed oesophagitis[11] (*level of evidence 2 a; degree of recommendation B*).

2. **Is 24 h pH monitoring such an easy and readily available exploratory procedure that it might be considered first-line in the diagnosis of GORD?**

   The procedure of 24 h pH monitoring itself is not difficult, although it requires considerable attention and technical refinement (co-operation – even complicity – on the part of the patient, good catheter placement, adequate evaluation of the results, etc.).[12] Its cost is high[12] and, although the procedure is well tolerated, it requires the patient to carry a nasal catheter for 24 h, with the obvious accompanying discomfort and inconvenience. Even so, it is a very good exploratory procedure for firm indications that is quite helpful in the management of patients with suspected GORD and with diagnostic or therapeutic difficulties. Nevertheless, it is by no means a first-line exploratory procedure (*level of evidence 2 b; degree of recommendation B*).

3. Is it true that both 24 h pH monitoring and endoscopy are necessary for establishing a prognosis and a therapeutic strategy in the treatment of GORD?

It is recommended and accepted, although irrefutable evidence in support of this attitude is still lacking, that, in a patient with GORD without oesophagitis or in whom pH monitoring is normal, and after a course of treatment with PPIs, this medication may be withdrawn and reinstituted only in the case of a recurrence, or even be recommended only as on-demand therapy. However, in patients with severe oesophagitis (grades C or D according to the Los Angeles classification) or with grossly abnormal results from pH monitoring, maintenance treatment with PPIs is recommended, as recurrence is almost certain to occur.[13] However, these therapeutic recommendations are not as clear-cut as they would appear in theory (*degree of recommendation C*).

4. The Diagnostic PPI Test

In view of the above, and with the demonstration that antisecretory treatment with a powerful PPI or high doses of other PPIs, or both, for 1 or 2 weeks achieves significant improvement or even remission of the symptoms of GORD, it is not surprising that a considerable number of experts have, for some years, proposed that treatment with PPIs be considered as a diagnostic test for the disease[14] and that it be recognised – as it indeed has been in recent reviews[15] – by the name of 'PPI test'.

In a study published in 1999, Bate et al.[16] performed endoscopy and 24 h pH monitoring in 69 patients with clinical features suggestive of GORD. They also performed a PPI test with omeprazole 40 mg/day for 2 weeks, and compared the results. There was a significant correlation between the pH monitoring and the PPI test results, but not between those of pH monitoring and endoscopy. When the criterion for a positive PPI test was total disappearance of symptoms, the sensitivity of the test was 70% and its specificity 58%; using a substantial improvement in symptoms as the positivity criterion, the sensitivity increased to 90% and the specificity, logically, decreased to 31%. In the light of these results, the authors considered the PPI test to be simple, easy to perform and sufficiently sensitive for it to be recommended as a first-line procedure in the diagnosis of GORD.

Juul-Hansen et al.,[17] in 2001, published their experience regarding the value of the PPI test in patients with symptoms of GORD and abnormal results from pH monitoring. The patients received lansoprazole 60 mg/day or placebo for 5 days. The sensitivity of the test was considered to be very good, at 85%, with quite acceptable specificity (73%).

Fass et al.[18] assessed the diagnostic efficacy of the PPI test (with omeprazole 40 mg in the morning and 20 mg in the evening, for a total of 60 mg/day, over 1 week) as compared with 24 h pH monitoring, in patients with oesophagitis. The PPI test was more sensitive than 24 h pH monitoring (83% *vs* 60%; $p < 0.03$). When results from pH monitoring that also had a positive symptomatic index (coincidence of symptoms with the observation of a decrease in pH to less than 4) were considered abnormal, the sensitivity of 24 h pH monitoring increased from 60 to 80%.

Esomeprazole 40 mg/day in a single dose or 20mg twice daily for 2 weeks was used for PPI testing by Johnsson et al.[19], who reasoned that, by taking advantage of the greater antisecretory efficacy of this PPI, a greater diagnostic accuracy might be achieved in the test. The sensitivity of the 'esomeprazole test' from day 5 onwards was 80% and 86% with 40 mg/day and 20mg twice daily, respectively, compared with 36% with placebo. However, the specificity was rather low, at 45%. The authors concluded that the esomeprazole test with 40 mg/day for 1 week has a high sensitivity in the diagnosis of GORD.

Juul-Hansen and Ryding[20] performed the PPI test (lansoprazole 60 mg/day for 1 week) in patients with symptoms compatible with GORD and without oesophagitis. pH monitoring was abnormal in 65% of the patients. The PPI test was positive in all patients with abnormal pH monitoring findings, but also in most of those with

normal results from the monitoring. If pH monitoring were accepted as the gold standard in the diagnosis of GORD, the sensitivity of the PPI test was 97%, but its specificity was unacceptably low, at 6%. However, it does not seem reasonable to accept pH monitoring as the gold standard for diagnosis; instead, it should be considered an excellent diagnostic test in those indications for which its usefulness has been demonstrated.

Finally, in a meta-analysis published in 2004, Numans et al.[21] reviewed 15 studies with pH monitoring as the gold standard for the diagnosis of GORD. The sensitivity of the PPI test was 78% and its specificity 54%. The conclusion of this meta-analysis was that 'short-term treatment with PPI in patients suspected of having GORD does not confidently establish or exclude the diagnosis when GORD is defined by currently accepted reference standards'. However, 'many patients will respond to an empirical trial of a PPI, suggesting that a PPI trial might be reasonable in patients without alarm symptoms or other suspected complications of GORD'. Of particular interest are the comments on this paper in the Editors' patient information page (Summaries for Patients[22]):

(i) To the question '*Who was studied?*', the answer is: The authors review the results of the diagnostic tests performed in 2,750 patients with suspected GORD and compare them with those of the PPI test.

(ii) To the question '*What did the researchers find?*', the Editors answer: With the intake of these drugs over one week about 70% of the patients reduce their symptoms, even though in a considerable proportion of those patients (about 30%) the objective tests of endoscopy and pH-metry did not demonstrate reflux. On the other hand, in 30% of the patients with confirmed reflux the PPIs did not achieve significant amelioration of the symptoms.

(iii) They conclude, for the information of the patients who visit the Annals' website, that the PPI test cannot be considered to be unequivocally diagnostic for GORD, but it does help in its assessment as a first-line diagnostic test.

The negative aspects of the PPI test are derived from its low specificity (about 50–60%). This in turn is attributable to the fact that the PPIs are potent antisecretory drugs that achieve improvement, not only in patients with GORD, but also in almost all patients with duodenal or gastric ulcer and in some 25–50% of those with functional dyspepsia. This aspect should be addressed and assessed in cost-efficacy studies, as the low specificity of the test may cause a diagnostic delay in peptic ulcer disease, which may then be diagnosed at a later time when it causes complications such as upper gastrointestinal bleeding.[23]

The cost studies[14,15,23] show that the strategy of initiating the diagnostic work-up with the PPI test instead of endoscopy or pH monitoring reduces the number of endoscopies by 64% and pH monitoring by 53%, with a saving of €300–400 for each patient with symptoms compatible with GORD (*level of evidence 2 a; degree of recommendation B*).

5. The Diagnostic PPI Test in Atypical Manifestations of GORD

5.1 Non-Cardiac Chest Pain

Non-cardiac chest pain is a common complaint in everyday clinical practice, and a number of studies have shown that at least 50% of patients with thoracic pain have no evidence of coronary artery disease. The causes of this 'non-coronary chest pain' are quite varied, but there is no doubt that GORD is numerically the most important one, as it represents some 60% of the cases. The remaining 40% encompass motor disorders, visceral hypersensitivity, musculoskeletal disorders and psychological conditions. The PPI test has therefore been proposed for the diagnosis of GORD in cases of thoracic pain with normal coronary angiography.

One of the first studies in this area was that by Fass et al.[24] in 1998, in which endoscopy and 24 h pH monitoring were performed in 37 patients. Sixty-two percent of the patients had GORD and 38% had negative results in the two 'objective'

tests. Seventy-eight percent of the patients considered to be GORD-positive (according to those criteria) and 14% of those considered GORD-negative had a positive PPI test (omeprazole 40mg in the morning and 20mg in the evening for 7 days, compared with placebo), yielding 78% sensitivity and 86% specificity.

More recently, Xia et al.[25] studied 68 patients with non-cardiac chest pain and normal findings on coronary angiography, endoscopy and pH monitoring, who received lansoprazole 30 mg/day or placebo for 4 weeks. The 'therapeutic PPI test' was considered to be positive when a symptomatic decrease of more than 50% occurred in the lansoprazole group. A greater number of patients with abnormal reflux improved as compared with those without reflux (92% compared with 33%), whereas in the placebo group the improvement rate was similar (34%) in the groups with or without abnormal reflux. On the basis of these findings, the authors concluded that the therapeutic PPI test over 1 month is useful for the diagnosis of GORD with negative endoscopy in patients with non-cardiac thoracic pain (*level of evidence 2 a; degree of recommendation B*).

5.2 Laryngitis

Otolaryngological manifestations of acid reflux include a wide range of pharyngeal and laryngeal symptoms. The most reliable symptoms are voice change, sore throat, globus and cough.[26]. Sermon et al.[27] demonstrated that ambulatory 24 h dual-probe monitoring is useful in the assessment of patients with suspected ear, nose and throat (ENT) manifestations of GORD, especially in the case of abnormal laryngoscopy. However, potent inhibition of the acid secretion with a PPI for a mean of 3–4 months is probably the best diagnostic test for reflux laryngitis,[28] as two-channel pH monitoring has often failed to show differences between controls and patients with pharyngitis that is probably reflux-induced.[29] The 'short-term PPI test' is of no use in this manifestation of reflux and a therapeutic PPI test with potent acid inhibition for at least 3 months is required.

In a recent study, DelGaudio and Waring[30] investigated the efficacy of empirical treatment with esomeprazole in patients diagnosed with laryngopharyngeal reflux, with the aim of establishing a therapeutic model for this population. Thirty patients with reflux pharyngolaryngitis received esomeprazole 40 mg/day. Improvement of the ENT symptoms was achieved by week 4 in eight patients (26%) and by week 8 in 19 patients (63%). Ten of the 11 non-responding patients continued in the study, receiving double-dose esomeprazole; four of them (40%) responded after 2 months.

On the basis of their findings, DelGaudio and Waring[30] proposed the following therapeutic intervention model. Patients with suspected reflux pharyngolaryngitis should be treated initially with esomeprazole at the standard dose of 40 mg/day for 8 weeks. Those who do not improve should receive a doubled dose for a further 8 weeks. Non-responders should undergo 24 h two-channel pH monitoring while still receiving medication, in order to determine whether there is sufficient control of acid reflux. A positive result (insufficient control) might lead to a further increase in the dose of PPI or to antireflux surgery. A negative result (no abnormal reflux) presents the possibilities that the reflux is: (i) well under control; (ii) intermittent; or (iii) never existed. When faced with these doubts, it is advisable to repeat the pH monitoring after withdrawing the medication (*level of evidence 3 b; degree of recommendation B*).

5.3 Chronic Cough

Chronic cough is a common problem and is a frequent cause for medical consultation. Approximately 10% of new patients seen in respiratory clinics are referred with an isolated chronic cough.[31] In patients who are non-smokers, who are not taking angiotensin converting enzyme inhibitors and who have a normal chest X-ray, the three most frequent causes of chronic cough (cough lasting more than 3 weeks) are bronchial asthma, postnasal drip, and GORD.[32] GORD might be the underlying responsible cause in 10–25% of the

patients with chronic cough; it might induce cough through the activation of an oesophago-bronchial tussigenic reflex in the distal oesophagus.

The most sensitive and specific test for diagnosis of GORD is 24 h oesophageal pH monitoring, evaluating the duration and frequency of the reflux episodes and the temporal relationship between reflux and cough episodes. When 24 h oesophageal pH monitoring cannot be done or is not available, an empirical antireflux medical treatment is appropriate when GORD is a likely cause of chronic cough. However, if a PPI test fails, it cannot be assumed that GORD has been excluded as a cause of chronic cough.

Bilgen et al.[33] compared an empirical PPI trial and 24 h double-probe pH monitoring in laryngopharyngeal reflux and concluded that 'the best diagnostic tool for ascertaining whether chronic cough is secondary to GORD, after ruling out asthma and postnasal drip, is therapy with high-dose PPIs for two weeks in order to achieve potent acid inhibition' (*degree of recommendation C*).

In summary, and as stated by Dekel et al.[15] in a recent review, the use of PPIs both as a diagnostic test (1–2 weeks) and as a diagnostic-therapeutic test (1–4 months) has a moderate usefulness and may be used especially in those environments in which there are difficulties in performing the objective tests (*level of evidence 2 b; degree of recommendation B*).

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