

REVIEW

Acid suppression in gastro-oesophageal reflux disease: Why? How? How much and when?

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For patients with suboptimal relief from lifestyle modifications, acid suppressive therapy remains a cornerstone of treatment for gastro-oesophageal reflux disease (GORD). While a great deal of attention is focused on complications of GORD, adequate symptom relief remains an important and practical therapeutic goal. Adequate symptom relief is an achievable and easily measurable endpoint that both restores quality of life and prevents many potential complications.

Prevalence studies have shown that at one time or another, about half of all adults in the United States have experienced symptoms of gastro-oesophageal reflux disease (GORD). Classic symptoms of heartburn or acid regurgitation occur in approximately 40% of adults monthly and in about 14% to 20% weekly. Heartburn was the primary or secondary reason for more than 2.5 million visits to doctors in the United States in 1985.¹ For many patients the disease is chronic and associated with significant impairment in quality of life.² The combination of high prevalence rates, impaired quality of life, and chronicity result in a substantial burden of disease with tremendous socioeconomic impact.

IMPACT OF GORD ON QUALITY OF LIFE AND HEALTH CARE COSTS

When health care providers think of the cost of a disease, they most often think first of direct expenses such as the costs of visits to doctors' offices, tests, and medications. The direct health care costs of GORD are high due to both the prevalence and chronicity of the disorder. Direct expenses attributable to acid peptic disorders among the 2.4 million members of the Kaiser

Permanente Medical Care Program of Northern California amounted to \$59.4 million, of which \$24.1 million was attributable to GORD.³ Industry estimates suggest that sales of proton pump inhibitors will exceed 11 billion dollars in 2002.

The indirect costs of GORD likely exceed the direct costs, but they are harder to measure and good published data are lacking. Indirect costs reflect the societal and economic impact of GORD beyond the direct expenses to the health care system. These costs include principally absenteeism and loss of workplace productivity. Indirect costs are largely attributable to diminished quality of life, and the impact of GORD on quality of life is considerable. Dimenas demonstrated that using a generalised quality of life measure, untreated GORD was associated with a greater negative impact on wellbeing than hypertension, compensated congestive heart failure, menopause, or angina (fig 1).⁴ Resolution of symptoms in GORD results in normalisation of quality of life and, by inference, diminution of associated indirect health care costs.³ Clearly, effective treatment of GORD, or any chronic disease for that matter, has implications both for individual wellbeing and the associated socioeconomic scenario.

DEFINING GOALS OF GORD THERAPY

Prevention of oesophageal adenocarcinoma and management of Barrett's oesophagus

The goals of GORD therapy are to provide adequate symptom relief and prevent complications. The most severe complication of GORD is oesophageal adenocarcinoma. Oesophageal cancer remains relatively uncommon but has a poor prognosis. While the overall incidence of oesophageal carcinoma has not significantly changed, the incidence of oesophageal adenocarcinoma has nearly doubled in the past 20 years so oesophageal carcinoma is now more likely to be an adenocarcinoma rather than a squamous cell cancer. While strongly associated with intestinal metaplasia (Barrett's oesophagus), it has recently been shown that GORD alone is a risk factor for the development of oesophageal adenocarcinoma.⁶ Lagergren and colleagues demonstrated in a well constructed epidemiological trial that the duration, severity, and frequency of heartburn are all independent predictors of risk for the development of oesophageal adenocarcinoma. For patients with severe symptoms of

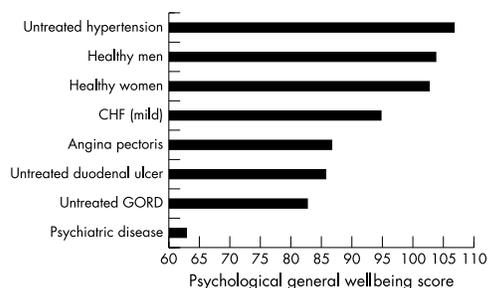


Figure 1 Gastro-oesophageal reflux disease (GORD) and diminished quality of life (CHF, congestive heart failure). Adapted with permission from E Dimenas. *Scand J Gastroenterol Suppl* 1993;199:18-21.⁴

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Abbreviations: GORD, gastro-oesophageal reflux disease; H₂RA, histamine-2 receptor antagonist

greater than 20 years' duration, the adjusted odds ratio for the development of this malignancy was 43.5 (95% confidence interval 18.3 to 103.5) as compared with asymptomatic persons.⁶

This same study also reported that treatment of GORD did not reduce the risk for the development of oesophageal adenocarcinoma.⁶ In fact, no data presently exist that demonstrate the efficacy of medical or surgical therapy in reducing either the extent of intestinal metaplasia or the risk of oesophageal adenocarcinoma. Despite this, many gastroenterologists empirically place patients with Barrett's oesophagus on a proton pump inhibitor regardless of symptoms. At present, conservative interpretation of the available literature supports treatment of Barrett's patients with therapy that provides adequate symptom control.

Healing of oesophagitis and endoscopy

Oesophagitis is present in 30%–40% of patients with GORD and can result in anaemia, bleeding, or dysphagia due to either dysmotility or peptic stricture. These complications are generally seen in more severe grades of oesophagitis. Control of oesophageal acid exposure heals oesophagitis and reduces complications. This is particularly true for peptic strictures in which the need for redilation is markedly decreased among patients treated with proton pump inhibitors.⁷

Healing of oesophagitis and, perhaps more importantly, maintenance of oesophagitis healing occurs in 80%–90% of patients treated with standard doses of proton pump inhibitors.⁸ This is in contrast to the 40%–70% healing seen with histamine-2 receptor antagonists (H₂RAs).⁹ Because of their obvious clinical superiority in the setting of complicated GORD, proton pump inhibitors should be used to treat and maintain any patient presenting with a complication of GORD.

Arguing from the other side, most patients with GORD don't have oesophagitis and most patients with oesophagitis won't develop complications. How are these patients best managed? Does everyone with longstanding or frequent GORD symptoms require endoscopy? This is clearly a confusing area. While it is presently not possible to draw firm conclusions in these areas, a few simple observations may simplify and demystify the problem.

First, the role of endoscopy is to evaluate and treat complications related to GORD and, arguably, to evaluate for the presence of Barrett's oesophagus. Endoscopy is an insensitive test for the diagnosis of GORD since oesophagitis is present in only 30%–40%. This appears to be particularly true in the evaluation of patients with possible extraoesophageal GORD symptoms, in whom the prevalence of endoscopic oesophagitis is substantially lower than for typical GORD. Various authors have advocated endoscopic detection of oesophagitis as a tool to guide therapy. The utility of this approach in clinical practice is dubious since accurate determination of oesophagitis presence and severity requires withholding treatment before endoscopy, which is neither good medicine nor good business.

Secondly, in clinical practice, relapse is generally defined symptomatically and not endoscopically. Third, detecting persistent oesophagitis does not influence practice decisions to the extent that persistent symptoms do. A recent study testing the utility of endoscopy in 742 patients with uncomplicated GORD found no correlation between endoscopic findings and subsequent therapy decisions.¹⁰ Patients with persistent symptoms received therapeutic escalation regardless of endoscopic findings.

Oesophagitis severity weakly correlates with symptoms, and improvement in quality of life after GORD therapy is dependent on symptom resolution rather than oesophagitis healing. It should also be recognised that it is easier to heal oesophagitis than to resolve symptoms. A recent study evaluating rabeprazole 20 mg daily and ranitidine 150 mg four

times a day showed that after eight weeks, both regimens provided reasonable healing of oesophagitis (92% for rabeprazole and 71% for ranitidine), but the percentage of symptom-free patients was less (50% for rabeprazole and 28% for ranitidine).¹¹ Similar results have been obtained in studies using various doses of omeprazole. After four weeks, oesophagitis healing rates were 76% for omeprazole 20 mg every day and 56% for omeprazole 10 mg every day. Complete symptom relief was obtained in 41% of patients taking omeprazole 20 mg every day and 35% of those taking omeprazole 10 mg every day.¹²

On balance, consideration of the above argument builds a strong case for symptom driven management in uncomplicated GORD. Using symptom resolution as a goal reasonably assures healing of associated oesophagitis.

Symptom relief and symptom driven therapy

Most physicians are well acquainted with step up or step down approaches to GORD management. These are chiefly pharmacoeconomic models that have not been critically evaluated in practice. A recent randomised, double blind controlled trial involving 593 adults with heartburn did demonstrate the clinical superiority of lansoprazole over either fixed dose ranitidine or regimens using step up or step down approaches.¹³ This important prospective study demonstrates that typical GORD symptoms are best managed not by stepping up or stepping down, but by stepping in with targeted therapy that meets treatment goals.

Symptom appropriate treatment is not difficult to implement. Many patients being evaluated with classic GORD symptoms have self medicated before seeing a physician. Additionally, many of these patients can identify exacerbating factors that are most often dietary or situational. In these situations, physicians should institute a treatment with a high probability of providing prompt and sustained relief. The appropriate treatment is dictated by the patient's symptomatology and the degree of relief provided by previous therapies employed by the patient. If, for example, a patient reports 70% symptom reduction with two or three antacid tablets each day, a prescription strength H₂RA is probably an appropriate choice. If, on the other hand, there is modest symptom reduction using generous amounts of over-the-counter H₂RA, a proton pump inhibitor, rather than a prescription strength H₂RA, is a logical choice.

The corollary to this approach resides with patients refractory to acid suppressive therapy. As there is a strong correlation between the degree of acid suppression and heartburn relief, a brief course of acid suppressive therapy with proton pump inhibitors dosed twice daily is valuable not only for its prompt therapeutic effect but also for its inherent diagnostic value. Recent trials have supported this approach and shown it to compare favourably with more onerous oesophageal pH monitoring.¹⁴ Patients with suspected GORD who respond to a brief trial of proton pump inhibitor therapy can be further managed by scaling down treatment to the lowest dose of acid suppressive therapy that provides adequate symptom relief.

Patients not responding to a therapeutic trial of high dose proton pump inhibitors should undergo ambulatory 24 hour oesophageal pH monitoring performed while taking acid suppressive therapy. The purpose of the study in this setting is not to prove or disprove the diagnosis of GORD, but to prove or disprove the association of the patient's symptoms with oesophageal acid exposure. As such, the study should determine not only the degree of total oesophageal acid exposure but also the correlation of the patient's symptoms with acid exposure.

Persistent abnormal oesophageal acid exposure is present in the minority of patients taking proton pump inhibitors once or twice daily. These patients can be managed by reviewing compliance and dosing issues and escalating therapy as needed.

The majority of patients will not have abnormal oesophageal acid exposure and their management is more problematic. Many of these patients have a functional oesophageal syndrome, disorders of gastric or oesophageal motility, or anxiety or depressive disorders. Additionally, there exists the possibility of non-acid reflux as a cause of persistent symptoms, although studies supporting this hypothesis are controversial.

Physician driven versus patient driven therapy

For most patients with GORD, the ultimate benchmark of clinical efficacy is patient satisfaction. The approach outlined thus far for patients with typical GORD symptoms is based on that premise. Additionally, this approach ensures oesophagitis healing and avoidance of complications in patients treated with acid suppressive therapy on a daily basis. Many patients with GORD, however, take medications only when symptomatic. A recent Gallup survey showed that among patients with prescriptions calling for the daily use of omeprazole or lansoprazole, 45% of patients were using the medication less than daily.¹⁵ These patients are treating their symptoms in an "on-demand" fashion.

On-demand therapy appears safe for most patients with GORD, particularly those with normal endoscopic findings. Symptom resolution is strongly associated with oesophagitis healing and a recent working group on the management of reflux disease thought existing evidence showed that control of reflux symptoms to less than two episodes per week was associated with healing of oesophagitis in more than 75% of patients.¹⁶ Additionally, endoscopy negative GORD does not progress to ulcerative disease.

On-demand therapy appears efficacious, although the practice has not been assessed in a large number of trials. The choice of a therapeutic agent is dependent on symptom severity and the rapidity with which symptom relief is desired. Nothing provides more rapid relief of heartburn than antacids. Unfortunately, no other agent also provides relief of such short duration. H₂RAs have been shown to be effective as on-demand agents in GORD and have the advantage of fairly rapid onset of action.¹⁷ These agents are widely available in both prescription and over-the-counter dosing, which makes them convenient. Unfortunately, they may provide suboptimal symptom relief for patients with more severe GORD. Proton pump inhibitors are considered the most efficacious agents for healing oesophagitis and providing symptom relief in GORD. This is attributable to their ability to provide profound and sustained suppression of gastric acid secretion. Although proton pump inhibitors are somewhat slower than H₂RAs in initiating inhibition of acid secretion, they are superior to H₂RAs with respect to rapidity and completeness of symptom relief as well as duration of remission. This has been shown for both maintenance and on-demand treatment strategies.¹⁸

Although data are limited, several studies have shown that intermittent or on-demand therapy with proton pump inhibitors is efficacious. Bardhan *et al* evaluated intermittent treatment with either omeprazole 10 mg or 20 mg daily or ranitidine 150 mg twice daily in patients who either were endoscopy negative or had mild oesophagitis.¹⁸ Of 677 patients, 318 (47%) used intermittent therapy to maintain symptom control over a 12 month period without having to resort to maintenance antisecretory drugs. There was no significant difference in efficacy between omeprazole and ranitidine, although omeprazole did provide faster relief of heartburn. Lind compared omeprazole 10 mg or 20 mg daily with placebo in heartburn sufferers who were endoscopy negative.¹⁹ Remission rates after six months were 83% with 20 mg of omeprazole, 69% with 10 mg of omeprazole, and 56% with placebo. Patients required medication slightly less often than every other day. These studies demonstrate that proton pump inhibitors can be used successfully to safely provide

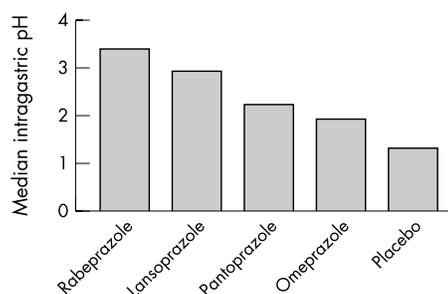


Figure 2 Day 1 antisecretory effects of proton pump inhibitors in 18 *Helicobacter pylori* negative subjects. All agents were significantly superior to placebo ($p < 0.05$). Rabeprozole and lansoprazole produced increases in gastric pH that were superior to pantoprazole and omeprazole ($p < 0.05$). Rabeprozole was also superior to lansoprazole in its effects on gastric pH ($p < 0.05$). Adapted from D Pantoflickova *et al*. *Gastroenterology* 2001;118:A5895.

adequate symptom relief in most patients with uncomplicated GORD. Comparative studies of proton pump inhibitors show little overall difference in outcome between available agents. Rabeprozole and lansoprazole have provided earlier and better symptom relief than other proton pump inhibitors in some studies of peptic ulcer treatment. Several studies have shown a trend for lansoprazole 30 mg daily to provide earlier symptom relief than omeprazole.^{20,21} Preliminary data suggest that rabeprozole 20 mg daily is more effective than omeprazole 20 mg daily in reducing heartburn scores within the first three and seven days of treatment.²²

Rabeprozole and lansoprazole appear to offer superior early symptom relief because of more effective early inhibition of acid secretion. In 18 subjects given a single dose of various proton pump inhibitors, the median 24 hour intra-gastric pH on the first day of dosing was significantly higher with rabeprozole 20 mg (pH = 3.4) than with lansoprazole 30 mg (pH = 2.9), pantoprazole 40 mg (pH = 2.2), or omeprazole 20 mg (pH = 1.9) (fig 2).²³ On balance, existing evidence suggests that differences between proton pump inhibitors are minimal when these agents are used chronically. The superior control of gastric acid secretion seen particularly with rabeprozole and also lansoprazole during the first days of administration would seem to favour the use of these agents in the setting of intermittent or on-demand use. This is an area that requires comparative studies using clinical outcomes as endpoints.

CONCLUSION

Gastro-oesophageal reflux disease is common and affects a large segment of the population. Much attention has focused on adenocarcinoma of the oesophagus and complications attributable to oesophagitis. While investigative efforts in these areas are essential to further our understanding and management of GORD, it is important for clinicians to remain aware of the overall low incidence of adenocarcinoma of the oesophagogastric junction despite its increased incidence. Additionally, there is a high probability that oesophagitis will be healed using therapy that provides symptom resolution. Effective symptom resolution can be reasonably and effectively delivered via treatment based on assessment of symptom severity, chronicity, and response to existing therapies. The delivery of targeted therapy based on patient assessment will not only provide prompt, sustained symptom relief but is also likely to be economically advantageous.

Patients with GORD complicated by bleeding or stricture should be maintained chronically on proton pump inhibitors. The role of acid suppressive therapy in Barrett's oesophagus is principally to provide symptom relief. Empiric use of proton pump inhibitors in these patients, though appealing and commonly practised, lacks supporting evidence at this time.

Most patients with GORD do not have oesophagitis but do have a chronic, remitting/relapsing course. Prompt, complete, and sustained symptom resolution is clearly the principal goal for these patients. This will restore quality of life, which is greatly impaired in many GORD sufferers. Achieving this endpoint not only fulfills the primary mission of the clinician but also decreases both direct and indirect costs of disease management. Ultimately, good clinical practice is good economic practice.

Finally, for patients with uncomplicated GORD, it may be time to become more comfortable in allowing patients to manage their own symptoms. The practice of on-demand or intermittent treatment has been occurring without our blessing for some time now. While additional studies are needed in this area, the strategy appears safe and effective, and it makes economic and clinical sense. After all, who has a more vested interest in symptom relief than the heartburn sufferer?

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