

# Correct use of proton pump inhibitors for gastro-oesophageal reflux disease

Proton pump inhibitors (PPI) are the most widely used prescription drugs for gastro-oesophageal reflux disease (GORD). Surveys indicate varying prescription practice by doctors and varying use by patients. What is the most correct way to use these drugs, for patients with different treatment needs and in different situations?

Gastro-oesophageal reflux disease is the most common disease affecting the upper gastrointestinal tract and affects all age groups, from infants to the aged. Approximately 8 % of adults meet the diagnostic criteria for GORD. In many cases the symptoms act as a constraint on everyday living and quality of life (1), and the indirect costs to society in terms of reduced productivity may be substantial (2). The disease is chronic in most cases, but often with varying need for treatment over time.

The most effective medical treatment for acid reflux is proton pump inhibitors (PPI), which inhibit the acid secretion of the stomach more strongly and with a longer duration of action than other available drugs (3). The consumption of these medicines in Norway is lower than elsewhere in Europe, but has increased by up to 10 % annually in the period 2003–2008 (4). Both overuse and under-use are undesirable, and it is important that the drugs be used optimally.

This article is intended to provide practice advice on the use of proton pump inhibitors for acid reflux disease and is based on searches in PubMed, the authors' own clinical experience and research, and Norwegian reimbursement rules for prescription drugs.

## Pathophysiology

GORD is characterised by a retrosternal burning pain («heartburn») and regurgitation to the pharynx. This is due to the contents of the stomach flowing back into the oesophagus. The closure mechanisms at the cardia, primarily the physiological sphincter, fail for various reasons, most commonly in the hours following meals. The refluxate damages the mucous membranes with its content of HCl, pepsin and to a varying degree bile, while proton pump inhibitors reduce this damage to the tissues. Gastroscopy reveals reflux oesophagitis in approximately 40–50 % of the patients with typical reflux symptoms (5).

Even if gastroscopy findings are normal, the mucous membrane is often abnormal, with increased permeability and inflammation (6). The sensitivity of the oesophagus to

acid reflux varies considerably (7), which may partly explain different needs for acid secretion inhibition in order to relieve symptoms.

## Treatment goals

The primary treatment goal for GORD is to relieve or prevent symptoms and thereby enhance the patient's quality of life. Healing in patients with substantial mucosal injury in the form of reflux oesophagitis grades C-D should be verified by means of a follow-up gastroscopy. It is hoped that healing will prevent complications, primarily metaplasia (Barrett's oesophagus) and adenocarcinoma in the oesophagus, an effect that has not been documented. On the other hand, we very seldom observe peptic strictures in patients who use proton pump inhibitors regularly.

## Pharmacology

Proton pump inhibitors are substituted benzimidazoles that bond almost irreversibly with active proton pumps (H<sup>+</sup>K<sup>+</sup>ATPase). Acid secretion is inhibited irrespective of the stimulus; it is particularly effective for meal-induced acid secretion. The effect increases over days, until stable inhibition of acid secretion is achieved on about day 4–5. Wide interindividual differences in pharmacokinetics mean that the same dose may have a different effect and duration of action in different patients (8). In Norway, omeprazole, lansoprazole, pantoprazole and esomeprazole are all marketed in two tablet strengths. The drugs are not equivalent mg for mg. There is a wide range in efficacy, from pantoprazole 20 mg to esomeprazole 40 mg (9). In clinical use, the «standard doses» omeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg and esomeprazole 20 mg appear to be fairly equivalent, while esomeprazole 40 mg has proved to result in better healing and symptom relief with severe reflux oesophagitis (10). Lower doses than these can be tried as maintenance treatment. Generic lansoprazole 30 mg and pantoprazole 40 mg are often lowest in price and most cost-effective for the majority of patients (11).

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## MAIN POINTS

Treatment with proton pump inhibitors is the most effective for the majority of reflux patients, but doses should be kept to the minimum required for effective symptom relief

In younger patients with typical symptoms of short duration, treatment with proton pump inhibitors without gastroscopy may be attempted; in other cases gastroscopy is indicated

Some patients require a higher dose, but it is seldom effective to increase it to more than double the standard dose

Proton pump inhibitors can be combined with an H<sub>2</sub> receptor antagonist taken as needed

When you think of the symptoms you have had in the last 7 days, how did you experience the following:

Answer the questions by setting a cross in one square in each row.

	No. of days			
	0	1	2–3	4–7
1. How often did you have a burning feeling behind your breastbone (heartburn)?	<input type="checkbox"/> (0)	<input type="checkbox"/> (1)	<input type="checkbox"/> (2)	<input type="checkbox"/> (3)
2. How often did you have stomach contents (liquid or food) moving upwards to your throat or mouth (regurgitation)?	<input type="checkbox"/> (0)	<input type="checkbox"/> (1)	<input type="checkbox"/> (2)	<input type="checkbox"/> (3)
3. How often did you have a pain in the middle of the upper stomach?	<input type="checkbox"/> (3)	<input type="checkbox"/> (2)	<input type="checkbox"/> (1)	<input type="checkbox"/> (0)
4. How often did you have nausea?	<input type="checkbox"/> (3)	<input type="checkbox"/> (2)	<input type="checkbox"/> (1)	<input type="checkbox"/> (0)
5. How often did you have difficulty getting a good night's sleep because of your heartburn and/or regurgitation?	<input type="checkbox"/> (0)	<input type="checkbox"/> (1)	<input type="checkbox"/> (2)	<input type="checkbox"/> (3)
6. How often did you take additional medication for your heartburn and/or regurgitation in other than what the physician told you to take? [e.g. Titalac, Link, Novaluzid, Zantac, PepsiDuo)?	<input type="checkbox"/> (0)	<input type="checkbox"/> (1)	<input type="checkbox"/> (2)	<input type="checkbox"/> (3)

**Figure 1** The GerdQ questionnaire for assessing reflux disease [12, 13]. The patients complete the questionnaire themselves. Scores for the different responses are given in red in brackets. The points are added together. A score of  $\geq 8$  means a high probability of reflux disease. A change in score such that none of the questions 1, 2, 5 or 6 scores more than 1 is regarded as a good response to treatment. Reproduced with the permission of AstraZeneca.

## Assessment of reflux disease

When patients first consult for reflux symptoms, their needs may vary considerably. GerdQ is a questionnaire that can largely distinguish reflux disease from other abdominal conditions that must be assessed endoscopically, and identify the degree of symptom burden [12, 13]. It consists of only six questions, and is also useful in follow-up of patients undergoing medical treatment (Fig. 1). As a general rule, younger people with typical, moderate reflux symptoms of short duration and without alarm symptoms (bleeding, anaemia, dysphagia, weight loss) do not need endoscopic examination. They should be given lifestyle advice and offered  $H_2$  blocker as needed («white» prescription, not reimbursed) (Fig. 2). If the symptom burden is limited, medical treatment may not be necessary. If the disease is clearly affecting quality of life, a proton pump inhibitor can be administered on «white» prescription for a period without first performing a gastroscopy (Fig. 2). A number of studies have shown that serious illness is not overlooked if this course is followed [5, 13]. The costs to patients of a generic proton pump inhibitor on a «white» prescription are low.

It is doubtful whether an effect of proton pump inhibitors on chest pain, reflux symptoms and dyspepsia can be taken as evidence of the diagnosis acid reflux disease [14]. This can be attributed partly to a placebo effect and partly to unclear response parameters.

The main indications for gastroscopy are alarm symptoms (as mentioned above), airway symptoms, age of over 50, symptoms

for more than five years, or symptoms that occur during the night. Patients who are worried about cancer should also be offered gastroscopy. If there is a long wait for endoscopy, a proton pump inhibitor can be administered. This should be discontinued two weeks at the latest before the procedure. Information about the effect of both starting and stopping medication is useful when evaluating the need for further treatment. Manometry and 24-hour pH monitoring are primarily indicated for patients for whom surgery is being considered, patients who have not benefited from treatment with proton pump inhibitors or patients with atypical symptoms when gastroscopy reveals normal mucous membranes.

## Prescription rules in Norway

Proton pump inhibitors are indicated for reflux disease when patients continue to experience severe symptoms despite the use of  $H_2$  blockers and antacids. Reimbursement is given only after a first time prescription by a specialist in internal medicine or surgery, and when the disease has been documented by endoscopic findings of reflux oesophagitis or a pathological result of 24-hour pH monitoring. 24-hour pH monitoring aims to detect either abnormally increased exposure to acid in the oesophagus or a significant time correlation between symptom episodes and reflux. One of the most reasonably priced drugs, lansoprazole, omeprazole or pantoprazole must be tried first. Only when symptom relief is inadequate after at least four weeks of regular use can prescription be shifted to esomeprazole. Additional indica-

tions for esomeprazole are severe reflux oesophagitis, peptic strictures or metaplasia.

## Short-term treatment with proton pump inhibitors

Initial treatment for reflux symptoms, particularly in the absence of reflux oesophagitis, should be given for 1–2 months, after which the result of the treatment should be evaluated, for example by means of a questionnaire (Fig. 2):

– If, after 1–2 months, the patient is satisfied with the symptom relief (whether or not the patient has undergone gastroscopy), a trial of discontinuing proton pump inhibitors should be made, unless endoscopy has revealed severe oesophagitis. After 1–2 months of treatment, reflux oesophagitis will have been healed in  $> 80\%$  [11] and the sensitivity of the oesophagus to acid reduced. In the event of rapid and pronounced return of symptoms after discontinuation, maintenance treatment is generally indicated (Fig. 3), i.e. resuming the same dose of the same proton pump inhibitor. An attempt should nonetheless be made to reduce the maintenance dose to the lowest effective dose, whilst reminding the patient of simple lifestyle advice to limit symptom breakthrough.

– If relief of reflux symptoms is not satisfactory, the dose of proton pump inhibitor can be doubled for a period, or esomeprazole 40 mg daily can be tried. Experience shows that a simple morning dose 15–30 minutes before breakfast results in the best adherence with medication. If the patient has symptoms in the evening and at night, it is

logical to divide the daily dose into a morning dose before breakfast and an evening dose before a meal in the period 6–8 p.m. We seldom see that increasing the daily dose to more than double the standard dose has any effect. If therapy continues to fail, the patient should be assessed as indicated in the section on resistance to treatment below.

Many patients have intermittent symptoms and wish to treat symptoms only when they occur. Proton pump inhibitors in the formulations now available in Norway are less appropriate than  $H_2$  receptor antagonists for such use since an effect is only achieved after 1–2 days. Proton pump inhibitors, on the other hand, can be used preventively for shorter and longer periods when symptoms are expected (holiday travel, periods with increased physical exertion etc.).

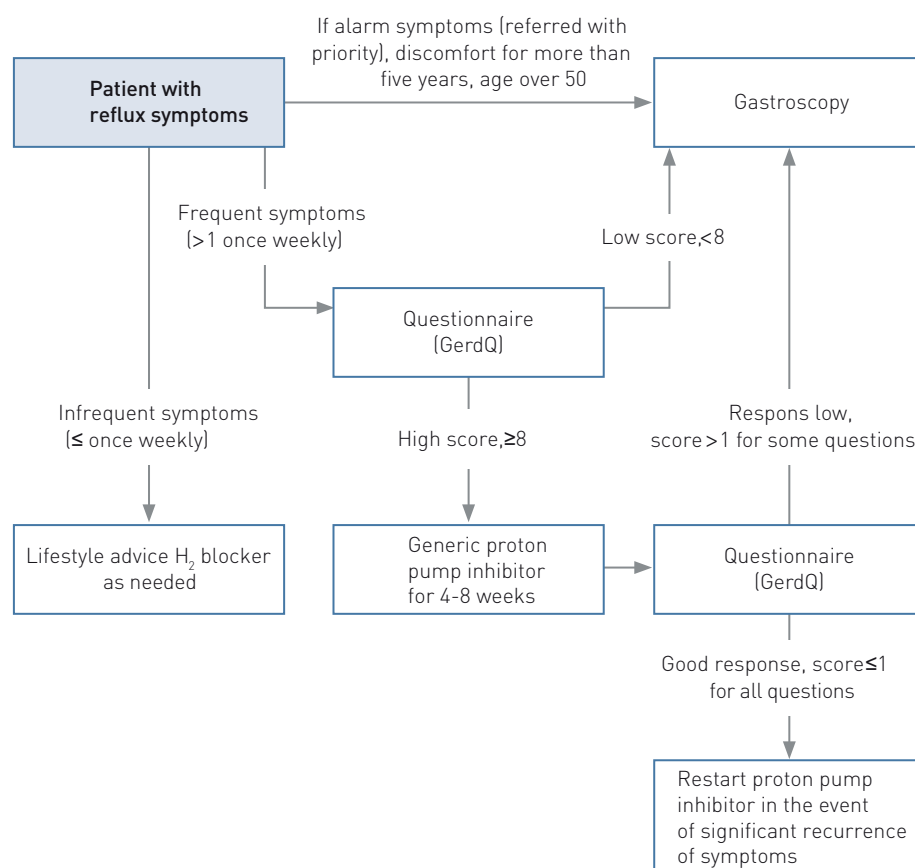
### Resistance to treatment

Patients who do not obtain satisfactory symptom relief from proton pump inhibitors, even in a double dose, must be investigated further. It must first be ensured that the patient has taken the medicine as prescribed (taken daily, fasting before normal sized meals). Careful questioning will often reveal that the reflux symptoms have in fact disappeared, but that the patient still has other discomfort that cannot be expected to be relieved by inhibition of acid secretion (dyspepsia, irritable bowel etc.). Others find that reflux symptoms return during treatment, possibly because the person concerned has relaxed dietary constraints, increased physical activity etc.

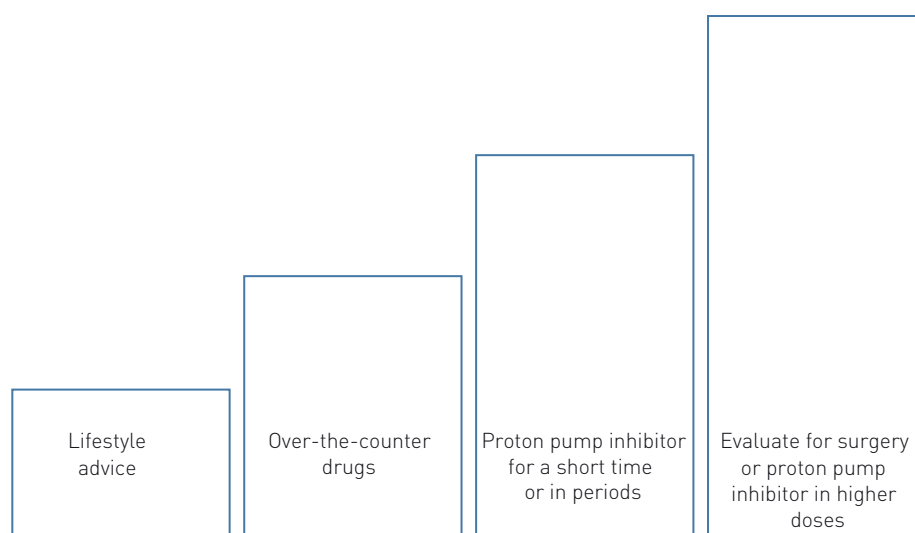
We do not assess patients with a poor response to treatment before they have used the standard dose twice a day for > 4 weeks. With this patient group, proton pump inhibitors are not discontinued before assessment, which consists of gastroscopy and impedance-pH monitoring. If pH-metry shows that symptom episodes are significantly time-associated with reflux episodes, the strength of the proton pump inhibitor can be increased or antireflux surgery can be considered, particularly for patients who have regurgitation as a residual symptom. Some patients benefit from supplementing PPI therapy with an  $H_2$  receptor antagonist (commonly effervescent tablets) taken only when symptoms break through, or an alginate taken as prophylaxis at bed-time.

### Long-term treatment with proton pump inhibitor or antireflux surgery?

Randomised comparative studies have not disclosed important differences in efficacy between antireflux surgery and maintenance treatment with proton pump inhibitors (15), with respect to symptom relief, quality of life or safety, within a time period of up to 12 years. Probably only a sub-group of patients benefit significantly more from the reduced frequency and volume of reflux to the oeso-



**Figure 2** Proposed algorithm for simple assessment and initial treatment of younger patients (< 50) with reflux symptoms but no alarm symptoms (bleeding, anaemia, weight loss, dysphagia). A questionnaire (GerdQ, Fig. 1) can be used to distinguish patients with pure reflux discomfort, who can be treated without gastroscopy initially



**Figure 3** Treatment stages when reflux disease is diagnosed. Patients with minor discomfort can be treated with  $H_2$  blockers as needed, more serious problems are treated with proton pump inhibitors for periods, continuously and in some cases with a double dose

phagus brought about by surgery. As many as 10–15% of patients who are operated upon experience substantial new discomfort after the procedure, often in the form of bloating and increased intestinal gas (16). For the majority of the many reflux patients,

maintenance therapy with proton pump inhibitors is the preferred treatment strategy. *Helicobacter pylori*-associated gastritis and atrophy may be exacerbated through the use of PPI (17) and eradication of the bacteria may be reasonable before long-term use.

## Discussion

Proton pump inhibitors have become standard treatment for patients with gastro-oesophageal reflux disease when the symptoms are substantially affecting the patient's quality of life. Short-term use is associated with very little discomfort (10). Research on health registers, on the other hand, has shown a moderately increased incidence of pneumonia and intestinal infections, including *Clostridium difficile* (18). There has been discussion as to whether there is increased risk of osteoporosis with a risk of fractures in patients who have used proton pump inhibitors for a long period (19–21). New data weigh against interaction with activation of clopidogrel at the CYP 2C19 level being of clinical significance in the form of increased cardiovascular risk (21). Today there is little evidence for an actual increase in malignant disease even with prolonged PPI use (22). Nevertheless, there is every reason to restrict the treatment periods and dose to the lowest that are effective. In young patients, empirical short-term treatment for classic reflux symptoms is reasonable, while long-term treatment may be indicated in the event of recurrence of distressing symptoms. Lifestyle advice must often be repeated in order to maintain a good therapeutic effect. Long-term treatment with proton pump inhibitors on unclear indications must be avoided.

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