



Long-term management of patients taking proton pump inhibitors

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Summary

Proton pump inhibitors have changed the management of acid-related upper gastrointestinal disorders. Other effective strategies for reducing upper gastrointestinal morbidity include lifestyle modification, *Helicobacter pylori* eradication for patients with present or past peptic ulcer disease and infection, and less potent therapy for mild dyspepsia and gastro-oesophageal reflux. Proton pump inhibitors have a definite role in the prevention of recurrence of oesophageal strictures. They can also be used to prevent the ulcerative complications of non-steroidal anti-inflammatory drugs in patients at high risk. In Barrett's oesophagus the efficacy of proton pump inhibitors in preventing disease progression and the development of adenocarcinoma is unclear.

Key words: dyspepsia, gastro-oesophageal reflux disease, *Helicobacter pylori*.

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Introduction

The discovery of *Helicobacter pylori* and the introduction of proton pump inhibitors (PPIs) in the 1980s were major advances in our understanding and management of upper gastrointestinal disorders. These advances made surgery for peptic ulcer disease largely obsolete. In Australia, general practitioners and gastroenterologists now prescribe PPIs to the extent that they are in the top 10 drugs, by prescription counts and cost.¹ Prescribing patterns reflect recent changes in the epidemiology of acid-related disorders, failure of a multi-pronged approach to chronic upper gastrointestinal disorders, uncertainty about the prevention of long-term complications and confidence about the relative safety of PPIs.

Clinical pharmacology

Gastric acid secretion by the parietal cells is controlled through food-stimulated and neuroendocrine pathways involving the

activity of gastrin, histamine, acetylcholine, and pituitary adenylate cyclase activating peptide. PPIs irreversibly inactivate the final effector in the secretion pathway (gastric hydrogen potassium ATPase in the parietal cell). As PPIs suppress stimulated, as well as basal, acid secretion they are best taken before a meal. They are usually taken once daily as the recovery half-life of gastric acid secretion ranges from 15 to 46 hours. The anti-secretory effect increases within the first few days of oral dosing.

There are few clinically significant drug interactions with PPIs. Occasionally, the concentrations of drugs such as phenytoin and warfarin may be affected due to inhibition of the cytochrome P450 system. The absorption of other drugs (for example, quinolones, ketoconazole) may be affected by an increased gastric PH.

Indications

In the long-term management of patients taking PPIs, the initial indication for prescription always needs review. Persistent symptoms may require further investigation.

Gastro-oesophageal reflux disease

Gastro-oesophageal reflux disease is probably the most frequent indication for prescribing PPIs. For patients with symptoms typical of gastro-oesophageal reflux disease, a therapeutic trial of PPIs can be started as a first step. If symptoms are relieved, this serves to support the diagnosis. After diagnosis, most of the controversy about the management of gastro-oesophageal reflux disease has been about pharmacological therapy. Should treatment be stepped up from the least potent towards the most potent therapy or stepped down from most towards least potent, with the end point being symptom control? This will be guided by the symptoms and, if indicated, endoscopy.

Whether the goal of therapy is symptomatic relief or reduction of adenocarcinoma risk, patients should be informed of the importance of risk factors for symptom generation and adenocarcinoma development. Obesity, smoking, alcohol and fatty foods all exacerbate gastro-oesophageal reflux disease and are risk factors for oesophageal carcinoma.² While the absolute risk of adenocarcinoma is small, overweight people and obese

people have about 1.5 and 4 times the risk of individuals with normal weight. Once lifestyle is addressed, the key questions determining the appropriate use of PPIs are:

- What is the natural history of gastro-oesophageal reflux disease?
- Does long-term treatment reduce complications?

Long-term studies of patients with dyspepsia and gastro-oesophageal reflux disease show that many patients' symptoms resolve and they stop treatment. While PPIs provide more effective symptom control than histamine (H₂) receptor antagonists there are also overwhelming long-term data that a substantial proportion of patients can control their symptoms with lifestyle interventions, antacids, H₂ receptor antagonists or PPIs taken when required.

PPIs should be prescribed regularly when there is a history of oesophageal stricture as, unlike H₂ receptor antagonists, they reduce stricture recurrence. The elderly also require regular therapy as they are more likely to have severe oesophagitis despite milder non-specific symptoms.³

Barrett's oesophagus

Long-term PPI therapy is currently recommended for all patients with Barrett's oesophagus although treatment is yet to be shown to reduce the risk of adenocarcinoma. A large randomised trial is investigating if a combination of low-dose aspirin and a PPI may reduce the development of adenocarcinoma in patients with Barrett's oesophagus.⁴

Gastric and duodenal ulcer disease

In patients who are not taking non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin, *H. pylori* is a key cause of peptic ulcer disease. Its eradication effects a cure. Everyone with a documented history of peptic ulcer disease and evidence of *H. pylori* infection should therefore be offered eradication therapy rather than be subjected to long-term PPI therapy. PPIs do have some antibacterial activity against *H. pylori*, but must be used in combination with antibiotics to achieve eradication. This simple and effective strategy is underutilised.

Patients taking long-term NSAIDs who also have *H. pylori* infection have a six-fold increase in the risk of ulcer bleeding, in contrast to a risk of less than two-fold for patients with *H. pylori* infection alone and almost five-fold for patients on NSAIDs with no *H. pylori* infection. The approach to primary prevention of ulcer disease in patients taking long-term NSAID and antiplatelet therapy will depend on clinical circumstances. Serious NSAID-induced gastrointestinal complications occur in about 1.5% of patients per year. This risk increases with the type of NSAID and dosage, concurrent warfarin or antiplatelet therapy, age and a past history of ulcer disease. Patients requiring NSAIDs, aspirin or clopidogrel, who are at increased risk of peptic ulcer complications should be considered for concurrent treatment with a PPI.⁵

Other indications

PPIs may be indicated in the prevention of stress-related mucosal injury in the critically ill. The long-term impact of PPIs on symptoms and quality of life in patients with functional dyspepsia is debatable. Empirical use of PPIs is not indicated in patients taking corticosteroids.

Zollinger-Ellison syndrome is a rare condition characterised by severe peptic ulceration resulting from the release of gastrin by a pancreatic tumour. High doses of PPIs may be needed.

Safety of long-term therapy

PPIs are well tolerated and most adverse effects are mild and transient. Common adverse effects, observed in up to 10% of patients, are headache, diarrhoea, gastrointestinal upset, constipation and flatulence. Rare but important adverse events include acute interstitial nephritis, hyponatraemia, hypokalaemia, hypomagnesaemia⁶, pancreatitis and Stevens-Johnson syndrome. There are reports of an increased risk of pneumonia and *Clostridium difficile* colitis in long-term users of PPIs.⁷

Gastric atrophy and cancer

Long-term use of PPIs leads to hypergastrinaemia in most patients. The gastrin concentration is usually less than four times the upper limit of normal and quickly normalises after the PPI is stopped. Higher concentrations may be seen in patients with atrophic gastritis and with *H. pylori* infection. In these patients particularly, enterochromaffin-like cell hyperplasia may be seen, however there are no reported cases of dysplasia or carcinoid development. Fundic gland polyps may also be induced by prolonged hypergastrinaemia, but again despite their frequency dysplasia has rarely been reported.

Concern about the risk of gastric cancer with long-term PPI therapy largely relates to the interaction between the drugs and *H. pylori*. In infected patients PPI-induced changes in gastric pH drive the infection proximally and induce corpus gastritis and a progression to atrophic gastritis. There is currently no proof that this increases the incidence of gastric cancer among long-term PPI users, but in 2006 the Maastricht consensus panel recommended *H. pylori* eradication for patients with atrophic gastritis.

Enteric infection

Achlorhydria and hypochlorhydria increase the risk of enteric infections. A number of case control studies have investigated whether long-term PPI therapy increases the risk, particularly in the elderly. The results are inconclusive with some studies finding an increased risk of infection (for example with *Campylobacter* species) and others finding no significantly increased risk. Studies of community and of hospital-acquired *Clostridium difficile* infection have found PPI therapy to be a risk factor. This may be of particular relevance in hospitals where

high doses of PPI therapy are used, but further studies are needed to assess these findings.

Malabsorption

The effect of PPI therapy on the bioavailability of minerals, such as calcium, has been extensively studied. Although PPIs change pH and bioavailability this does not appear to be clinically relevant. A recent case control study found a higher incidence of hip fracture among long-term PPI users, but did not control for coeliac disease.⁸

Acid suppression therapy may inhibit B₁₂ absorption as ingested B₁₂ is protein bound and its release from foods is facilitated by gastric acid. Studies to date suggest only patients with profound acid suppression over many years, such as those treated for Zollinger-Ellison syndrome, are at risk of developing clinically relevant B₁₂ deficiency and should be monitored.

Conclusion

The use of PPIs is widespread. Gastro-oesophageal reflux disease is a major indication but it should be addressed with lifestyle modification before acid suppression. For the majority of patients who remain symptomatic the objective is symptom control and this can often be achieved with intermittent treatment. Long-term maintenance therapy has a clear role in preventing NSAID/aspirin-induced ulceration and the recurrence of oesophageal strictures. Its capacity to reduce Barrett's oesophagus and adenocarcinoma development is less clear and awaits further studies.

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Further reading

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 27)

1. Proton pump inhibitors reduce the recurrence of oesophageal strictures.
2. Most people with gastro-oesophageal reflux disease do not need continuous daily therapy with a proton pump inhibitor.

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