Therapeutic brief 7

PPIs in GORD: Reduce the dose – Keep the benefits

Low dose proton pump inhibitors (PPIs) control dyspepsia in 70-80% of patients with healed oesophagitis.[1-3]

This therapeutic brief asks you to review the management of your veteran patients who take PPIs for gastroesophageal reflux disease (GORD) and to consider the 'step-down' approach.

In 2004, over one third of medicine-taking veterans were dispensed a medicine to treat gastric acid-related disorders, of which 78% were PPIs.[4] Analysis of PPI dispensings by strength over the same period showed that the majority were for the higher strength products (refer to Table 1 for low and high strength product listings)[4].

Inside

Since 1999, there has been a slow but steady rise in the proportion of lower strength products dispensed. In the year 2004/2005 approximately 18 % of dispensings were for the lower strength products (see figure 1)[5].

When treating GORD, prolonged therapy with high PPI doses is rarely more effective than low doses.[6]

The high prevalence of regular use of PPIs means that rare but serious adverse effects such as acute interstitial nephritis and microbiological infections are seen more often.

The 'step-down' approach is recommended for most people with mild to moderate GORD.[7,8] A 4 or 8 week course of PPI (e.g. 20mg omeprazole once daily) usually results in symptom control and healing of oesophagitis. Treatment can then be 'stepped-down' to the minimum dose for symptom control, which may include intermittent, patient-driven therapy.

The 'step-down' approach is not recommended for patients with severe oesophagitis, strictures, Zollinger-Ellison syndrome or Barrett's oesophagus who will require regular rather than intermittent PPI therapy.[7,9]

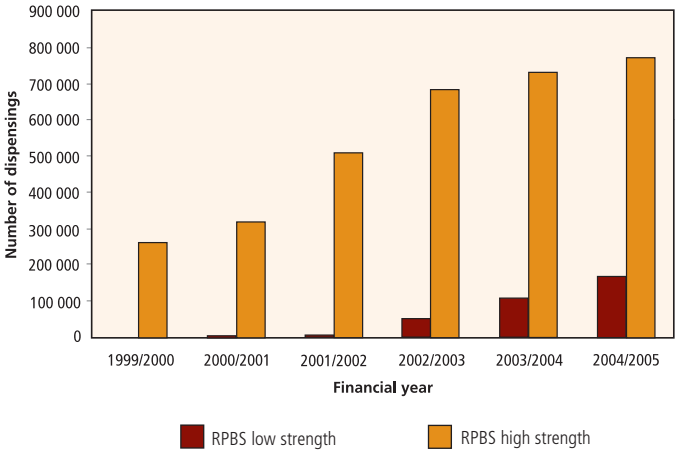

Figure 1: RPBS dispensings of low and high strength PPI products

Key Points

- Review patients on prolonged PPI therapy for GORD for both indication and dose.
- Use 'step-down' approach for maintenance therapy.
- Low dose PPI controls dyspepsia in 70-80% of patients with healed oesophagitis.
- Lifestyle interventions may improve symptom control for some patients.

2 Review PPI Therapy

PPIs are effective in controlling symptoms of dyspepsia due to GORD.[8] Use higher strength PPI products (see Table 1) for 4 or 8 weeks to control symptoms and heal oesophagitis. Then review with a view to 'step-down' treatment to the minimum dose of PPI that controls symptoms.[7]

All patients on PPI therapy should be reviewed:

- after an initial 4 weeks of therapy for GORD or oesophagitis;[7,9] and
- on completion of 8 weeks of therapy for GORD or oesophagitis.[7,9]

The need for ongoing therapy should be established when repeat prescriptions are requested.

PPI therapy may fail to give symptomatic relief due to an inadequate effect on lowering gastric acid secretion, a misdiagnosis, or major complications from oesophagitis. If higher dose PPI therapy is required, twice daily dosing may be more effective than once daily dosing.[9] Also, changing to another PPI may be effective.

Hospital-initiated PPI therapy should be reviewed after discharge to confirm an ongoing indication for the medicine and a plan developed for future review and dose reduction.

Review the need for medications that may induce/ exacerbate dyspepsia

Certain drugs may induce or worsen symptoms of dyspepsia. These drugs include aspirin, cholinesterase inhibitors, conventional NSAIDs, COX-2 selective NSAIDs, bisphosphonates, calcium channel blockers, clopidogrel, corticosteroids, iron, nitrates, tetracyclines, SSRIs, venlafaxine and theophylline.[7,8,10]

Avoid use of all NSAIDs in patients with symptoms of dyspepsia.

If continued NSAID use is required, prophylactic PPI therapy should be considered in patients with risk factors for gastrointestinal bleeding.[7,11]

Omeprazole and pantoprazole are currently approved for NSAID-induced ulcer prophylaxis in Australia, although neither is listed as a concessional benefit for this indication.

The 'step-down' approach

Following a satisfactory response to initial standard dose PPI therapy for 4 or 8 weeks 'step down' options include:

Reducing the dose

A recommended approach is to continue the same PPI and prescribe either half the daily dose or alternate daily dosing, depending on patient preference. Low dose PPIs control symptoms of dyspepsia in 70-80% of patients with healed oesophagitis.[1-3] Refer to Table 1 for dosing advice.

Intermittent symptom-driven PPI

E.g. Use omeprazole 10mg or equivalent on days when symptoms occur. On average, tablets are taken two to three days per week[7]. This dosage controls symptoms in most people with endoscopy negative GORD.[12,13]

Trial cessation

In a significant minority of patients (up to 40%) cessation of PPI therapy does not cause symptom relapse.[6,7] The decision to cease therapy should be guided by symptom control and each patient's ability to report return of symptoms.

Table 1: Safety, efficacy, strength and dose comparison for proton pump inhibitors.

	Safety and efficacy equivalence of PPIs*	Usual daily dose for healing GORD	Consider for maintenance therapy for GORD+
		High strength product	Low strength product
Omeprazole (Acimax, Losec, Meprazol, (robitor) tablet, capsule	20 mg	20 mg	10 mg
Lansoprazole (Zoton) capsule, granules (for suspension)	30 mg	30 mg	15 mg
Pantoprazole (Somac) tablet	40 mg	40 mg	20 mg
Rabeprazole (Pariet) tablet	20 mg	20 mg	10 mg
Esomeprazole (Nexium) tablet	20 mg	40 mg	20 mg

*Provided by the Pharmaceutical Benefits Pricing Authority 04/04.
+Recommended "Step-down dose" – is half the daily dose for healing GORD or half the current daily dose which gives symptom control.

Adverse effects

PPIs are generally well tolerated and all agents have a similar adverse effect profile with few contraindications for use.[8]

The exception to the above statement is lansoprazole, which has been associated with a higher reported incidence of diarrhoea. It has been suggested that the diarrhoea is due to drug-induced microscopic colitis[14,15] and may occur more frequently in the elderly.[16]

The high prevalence of use of PPIs amongst veterans may result in a higher burden of rare adverse effects than anticipated, so regular review of the need for ongoing therapy and monitoring of adverse effects is necessary. For example, in Australia, PPIs are the third most reported group of medicines associated with the rare adverse effect, interstitial nephritis.[17] Research in the United Kingdom supports this observation.[18]

There is evidence from observational trials that long-term PPI use is associated with an increased risk of community-acquired pneumonia compared to non-users in a dose-related manner.[19,20] If confirmed by larger prospective trials, this risk is roughly comparable to that of upper gastrointestinal bleeding caused by non-steroidal anti-inflammatory drugs.[21]

In addition, PPIs have been reported as a risk factor for *Clostridium difficile* diarrhoea.[22] Other risk factors for infection with *Clostridium difficile* include concomitant treatment with broad spectrum antibiotics, chemotherapeutic agents and advancing age.[23]

H. pylori infection

The preponderance of evidence suggests that neither *H. pylori* infection nor eradication cause or exacerbate GORD in the majority of patients.[7,24] However, long term PPI use in the presence of *H. pylori* infection increases the risk of gastric mucosal atrophy . Eradication of *H. pylori* reduces this risk.[7]

The Gastroenterology Society of Australia (GESA) and the Maastricht report[24] advocate that consideration be given to testing for *H. pylori* in patients with GORD who are long term PPI users, followed by eradication therapy in patients testing positive for the bacterium. However, this approach is not universally accepted because gastric mucosal atrophy associated with long-term PPI use has not unequivocally shown to lead to neoplasia.

A non-invasive test such as urea breath test (UBT) , faecal antigen test (FAT), or serology may be used to detect active infection. PPIs must be withheld for at least one week, and antibiotics for at least 4 weeks, prior to either the UBT or FAT to avoid false negatives. Confirming the eradication of *H. pylori* following eradication therapy is performed using either the UBT or FAT. Serology is not suitable for confirming eradication, because antibody titres can remain elevated for months following successful eradication.

Of the veterans dispensed medicine for gastric acid-related disorders in 2004, only 1.1% were also dispensed *H. pylori* eradication therapy.[4] As the bacterium has a prevalence of 40% in people over 40 years of age,[7] testing for *H. pylori* when prescribing long-term PPI therapy may be considered.

Patient directed use of antacids and H_2 antagonists

Symptom-driven use of antacids, antacid/alginate combination, or 'over-the-counter' H2 antagonists may be helpful for the relief of mild, occasional reflux symptoms.[7] However, patients who require frequent self-medication should be assessed for more effective treatment.

Regular antacid use in patients with endoscopically significant reflux is ineffective and has not been shown to heal oesophagitis;[7] however it can be effective in patients with endoscopically negative reflux who have intermittent symptoms.

4

Lifestyle interventions

For patients with GORD, lifestyle interventions can be used as adjuncts to appropriate pharmacologic therapy.[7]

The main lifestyle interventions are:

- Diet modification: identify and avoid foods that precipitate reflux episodes e.g. fatty and spicy foods and excess coffee, tomato and orange juice.
- Physical adjustments and accommodations: avoid large meals and refrain from lying down, bending or straining soon after meals. Avoid tight fitting clothing, particularly after meals. Raising the bed head may decrease the occurrence of night-time reflux.
- Moderation of alcohol consumption: avoid excessive alcohol intake.
- Obesity: obese patients should lose weight.
- Smoking cessation: cease smoking as it aggravates reflux and increases the risk of oesophageal and other cancers. The Quitline is available 24 hours a day for information and support – 137 848.

What to tell your patient

- Expect the same benefits from lower dose PPI therapy.
- Potentially fewer tablets/capsules to take with 'step-down' approach.
- The less medicine you take, the less risk of unwanted effects.
- Once symptoms are controlled, you may be able to take when needed.
- Report any abdominal symptoms immediately.
- Lifestyle interventions can improve symptom control.
- Bring a list of all medicines to each visit for review.

Useful websites for more information on the treatment of GORD include:

- **www.nice.org.uk and**
- **www.gesa.org.au**

Patients can be referred to **www.quit.org.au** for advice and support on how to quit smoking.

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