Topic 32: Proton Pump Inhibitors – How much for how long?

The considerable benefits and perceived safety of proton pump inhibitors (PPIs) in the management of acid-related gastrointestinal (GI) disorders means they are often used for long periods without ongoing review.

In Australia the use of PPIs increased 1318% between 1995 and 2006. Currently there are enough PPIs dispensed to treat seven percent of the Australian population every day. This translates to 1.6 million Australians taking a PPI daily.

Despite their perceived safety, emerging evidence suggests PPIs are associated with a range of rare but serious adverse effects. These include osteoporosis and fractures, hypomagnesaemia, interstitial nephritis, enteric infection and community acquired pneumonia. This therapeutic brief advocates the benefits of a step-down approach: reducing the dose, adopting intermittent use or trialling cessation, while maintaining adequate symptom control.

Key points

In the treatment of GORD, review patients:
- after four to eight weeks of initial full-dose PPI treatment
- if PPI medicines were initiated in hospital

Consider a step-down approach for the maintenance of symptoms:
- reduce the dose
- adopt intermittent symptom-driven use
- trial cessation

Due to high prevalence of extended use of PPIs, rare but potentially serious adverse effects are often observed.

Prescribing for gastro-oesophageal reflux disease (GORD)

The initial course of treatment usually involves the prescribing of a full-dose PPI (see table 1) for four to eight weeks, after which treatment should be reviewed. If response is adequate, consider ‘stepping-down’ to maintenance dose, switching to intermittent dosing or trialling cessation (see table 1). For many patients symptoms will have resolved and extended treatment may be unnecessary. If response is inadequate after two to four weeks, check adherence.

If adherence to the PPI is satisfactory, then endoscopy may be required to exclude other conditions. If after endoscopy no underlying cause is found, it may be necessary to double the dose for four weeks before ‘stepping-down’ to the lowest effective dose or trialling cessation. Patients initiated on PPIs in hospitals should be reviewed as they may not require ongoing treatment following discharge. Ongoing use of PPIs may expose patients to adverse effects.
Reduce the dose

A recommended approach is to prescribe either half the daily dose or alternate daily dosing, depending on patient preference. At least 80% of patients with GORD presenting with healed oesophagitis can achieve symptomatic remission with lower (maintenance) doses of PPIs.

Intermittent symptom-driven PPI

As an example, use omeprazole 10mg or equivalent on days when symptoms occur. This dosage controls symptoms in most people with endoscopy negative GORD.

Trial cessation

In a significant minority of patients (up to 30%) symptoms will not return after cessation of PPI therapy. The decision to cease therapy should be guided by symptom control and each patient’s ability to report return of symptoms.

If the initial attempt to step-down or discontinue PPI therapy is unsuccessful, the PPI may be continued for a few weeks before considering another attempt to reduce the dose or cease treatment.

Following cessation, antacids, histamine H2 receptor antagonists (H2RAs) or PPIs at the lowest effective dose may be used as needed for the relief of mild, occasional reflux symptoms.

Rebound activation of proton pumps resulting in rebound acid hypersecretion may occur following cessation of PPIs. Gradual dose tapering or switching to alternate day therapy for one to two weeks before cessation may prevent rebound symptoms.

---

**Table 1: Initial and maintenance proton-pump inhibitors therapy for gastro-oesophageal reflux disease**

<table>
<thead>
<tr>
<th></th>
<th>Omeprazole</th>
<th>Lansoprazole</th>
<th>Pantoprazole</th>
<th>Rabeprazole</th>
<th>Esomeprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Losec®, Acimax®, Meprazol®, Ozmap®, Omepr®, Omepral®, Maxor®, Pemzo®, Probitor®) tablet, capsule</td>
<td>(Zoton FasTabs®, Zopral®, Lanzopran®) tablet, capsule</td>
<td>(Somac®, Ozpan®, Gastenz®, Salpraz®, PantoFast®, PantoLoc®, Panto®, Sozo®, Suvacid®) tablet, granules</td>
<td>(Pariet®) tablet</td>
<td>(Nexium®) tablet</td>
</tr>
<tr>
<td>Initial therapy</td>
<td>20mg</td>
<td>30mg</td>
<td>40mg</td>
<td>20mg</td>
<td>20mg *</td>
</tr>
<tr>
<td>(full-dose PPI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maintenance therapy</td>
<td>10mg</td>
<td>15mg</td>
<td>20mg</td>
<td>10mg</td>
<td>See note**</td>
</tr>
<tr>
<td>(lower dose PPI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Not all strengths and formulations of PPIs are included in the Table. Table excludes injections.

* While many patients may be initially treated with esomeprazole 40mg, 20mg is recommended initial therapy; esomeprazole 40mg is appropriate if endoscopy reveals severe erosive disease or ulceration in previously untreated patient or response to esomeprazole 20mg is inadequate after initial 4 weeks. The advantage of starting on 20mg esomeprazole is that it reduces the number of steps required in the step-down process.

** Step-down strategy: 10mg omeprazole is appropriate step-down therapy from 20mg esomeprazole.

---

**Step-down strategies and PPI withdrawal plan**

In patients who have had an adequate response to initial full-dose PPI therapy, it is appropriate to cease or reduce PPI therapy using a ‘step down’ approach:

- Reduce the dose
- Trial cessation
- Intermittent symptom-driven PPI

---

**Veterans’ Medicines Advice and Therapeutics Education Services**

What to discuss with your patient

Patients with mild or infrequent symptoms can often be managed with simple non-drug measures. Advise patients about lifestyle modifications as appropriate, such as weight loss, moderation of alcohol consumption, smoking cessation, elevation of bed head and avoidance of precipitating foods.

Patients achieving good symptom control may be hesitant to trial dose reduction or cessation. For these patients it may be worthwhile highlighting that by using a step-down approach it is often possible to maintain symptom relief while avoiding potential adverse effects.

Encourage patients to try again if attempt to step-down PPI therapy is unsuccessful.

Adverse effects

The high prevalence of extended use of PPIs means that rare but potentially serious adverse effects are being seen more often.

Fractures

Recent meta-analyses and regulatory agencies have identified an association between use of PPIs and fractures, including hip and spinal fractures. This may be due to impaired calcium absorption. Patients at risk of osteoporotic fractures are advised to maintain an adequate intake of calcium and vitamin D. Bone mineral density tests are recommended for high-risk patients using a high-dose PPI on a long-term basis. These may include older patients and postmenopausal females.

Acute interstitial nephritis

Acute interstitial nephritis (AIN) is a rare adverse event (approximately 8 cases per 100,000 patient years in one study). The TGA has warned that PPIs are now a leading cause of AIN in Australia.

Hypomagnesaemia

Clinicians should be alert to the possibility of PPI-associated hypomagnesaemia. Patients may present with clinical symptoms such as nausea and vomiting, anorexia, weakness and fatigue, dizziness, decreased mobility, paraesthesia or severe muscle cramps. Use of magnesium supplements may be insufficient to correct a magnesium deficiency associated with long-term PPI use, and the PPI may need to be discontinued.

Enteric infection

PPIs may increase susceptibility to enteric bacterial infection, including Clostridium difficile infection due to the reduction in gastric acidity. The use of probiotics for the prevention or treatment of Clostridium difficile is not warranted. The US Food and Drug Administration recommends patients using PPIs contact their health professional if they develop persistent diarrhoea. Patients using PPIs may be at increased risk of traveller’s diarrhoea, and the ongoing need for PPI therapy in patients travelling to high risk areas should be reviewed.

Pneumonia

Epidemiological studies suggest an association between use of PPIs and both community and hospital-acquired pneumonia, possibly due to the reduction in gastric acidity which allows bacterial colonization. The greatest risk of developing pneumonia happens shortly after initiating treatment.

Vitamin B12 deficiency

Long-term use of PPIs may decrease the absorption of Vitamin B12, although the clinical relevance is uncertain.

PPIs and clopidogrel

Regulatory agencies have warned that PPIs, particularly omeprazole and esomeprazole, may reduce the antiplatelet effect of clopidogrel. However, a recent meta-analysis has not found strong evidence to suggest that the interaction is clinically significant.
When is long term treatment appropriate?

Some patients may require long term treatment with PPIs. This includes patients with severe oesophagitis, oesophageal stricture or scleroderma, Zollinger-Ellison syndrome or Barrett’s oesophagus. Patients who require long-term treatment with a NSAID, including low-dose aspirin, may be co-prescribed a low-strength PPI for ulcer prophylaxis in some circumstances. Prophylaxis with a PPI may also be clinically appropriate in other patients at high risk of bleeding.

Further information:
- Gastroenterological Society of Australia www.gesa.org.au

References