Proton pump inhibitors

Uncommon adverse effects

**Background**
Proton pump inhibitors (PPIs) are one of the most popularly prescribed drugs in Australia for conditions such as gastro-oesophageal reflux disease, peptic ulcer disease and functional dyspepsia. Despite their good safety profile, PPIs have potential adverse effects, yet they are often overprescribed and without a clear indication.

**Objective**
This article reviews the uncommon adverse effects of PPIs and provides recommendations for managing patients receiving this therapy.

**Discussion**
Uncommon adverse effects include rebound acid hypersecretion syndrome, fragility fractures, interstitial nephritis, electrolyte derangements, pneumonia, enteric infection and vitamin B12 deficiency. General practitioners should be aware of these potential adverse effects and ensure that PPIs are used appropriately and where benefit clearly outweighs any harmful effects.

**Keywords:** proton pump inhibitors/adverse effects; gastrointestinal disease; therapeutics

Proton pump inhibitors (PPIs) are one of the most widely used classes of drug in Australia, with more than 130 million Pharmaceutical Benefits Scheme (PBS) prescriptions dispensed since 1992. Both esomeprazole and pantoprazole are placed in the list of top 10 drugs by prescription counts (Table 1). Overprescription inevitably adds burden to the healthcare system, with esomeprazole costing more than $200 million in 2008–2009.

**Reasons for common usage**
Proton pump inhibitors are prescribed for common conditions such as gastro-oesophageal reflux disease, peptic ulcer disease and functional dyspepsia. Gastro-oesophageal reflux disease (GORD) affects up to 20% of the Western population whereas dyspepsia, defined as the presence of symptoms thought to originate in the gastroduodenal region (early satiation, postprandial fullness, epigastric pain or burning), is reported in 25% of adults. Functional dyspepsia without any organic disease is a common trigger for clinicians to prescribe a PPI.

Proton pump inhibitors work effectively at reducing symptoms without many immediate side effects that would dissuade patients from using them. Up to 33% of patients who initiate PPI treatment redeem repeated prescriptions without an obvious indication for maintenance therapy such as GORD (Table 2). Other contributing factors include its easy accessibility as an over-the-counter medication (pantoprazole 20 mg/day) and the lack of alternative therapies other than histamine type 2 receptor antagonists (H2RA). Above all, there is little concern about the potential adverse effects of PPI therapy.

Recently however, PPI therapy has received increasing attention from Therapeutic Goods Administration (TGA) and warnings with regard to adverse effects have been released. Many of these adverse effects are also addressed in the current Gastroenterological Society of Australia (GESA) guidelines on GORD. It is essential that clinicians are aware of the potential adverse effects and use the drug only in appropriate clinical settings.

**Uncommon adverse effects**

**Rebound acid hypersecretion syndrome**
Rebound acid hypersecretion syndrome (Figure 1) was demonstrated in a recent randomised study involving 118 healthy asymptomatic patients who received esomeprazole for 8 weeks followed by 4 weeks of placebo versus placebo for 12 weeks. There was significantly higher rate of dyspepsia, heartburn and reflux in the group where esomeprazole was withdrawn after 8 weeks, compared with those receiving placebo (44% vs. 15%, p<0.0001). Similarly, Niklasson et al randomised 48 healthy subjects to 4 weeks of...
Pantoprazole or placebo and found that subjects who received pantoprazole had significantly higher dyspeptic symptoms during the first 2 weeks after withdrawal of the study drug. Hence, it is conceivable that PPI withdrawal induces the underlying symptoms that they were initially used to treat.11

### Osteoporosis

Proton pump inhibitor therapy can influence bone metabolism. Specifically, inhibition of the osteoclastic proton pumps may reduce bone resorption, while profound acid suppression could potentially hamper intestinal calcium absorption, and secondary hypergastrinaemia may enhance bone resorption through the induction of parathyroid gland hyperplasia.12 Several case control studies demonstrated an increased risk of osteoporosis and hip fractures with increasing duration and dosage of the PPI.13,14 One study concluded that the calculated risk was small, as 1283 patients aged over 50 years would need to be treated with a PPI for 1 year to identify one excess hip fracture.14 It may be worth considering increasing calcium intake for prevention and assessing bone mineral density in those requiring pantoprazole or placebo for more than 5 years.15

The TGA is currently considering upgrading warnings about the increased risk of osteoporosis16 and further studies are awaited to confirm this association.

### Enteric infection

Loss of the normal stomach acidity has been associated with colonisation of the normally sterile upper gastrointestinal tract.17 Therefore it is biologically plausible that raising the pH of the stomach with acid suppressive therapy may result in an increased load of pathogenic microbes. A systematic review of 12 papers evaluating 2948 patients receiving a PPI demonstrated an increased risk of *Clostridium difficile* (odds ratio [OR] 1.95; 95% CI: 1.48–2.58) and salmonella, campylobacter, or shigella infection (OR 2.55; 95% CI: 1.53–4.26).18 One study found that, compared with patients receiving no acid suppression therapy, the risk of *C. difficile* infection increased an estimated 53% for those receiving H2RA, 74% for those receiving daily PPI dosing, and more than doubled for those receiving more frequent PPI dosing,19 suggesting a dose dependent relationship. One needs to consider the limitations of these studies due to significant study heterogeneity in the meta-analysis and confounding factors such as comorbid conditions in case control studies which could have contributed to the association. Nevertheless, PPI therapy should be used with caution, particularly for high risk groups including the elderly, hospitalised patients on antibiotics, and those travelling to high risk countries including Southeast Asia, Africa, South America and the Middle East.

### Pneumonia

Gastric acid suppression leads to increased bacterial colonisation in the upper gastrointestinal tract and aspiration of the gut flora during physiological reflux. Three large case control studies involving up to 360 000 participants and 7 years of follow up demonstrated a 16–50% increased risk of pneumonia in PPI users.20–22 The risk appears modest, however, as one study showed that the increased risk equated to four extra hospitalisations for pneumonia each year for every 1000 people prescribed a PPI.22 Similar to the studies examining the risk of enteric infection, comorbid conditions such as...
underlying stroke, chronic illness and alcoholism may have had added risk to the pneumonia in the first place.

Acute interstitial nephritis
Proton pump inhibitor induced acute interstitial nephritis is uncommon, however increasing numbers of cases are being reported.23,24 The underlying mechanism is thought to involve an immune component.24 Symptoms are nonspecific and include weight loss, fatigue, malaise, nausea and vomiting. A dose response relationship has not been established and onset may be delayed up to several months.25 Renal function should be checked and a nephrologist opinion should be sought if acute interstitial nephritis is suspected.

Hypomagnesaemia and hypocalcaemia
The TGA has recently released warning about serious hypomagnesaemia and hypocalcaemia related adverse events including tetany, seizures, delirium and cardiac arrhythmias.1 Since 2002, there have been several reports describing a wide range of clinical features from asymptomatic hypomagnesaemia to carpopedal spasm, severe muscle cramping or seizures.26,27 Extra renal magnesium wasting by impaired intestinal magnesium transport or intestinal loss has been speculated as underlying mechanism.27

Clinicians should consider cessation of PPI therapy in patients with otherwise unexplained symptomatic hypomagnesaemia and/or hypocalcaemia.

Vitamin B12 deficiency
Proton pump inhibitor therapy reduces the absorption of vitamin B12, probably by inhibiting intragastric proteolysis and, therefore, its release from food required before binding to R-proteins and gastric intrinsic factor in order to be released from the terminal ileum.28 Two studies examining vitamin B12 level in subjects on omeprazole indicated that certain circumstances predict the fall in vitamin B12 levels.29,30 Such circumstances include patients who are genetically slow metabolisers of PPI, those with Helicobacter pylori gastritis at risk of developing atrophic gastritis, and those on high doses of a PPI for several years. At present, there is little evidence to suggest vitamin B12 monitoring is required routinely in all patients on PPI therapy, although the effects of long term treatment should be kept under review.

Fundic gastric polyps
The development of fundic gastric polyps appears to be a cystic response of gastric mucosa to the physiological alterations induced by profound acid inhibition over many years.31 A study involving 598 patients undergoing gastroscopy showed that long term PPI use was associated with an up to fourfold increased incidence of fundic gastric polyps but the risk of dysplasia was negligible.32 Progression to dysplastic polyp is almost exclusively seen in those with familial adenomatous polyposis.33

PPIs and clopidogrel
Proton pump inhibitor therapy is commonly prescribed as a prophylaxis for gastrointestinal bleeding in patients receiving antiplatelet agents, but there is potential concern for PPIs to blunt the efficacy of clopidogrel by competitively inhibiting CYP2C10 metabolism.34 A recent, large randomised trial involving 3873 patients receiving dual antiplatelet therapy did not show any significant increases in the risk of cardiovascular events with concomitant use of clopidogrel and omeprazole.35 A meta-analysis including 23 studies involving 93 278 patients also did not demonstrate significant association between PPI use and overall mortality.36 Therefore PPI therapy can be prescribed as ulcer prophylaxis for patients on antiplatelet agents.

Recommendations
The following recommendations in managing patients on PPI therapy for GORD and dyspepsia comply with GESA guidelines:

- Consider a trial of cessation of therapy, stepping down to the lowest effective dose or intermittent therapy on demand if initial treatment is successful or symptoms are mild.8
- In randomised trials of patients with mild to moderate GORD, symptom relief and patient satisfaction with low dose, symptom driven therapy was similar to that of continuous low dose therapy.37,38 Exceptions include those with severe oesophagitis, oesophageal stricture or scleroderma, Barrett oesophagus, or Zollinger-Ellison syndrome.
- Consider lifestyle modifications for patients with GORD, including avoidance of precipitating foods, weight loss and nocturnal posture (elevation of torso).8 Patients with mild or infrequent symptoms can often be managed with these measures.
- Review medications and discontinue or reduce the dose of any medicine that could contribute to symptoms (eg. calcium channel blockers, nitrates, nonsteroidal anti-inflammatory drugs [NSAIDs], theophylline) where appropriate.
- Warn patients about the potential adverse effects of PPI therapy.
- Emphasise the benefits of reduced PPI therapy including:
  - fewer tablets to be taken
  - lower prescription costs
  - less risk of unwanted side effects
- Manage patients with severe symptoms in consultation with a gastroenterologist.

Summary
Proton pump inhibitor therapy remains an important, valuable and safe intervention in patients with an appropriate indication. However, overuse of the drug may expose patients to serious (albeit rare) adverse effects and create significant financial burden on the healthcare system as a result of increased PBS prescriptions.

Therefore, clinicians should make active efforts to minimise the unnecessary use of PPIs, warn patients about the potential adverse effects of PPI therapy, and identify and correct these effects.

Author
Stephen Oh MBBS, BSc, is an advanced trainee in gastroenterology, Royal North Shore Hospital, Sydney, New South Wales. oys120_@hotmail.com.

Conflict of interest: none declared.

References