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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.[1] Both esomeprazole and pantoprazole are placed in the list of top 10 drugs by prescription counts (*Table 1*).[2] Overprescription inevitably adds burden to the healthcare system, with esomeprazole costing more than $200 million in 2008–2009.[2]

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[3] whereas dyspepsia, defined as the presence of symptoms thought to originate in the gastroduodenal region (early satiation, postprandial fullness, epigastric pain or burning),[4] is reported in 25% of adults.[5] 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[6] (*Table 2*).[7]

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.

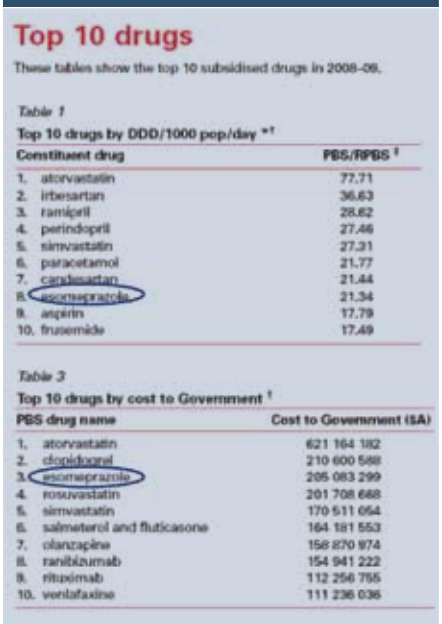
Recently however, PPI therapy has received increasing attention from Therapeutic Goods Administration (TGA) and warnings with regard to adverse effects have been released. Many of these adverse effects are also addressed in the current Gastroenterological Society of Australia (GESA) guidelines on GORD.[8] 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%, $p<0.0001$).[9] Similarly, Niklasson et al[10] randomised 48 healthy subjects to 4 weeks of

Table 1. Top 10 subsidised drugs in 2008–2009[1]



Top 10 drugs

These tables show the top 10 subsidised drugs in 2008–09.

Table 1

Top 10 drugs by DDD/1000 pop/day *†

Constituent drug	PBS/RPBS ‡
1. atorvastatin	77.71
2. irbesartan	36.63
3. ramipril	28.82
4. perindopril	27.46
5. simvastatin	27.31
6. paracetamol	21.77
7. candesartan	21.44
8. esomeprazole	21.34
9. aspirin	17.79
10. frusemide	17.49

Table 3

Top 10 drugs by cost to Government †

PBS drug name	Cost to Government ($A)
1. atorvastatin	621 164 182
2. clopidogrel	210 600 588
3. esomeprazole	205 083 299
4. rosuvastatin	201 708 668
5. simvastatin	170 511 054
6. salmeterol and fluticasone	164 181 553
7. olanzapine	158 870 974
8. ranibizumab	154 941 222
9. rituximab	112 256 755
10. venlafaxine	111 236 036

Esomeprazole was the eighth most commonly prescribed drug in 2008–2009, based on the defined daily dose/thousand population/day[2]

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 1263 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 a daily PPI for more than 5 years.[15]

The TGA is currently considering upgrading warnings about the increased risk of osteoporosis[16] 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

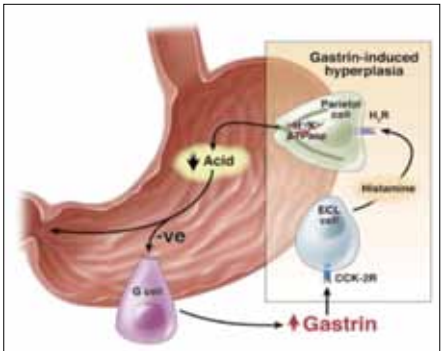


Figure 1. Rebound acid hypersecretion syndrome
The increased gastrin concentration during PPI therapy exerts trophic effects on the oxyntic mucosa causing hyperplasia and increased functional capacity of the enterochromaffin-like cell and parietal cell. As a consequence, on discontinuing PPI therapy there is rebound acid hypersecretion which persists for at least 2 months

Table 2. Indications for PPI therapy[7]

- Gastro-oesophageal reflux disease
- Endoscopically confirmed peptic ulcer disease
- Investigated nonulcer dyspepsia
- Endoscopy negative reflux disease
- Erosive and ulcerative oesophagitis
- Barrett esophagus
- Zollinger-Ellison syndrome
- Scleroderma induced strictures
- Short term treatment of ulcer disease, as part of a combination regimen for *Helicobacter pylori* eradication
- Prophylaxis of NSAID induced dyspepsia/ulceration

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.

Hypomagnaesaemia 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 599 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[8]:

- 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[39]
- 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[50]
- 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[39]
  - 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.

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References

1. Therapeutic Goods Administration. Medicines safety update. Available at www.tga.gov.au/hp/msu-2011-03.htm [Accessed 16 May 2011].
2. Commonwealth of Australia. Drug Utilisation Sub-Committee (DUSC) database. September 2009. Available at www.australianprescriber.com/magazine/32/6/artid/1063 [Accessed 16 may 2011].
3. Dent J, El-Serag HB, Wallander MA, Johansson S. Epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut 2005;54:710.
4. Tack J, Talley NJ. Rome foundation diagnostic algorithms – gastroduodenal disorders. Am J Gastroenterol 2010;105:757–63.
5. Katz MH. Failing the acid test. Arch Intern Med 2010;170:747–8.

6. Raghunath AS, O'Morain C, McLoughlin RC. The long-term use of proton-pump inhibitors. Aliment Pharmacol Ther 2005;22(Suppl 1):55–63.
7. National Prescribing Service. Proton pump inhibitors. Available at www.nps.org.au/__data/assets/pdf_file/0012/111423/Clinical_guidance_final_PPI.pdf [Accessed 16 May 2011].
8. Gastroenterological Society of Australia. Gastro-oesophageal reflux disease in adults. 2008. Available at www.gesa.org.au/pdf/RefluxDisease4Ed08.pdf [Accessed 16 May 2011].
9. Reimer C, Søndergaard B, Hilstead L, Bytzer P. Proton-pump inhibitor therapy induces acid-related symptoms in healthy volunteers after withdrawal of therapy. Gastroenterology 2009;137:80–7.
10. Niklasson A, Lindstrom L, Simren M, et al. Dyspeptic symptoms development after discontinuation of a proton pump inhibitor: a double-blind placebo-controlled trial. Am J Gastroenterol 2010;105:1531–7.
11. McColl KE, Gillen D. Evidence that proton-pump inhibitor therapy induces the symptoms it is used to treat. Gastroenterology 2009;137:20–39.
12. Wright MJ, Proctor DD, Insogna KL, Kerstetter JE. Proton pump-inhibiting drugs, calcium homeostasis, and bone health. Nutr Rev 2008;66:103–8.
13. Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. JAMA 2006;296:2947–53.
14. Targownik LE, Lix LM, Metge CJ, et al. Use of proton pump inhibitors and risk of osteoporosis-related fractures. CMAJ 2008;179:319–26.
15. Talley NJ, Jung HK, Jiang X, Locke GR. Is there an increased risk of hip fracture in patients on long-term PPI therapy? Nat Clin Pract Gastroenterol Hepatol 2007;4:420–1.
16. Medical Observer. TGA to consider upgrading warnings on PPIs after fracture concerns. July 2010. Available at www.medicalobserver.com.au/news/tga-to-consider-upgrading-warning-on-ppis-after-fracture-concerns [Accessed 16 May 2011].
17. Thorens J, Froehlich F, Schwizer W, et al. Bacterial overgrowth during treatment with omeprazole compared with cimetidine. Gut 1996;39:54–9.
18. Leonard J, Marshall JK, Moayyedi PI. Systematic review of the risk of enteric infection in patients taking acid suppression. Am J Gastroenterol 2007;102:2047–56.
19. Howell MD, Novack V, Grgurich P, et al. Iatrogenic gastric acid suppression and the risk of nosocomial Clostridium difficile infection. Arch Intern Med 2010;170:784–90.
20. Laheij RJ, Miriam C, Sturkenboom JM, et al. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. JAMA 2004;292:1955–60.
21. Gulmez SE, Holm A, Frederiksen H, Jensen TG, Pedersen C, Hallas J. Use of proton pump inhibitors and the risk of community-acquired pneumonia: a population-based case-control study. Arch Intern Med 2007;167:950–5.
22. Roughead EE, Ramsay EN, Pratt NL, et al. Proton-pump inhibitors and the risk of antibiotic use and hospitalisation for pneumonia. Med J Aust 2009;190:114–6.
23. Simpson IJ, Marshall MR, Pilmore H, et al. Proton pump inhibitors and acute interstitial nephritis: report and analysis of 15 cases. Nephrology 2006;11:381–5.
24. Ray S, Delaney M, Muller AF. Proton pump inhibitors and acute interstitial nephritis. BMJ 2010;341:4412.
25. Sierra F, Suarez M, Rey M, Vela MF. Proton pump inhibitor-associated acute interstitial nephritis. Aliment Pharmacol Ther 2007;26:545–53.
26. Mackay JD, Bladon PT. Hypomagnesaemia due to proton-pump inhibitor therapy: a clinical case series. Q J Med 2010;103:387–95.
27. Cundy T, Mackay J. Proton pump inhibitors and severe hypomagnesaemia. Curr Opin Gastroenterol 2011;27:180–5.
28. Allen RH, Seetharam B, Podell E, Alpers DH. Effect of proteolytic enzymes on the binding of cobalamin to R protein and intrinsic factor. In vitro evidence that a failure to partially degrade R protein is responsible for cobalamin malabsorption in pancreatic insufficiency. J Clin Invest 1978;61:47–54.
29. Sagar M, Kanczewska L, Ljungdahl A, et al. Effect of CYP2C19 polymorphism on serum levels of vitamin B12 in patients on long-term omeprazole treatment. Aliment Pharmacol 1999;13:453–8.
30. Schenk BE, Ukipers EJ, Jlinkenberg-Knol EC, et al. Atrophic gastritis during long-term omeprazole therapy affects serum vitamin B12 levels. Aliment Pharmacol 1999;13:1343–6.
31. Yeomans ND, Dent J. Personal review: alarmism or legitimate concerns about long-term suppression of gastric acid suppression? Aliment Pharmacol Ther 2000;14:267–71.
32. Jalving M, Koornstra JJ, Wesseling J, Boezen HM, DE Jong S, Kleibeuker JH. Increased risk of fundic gland polyps during long-term proton pump inhibitor therapy. Aliment Pharmacol Ther 2006;24:1341–8.
33. Jalving M, Koornstra JJ, Götz JM, et al. High-grade dysplasia in sporadic fundic gland polyps: a case report and review of the literature. Eur J Gastroenterol Hepatol 2003;15:1229–33.
34. Li XQ, Andersson TB, Ahlstrom M, Weidolf L. Comparison of inhibitory effects of the proton pump-inhibiting drugs omaprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole on human cytochrome P450 activities. Drug Metab Dispos 2004;32:821–7.
35. Bhatt DL. Cryer BL. Constant CF, et al. Clopidogrel with or without omeprazole in coronary artery disease. N Engl J Med 2010;363:1909–17.
36. Kwok CS, Loke YK. Meta-analysis: the effects of proton pump inhibitors on cardiovascular events and mortality in patients receiving clopidogrel. Aliment Pharmacol Ther 2010;8:810–23.
37. Bour B, Staub J, Chousterman M, et al. Long-term treatment of gastro-oesophageal reflux disease patients with frequent symptomatic relapses using rabeprazole: on-demand treatment compared with continuous treatment. Aliment Pharmacol Ther 2005;21:805–12.
38. Janssen W, Meier E, Gatz G, et al. Effects of pantoprazole 20mg in mild gastroesophageal reflux disease: Once-daily treatment in the acute phases, and comparison of on-demand versus continuous treatment in long term. Curr Ther Res Clin Exp 2005;66:345–63.
39. National Prescribing Service. News 46. Proton pump inhibitors: step down to symptom control. May 2009. Available at www.nps.org.au/__data/assets/pdf_file/0016/23821/ news46.pdf [Accessed 16 May 2011].
40. Drugs for dyspepsia, reflux and peptic ulcers. In: Australian Medicines Handbook. Adelaide: Australian Medicines Handbook, 2010.

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