The dangers of proton pump inhibitor therapy

Proton pump inhibitors are used for the treatment of peptic ulceration, severe gastro-oesophageal reflux, scleroderma oesophagitis and Zollinger–Ellison syndrome. They may also be used prophylactically to prevent gastric ulcers induced by non-steroidal anti-inflammatory drugs and aspirin. Proton pump inhibitors are substantially more potent and longer acting than currently available H_2 receptor antagonists and produce faster, more complete healing of oesophagitis and relief of heartburn.

As a consequence, they are among the most widely prescribed medications in the UK (*Figure 1*) and perceived to be very safe and cost effective. Nonetheless, emerging evidence suggests an increased incidence of adverse events associated with chronic use (*Table 1*). This article gives an overview of the potential risks of proton pump inhibitor therapy, and advises on strategies to reduce their over-prescription.

Diarrhoea and *Clostridium difficile* infection

The most widely studied potential risk associated with proton pump inhibitors is *Clostridium difficile* infection. A growing body of evidence demonstrates a link between *C. difficile* infection and proton pump inhibitor use. A meta-analysis, which included 23 cohort and case-control studies involving almost 300 000 patients, found a 65% increase (summary risk estimate = 1.69, 95% confidence interval = 1.395–1.974) in *C. difficile*-associated diarrhoea among proton pump inhibitor users (Janarthanan et al, 2012). Although this translates into only a small absolute increase in individual risk of 1.01 (95% confidence interval 1.00–1.02) per day of inpatient stay on a proton pump inhibitor (Dalton et al, 2009), the prevalence and long duration of proton pump inhibitor use nonetheless results in substantial population attributable risk (Nardino et al, 2000; George et al, 2008; Eid et al, 2010).

The underlying mechanism of the predisposition remains unclear, but may be directly caused by acid suppression. *C. difficile* is acid-resistant in its spore form but acid-sensitive in the vegetative state, which is thought to be important in mounting clinically symptomatic infection. Proton pump inhibitors also increase the incidences of *Campylobacter* and *Salmonella*-induced diarrhoea, both of which are acid-sensitive organisms. H_2 receptor antagonists are less potent gastric acid suppressors, which may be used as alternatives to proton pump inhibitors for symptomatic treatment of dyspepsia or stress ulcer prophylaxis. In line with their less potent acid-suppressive actions, there is evidence that they confer significantly lower risks of *C. difficile* infection (Kwok et al, 2012).

Pneumonia

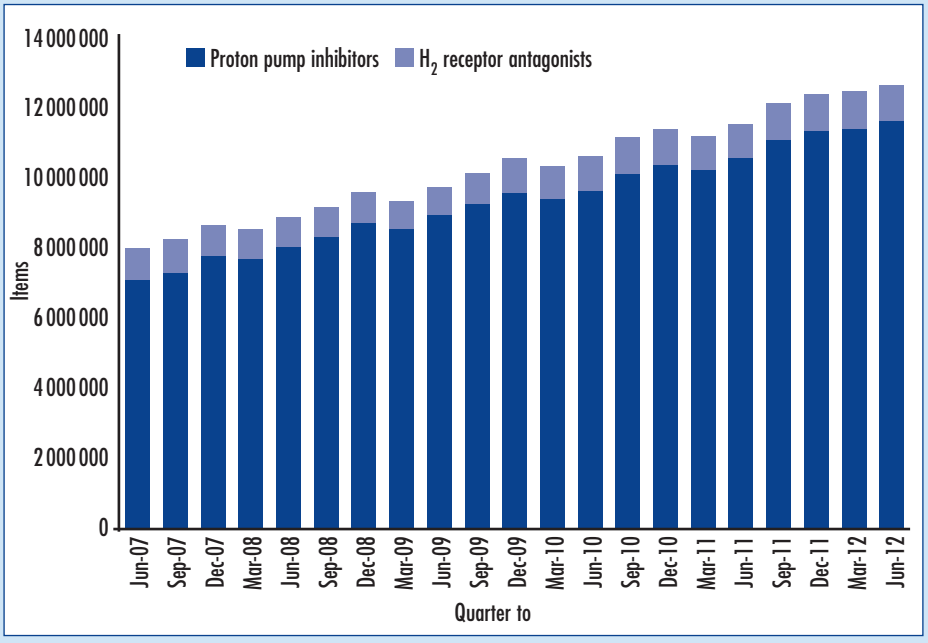
The mechanism by which proton pump inhibitors are thought to cause pneumonia is again directly linked to acid suppression, which leads to gastric bacterial overgrowth creating an opportunity for translocation of gut bacteria to the lungs through reflux and micro-aspiration.

Proton pump inhibitors have been associated with increased risk of pneumonia in a number of case-control and cohort studies. Eight of these were examined in a meta-analysis (Eom et al, 2011a), which found an odds ratio of 1.27 (95% confidence interval 1.11–1.46). However, these were retrospective studies, and as such potentially vulnerable to confounding

Table 1. Adverse effects associated with proton pump inhibitors

Clostridium difficile infection
Pneumonia
Fractures
Vitamin B_{12} deficiency
Hypomagnesaemia
Acute interstitial nephritis
Possible interaction with clopidogrel
Oligouria or anuria
Typical renal biopsy features

Figure 1. Trends in prescribing of ulcer healing drugs in general practice in England. From NHS Prescription Services (2012).



Dr Carina Owen *is Foundation Year 2,* **Ms Preet Panesar** *is Lead Pharmacist in Microbiology,* **Dr Daniel JB Marks** *is Specialty Registrar in Clinical Pharmacology and Therapeutics and* **Dr Matthew Banks** *is Consultant Gastroenterologist, University College London Hospital NHS Foundation Trust, London NW1 2BU*

Correspondence to: Dr C Owen (carinaowen@hotmail.com)

patient and prescriber selection bias and ascertainment errors. A more recently published prospective cohort study (Filion et al, 2013) examined rates of hospitalization for community-acquired pneumonia in new users of proton pump inhibitors as prophylaxis for side effects of non-steroidal anti-inflammatory drugs, and found no significant difference.

Fracture risk

Several studies have examined the potential association between proton pump inhibitors and fracture. Once again, the evidence relies principally upon observational studies, but significant low magnitude associations are replicated in the literature (Yang et al, 2006; Eom et al, 2011b).

Khalili et al (2012) conducted a prospective cohort study using the Nurses Health Study, which included 79 899 female participants followed up over an 8-year period. The outcome measure was incident hip fracture, with 893 events documented over the duration of the study. The risk was 35% greater in participants who used proton pump inhibitors for more than 2 years (age-adjusted hazard ratio 1.35, 95% confidence interval 1.13–1.62). This study was notable for the collection of detailed information on several potential confounding risk factors, including body mass index, use of postmenopausal hormones, smoking, calcium intake and physical activity. Importantly, the influence of proton pump inhibitors varied according to smoking history, with the significantly increased risk of hip fracture restricted to women with a smoking history (adjusted hazard ratio 1.51, 95% confidence interval 1.20–1.91). Broadly, this suggests that any association between proton pump inhibitor use and fracture is most relevant to patients who possess additional risk factors.

There are several plausible mechanisms through which proton pump inhibitors may increase fracture risk. Their use may reduce calcium absorption, contributing to development of osteoporosis. This has been demonstrated in elderly women on calcium carbonate supplements (O'Connell et al, 2005) and more broadly in the general population in relation to dietary calcium absorption (Graziani et al, 1995).

Conversely, the relationship between chronic proton pump inhibitor use and osteoporosis was examined in a cross-sectional study of hip and lumbar spine bone mineral density readings in osteoporosis patients and matched controls (Targownik et al, 2010). No significant association was identified, nor was there any difference in the rates of bone mineral density decline between patients on proton pump inhibitors and those not receiving these medications over 3 years in a longitudinal analysis of 2549 subjects.

These data call into question any proposed causal association between proton pump inhibitors and osteoporosis. It remains possible that the observed increased fracture risk with proton pump inhibitors reflects confounding rather than a true causal association or that their influence is independent of changes in bone mineral density. In support of the latter, osteoclasts use a proton pump for bone resorption and it has been speculated that proton pump inhibitors compete at this site to impede bone remodelling (Costa-Rodrigues et al, 2013).

Vitamin and mineral deficiencies

Vitamin B_{12}, iron and magnesium require gastric acid for effective absorption, and therefore proton pump inhibitor use may lead to deficiencies. Studies have consistently demonstrated reduced vitamin B_{12} absorption in patients taking proton pump inhibitors (Marcaud et al, 1994; Valuck and Ruscin, 2004), which persists despite supplementation (Dharmarajan et al, 2008). These studies used serum vitamin B_{12} concentrations as the principal marker, which may in fact underestimate the prevalence of subclinical deficiency (Stabler, 2013). Hirschowitz et al (2008) examined levels of vitamin B_{12} deficiency in acid hypersecretors on lansoprazole, but compared the results of measured serum vitamin B_{12} with those of the more sensitive markers methylmalonic acid and homocysteine. Use of the former identified a 10% rate of deficiency, whereas use of the additional tests uncovered insufficiency in 31% of patients.

Iron deficiency de novo has not been reported with proton pump inhibitor use but there are case reports of patients not responding to iron supplementation, which improved after proton pump inhibitor cessation. This may relate to the redox state, with acidic environments favouring formation of the better absorbed Fe^{2+} ion (McColl, 2009).

Severe hypomagnesaemia is a rare, unpredictable complication of proton pump inhibitor use. Several published case reports have described symptomatic proton pump inhibitor-induced hypomagnesaemia with serum concentrations between 0.05 and 0.35 mmol/litre, mandating in-patient therapy. These occurred in patients on a variety of proton pump inhibitors for a range of indications, but consistently occurred in individuals using these on a long-term (over 1 year) basis and resolved within 2 weeks of proton pump inhibitor cessation.

Hess et al (2012) performed a statistical analysis of 35 case reports of severe proton pump inhibitor-induced hypomagnesaemia, using extracted data on serum magnesium. They showed that not only did magnesium levels recover quickly in all cases of proton pump inhibitor-induced hypomagnesaemia on drug withdrawal, but in patients who were subsequently re-challenged with proton pump inhibitors, hypomagnesaemia invariably recurred. When patients were switched to H_2 receptor antagonists, magnesium levels remained normal. A secondary end point of their study was to profile the 'patient-at-risk' of proton pump inhibitor-induced hypomagnesaemia, but no significant unifying factors were identified. Interestingly, renal magnesium excretion in all documented cases was appropriately low given the level of hypomagnesaemia.

This is in contrast to most cases of drug-induced hypomagnesaemia, where the mechanism is renal wasting secondary to tubular damage. Instead, the mechanism for proton pump inhibitor-induced hypomagnesaemia is thought to be intestinal, with in vitro evidence of reduced cation transport though colonic cells caused by proton pump inhibitors. Health-care professionals should consider measuring magnesium levels before starting proton pump inhibitor therapy and monitoring concentrations in those on prolonged treatment, particularly in patients prescribed a proton pump inhibitor concomitantly with digoxin or other drugs that may cause hypomagnesaemia (such as loop or thiazide diuretics).

Case reports of hyponatraemia and hypokalaemia related to proton pump inhibitor use have also been published (Melville et al, 1994; Maeda et al, 2011), although these are not widely recognized complications.

Acute interstitial nephritis

Proton pump inhibitors are recognized to cause acute interstitial nephritis. This was first reported in 1992 as a complication of omeprazole, followed by a collection of case reports and series further linking lansoprazole, esomeprazole, pantoprazole and rabeprazole to acute interstitial nephritis, suggestive of a class effect (Geevasinga et al, 2006). More recently, the association has been confirmed by a nested case-control study of 572 661 patients, which found an odds ratio of 5.16 (95% confidence interval 2.21–12.05) leading to a crude incidence of 11.98 per 100 000 person-years (Blank et al, 2014). Early recognition of acute interstitial nephritis and discontinuation of the causative agent are crucial to maximize recovery of renal function.

Drug interactions

The major concern with proton pump inhibitors in this regard has centred on a potential interaction with the antiplatelet drug clopidogrel. This is based on pharmacokinetic evidence that proton pump inhibitors inhibit certain hepatic cytochrome P450 enzymes required to convert clopidogrel to its active metabolite. The pharmacological efficacy of clopidogrel can be assessed by measuring changes in the platelet reactivity index, and early studies focussed on this as an outcome.

Gilard et al (2008) conducted a randomized control trial of 140 patients, in which they demonstrated a significant difference in platelet reactivity index after 1 week in patients receiving clopidogrel with omeprazole compared to clopidogrel and placebo. They concluded that omeprazole significantly decreased the potency of clopidogrel to inhibit platelets, and subsequently the Food and Drug Administration and Medicines and Healthcare products Regulatory Agency advised that omeprazole and esomeprazole should be avoided in patients prescribed clopidogrel.

The clinical relevance of this interaction has nevertheless been called into question, with data from a randomized controlled trial showing no increase in cardiovascular events in patients concomitantly using clopidogrel with omeprazole. The COGENT trial (Bhatt et al, 2010) measured cardiovascular events as an end point in 3761 patients with an indication for dual antiplatelet therapy, who were randomized to receive clopidogrel with either omeprazole or placebo. There were 54 cardiovascular events in the placebo group and 55 in the omeprazole group (hazard ratio 0.99, 95% confidence interval 0.68–1.44, P=0.98). The trial power was limited by its premature termination when the sponsor lost financing, and the authors concede that the findings cannot therefore be viewed as definitive. However, a review by Focks et al (2013) of all available clinical evidence concluded that, while there was clear evidence for ex vivo interaction, the case for adverse events in patients as a result of co-administration has not been made.

The cost and epidemiology of proton pump inhibitor overuse

The consequences of long-term proton pump inhibitor use are complex, and the financial impact substantial. In 2001, the NHS in England and Wales spent over £300 million on these drugs (National Institute for Health and Care Excellence, 2004). The introduction of generic preparations saw a huge reduction in expenditure. However, despite an overall decrease in spending on proton pump inhibitors, over £10 million was spent on high cost proton pump inhibitors in general practice in England in the first quarter of 2011. This is particularly pertinent bearing in mind that high cost proton pump inhibitors (such as esomeprazole and rabeprazole) offer no proven advantages over low cost equivalents (such as lansoprazole, omeprazole or pantoprazole) (*Table 2*). The more recently licensed proton pump inhibitor, esomeprazole, was ranked the fourth highest grossing drug in the world, with a total of US$7.5 bn worth of sales in 2012.

Several studies have examined the extent of inappropriate overuse of proton pump inhibitors in both primary and secondary health-care systems (Nardino et al, 2000; George et al, 2008; Eid et al, 2010). Data suggest that 40–65% of proton pump inhibitor prescriptions are inappropriate. The most common reasons for overuse in secondary care include prophylaxis for patients on non-steroidal anti-inflammatory drugs or corticosteroids, stress ulcer prophylaxis and treatment of dyspepsia. An audit in the authors' centre substantiated published studies in the literature, with over 50% of inpatients found to be on a proton pump inhibitor (Owen et al, 2014). Furthermore, a clear indication for proton pump inhibitor use was only documented for half of the prescriptions, and the vast majority did not specify a defined stop date.

Guidelines

Proton pump inhibitors are perceived to be cheap and safe medications, and are commonly started by clinicians outside of evidence-based scenarios or continued indefinitely without review. Given the risks associated with their widespread long-term use, a robust strategy is necessary when initiating therapy to ensure these drugs are actively reviewed and discontinued when no longer required.

Indications for proton pump inhibitor prescription can be divided into treatment and prophylaxis. *Table 3* provides an overview of indications for proton pump inhibitor treatment, with recommendations based on National Institute for Health and Care Excellence (2004) guidelines. For the majority of clinical presentations, guidelines suggest proton pump inhibitors should be used as a short-term treatment, much in the same way that antibiotics are

Table 2. Pharmacokinetics of proton pump inhibitors

	Bioavailability (%)	Time to peak concentration (hrs)	Half-life (hrs)	Protein binding (%)	Metabolism
Esomeprazole	50–68	1–2	1.3	97	Hepatic (CYP2C19, CYP3A4)
Lansoprazole	80–85	1.5–2	1.3–1.7	97	Hepatic (CYP2C19, CYP3A4)
Omeprazole	30–40	0.5–3.5	0.5–1	95	Hepatic (CYP2C19, CYP3A4)
Pantoprazole	77	1.1–3.1	1–1.9	98	Hepatic (CYP2C19, CYP3A4)
Rabeprazole	52	1–2	0.7–1.5	96	Non-enzymatic reduction (CYP2C19, CYP3A4)

From Vanderhoff and Tahboub (2002)

used to treat infections. In certain conditions (such as severe gastro-oesophageal reflux, Zollinger–Ellison syndrome or Barrett's oesophagus), long-term proton pump inhibitor use may be required, often in high dose.

Proton pump inhibitors are commonly prescribed as prophylaxis against gastrointestinal ulceration caused by non-steroidal anti-inflammatory drugs or antiplatelet agents. Other agents may also increase the risk of haemorrhage but to a lesser degree, including high-dose steroids, anticoagulants and selective serotonin-reuptake inhibitors. Selective serotonin-reuptake inhibitors vary in their affinity for the serotonin transporter, and it is those with a high affinity (fluoxetine, sertraline, paroxetine and clomipramine) that are considered more likely to increase gastrointestinal risk (Paton and Ferrier, 2005). Prescribers must balance this risk against those associated with proton pump inhibitor use to decide whether prophylaxis is warranted.

There are no current UK guidelines to aid decision making, although American College of Gastroenterology guidelines (Bhatt et al, 2008; Lanza et al, 2009) suggest that proton pump inhibitor prophylaxis is only required for 'high risk' patients (*Table 4*), or where multiple agents conferring risk of gastrointestinal complications are used. Such patients should receive standard dose proton pump inhibitor (e.g. lansoprazole 30 mg daily or omeprazole 20 mg daily) for the duration of antiplatelet or non-steroidal anti-inflammatory drug therapy. Prophylaxis for non-steroidal anti-inflammatory drugs is only required for regular, ongoing prescription and not for short-term or as-required use. High-dose steroids (>30 mg prednisolone or >4 mg dexamethasone daily, or equivalent), anticoagulants and selective serotonin-reuptake inhibitors may all contribute to increased risk of gastrointestinal complications in patients already taking regular non-steroidal anti-inflammatory drugs or antiplatelet medications (Hernandez-Diaz and Rodriguez, 2001; Paton and Ferrier, 2005; Bhatt et al, 2008) and as such proton pump inhibitor prophylaxis is recommended for patients taking any of these in addition to non-steroidal anti-inflammatory drugs or antiplatelet agents, but not for individuals receiving these agents alone.

Conclusions

Although broadly considered safe and effective medications, proton pump inhibitors have been associated with a number of adverse effects, particularly with chronic administration. When used appropriately, their prescription should be evidence-based and time-limited. Nonetheless, over-prescription of proton pump inhibitors remains common and carries significant financial implications. A multi-faceted approach is required to address this problem, with both primary and secondary care institutions developing and disseminating robust guidelines to limit the prescription of proton pump inhibitors to those individuals who are likely to derive benefit and minimize the physical and economic harms that can otherwise arise. BJHM

Figure 1 *is reproduced from NHS Prescription Services (2012) with kind permission of the NHS Business Services Authority.*

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Table 3. Evidence-based indications for proton pump inhibitor therapy

Heartburn, gastro-oesophageal reflux disease, dyspepsia	Third line treatment after failed symptomatic control with antacid and ranitidine. Treat for 1 month then discontinue
Endoscopically-proven disease peptic ulceration or oesophagitis	Treat for 1 month then discontinue
Helicobacter pylori eradication	Treat for 1 week with two antibiotics
Post-variceal haemorrhage	Treat for 10 days then discontinue
Acute upper gastrointestinal haemorrhage	Indicated along with therapeutic endoscopy. Duration then as per guidance for underlying cause of haemorrhage
Short bowel syndrome	Indicated long term to reduce gastrointestinal secretions

From National Institute for Health and Care Excellence (2004)

Table 4. 'High risk' factors that may warrant stress ulcer prophylaxis

Age >65 years
History of peptic ulcer disease
History of upper gastrointestinal bleed
Use of multiple agents with risks of gastrointestinal complications

KEY POINTS

- The number of proton pump inhibitor prescriptions in the UK increases year on year.
- A growing body of evidence has identified adverse effects with chronic proton pump inhibitor use.
- The risk of *Clostridium difficile* infection is increased in patients receiving proton pump inhibitors.
- Other potential adverse effects include increased risks of pneumonia, fracture in high risk individuals, severe hypomagnesaemia, impaired vitamin B_{12} and iron absorption, acute interstitial nephritis and reduced efficacy of clopidogrel.
- In most circumstances, proton pump inhibitors should be prescribed as a limited course.
- Prescribers should consider using antacids or histamine H_2-receptor antagonists as alternatives to proton pump inhibitors where only symptomatic relief is required.

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