Time to halt the overprescribing of proton pump inhibitor therapy

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Proton pump inhibitors (PPIs) are among the most frequently prescribed drugs globally. While they are highly cost-effective when used appropriately, studies across a wide range of populations continue to identify that they are prescribed without a clear indication in up to 70% of cases. This results in a cost to the NHS in excess of £100m each year[1]. In addition, although the absolute risk of harm to individuals from PPIs is low, their widespread long-term use is accompanied by a number of adverse effects that contribute significant negative impacts at a population level. Action is now required to limit the inappropriate prescribing of PPIs, and support deprescribing in patients on long-term therapy in whom the original indications no longer apply.

The rise of PPIs

PPIs were introduced in the 1980s, and rapidly became some of the best-selling medicines of all time. They inhibit gastric acid secretion through blockade of H^+/K^+-ATPases in parietal cells, and are highly effective for treating peptic ulceration, oesophagitis and gastro-oesophageal reflux[2,3]. They are also important components of *Helicobacter pylori* eradication regimens[4], and useful for prophylaxis against non-steroidal anti-inflammatory drug (NSAID) induced upper gastrointestinal injury[5]. For most of these presentations, they are only intended for short-term use and rarely required beyond four to eight weeks. In a minority of conditions (for example, severe Barrett's oesophagus, gastrinoma and eosinophilic oesophagitis), protracted courses may be required[6].

PPIs combine high efficacy with low toxicity, and are perceived to be safe and cost-effective[1]. Consequently, they are widely prescribed. Their use costs the NHS over £100m, and global spend is in excess of £2bn. Five PPIs are currently licensed in the UK: omeprazole, lansoprazole, pantoprazole, esomeprazole and rabeprazole. In most scenarios, there is no clear evidence to support use of one over another, and class effects can be assumed[7].

Overprescribing is the norm

Studies consistently find that PPIs are overprescribed, globally, in both primary and secondary care. Their prevalence continues to increase: in Australia, prescriptions rose by 1318% over one decade[8]. Most of this occurs in primary care, with increasing numbers treated for longer durations[9]. Part of this relates to substitution of histamine-2 receptor antagonists, but the bulk represents expanded use of acid suppression therapy. A proportion of this increase will be legitimate, due to rising groups of patients treated with dual antiplatelet therapy for coronary artery or cerebrovascular disease, or bisphosphonates (for which PPIs partially mitigate risk of oesophagitis[10]). There is also a small cohort of patients with chronic cough in whom gastro-oesophageal reflux is believed to be a contributor[11]. The recent approvals of esomeprazole for general sale, and

pantoprazole as an over-the-counter medicine, may further drive consumer use in the UK.

A number of studies have examined the appropriateness of PPI prescriptions. In one series looking at medicines in elderly patients in Italy, 30% were receiving a PPI with no clear indication, although a further 11% of this cohort possessed a recognised indication and were not on treatment (that is, PPIs were underprescribed)[12]. A study of 124,133 first-time adult users from Denmark found that only one-third met criteria for potential long-term use, and that there were significant variations in initiating such therapy related to both patient and prescriber characteristics[13]. In contrast, in the same catchment population, only 4% of pre-existing long-term users (defined as more than 60 daily doses over a six-month period) had a diagnosis that overtly merited such management[14].

Within hospitals, a retrospective study of surgical inpatients from The Netherlands identified non-compliance with guidelines in 46.6%; 93.1% of these represented overprescribing[15]. Audits of medical inpatients in the UK show inappropriate prescribing rates of 40.7–54%, of which 86% are overprescribing.[16,17] Data from other countries are comparable, associated with substantial costs[8,18-21].

A number of studies have probed the underlying rationales for PPI prescription and their continued use[22-24]. The reasons are frequently questionable, and adherence to guidelines poor with behaviour challenging to adapt despite educational and stewardship strategies[25]. The most common explanations were inappropriate treatment of dyspepsia, prophylaxis for low-risk patients on NSAIDs or corticosteroids, and stress ulcer prophylaxis (in secondary care).

Communication is poor. In one UK centre, suggested duration of treatment was specified in fewer than 20% of hospital discharge letters, less than one-third indicated that prescriptions needed to be reviewed, and only half contained information as to why the drug was started[26].

Overprescribing is more common in those with increasing numbers of co-morbidities and polypharmacy, likely due in part to a belief that PPIs have greater benefits and safety profiles than have actually been demonstrated. Additionally, patients receiving multiple medicines are likely to see several specialists. This increases the chance of a drug being prescribed and renders it less likely that one clinician takes overall responsibility for the therapeutic repertoire or questions a prescription from a colleague. A number of cognitive biases come into play, including a preference to maintain the status quo, and fear of criticism should harm arise because of a perceived (if justified) omission[27].

One further specific problem is that, once a patient has taken a PPI for any more than a few weeks, acid hypersecretion can occur on discontinuation. This causes rebound symptoms, and frequently establishes a vicious cycle of drug reinitiation and long-term continuation[28].

Harms of PPI therapy

Over the past decade, a range of adverse effects from PPI therapy have been identified. Although most studies are retrospective, a signal has evolved that PPIs are not as benign as originally perceived. Most of these translate into small absolute risks at an individual level, but because of prevalence and chronic use contribute substantial population attributable risk.

The most widely studied and publicised of these is *Clostridium difficile* infection. A meta-analysis of 23 cohort and case-control studies, involving almost 300,000 patients, identified a 65% increase in the relative risk of *C. difficile*-associated diarrhoea[29]. The mechanism remains unproven, but may be that acid suppression permits viability of the *C. difficile* vegetative state, subsequently leading to clinically symptomatic infection. There are suggestions that PPIs also increase risks of *Campylobacter* and *Salmonella* gastroenteritis (both are acid-sensitive organisms)[30], and two recent studies demonstrate alterations in the gut microbiome[31].

PPIs have been provisionally associated with increased risk of pneumonia (odds ratio on meta-analysis 1.27%)[32]. The proposed mechanism relates to acid suppression permitting gastric bacterial overgrowth, leading to respiratory tract infection through reflux and micro-aspiration. The caveat is that most data derive from retrospective studies, and at least one prospective study failed to verify the association[33].

Increased fracture risk has been reported, most notably in the Nurses Health Study, which included 79,899 female participants followed for eight years[34]. The age-adjusted hazard ratio of hip fracture was 1.35 with more than 2 years of PPI use, and even higher in smokers. Possible explanations include reduced calcium absorption[35], or competition with osteoblast and osteoclast proton pumps that impedes bone remodelling[36]. Deficiencies have also been reported in both iron[37] and vitamin B_{12}[38] absorption, and a major issue in a small subset of patients is severe hypomagnesaemia[39]. If the latter occurs it is typically a drug class effect, likely due to inhibition of cation transport in the colon.

PPIs are now well recognised as a cause of acute interstitial nephritis, which, in a nested case-control study of 572,661 patients, occurred with an odds ratio of 5.16 (translating into an incidence of 11.98 per 100,000 person-years)[40]. Early recognition and drug discontinuation are crucial for maximising renal recovery. There have also been a number of reports of PPIs triggering subacute cutaneous lupus erythematosus[41].

Finally, increased rates of chronic kidney disease and myocardial infarction have recently been reported among PPI users. In one study of 173,321 people, the hazard ratio of developing chronic renal impairment was 1.22, rising with increasing duration of exposure[42]. In a further data-mining exercise examining records from 2.9 million patients, PPIs were associated with a 1.16-fold risk of myocardial infarction, and a 2-fold increased risk of cardiovascular mortality[43]. The cause was not ascertained, and although the authors speculated about interference with nitric oxide signalling, an alternative explanation would be

confounding due to increased use of acid suppression in patients with greater numbers of comorbidities and polypharmacy (and hence overall cardiovascular risk).

Drug interactions

The extensive, long-term use of PPIs in patients with multiple comorbidities and polypharmacy renders them high risk for drug-drug interactions. Specifically, their alteration of pH in the gastrointestinal tract can impact on drug absorption, and they inhibit (to varying degrees) cytochrome (CYP) p450 and the p-glycoprotein pathway[44]. This may be a particular issue for omeprazole, which has high affinity for CYP2C19 and moderate affinity for CYP3A4[45].

Drug interactions were raised as a major concern in the case of clopidogrel, which requires CYP2C19 for conversion to its active metabolite. An initial randomised controlled trial of 140 patients found a reduction in the platelet reactivity index after one week in patients receiving clopidogrel with omeprazole[46], and on this basis a number of regulatory agencies counselled that both omeprazole and esomeprazole should be avoided in this context. The clinical relevance of the interaction has, however, been called into question, with the prospective COGENT trial reporting no increase in cardiovascular events in 3,761 patients on omeprazole and dual antiplatelet therapy[47]. The trial was terminated prematurely due to lack of funding but, while this did restrict statistical power, a subsequent review concluded that, with all currently available clinical data, despite evidence of an *ex vivo* interaction, the case for adverse impact in patients *in vivo* had not been made[48].

Others have also highlighted the significant risk of bias in many of the retrospective studies reporting harmful interactions between PPIs and clopidogrel[49], and pointed out that concomitant use does halve the risk of gastrointestinal bleeding[50]. Consequently, some authorities advocate preferential use of alternative PPIs with lower CYP2C19 affinity (such as pantoprazole or rabeprazole) in this patient cohort, although this strategy has not been subject to well-designed clinical trials.

Although studies on drug interactions have been dominated by those focusing on antiplatelet therapies, PPIs can also decrease plasma concentrations of several anti-retroviral agents, dabigatran, mycophenolate mofetil, and targeted oncological signal pathway inhibitors, as well as increase the concentrations of calcineurin inhibitors, methotrexate and metformin[51]. As with clopidogrel, little evidence has emerged to date that these result in clinically meaningful harm, although it would still be prudent to take care when prescribing PPIs with drugs that have potential for an interaction to occur.

Minimising overprescribing

The steps required to curb and subsequently reduce inappropriate prescribing include: recognition of the problem; use of alternative approaches to manage conditions currently treated “by default” with PPIs; education regarding appropriate indications and durations for their use; and enhanced drug stewardship akin to that employed widely for antimicrobials, mandating better

documentation around PPI prescriptions and regular review. Patient involvement and shared decision-making are also key[52].

One of the most frequent reasons for long-term PPI prescribing is dyspepsia. This is a condition that can often be significantly ameliorated by lifestyle modification or medication rationalisation[3]. Weight loss (if overweight) and smoking cessation should be strongly encouraged. Possible drug contributors to dyspepsia include calcium channel blockers, nitrates, theophyllines, bisphosphonates, antiplatelet agents and NSAIDs, and a therapeutics review should be conducted to consider whether these are still indicated or could be appropriately substituted. Where PPIs are prescribed, the lowest effective dose should be used, for the shortest possible duration. Low-cost PPIs should generally be used in preference to more expensive agents, although whether this extends to situations where drug-drug interactions could occur remains an open question. The indications and intended durations should be clearly documented and communicated to the primary care provider and pharmacy.

Patients on long-term therapy should be reviewed on (at minimum) an annual basis and, if the indication for treatment was dyspepsia, encouraged to step-down therapy gradually, aiming for the lowest effective dose. Substitution of PPIs with antacid or alginate therapy, or H_2 receptor antagonists, can also be considered. Patients should be counselled regarding rebound acid secretion on drug discontinuation, that this does not necessarily represent recurrence of disease, and on strategies to manage this (preferably without re-escalating PPI dose)[28].

The other common rationale for long-term PPI prescribing is prophylaxis when receiving antiplatelet agents or NSAIDs. Most guidelines suggest this is only required for high-risk patients, specifically those over 65 years of age, with a history of peptic ulcer disease or upper gastrointestinal haemorrhage, or taking multiple medicines that augment gastrointestinal adverse effects[53,54]. The latter include high-dose steroids (dose equivalent greater than 30mg prednisolone/day), anticoagulants, and selective serotonin reuptake inhibitors.

Time to deprescribe

Prescribing of PPIs has skyrocketed over the past decade. These drugs can be effective, but are principally intended for short-term use yet often not discontinued. There is clear and consistent evidence of overprescribing as clinicians overestimate benefits and underestimate harms, associated with substantial costs to healthcare providers. Measures should be put in place to educate prescribers as to appropriate indications and durations for PPI use, provide a degree of stewardship, and facilitate long-term users in de-escalating therapy.

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