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REVIEW

Proton-pump inhibitors

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Abstract

Proton-pump inhibitors (PPIs) are a class of drugs that profoundly suppress gastric acid secretion, and thus have become the treatment of choice for gastro-oesophageal reflux disease and peptic ulcer disease. PPIs are considered safe and effective. It is essential that clinicians understand the appropriate use of PPIs, given the significant economic burden of inappropriate prescribing and safety concerns. Long-term safety concerns and possible drug interactions have led to a more conservative approach to PPI use. Some of these concerns may have been overstated, but they serve to highlight the need for ongoing vigilance because even a small increased risk of an adverse event may translate to a large number, considering that the use of PPIs is widespread. This review focuses on the use of oral PPIs in the ambulatory setting, and recent concerns regarding the adverse effects of PPIs.

Keywords: proton-pump inhibitors, PPIs, gastro-oeseophageal reflux disease, GORD, PUD

Introduction

Proton-pump inhibitors (PPIs) work by binding irreversibly to the H+/K+-ATPase pump of the parietal cell, leading to inhibition of acid production in approximately 70% of active pumps.[1] The result is a dramatic increase in gastric pH mitigating the deleterious effects of acid in gastro-oesophageal reflux disease (GORD) and peptic ulcer disease (PUD).[2] Thus, PPIs are among the most sold drugs worldwide.[3] Concern exists regarding the appropriate prescribing of this class of drugs not just for well documented indications, but also as a panacea for all upper gastrointestinal maladies.[4] This places an unnecessary and appreciable economic burden on whoever is paying the bill. In addition, despite the excellent safety profile of these drugs, there is potential for long-term adverse effects of acid suppression.[5] Ultimately, it is the decision of the clinician to use a drug, withhold it, increase the dose or withdraw it. This decision must be rational and evidence based. Unfortunately, functional gastrointestinal disorders tend to distort the clinical picture, and good clinical judgement is necessary in this difficult group of patients who invariably end up taking PPIs.[6] This review focuses on the indications and use of PPIs in conditions commonly encountered in adult family practice, and attempts to address concerns about their adverse effects. Guidance on PPI use that is advocated and practised is provided.

Indications for proton-pump inhibitors

Gastro-oesophageal reflux disease

The first step is to ensure that you are treating GORD. A classical description of "heartburn" or a feeling of "acid coming up the chest" in a patient aged 40 years and younger may be sufficient when considering a trial of PPIs.[7,8] This has become common practice and a simple GORD questionnaire may enhance diagnostic confidence without the need for further testing.[9,10] A trial of PPIs may then be commenced, provided that alarm symptoms have not been identified. There is no standard definition of what constitutes an adequate trial of PPIs. Six weeks of a daily PPI at a standard dose equivalent to omeprazole 20 mg ingested 30 minutes before breakfast could be considered adequate as a trial.

Any features that might cause alarm should be identified and patients referred for further tests. This includes being > 40 years of age, having had the symptoms > 5 years, dysphagia, weight loss and anaemia. Any concern about possible ischaemic heart disease should prompt an immediate cardiac assessment. GORD is a common condition. Thus, it may coexist with other more serious conditions.[11] The best response to PPIs is observed in those with documented erosive oesophagitis observed at endoscopy.[12] It is becoming an uncommon finding at endoscopy owing to the widespread empiric treatment of GORD with potent PPIs, which leads to healing of the oesophageal erosions. PPIs are less effective in non-erosive GORD, and it is thus this group that comes to specialist attention, often requiring evaluation with endoscopy, manometry, pH studies and impedance monitoring, if available.[13] It is important to ensure that PPIs are given for an adequate duration in this group of patients as an incremental benefit may only be observed over a sustained period.[14] Two weeks of PPI therapy is simply inadequate. A good response to PPIs in GORD should lead to sustained daily treatment for approximately six months. At some point after this, the patient should be encouraged to try weaning him- or herself off the daily PPI dose, i.e. to take it on alternate days, and then try using PPIs on demand.[15] The "weaning off" concept is applied to avoid possible rebound acid hypersecretion which may occur following abrupt cessation of the PPI. On-demand

therapy allows the patient to reinstitute therapy for a week or two should troublesome symptoms recur, or if he or she anticipates that symptoms will occur during a planned holiday or a weekend of excess. PPIs can be used effectively in this manner to control symptoms, and ensure good quality of life for most GORD patients, while simultaneously reducing the long-term "pill burden". Alginates,such as Gaviscon® (used after meals for symptom relief as required) and lifestyle modifications especially moderate weight loss can augment GORD management.[16]

Some patients achieve a partial response to PPIs and are not completely satisfied. Consideration may be given to trying a twice-daily dosing regimen, i.e. a standard dose should then be taken 30 minutes before breakfast and supper, and the patient's response reassessed after 4-6 weeks.[17] In addition, therapeutic targets should be discussed with the patient. One hundred per cent satisfaction with PPIs may not be an achievable target in all patients. The patient and clinician may agree that a reduction in symptoms is acceptable with a standard daily dose, despite the occasional breakthrough episode. Trying to use a different PPI, which for unclear reasons may prove to be effective in an individual patient, is another strategy that can be used.[18] There is a lack of quality head-to-head trials which compare different PPIs. Excessively high doses of PPIs should be avoided.

Patients who report minimal improvement in their GORD symptoms on an appropriate daily PPI dose taken at the correct time, or those with volume reflux, should be referred to a gastroenterology specialist.

Peptic ulcer disease

The first step in PUD is to establish a diagnosis. Uncomplicated PUD is an endoscopic diagnosis and cannot be reliably diagnosed clinically. There is no place for a trial of PPIs or empiric eradication therapy if a clinician suspects PUD, and prompt referral to a gastroenterologist for an endoscopy should be the priority.[19] PPIs may be given for a few days while awaiting endoscopy. Complications such as bleeding, perforation and gastric outlet obstruction are clear indications for hospitalisation and in-patient management. Upper gastrointestinal bleeding from PUD can be managed with resuscitation and an intravenous PPI, i.e. an 80 mg bolus, followed by 8 mg/hour infusion.[20] This should not replace early endoscopy and the application of haemostatic techniques for ulcers with high-risk stigmata. There is a lack of evidence comparing intravenous and high dose PPIs in this situation. *Helicobacter pylori*-related ulcers should receive eradication therapy which includes twice-daily PPI for the duration of the dual antibiotic therapy, followed by a daily PPI.[21] Increasing the gastric pH during this period improves the efficacy of antibiotic therapy, stabilises clot formation and promotes ulcer healing. It is not clear for how long PPI therapy should be maintained. Recommendations include a minimum of four weeks for duodenal, and eight weeks for gastric, ulcers.[22] PPI treatment for nonsteroidal anti-inflammatory drug (NSAID) ulcers should probably be continued for a longer duration, and possibly indefinitely if the patient requires continued NSAID use.[23]

Non-ulcer dyspepsia and functional dyspepsia

Functional dyspepsia can be a difficult diagnosis to establish. This is mainly because there is a wide range of causes of epigastric discomfort, including *H. pylori,* biliary colic, early chronic pancreatitis, diabetic gastroparesis, and a number of medications. Frequently there is also an overlap with GORD symptoms.[24] Taking a careful history, and conducting an examination, upper gastrointestinal endoscopy and abdominal ultrasound is usually required in this difficult group of patients. The rationale for PPI use for this condition stems from evidence that the antroduodenal region in these patients may be unusually acid sensitive and from observed clinical response.[25] Not all patients experience a satisfactory response, but it is worth allowing an adequate duration of PPI treatment, i.e. 8-12 weeks, before declaring the PPI treatment to have failed and before trying alternate therapies. Organic causes of dyspeptic symptoms should always be considered while managing these patients.

Proton-pump inhibitor prophylaxis in patients on nonsteroidal anti-inflammatory drugs, including aspirin

PPIs provide gastroprotection in patients using chronic NSAIDs, including low-dose aspirin. Not all patients need to be on PPI prophylaxis. Consensus recommendations advise PPI prophylaxis in those who have additional risk factors for gastrointestinal bleeding. This includes the elderly (> 70 years), those on wafarin and chronic steroid use, the *H. pylori*-infected and those with a prior history of documented peptic ulcers and gastrointestinal bleeding. PPIs have been shown to reduce adverse gastrointestinal events in patients on long-term NSAIDs.[26] However, many patients are not receiving PPI gastroprotection as recommended in the guidelines, and many patients who are on low-dose aspirin are receiving PPIs when no recommendation exists.[27]

Concerns about long-term proton-pump inhibitor use

Osteoporosis and fracture risk

Epidemiological evidence of PPIs being directly responsible for osteoporosis and fractures remain weak.[28] The biological plausibility for this concern is that of reduced calcium absorption due to the increased pH caused by PPI use.[29] However, these are usually elderly patients with other risk factors for fractures who are also on PPIs. Initial concerns served to alert the medical community that even a safe and effective class of drugs should only be prescribed if a clear clinical indication exists. Osteoporosis should be investigated and treated on its merit, and PPI therapy should not be withheld if it is definitely needed.[28]

Gastric fundal polyps

PPIs are associated with the increased development of gastric fundal hyperplastic polyps.[30] There does not appear to be any evidence to suggest an increased risk of dysplasia and progression to cancer.[31] In addition, there is no clear evidence that long-term PPI use increases the risk of the development of gastric neuroendocrine tumours in humans.[32]

Vitamin B_{12} deficiency

There have been recent concerns about an association between chronic PPI use and vitamin B_{12} deficiency.[33] Thus, it is prudent to check vitamin B_{12} levels, especially in older patients on PPIs, given the serious consequences of vitamin B_{12} deficiency and the ease of vitamin B_{12} replacement. However, a clear recommendation does not exist that all elderly patients using PPIs should be regularly screened for vitamin B_{12} deficiency.[34] Further studies in this regard would be of value to establish this risk.

Proton-pump inhibitors and clopidigrel

There was immense worry that PPIs significantly reduce the efficacy of clopidogrel, thus placing patients with coronary artery disease at risk of myocardial infarction. There is in-vitro evidence of this effect as both drugs share similar hepatic metabolism pathways.[35] The concern arising from this effect led to the US Food and Drug Administration adding a "black box" warning to practitioners who prescribe PPIs to patients on clopidigrel. Certain PPIs, such as rabeprazole and pantoprazole, do not appear to have such a significant effect.[36] In fact, PPIs have been effective in reducing gastrointestinal bleeding associated with dual antiplatelet therapy. What is the recommended course of action from a practical point of view if a patient needs a PPI and dual antiplatelet therapy? One option would be to use a "safe" PPI, such as rabeprazole or pantoprazole. Another option would be to separate the dosing of the PPI and clopidogrel by 12 hours. In general, the initial concerns and clinical significance of this drug-drug interaction may have been overstated.[37]

Proton-pump inhibitors and Clostridium difficile*-associated diarrhoea*

The rise in *Clostridium difficile*-associated diarrhoea appears to have emerged with the increased prescribing of PPIs. This may also relate to the emergence of virulent strains. There is reasonable evidence to support this association, particularly in community-acquired *C. difficile*-associated diarrhoea.[38,39] Exposure to antibiotics and age are the strongest risk factors for *C. difficile*-associated diarrhoea. Not surprisingly, it is the elderly who are often on multiple drugs, including PPIs, and who are likely to receive broad-spectrum antibiotics. Maintaining an acidic gastric pH may be protective against the development of enteric infections, including *C. difficile*-associated diarrhoea. Given the seriousness of *C. difficile*-associated diarrhoea and the potential for the precipitation of hospital or nursing home outbreaks, a high index of suspicion for this infection should be maintained. If there is no essential need for a PPI, such as a recently diagnosed peptic ulcer, stopping the PPI while managing the *C. difficile*-associated diarrhoea is recommended. Clinicians may consider temporarily stopping PPIs in patients who are, or were, in close proximity to the index case, provided it is not essential. Alternative antacids can be used in the interim. Patient isolation and strict hand washing with soap to destroy resistant spores are important measures to prevent spread.[40] C. *difficile* associated diarrhoea and the PPI association alerts clinicians to use PPIs responsibly, as is also the case with antibiotics.

Proton-pump inhibitors and community-acquired pneumonia

The association of PPIs and community-acquired pneumonia remains controversial owing to confounding factors. Affected patients tend to be elderly with other risk factors for pneumonia.[41,42] PPIs should be used if clearly indicated, but clinicians must remain alert to the patient profile in whom the risk of pneumonia is increased.

Conclusion

PPIs remain a powerful class of drugs in the treatment of common and important upper gastrointestinal disorders. However, there is substantial evidence that they are inappropriately prescribed and overused. PPI therapy should not be a substitute for an upper gastrointestinal endoscopy and other investigations, when indicated. It is important that a PPI is taken at least 30 minutes before a meal to maximise inhibition of the proton pumps. Where no clear indication exists, and in GORD patients who may be satisfied with on-demand therapy, weaning the patient off the PPI therapy should be attempted. Practitioners must appreciate the cumulative economic burden of chronic PPI use. PPIs have a good safety record, but emerging concerns about undesirable long-term effects will hopefully lead to more prudent prescribing habits.

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