

Proton pump inhibitors

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Abstract

Proton pump inhibitors (PPI's) are a class of drugs that profoundly suppress gastric acid secretion and have thus become the treatment of choice for gastro-oesophageal reflux disease (GORD) and peptic ulcer disease (PUD). PPI's are considered safe and effective. It is essential that clinicians understand the appropriate use of PPI's 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 it does serve to highlight the need for ongoing vigilance as even a small increased risk for an adverse event may translate to large numbers considering the widespread use of PPI's. This review will focus on the use of oral PPI's in the ambulatory setting and recent concerns regarding adverse effects of PPI's.

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Introduction

PPI's work by binding irreversibly to H⁺/K⁺ 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 GORD and PUD.² PPI's are thus among the most sold drugs worldwide.³ Concern does exist regarding the appropriate prescribing of this class of drugs not just for well documented indications but 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 may be potential long term adverse effects of acid suppression.⁵ Ultimately, it is the decision of the clinician to use, withhold, increase dose or withdraw a drug. This decision must be rational and evidence based. Unfortunately, functional gastrointestinal disorders tend to distort the clinical picture and one depends on good clinical judgement in this difficult group of patients who invariably end up on PPI's.⁶ In this review I will focus on the indications and use of PPI's in conditions commonly encountered in adult family practice and try to address some of the concerns regarding adverse effects. I will also try to provide some guidance on PPI use that I advocate and practice.

Indications for PPI's

GORD

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 less than 40 years may be sufficient to consider a trial of PPI's.^{7,8} This has become common practice and simple GORD questionnaires may enhance diagnostic confidence without the need for further testing.^{9,10} A trial of PPI's may then be commenced provided there are no alarm symptoms. There is no standard definition of what constitutes an adequate trial of PPI's. Six weeks of daily PPI at standard doses (equivalent to Omeprazole 20mg) ingested 30 minutes before breakfast may be considered an adequate trial. Any alarm features should be sought and these patients should be referred for further tests. This includes age > 40yrs, symptoms > 5yrs, dysphagia, weight loss and anaemia. Any concern about possible ischaemic heart disease should prompt immediate cardiac assessment. GORD is a common condition and may thus co-exist with other more serious conditions.¹¹ The best response to PPI's is observed in those with documented erosive oesophagitis observed at endoscopy.¹² It is becoming an uncommon finding at endoscopy due to the widespread empiric treatment of GORD with potent PPI's which leads to healing of oesophageal erosions. PPI's 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 PPI's are given for an adequate duration in this group of patients as there may be incremental benefit over a sustained period.¹⁴ Two weeks of PPI therapy is simply inadequate. A good response to PPI's in GORD should lead to sustained daily treatment for about 6 months (30min daily before breakfast). At some point after this the patient should be encouraged to try weaning off their daily PPI dose to alternate days and then try

using PPI's on demand.¹⁵ The "weaning off" concept is to avoid possible rebound acid hypersecretion that may occur with abrupt cessation. On demand therapy allows the patient to re-institute therapy for a week or two should troublesome symptoms recur or if they anticipate symptoms such as during a planned holiday or a weekend of excess. PPI's can be used effectively in this manner to control symptoms and ensure a good quality of life for most GORD patients while reducing the long term "pill burden". Alginates such as Gaviscon (use after meal for symptom relief as required) and lifestyle modifications (especially moderate weight loss) can augment GORD management.¹⁶

Some patients achieve a partial response to PPI's and are not completely satisfied. Consideration may be given to trying a twice daily dosing regimen (30 minutes before breakfast and supper) using standard doses and re-assess response after 4 to 6 weeks.¹⁷ In addition, one needs to discuss therapeutic targets with such patients. One hundred percent satisfaction with PPI's may not be an achievable target in all patients. Patient and clinician may agree that a reduction in symptoms on daily doses despite the occasional breakthrough episode may be acceptable. Another strategy is to try using a different PPI which for unclear reasons may prove effective in an individual patient.¹⁸ There is a lack of quality head-to-head trials comparing different PPI's. Excessive high doses of PPI's should be avoided.

Patients who report minimal improvement in 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 PPI's or empiric eradication therapy if a clinician suspects PUD and prompt referral to a gastroenterologist for an endoscopy should be the priority.¹⁹ PPI's 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 intravenous PPI's (80mg bolus followed by 8mg/hour infusion).²⁰ This should not replace early endoscopy and application of haemostatic techniques for ulcers with high risk stigmata. There is a lack of evidence comparing intravenous versus high dose oral PPI's in this situation. Helicobacter pylori related ulcers should receive eradication therapy which includes twice daily PPI for the duration of dual antibiotic therapy followed by daily PPI.²¹ Increasing gastric pH during this period improves the efficacy of antibiotic therapy, stabilises clot formation and promotes ulcer healing. It is not clear how long PPI therapy should be maintained. Recommendations include a minimum of 4 weeks for duodenal ulcers and 8 weeks for gastric ulcers.²² PPI treatment for non-steroidal 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 / Functional dyspepsia

Functional dyspepsia can be a difficult diagnosis to establish. This is mainly due to a wide range of causes of epigastric discomfort including Helicobacter pylori, biliary colic, early chronic pancreatitis, diabetic gastroparesis and a number of medications to name a few. In addition there is frequent overlap with GORD symptoms.²⁴ A careful history, examination, upper GI endoscopy and abdominal ultrasound are usually required for this difficult group of patients. The rationale for PPI use in this condition stems from evidence that the antro-duodenal region in these patients may be unusually acid sensitive and observed clinical response.²⁵ Not all patients will have a satisfactory response but it is worth giving an adequate duration of PPI treatment (8 to 12 weeks) before declaring failed PPI treatment and trying alternate therapies. Organic causes for dyspeptic symptoms should always be considered while managing these patients.

PPI prophylaxis in patient's on NSAID's including aspirin

PPI's provide gastroprotection in patients using chronic NSAID's including low dose aspirin. Not all patients need to be on PPI prophylaxis. Consensus recommendations advise PPI prophylaxis in those that have additional risk factors for gastrointestinal bleeding. This includes the elderly (>70yrs), warfarin use, chronic steroid use, Helicobacter pylori infected and a prior history of documented peptic ulcers and gastrointestinal bleeding. PPI's have been shown to reduce adverse gastrointestinal events in patients on long term NSAID's.²⁶ However, many patients are not receiving PPI gastroprotection as recommended in guidelines and many patients on low dose aspirin are receiving PPI's where no recommendation exists.²⁷

Concerns about long-term PPI use

Osteoporosis and fracture risk

Epidemiological evidence for PPI's 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 happen to be on PPI's. The initial concerns however did serve to alert the medical community that even a safe and effective class of drugs should only be prescribed if there is a clear clinical indication. Osteoporosis should be investigated and treated on its merits and PPI therapy should not be withheld if it is definitely needed.²⁸

Gastric Fundal Polyps

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

Vitamin B12 deficiency

There have been recent concerns about an association between chronic PPI use and Vitamin B12 deficiency.³³ It thus seems prudent to check Vitamin B12 levels especially in older patients on PPI's given the serious consequences of B12 deficiency and the ease of B12 replacement. However, there is no clear recommendation that all elderly patients using PPI's should be regularly screened for Vitamin B12 deficiency.³⁴ Further studies in this regard will be of value to establish this risk.

PPI's and Clopidogrel

There was immense worry that PPI's significantly reduces the efficacy of clopidogrel thus placing patients with coronary artery disease at risk for 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 Food and Drug Administration (FDA) adding a "black box" warning to practitioners who prescribe PPI's to patients on clopidogrel. Certain PPI's such as rabeprazole and pantoprazole does not appear to have such a significant effect.³⁶ PPI's have in fact been effective in reducing gastrointestinal bleeding related to dual antiplatelet therapy. What does one do 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

PPI's and Clostridium difficile associated diarrhoea (CDAD)

The rise in CDAD appears to have emerged with the increased prescribing of PPI's. This may also be related to the emergence of virulent strains. There is reasonable evidence to support this association particularly in community acquired CDAD.^{38,39} The strongest risk factors for CDAD are exposure to antibiotics and age. Not surprisingly, it is the elderly who are often on multiple drugs including PPI's and who are likely to receive broad spectrum antibiotics. Maintaining an acidic gastric pH may be protective against the development of enteric infections including CDAD. Given the seriousness of CDAD and potential for precipitation of hospital or nursing home outbreaks one must maintain a high index of suspicion for this infection. If there is no essential need for a PPI such as a recently diagnosed peptic ulcer I am happy to stop the PPI while managing the CDAD. Clinicians may consider temporarily stopping PPI's 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 The CDAD and PPI association alerts us to use PPI's responsibly as recommended for antibiotics.

PPI's and Community acquired pneumonia

This association remains controversial due to confounding factors. Affected patients tend to be elderly with other risk factors for pneumonia.^{41,42} The take home message here is to use PPI's if clearly indicated but remain alert to the patient profile that increases the risk for pneumonia.

Conclusion

PPI's will remain a powerful class of drugs in the treatment of common and important upper gastrointestinal disorders. There is substantial evidence that PPI's 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 the PPI should be taken at least 30 minutes before a meal to maximise inhibition of the proton pumps. Be prepared to wean off PPI therapy where no clear indication exists and in GORD patients who may be satisfied with on demand therapy. Practitioners should appreciate the cumulative economic burden of chronic PPI use. PPI's 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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