

# PPIs:

## Overused or Misused?

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The huge, worldwide sales figures for proton pump inhibitors (PPIs) may suggest that this class of drug is overused. Yet, it has earned a place of choice in the hearts and minds of countless patients afflicted with acid peptic-related disorders, though its use in treating peptic ulcer disease has fallen since the knowledge that *Helicobacter pylori* (HP) eradication is curative.

The use of PPIs for ulcer prophylaxis in the setting of non-steroidal anti-inflammatory drugs (NSAIDs) or acetylsalicylic acid (ASA), is an ever-growing enterprise—one with life-saving potential. Gastroesophageal reflux disease (GERD) is probably the best current indication for PPIs. Although some patients will get by with intermittent or on-demand treatment,<sup>1</sup> there is also a subset of refluxers who would do better with twice daily PPIs.<sup>2</sup> Their use for empiric treatment of HP-negative dyspepsia is common and those patients that do respond, likely have some degree of reflux, although placebo response rates are high. Quick tapering of PPIs for those without a clearcut response in the treatment of dyspepsia is probably an area where overuse may be curtailed.

Early concerns over risk of gastric neoplasia, both adenocarcinoma and carcinoid-like tumors do not appear to be founded.<sup>3</sup> However, there has recently been concern over a higher risk of infections such as *Clostridium difficile* associated with PPI use.<sup>4,5</sup> The success of PPIs in treating

### Bruce's case

- Bruce, a 45-year-old construction worker consults you for constrictive anterior chest pains.
- These have been occurring about five to six times a week since the last two years. After an adequate cardiac work up, you determine that these are non-cardiac chest pains.



### Discussion:

- Non-cardiac chest pain is most commonly due to gastroesophageal reflux disease (GERD). Other common causes include esophageal dysmotility, biliary colic, chest wall pain and others.
- Ruling out GERD may be difficult, since most people will have a normal endoscopy (non-erosive reflux). A 24-hour pH study has a good chance of making the diagnosis, but is not always readily available.
- A therapeutic trial with a proton pump inhibitor (PPI) would be a good alternative. A recent meta-analysis looked at this subject and concluded that a four-week trial of a PPI twice a day will identify 80% of patients likely to respond (defined as a 50% reduction in symptoms).<sup>9</sup>

For another case go to page 76

## Peter's case



- Peter, a 25-year-old man presents to your office with a six-month history of typical heartburn, occurring daily and occasionally at night.
- He smokes 15 cigarettes a day and has an irregular meal pattern related to a high-stress job. He often eats a quick fast food meal in the late evening.
- After discussing a few lifestyle changes with Peter and suggesting antacids for his symptoms, you see him back at your office a month later. He has made efforts to improve his eating habits, but still has a lot of symptoms which did not respond well to the antacids.

### Discussion:

- GERD can be safely diagnosed clinically without need for imaging or endoscopy in the absence of certain alarm symptoms, such as:

- Age over 50, if recent onset
- Unintended weight loss
- Dysphagia or odynophagia
- Anemia
- Hematemesis
- Abdominal mass or lymphadenopathy
- Family history of gastrointestinal cancer

Treatment should address lifestyle changes when appropriate, but some patients will require more aggressive treatment.

- PPIs have clearly demonstrated clear superiority over histamine receptor antagonists (*i.e.*, ranitidine, famotidine, *etc.*) in treating all degrees of GERD. This benefit is in regards to efficacy and lack of tolerance

over long term use. Most patients will do well with a once daily regimen, although up to 30% will need twice-daily dosing to completely control their symptoms.

- Patients with more severe symptoms may also benefit from twice-daily dosing for the first or second week, followed by reduction to once-daily dosing for the long term.
- After a period of about four to six months of daily treatment, a trial of tapering the PPI should be attempted by gradually reducing the frequency of use over two weeks (so as to avoid a rebound effect on acid secretion).
- Most patients, especially those with erosive esophagitis, will have recurrent symptoms and require long term daily dosing. However, a subset of patients may be able to take PPIs on demand or for short periods at a time and will be relatively asymptomatic.
- Long term effects on GERD complications, such as stricturing, have not been determined in patients on intermittent treatment.

traditional acid peptic disease has boiled over to some less clear-cut indications, such as reflux laryngitis (also called laryngo-pharyngeal reflux, or posterior laryngitis), chronic cough and asthma. These attempts have been mostly in the guise of therapeutic trials. The medical literature for these uses are mostly unimpressive,<sup>6-8</sup> yet most clinicians continue to hope that better ways to identify true responders will soon be at hand.

### Frequently Asked Questions:

#### 1) When is the best timing for PPI administration?

A PPI should be administered half an hour to one hour before breakfast and if an evening dose is

added, it should be given before supper.

#### 2) When a patient with GERD is not responding to a PPI, is it better to change or to double the dose?

The different PPIs are about equivalent in terms of efficacy; changing to a twice-daily dose is most likely to improve response. Non-response to several months of double-dose PPIs should be cause to question the diagnosis.



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## Olga's case




- Olga, a 73-year-old woman, recently had a myocardial infarction.
- While on acetylsalicylic acid (ASA) 81 mg daily, she presents with a bleeding gastric ulcer and is put on daily PPI. Her *Helicobacter pylori* (HP) was also successfully treated, but she became infected with *Clostridium difficile*. After initial treatment, the colitis recurred.

### Discussion:

- This case brings up a few issues, including the small but definite risk of gastrointestinal (GI) complications associated with low-dose ASA (and non-steroidal anti-inflammatory drugs [NSAIDs] in general), particularly for those patients with certain risk factors:
  - Age over 60
  - Previous history of peptic ulcer disease or NSAID-induced GI toxicity
  - High-dose NSAID use
  - NSAID (including coxib) and ASA use
  - NSAID and steroid or biphosphonate use
  - NSAID and anticoagulant use
- GI complications can be controlled by adding a PPI to the ASA or NSAID. PPIs are the most effective and best tolerated co-therapy for reducing ulcer risk.
- Replacing ASA with clopidogrel has been an alternative strategy, but recent evidence suggests that this medication may also cause ulcer bleeding.<sup>11</sup>
- HP eradication also was thought to reduce the risk of an ASA-induced ulcer, but the risk is reduced even further by adding a PPI.<sup>12</sup>
- However, in the case of Olga, another factor comes into play and that is the added risk of *C. difficile*-associated disease (CDAD) with PPI treatment. This risk is roughly increased by a factor of two to three times for both in- and out-patients. The risk of recurrent infection is also significantly increased. This is because of the role of gastric acid in host defence against ingested organisms.
- PPIs have also been shown to slightly increase the risk for community-acquired pneumonia and for enteric infections caused by several common pathogens. The best course of action in this case may be to temporarily stop PPI treatment and replace ASA with clopidogrel until the CDAD is eliminated as a problem. If the patient requires an NSAID rather than ASA, the continued use of a PPI vs. change to a cyclooxygenase 2 (Cox-2) inhibitor would have to be considered, once the ulcer was healed and assuming no ASA was used.

### 3) How long is it safe to give PPIs?

The global experience with this class of medication suggests that there are not any major, long term sequelae. The serum level of vitamin B12 may decrease over time and should probably be monitored. Clinicians should also be aware of the increased risk for *C. difficile* infection. 

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