Proton Pump Inhibitors Deprescribing?

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Deprescribing PPI Objectives

- Why?
- Who?
- How?

The mechanism of action of Proton Pump inhibitors are:

- A – Reversibly inhibiting the H+/K+ Adenosine triphosphatase in gastric parietal cells.
- B – Irreversibly inhibiting the H+/K+ Adenosine triphosphatase in gastric parietal cells.
- C - Reversibly inhibiting the cAMP in gastric parietal cells.
- D – Irreversibly inhibiting the cAMP in gastric parietal cells.

Proton Pump Inhibitors (PPI)

- Omeprazole was introduced in 1989
- Irreversibly Inhibits the H+/K+ Adenosine triphosphatase in gastric parietal cells
- Estimates 8-10% of ambulatory adults have been prescribed a PPI in the past 30 days
- 2009 > $7 billion was spent on PPI in the US and $13 billion worldwide (not including OTC)

Deprescribing

Refers to a patient or physician effort to either discontinue PPIs outright, decrease exposure to PPIs by stepping down to a lower dose or intermittent/on-demand treatment regimen, or substituting PPIs with a less costly and/or less potent form of gastric acid inhibition.

Disclosures

- None
Why?

- Over 2 dozen associated complications have been reported
- Adverse events
- Cost
- Polypharmacy

Idiosyncratic Reactions

- Acute interstitial nephritis (AIN)
- Hypomagnesemia
- Microscopic colitis

Further reading options for discussion of adverse events:
- Vaezi MF, Yang YX, Howden CW. Complications of proton pump inhibitor therapy. Gastroenterology 2017; 153: 35 – 48

Take Home Point 1:

- Define a clear indication for why your patient needs a PPI
  - Both Inpatient and Outpatient
Indications

- Inappropriate use or prescribing of PPI:
  - Heidelbaugh et al:
    - PPI use in and their indications in 946 patients in clinic.
      - 1/3 of patients didn’t have an indication
      - 10% for extraesophageal symptoms
    - Furthermore, ~ % of the 946 patients did not have
documentation of response to therapy
  - Ladd et al:
    - 201 inpatients who were newly prescribed PPI
    - 75% of those patients either had no documented indication or
an inappropriate indication.
    - Of those 75% → 40% were continued on the medication at
discharge

What are the indications?

- FDA Indications for PPI Use
  - Healing of erosive esophagitis
  - Maintenance of healed erosive esophagitis
  - Treatment of GERD
  - Risk reduction for gastric ulcer associated with NSAIDS
  - Helicobacter pylori eradication to reduce the risk of
duodenal ulcer recurrence in combination with
antibiotics
  - Hypersecretory conditions including Zollinger-Ellison
syndrome
  - Short-term and maintenance treatment of duodenal
ulcer

AR 2

- Proton Pump inhibitors are least effective at
treating which symptom?
  - A – gastric ulcers
  - B – Reflux erosive esophagitis
  - C – Hoarseness
  - D – Chest pain

Take Home Point #2

- Define an endpoint based on indication
  Or
  - Indications define the endpoint

Potential Indications for Long Term Therapy

- Erosive esophagitis
  - Cochrane review of 134 trials which included 36,978
patients with erosive esophagitis demonstrated that the
acute use of PPIs uniformly provided more rapid healing of
esophagitis and symptom resolution compared with HRAs
and/or prokinetics.
  - Standard Dose at 8 weeks relieved symptoms in ~86% of
patients
  - PPI are more effective than H2 blockers in maintaining
symptom free remission (91%H2 and 62% H2Blocker)
  - Consider discontinuation in patients with mild esophagitis
(LA class A/B) or in those patients with major predisposing
factors. (heavy alcohol)
Prevention of Peptic Ulcer Disease

- Highly efficacious in preventing gastric and duodenal ulceration in chronic users of nonsteroidal anti-inflammatory drugs
- Epidemiologic studies, PPIs concomitantly with NSAIDS reduce the odds of being hospitalized for complicated peptic ulcer disease ~50% to 80%.
  - NSAIDS, Severe Medical Comorbidities Plus:
    - Concomitant antiplatelet and/or anticoagulants
    - Concomitant systemic corticosteroids
    - Age >70
    - History of PUD

Barrett’s Esophagus Progression

- Acid-induced injury is a major etiologic factor in the development of intestinal metaplasia
- Conflicting data on if PPIs prevent cancer, but trend towards being protective
- All major guidelines strongly recommend PPI therapy

Zollinger – Ellison Syndrome

- Unregulated release of gastrin from a gastrinoma
- PPI are the most effective therapy at controlling symptoms
- Removal of the tumor may allow for discontinuation of PPI
  - Usually not possible for patients with:
    - metastatic disease
    - multiple endocrine neoplasia type 1.

GERD

- “symptoms or complications resulting from the reflux of gastric contents into the esophagus or beyond, into the oral cavity (including larynx) or lung”

Pathophysiological triggers of GERD symptoms


PPI efficacy for potential manifestations of GERD

Guidelines for the diagnosis and management of GERD. *Am J Gastroenterol.* 2013

**GERD Treatment**

- Optimize dosing – 30 minutes prior to breakfast
- Survey: 100 patients
  - Only 46% optimal dosing (prior to meal)
  - Only 12% prior to breakfast
- 2001 Survey of 491 physicians
  - 70% of PCPs and 20% of GIs advised their patients to take PPIs at bedtime or did not believe timing in relation to meals was important

**AR 3**

- What is one of the roles for endoscopy in the evaluation of GERD?
  - A – To ensure patients will have a response to PPI
  - B – Document pH within the stomach to ensure adequate response
  - C – Rule out other potential etiologies
  - D – Send kids to school

**Role of Endoscopy**

- Can detect alternative diagnoses
  - Eosinophilic Esophagitis
  - Infection
  - Pill injury
  - Achalasia
- Anatomical contributors or results
  - Hiatal hernia
  - Barrett’s
  - Peptic stricture

**pH/Impedance outcomes**

- 106 patients with refractory reflux symptoms despite BID PPI
- All underwent pH-Impedance testing
- Results:
  - 65% GERD
  - 30% Functional heartburn
  - 5% Other – Achalasia, Distal Esophageal Spasm
Follow up

**GERD:**
- Hypersensitivity (acid exposure <6% and (+) SAP)
  - 8 patients used amitriptyline with 75% beneficial effect
  - 13 patients used PPIs with 53% beneficial effect
- GERD/NERD (acid exposure >6% and (+) SAP)
  - 8 patients with Nissen Fundoplication – "all with great results"
  - 27 patients used PPIs with 77% having symptom relief >50%

Herregods, T., et al. Patients with refractory reflux symptoms often do not have GERD. Neurogastroenterol Motil. 2015 Sep;27(9):1267-7

**Functional Heartburn**
- Limited controlled studies of pharmacologic therapy

Herren and Shaheen, Management of Functional Heartburn, AGA, January 2016

Follow up

**Functional Heartburn**
- 8 patients used amitriptyline with 50% having a beneficial effect (>50% symptom relief)

Deprescribing Efforts

**Deprescribing Guideline in Long-term care facility**
- Measured:
  - Total Number of PPI prescriptions
  - Average PPI cost per resident
- Results:
  - PPI decreased in first 6 months after guidelines initiated, but then began to climb back
  - Suggesting it is hard to maintain PPI reduction

How Should PPI Therapy be Deprescribed

**Step-down regimens**
**Total Discontinuation**
**On-Demand dosing**
Effectiveness of Step Down

- On-demand therapy, where a patient uses PPIs only when symptoms occur and taken until symptoms are adequately relieved, is significantly more effective than placebo in providing adequate symptom relief (51% vs. 14%, \( P < 0.0001 \))
- A meta analysis comparing continuing PPI use to on-demand PPI use found that persons assigned to on-demand therapy has a increase in the risk of loss of symptom control (16% vs. 10%, RR 1.71, 95% CI: 1.31–2.21

Total Discontinuation

- Unclear indications
- Symptoms where there is little evidence
- Patient preference

- However, the sudden discontinuation of PPIs may cause a sudden and profound rise in gastric acid output (rebound)

Total Discontinuation

- Reimer et al:
  - Patients with no history of GERD all given PPI for 8 weeks, then randomized to placebo group and continuing PPI group for 4 additional weeks
  - 40% of the patients that stopped the PPI reported dyspepsia

- 28 residents who fit the criteria, and the recommendation to discontinue therapy was accepted for 27.
- 8 weeks after the intervention, 19 (70%) of these residents were still asymptomatic and did not require re-initiation of medication.
• Need to give patients a strategy to taper
  – Take every other day for 2 weeks, twice per week for 2 weeks and then discontinue
• Advise patients who discontinue PPIs to be mindful of rebound and not to immediately reintroduce at the first sign of a recurrent symptoms.

Summary
• Not yet definitive evidence of serious harm associated with PPI use, several associations exist where biologic plausibility exists
• Given uncertainty clinicians should try to limit long term PPI use
• Define Indications
• Define Duration
• Deprescribe when possible
• Advise about rebound

References
2. Vermeulen, M et al. We have had a gutful: The need for deprescribing proton pump inhibitors. J Clin Pharm Ther. 2017 Dec;42(6):677-681