PPI OVERUSE: CAN YOU STOMACH IT?

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Appropriate Prescribing & Safety Concerns

SCENARIO

Patient med refill request:
Omeprazole 20mg q12 hrs #60
- 67 yo male
- CAD w/ 2 stents
- HTN
- OA of knees
- Dyslipidemia

CURRENT OTHER MEDS

- Chlorthalidone
- Isosorbide Mononitrate
- Atorvastatin
- Clopidogrel
- Oxybutynin
- Amlodipine
- Naproxen PRN
YOU CHECK THE CHART.....

- Nothing GI on problem list . . .
- No notes in chart about abdominal pain
- Patient has not been seen in clinic since 2013
- Omeprazole on med list since 2006

SO, WHAT DO YOU DO?

A. Refill the 60/month w/ another 11 refills...
B. Deny the refill, requiring the patient be seen
C. Refill only 60 tabs, NO refills, requiring an appointment for any future refills
D. Deny the refill and send an Rx for Ranitidine instead

SO, WHY AM I HERE?

- Proton pump Inhibitors (PPIs) make up over 50% of the GI drug market in the USA
- Literature suggests that 2/3 of PPI usage may be inappropriate, lacking in evidence for utility.
- Adverse effects include infections (PNA, C diff, SIBO), decreased vitamin/mineral absorption, fractures, and possibly MI's?
GOALS OF PRESENTATION

- Review the literature of safety concerns for PPI’s.
- Discuss differential diagnosis and alternative treatment modalities.
- Describe how to taper and discontinue PPI’s, or give informed consent for patients who desire to continue them.

WHAT DRUGS ARE WE TALKING ABOUT?

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulations</th>
<th>OTC</th>
<th>Formulary (As of 11/3/2014)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabeprazole (Aciphex)</td>
<td>Tablets &amp; sprinkles</td>
<td>NO</td>
<td></td>
</tr>
<tr>
<td>Omeprazole (Prilosec)</td>
<td>Capsules, packets &amp; suspension</td>
<td>Yes</td>
<td>CD-D, CD-OHP, FC-D, FC-OHP, HCBD, MODA-OHP</td>
</tr>
<tr>
<td>Esomeprazole (Nexium)</td>
<td>Capsules, packets &amp; IV</td>
<td>No</td>
<td>FC-D (higher co-pay)</td>
</tr>
<tr>
<td>Lansoprazole (Prevacid)</td>
<td>Capsules, sol tab &amp; suspension</td>
<td>Yes</td>
<td>CD-D, MODA-OHP</td>
</tr>
<tr>
<td>Deslansoprazole (Dexilant)</td>
<td>Capsules</td>
<td>No</td>
<td>FC-D (higher co-pay)</td>
</tr>
<tr>
<td>Pantoprazole (Protonix)</td>
<td>Packet, solution &amp; tabs</td>
<td>NO</td>
<td>CD-D, CD-OHP, FC-D, FC-OHP, HCBD, MODA-OHP</td>
</tr>
</tbody>
</table>

PPI FINANCIALS..... THE BIG BUCKS!!!!!!

- >$2.5 million for PPI’s for OHP in 2014
- > 20 million Americans take PPI regularly
- In 2013, U.S. spent $6.1 BILLION dollars on Nexium (esomeprazole) alone!
- Cost of side effects?

The Oregon state drug review, August 2015, Volume 5, Issue 5 pharmacy.oregonstate.edu/drug-policy/newsletter
MEDICARE 2013 TOP TEN DRUG CLAIMS

<table>
<thead>
<tr>
<th>Rank</th>
<th>Drug</th>
<th>Claims #’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lisinopril</td>
<td>36k</td>
</tr>
<tr>
<td>2</td>
<td>Simvastatin</td>
<td>36k</td>
</tr>
<tr>
<td>3</td>
<td>Levothyroxine</td>
<td>35k</td>
</tr>
<tr>
<td>4</td>
<td>Hydrocodone-acetaminophen</td>
<td>34k</td>
</tr>
<tr>
<td>5</td>
<td>Amlodipine</td>
<td>34k</td>
</tr>
<tr>
<td>6</td>
<td>Omeprazole</td>
<td>33k</td>
</tr>
<tr>
<td>7</td>
<td>Atorvastatin</td>
<td>26k</td>
</tr>
<tr>
<td>8</td>
<td>Furosemide</td>
<td>26k</td>
</tr>
<tr>
<td>9</td>
<td>Metformin</td>
<td>22k</td>
</tr>
<tr>
<td>10</td>
<td>Metoprolol</td>
<td>21k</td>
</tr>
</tbody>
</table>


MEDICARE 2013 DRUG COSTS

<table>
<thead>
<tr>
<th>Rank</th>
<th>Drug</th>
<th>Cost in $ Billions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Esomeprazole (Nexium)</td>
<td>$2.5</td>
</tr>
<tr>
<td>2</td>
<td>Fluticasone Propionate &amp; Salmeterol (Advair)</td>
<td>$2.2</td>
</tr>
<tr>
<td>3</td>
<td>Rosuvastatin (Crestor)</td>
<td>$2.2</td>
</tr>
<tr>
<td>4</td>
<td>Aripiprazole (Abilify)</td>
<td>$2.1</td>
</tr>
<tr>
<td>5</td>
<td>Duloxetine (Cymbalta)</td>
<td>$1.9</td>
</tr>
<tr>
<td>6</td>
<td>Tiotropium (Spiriva)</td>
<td>$1.9</td>
</tr>
<tr>
<td>7</td>
<td>Memantine (Namenda)</td>
<td>$1.5</td>
</tr>
<tr>
<td>8</td>
<td>Sitagliptin (Januvia)</td>
<td>$1.4</td>
</tr>
<tr>
<td>9</td>
<td>Insulin Glargine (Lantus Solostar)</td>
<td>$1.3</td>
</tr>
<tr>
<td>10</td>
<td>Lenalidomid (Revlimid)</td>
<td>$1.3</td>
</tr>
</tbody>
</table>


“One nation, under GERD”

Niall Brenan, Medicare data officer
IS DYSPEPSIA THE NEW NORM?

- **Dyspepsia**: also known as indigestion (bloating, belching, nausea, pain, heartburn)
- **Common**: everyone experiences at some point.

Why USE PPIs?

- PPIs are often started inpatient, ED, specialist office, patients OTC w/ no clear indication.
- Lack of assessment for ongoing therapy or if current dose is the lowest effective dose needed.
- Assessing and discussing lifestyle and psychological factors is difficult in 15 minutes!
- Rebound hypersecretion reinforces the need for daily PPI, >50% of pts who abruptly discontinue. PPIs after 2-3 months of use will develop rebound hypersecretion.
INFANTS & GERD: DAILY PREVALENCE

<table>
<thead>
<tr>
<th>Age in months</th>
<th>% 1 time per day</th>
<th>&gt;4 times/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 3</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>4 to 6</td>
<td>70</td>
<td>30</td>
</tr>
<tr>
<td>7 to 9</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>10 to 12</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

Nelson et al. 1997 Arch Pediatric Adolescent Med

Fluid equivalents

Infant 5kg
180 ml bottle

= Adult 80kg
3 liter

PPI’s FOR CHILDREN WITH GERD

A LITERATURE REVIEW: RCT’s & CROSSOVER STUDIES:

- Infants: 4/5 studies showed no difference in PPI TX vs. Placebo
- Children/Adolescents: No difference PPI TX vs. Controls (ranitidine or alginites)
- Children w/ Histological abnormalities: No difference PPI TX vs. Controls

Van der Pol et al. 2011 Pediatrics Volume 127, number 5
**VITAMIN & MINERAL ABSORPTION**

Malabsorption of nutrients that require gastric acidity: calcium carbonate, iron, magnesium and vitamin B-12

- Clinical relevance of this interaction is not known, some experts and literature recommend using calcium citrate for calcium supplementation when patient is on chronic PPI as calcium citrate not affected by gastric acidity.
- Reduced magnesium absorption may be of concern in patients on diuretics or on digoxin therapy. Symptoms of hypomagnesemia: muscle cramps, heart palpitations, dizziness, tremors and seizures.

**FRACTURES AND BMD w/ PPI**

- Long-term PPI use is associated with a 25% increase in overall fracture risk in postmenopausal women.
- Risk of hip fracture is only increased in patients with other risk factors. NNH=1200
- This risk should not prevent use of PPI in patients with osteoporosis when there is an indication but evaluate risk, prescribe lowest effective dose, and discuss calcium/vitamin D supplementation.
- No documented effect on bone mineral density.

CLOSTRIDIUM DIFFICILE GASTROENTERITIS

- 2-fold increase in risk for C. diff infections w/ PPI use
- NNH = 533 inpatients and risk of recurrence is 42% in those who are taking a PPI.
- H2RAs also increase risk, but to a lesser extent

Deshpande et al. 2012, Clinical Gastroenterology and Hepatology

PPIs & INFECTION RISKS

Small intestinal bacterial overgrowth (SIBO):
- Association only found w/ aspirate diagnosis
- Greatest risk being for inpatients on vents

Pneumonia:
- Data has led to conflicting results regarding risk for CAP while on PPIs, some data showing a NNH = 226 when PPIs are used for 3 months.
- Associated w/ short term PPI use and NOT long-term PPI therapy

Peritonitis
- PPI use in patients with cirrhosis was independently associated with higher risk for infections (peritonitis, sepsis, others)

Lo & Chan: 2013, Clinical Gastroenterology and Hepatology
O'Leary et. Al. 2015, Clinical Gastroenterology and Hepatology

PPI’s & Myocardial Infarction?

- Large data mining study showed small increase in MI w/ PPI’s use (>2 million people, 2 distinct data sets)
- Incidence of death from MI doubled w/ long-term PPI use
- Independent of other variables (smoking, age, disease comorbidity, clopidogrel use, ect.)
- No association with H2 blockers

Shah et. al, 2015, PLOS one
PPI's & Myocardial Infarction?

Various theories:
- No smoking gun
- Interaction with clopidogrel (Plavix) activating isoenzyme?
- Black box warning about combining PPI with clopidogrel

https://www.youtube.com/watch?v=OBRKPAoXQEQ
REBOUND HYPERSECRETION

- Higher pH during treatment appears to stimulate hypersecretion of HCl upon PPI withdrawal
- Increased Gastrin (hormone which stimulates HCl production) during PPI tx
- Avoid rebound symptoms by tapering PPI q1-2 wks to lowest available dose and then every other day therapy for 1-2 weeks

Reimer et al. Gastro 2009; 137: 80-87

FDA APPROVED CONDITIONS FOR PPI TREATMENT

- GI ulcers
- H. Pylori
- Hypersecretory conditions (Zollinger Ellison)
FDA NOT APPROVED CONDITIONS FOR PPI TREATMENT

NOT APPROVED (but we do it anyway)
- Erosive esophagitis
- GI ulcer prophylaxis with NSAIDs
- Dyspepsia
- Asthma Symptoms
- Functional abdominal pain

OHP PPI COVERAGE CHANGES

Effective July 1st, 2015
- Omeprazole or Pantoprazole <8 weeks, no TAR
- >8 weeks needs prior authorization
- H2 blockers: Ranitidine preferred and no limitations
- Current patients on PPI will have 1 year of automatic approval

The Oregon state drug review, August 2015, Volume 5, Issue 5
pharmacy.oregonstate.edu/drug-policy/newsletter
ALTERNATIVE DIAGNOSIS

- Stress?
- Cultural?
- Hypochlorhydria: Normal gastric pH 1.5-2.5
  PPI makes symptoms of belching or gas in upper GI worse. Can check pH on EGD
- Post-cholecystectomy syndrome: lack of bile prevents fat digestion and indigestion. Consider Ox bile supplement w/ meals.
- DM Gastroparesis: a damaging of nerves for GI motility. Think as PN of autonomic system.
- Eosinophilic Esophagitis: allergen mediated?

ALTERNATIVES TO PPIs

- Lifestyle: mindfulness in eating (cephalic, oral-mastication, and then lower GI digestion)
- Diet: avoid acid provoking foods
- Marshmellow Root: cold extraction, coats mucous membranes
- Apple Cider Vinegar (1 Tablespoon in 8 ounces of water) or betaine HCl prior meals for hypochlorhydria

ALTERNATIVES TO PPIs

- Alginates (Gaviscon, ect.): from algae cell walls; creates gel to thicken liquid and coat esophagus
- Antacids: magnesium hydroxide, calcium (e.g. milk), bismuth sulfate, magnesium 400mg
- TCA's (Desipramin, Amitriptyline) for functional dyspepsia
- H2 blockers (Ranitidine, Famotidine)
THE 5 R’s

- Remove: stressors, parasites, food intolerances
- Replace: digestive enzymes, hydrochloric acid, bile acids that may be compromised by disease/surgery/lifestyle.
- Reinoculate: lactobacillus, sacchromyces boulardii (Red Star Yeast 1 tsp x2/day)-foods best source, prebiotics w/ inulin
- Repair: add key nutrients
- Rebalance: sleep, stress, exercise

PEARLS

- PPIs are 4th line treatment for GERD/dyspepsia
- Taper: for 1-2 weeks take PPI every other day +/- H2-blocker on the off days
- Informed consent if continuing long-term PPI
- Get pickled: introduce fermented foods back into the diet

REFERENCES

REFERENCES cont.

- Shah et al. Proton pump inhibitor usage and the risk of myocardial infection in the general population. PLOS one. 2013.