Understanding the Risk Benefit Ratio of Proton Pump Inhibitors

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95TH ANNUAL CONVENTION

History of Proton Pump Inhibitors

- PPIs were first released in 1989
  - Omeprazole followed by lansoprazole, rabeprazole, esomeprazole, pantoprazole and dexlansoprazole
- OCT use was first approved in 2003
  - Prilosec, Prevacid, Nexium
- Class demonstrated substantial efficacy over H2 receptor antagonists, excellent tolerability, minimal short term side effects and minimal drug interactions
- Current use
  - One of the most commonly prescribed medications in primary care
  - Commonly used without physician advise or prescription

Pharmacology

- Parietal Cells
  - Located in the gastric glands in the body and fundus of the stomach
  - Activated by stimuli
    - Acetylcholine
    - Histamine
    - Gastrin
  - Acid production
    - Acid released at the Hydrogen Potassium ATPase pump

- PPIs are absorbed in the proximal small bowel
  - Short half life of 1-2 hours
  - Lipophilic weak base crosses membrane of the parietal cell
  - Passes into the parietal cell canaliculus
  - In Acidic environment of canaliculus
    - Molecule become protonated
    - Activated sulphenamide form of drug
    - Binds covalently with the H+/K+ ATPase enzymes
    - Irreversible inhibition of the proton pump
    - Cell can activate other proton pumps or build new ones

Supports dosing 30 minutes before meals
Efficacy and Benefit

- Healing of reflux is superior to H2RA (omeprazole vs. ranitidine)
- Decreased risk of relapse in maintenance of GERD
- Effective in patients with reflux which is refractory to H2RA
- Superior healing of erosive esophagitis, both efficacy and rate of healing
- Superior healing for gastric and duodenal ulcers
- Significantly reduce the risk of re-bleeding or surgery in patients with peptic ulcer bleeding


FDA Indications

- Healing of erosive esophagitis
- Maintenance of healed erosive esophagitis
- Treatment of gastroesophageal reflux disease
- Risk reduction of gastric ulcer associated with NSAID use
- Helicobacter pylori eradication to reduce the risk of duodenum ulcer recurrence
- Pathological hypersecretory conditions (ZE syndrome)
- Short term treatment or maintenance of duodenal and gastric ulcers

- Dose and duration are different based on indications
  - GERD 14 days repeat at four month intervals
  - ZE life long

Centers for Medicare & Medicaid Services. Proton Pump Inhibitors use in adults October 2015
Trends....where are we going?

- Population study in Finland 1987-1999
  - Elective surgery and parietal cell vagotomy have become nearly obsolete
  - Increase in emergency surgery from 5.2 to 7.0 operations per 10(5)
  - Hospital admission rate increased by 79% and mortality rate increased 31%
    - Changes driven by bleeding gastric ulcers in elderly women

  - Decreased admissions for peptic ulcer disease in younger patients
  - H. pylori treatment
  - Substantial increase in admissions for both men and women age >75
  - Medication exposure
    - ASA 75mg increased 460%
    - Oral anticoagulants increased by 200%
    - NSAIDS increased by 13%

Challenges for the Clinician

- Epidemiological studies suggest increasing disease burden of acid peptic disease
  - Demographic shift for older age
  - Polypharmacy (NSAIDS, anticoagulants, ASA, SSRI)
  - Co-morbid conditions (obesity, OSA, renal failure, COPD)
  - Wide availability in the OTC market
- Observational studies have demonstrated positive associations
  - Osteoporosis
  - Vitamin and mineral deficiency
  - Chronic kidney disease
  - Myocardial Infarction
  - Stroke
  - Dementia
- Greater scrutiny of the drug class
  - Reluctance of clinicians to prescribe and patients to consume the medication


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Achlorhydria and Hypergastrinemia

- Animal studies in mice with high dose omeprazole
  - Profound achlorhydria
  - Sustained hormonal stimulation with gastrin
  - Development of carcinoid tumors of enterochromaffin-like cells

- Never seen in humans
  - Review of 10,000 patients on long term omeprazole showed no carcinoid tumors
  - Level of achlorhydria is NOT complete and is similar to that of selective proximal vagotomy

Achlorhydria and Hypergastrinemia

- Changes seen in humans
  - Rise in mean serum gastrin levels (110 to 200.2 ng/L)
  - Moderate initial increase in the enterochromaffin-like cell density over the first three years
  - Development of fundic gland polyps
    - Parietal cell hyperplasia with parietal cell protrusion
    - Due to acid suppression and resulting elevated gastrin levels
    - Associated with duration of use (>5 years OR 3.8, 95% CI 2.2-6.7)
  - Dysplasia and cancer risk determined to be negligible

- Calcium
  - 2010/2011 FDA released a letter warning of increased fracture risk for patients on high dose or long-term PPI use
  - Mechanism of calcium depletion (unproven)
    - An acidic environment may aid in the dissociation of calcium from the food bolus
    - Decreased absorption may cause increased bone resorption
  - Review of 14 observational studies (1980-Feb 2011)
    - Eight studies showed association with hip fracture
    - Five studies showed association with spine fracture
    - Three studies showed reduction in fracture risk after discontinuation of PPI

Jalving M, Koornstra JJ, Wesseling J et al. Increased risk of fundic gland polyps during long-term proton pump inhibitor therapy. Alimentary Pharm and Therap 2006 Nov;24(9) 1341-1348

Insonga, K. The effect of proton pump inhibiting drugs on mineral metabolism. Am J Gastroenterol 104 (Suppl. 2) S2-S4
Calcium Cause of Fracture Risk

- Bone Mineral Density (BMD)
  - Decreased BMD in osteoporosis is associated with fracture risk
  - Canadian population study of 8,340 patients
    - Decreased BMD in the PPI group on presentation
    - No evidence of accelerated bone loss in the PPI group over 10 years
    - Previous study with same group using a different Canadian data base showed no difference in BMD at baseline or follow up.

- Bone structure and strength
  - Evaluation for unknown factor in PPI exposed patients
  - Three dimensional quantitative computed tomography
  - Buckling ratio
  - In 104 patients there was no difference in bone structure or strength


Calcium Recommendations

- Currently there are no guidelines for screening, monitoring, or supplementation of calcium in patients on long term PPI therapy
- FDA reconfirmed the safety of OTC PPIs when used as directed
Vitamin B12

- Essential nutrient acquired from animal derived food (meat, eggs, dairy)
- Absorption
  - Pepsin is activated from pepsinogen in an acidic environment
  - Pepsin cleaves vitamin B12 from the food source
  - In an achlorhydric environment B12 may not be cleaved from the food source to bind R protein and would thus be degraded by pancreatic enzymes
- Data
  - Limited research in the form of case reports and cross-sectional observational trials

Vitamin B12 Recommendations

- There is insufficient data to recommend screening or supplementation in patients who are on long term PPIs
- Monitoring or screening may be reasonable in high risk groups
  - Elderly
  - Nursing home residents
  - Malnourished
  - People on a strict vegan diet
Vitamin C

- Water soluble molecule not synthesized by the body
- PPI therapy decreases vitamin C concentrations
  - Decreases biologically active compound, ascorbic acid
- Possible clinical significance
  - Ascorbic acid prevents conversion of nitrate to N-nitroso compounds
- Currently there are no guidelines for monitoring or replacement

Iron

- Dietary iron is present in two forms
  - Nonheme (66%)
  - Heme (32%)
- Acidic environment of stomach and proximal duodenum
  - Results in dissociation of nonheme iron from food
  - Dissociated nonheme becomes soluble iron salts
  - Forms complexes with sugars and amines to facilitate absorption
- Data
  - Case reports: impaired absorption in patients on PPI who fail to respond to replacement
  - Retrospective cohort of 98 patients demonstrated an OR of 5.03 (95% CI 1.71-14.78) for decrease in hemoglobin by 1 gram in patients on PPI
- Guidelines
  - No guidelines to monitoring or replacement
  - Index or suspicion is reasonable in high risk patients
Hypomagnesemia

- Rare with unknown mechanism
- Presentation
  - Concomitant hypokalemia, hypocalcemia, severe ataxia, paresthesia, seizures and confusion
  - Requires hospitalization
  - Median age 70
  - Associated with long term use
    - 5 years 61%
    - 10 years 29%
  - 25% do not respond to magnesium therapy
    - PPI MUST be discontinued
    - Switching to another PPI will result in recurrent symptoms
- Screening
  - Patients presenting with or history of arrhythmia on PPI therapy

Enteric infections

- Role of gastric acid
  - Highly acidic environment is effective at eliminating most potential enteric pathogens
- Common enteric pathogens
  - Salmonella, E. coli, Shigella, Campylobacter
- Clostridium difficile
  - Spore forming bacterium
  - Typically more resistant to environmental insults including heat, cold, desiccation, and acid
Common enteric pathogens
Salmonella, E coli, Shigella, Campylobacter

- Systematic review
  - Six papers with total of 11,280 patients with enteric infections
    - Any acid suppression OR 2.55 (95% CI 1.53-4.26)
    - H2RA OR 2.03 (95% CI 1.05-3.92)
    - PPI therapy OR 3.33 (95% CI 1.84-6.02)
  - Risk of H2RA vs PPI trended for increased safety but was not statistically significant
- Special attention for high risk populations
  - Those traveling to high risk areas
  - Antibiotic exposure
  - Malnourished
  - Elderly
  - Immunosuppression

Infection with C. difficile

- Analysis of 12 papers involving 2,984 patients with initial C. difficile infection
  - Risk on any acid suppression OR 1.94 (95% CI 1.37-2.75)
  - Risk on H2RA OR 1.40 (95% CI 0.85-2.29)
  - Risk on PPI OR 1.96 (95% CI 1.28-3.00)

Infection with C. difficile

- Recurrent C. difficile infection occurs in 20% of infection
  - Significant cost ($11,000) with high risk of morbidity, mortality, and subsequent infection
- Cohort study of 754 patients with recurrent C. difficile
  - Risk factors for recurrence
    - Age >75, continuous PPI use, length of hospital stay, vancomycin as initial treatment regimen
    - OR for recurrent antibiotic exposure 1.30 (95% CI 0.9-1.7)
    - OR for continuous PPI use 1.5 (95% CI 1.1-2.0)
  - Less than half of the patients studies had an evidence based indication for continuous PPI use
    - Only three were taken off of therapy with the goal of reducing recurrent C. difficile infection risk

McDonald E, Miligan J, Frenette C et al. Continuous proton pump therapy and the associated risk of recurrent Clostridium difficile infection. JAMA Intern Med. 2015; 175 (5): 784-791

Kidney Disease

- Scope of disease
  - Chronic kidney disease (CKD) affects approximately 13.6% of the US population
  - High costs
  - Increased risk of cardiac events and death
- Prevalence of CKD is increasing
  - Diabetes/Hypertension
  - Polypharmacy and medication exposure may be a risk as well
  - No proposed mechanism to explain association of PPI with risk of CKD
Incident and Progression of CKD

- VA cohort study of patients followed over 5 years
  - 173,321 new PPI prescriptions
  - 20,270 new H2RA prescriptions
  - Risk of new CKD diagnosis was OR 1.28 (95% CI 1.23-1.34) for PPI vs H2RA
  - Risk of doubling of creatinine was OR 1.53 (95% CI 1.42-1.65)
  - Graded association based on duration of exposure


Incident and Progression of CKD

- Atherosclerosis risk in communities (ARIC) database of 10,482 patients
  - Patients on PPI were more likely to be white, obese, and hypertensive
  - Incident CKD was 14.2/1000 person years for PPI group vs 10.7/1000 person years for non-PPI
  - OR for CKD was 1.5 (95% CI 1.14-1.96) in PPI group
  - 10 year absolute risk was 15.6% in the PPI group vs 13.9 in the non-PPI group
  - Absolute risk difference of 1.7
  - No increased risk of CKD was seen in the H2RA group

Dementia

- Progressive cognitive decline resulting in loss of functional independence
  - Incidence expected to increase from 35 million to 84 million by 2040
  - Global cost of dementia estimated at 604 Billion
  - Prevention is essential
- Proposed mechanisms of association
  - B12 deficiency
  - Increased beta amyloid in the brain (mice studies)
  - Modulation of beta amyloid degradation by PPIs (mice studies)

Dementia

- 73,679 patients analyzed from a German insurance data base
  - Patients all >75 years old at enrollment
  - Regular PPI use was associated with dementia OR 1.44 (95% CI 1.36-1.52)
  - Dementia is a multifactorial disease
    - Other factors identified: depression, stroke, female, diabetes, polypharmacy
    - Anticholinergic drugs were an independent risk factor OR 1.8 (95% CI 1.65-1.96)
    - Study did not differentiate different etiologies of dementia
  - Patients with intermittent PPI use had an OR of 1.16 (95% CI 1.13-1.19)
    - Suggests basis for dose reduction

Myocardial Infarction

- Multiple observational studies have associated MI with both GERD and PPI use
- Mechanism of association is unknown
  - Reflux patients have greater number of comorbidities
    - Hypertension, diabetes, hyperlipidemia, alcohol related illness, stroke, obesity, COPD, asthma, depression, and anxiety
  - PPI directly result in endothelial dysfunction
- Mouse study
  - PPIs inhibit enzymatic activity of dimethylarginine dimethylaminohydrolase which is responsible for the clearance of asymmetric dimethylarginine which is an endogenous molecule known to inhibit the activity of nitric oxide synthase
- Impairment of NOS can increase vascular resistance and promote inflammation and thrombosis


Cardiac Events
Long-term PPI use

- Large population based Chinese study
  - GERD patients were at increased risk for CAD OR 1.49 (95% CI 1.34-1.66)
  - PPI less than one year risk of CAD OR 1.56 (95% CI 1.39-1.74)
  - PPI greater than one year risk of CAD OR 1.67 (95% CI 1.34-2.08)
  - Demonstrates GERD to be an independent risk factor
  - Results confirmed in other large cohort study
  - Determined a number needed to harm NNH of 4,357
- Stanford study used data mining to review 16M clinical documents from 2.9M individuals
  - PPI use associated with an OR of 1.16 (95% CI 1.09-1.24)
  - No increased risk seen with H2RA
  - Researchers hypothesized that if data mining were available in 2000, association could be found “pharmacovigilance algorithms”

Cardiac Events

Short-term PPI use

- Canadian population based study
  - Identified 5,550 hospital admissions for acute MI
  - Patients had been started on PPI within 12 weeks of admission
    - Increased risk of MI with PPI exposure 1.8 (95% CI 1.7-1.9)
    - Study also showed increased risk with H2RA as well as benzodiazepines both of which have previously been considered not to be a risk for AMI
- Swedish study evaluated patients admitted with AMI
  - Started on PPI within three months
    - OR was 1.36 (95% CI 0.82-2.25)
      - Results not significant
      - Authors suggest that observed increased risk may be result of cardiac symptoms misdiagnosed as dyspepsia
- Recent PPI administration appears poorly associated with AMI


Ischemic Stroke

- Endothelial dysfunction suggested in patients with acute MI by also increase the risk of ischemic stroke
- Presented in abstract form American Heart Association meeting 11/2016
  - Nationwide Danish health registry
    - Identified 244,679 patients underwent gastroscopy and age >30
    - Forty percent of patients had filled a prescription for a PPI
      - PPI patients were older and had an increased risk of atrial fibrillation
    - Risk of first time ischemic stroke was 1.21 (95% CI 1.16-1.27)
    - No increased risk was seen with H2RA
    - No increased risk for: omeprazole 20mg, lansoprazole 15mg, esomeprazole 20mg
      - Risk was associated with higher dose formulations

“Popular heartburn medications linked to higher risk of stroke”

“Most serious warning yet”

- Immediately following oral presentation of abstract CNN released article with the above headline
  - The article has not been published in a peer reviewed journal
  - Population based cohort studies do not demonstrate causality
  - Results have not been replicated in other studies
  - Author is not a physician or hold a degree in statistics
  - Is this responsible?
  - Is this #FakeNews?

- Ben Tinker is a supervising producer for CNN Health. He primarily works with CNN Chief Medical Correspondent, Dr. Sanjay Gupta, telling the most compelling and newsworthy health and wellness stories. Tinker produced CNN’s weekly health and wellness show, Sanjay Gupta MD, providing consumers driven news and advice for living a longer, happier, healthier life. Prior to joining CNN Health, Tinker worked in New York for CNNMoney, where he produced Your Bottom Line, the network’s weekly personal finance program. He holds dual degrees in journalism and psychology from New York University.

Media Based Sensationalism

- Role of the physician
  - Understand the risk, benefits, alternatives of proposed treatment or therapy
  - Understand the strength and weakness of current research and data
  - Advocate for patient safety
  - Engage in shared decision making with our patients with the goal of good outcomes
  - The discussion should be shaped and guided by physicians advocating for the best interest of their patients, not the media
Mitigation of Risk
Practicing Evidence Based Medicine and Limiting Exposure

- Risk stratify patients based on pre-existing comorbidities
  - Elderly, frail, malnourished
  - Hospitalized, antibiotic exposed, renal failure
  - Diabetic, hypertensive
- Over half of all patients on PPIs do not have an evidence based indication for the drug
  - Review medications lists frequently especially at transition of care such as hospital discharge
  - Consider trial of H2RA or antacids
  - Discontinue PPI whenever possible

Mitigation of Risk
Practicing Evidence Based Medicine and Limiting Exposure

- Some patients are on a PPI for correct indication or do not tolerate discontinuation
  - Dose reduction has been shown to decrease risk of multiple disease associations
  - Intermittent dosing is tolerated in some patients
- High dose PPI not responding to therapy
  - Consider other diagnosis
  - Hypersensitive esophagus or functional heartburn
Lifestyle Modification

- The most common indication for PPIs is GERD
  - GERD symptoms are often driven by lifestyle issues
    - Dietary modification
    - Smoking cessation
    - Weight loss

- Dietary modification is free and low risk
  - Compliance has been shown to be low even for severely symptomatic patients
  - Requires frequent re-education and encouragement

Kubo A, Block G, Quesenberry C et al. Dietary guideline adherence for gastroesophageal reflux disease. BMC Gastroenterol. 2014; 14: 144

Smoking and Exercise

- Swedish study monitored patients with multiple gastrointestinal symptoms over an 18 year period
  - The OR was 3.5 for improvement of reflux with exercise
  - The OR was 3.45 for improvement of reflux with decreased smoking

- These interventions are free, no risk and will also reduce other comorbid diseases discussed in this talk

Obesity

- The incidence of obesity continues to increase in the US
  - In a study of patients on double dose PPI obesity was associated with persistent acid opposed to another diagnosis such as hypersensitive esophagus
  - A clear association with increased reflux episodes and increased BMI was demonstrated using impedance pH monitoring
  - These studies demonstrate a clear association between obesity and reflux disease
  - Western diet high in meat and processed foods is fueling an epidemic of disease which fosters a dependence on pharmacology (opinion)


Weight loss

- Study evaluating the effect of weight loss on 101 patients with GERD symptoms
  - Group A: personalized supervised hypocaloric diet and aerobic exercise program
  - Group B: given a standard of care diet
  - Both groups were placed on a PPI at enrollment

  Results
  - Group A
    - BMI decreased from 30.3 to 25.7
    - PPI was discontinued in 27/50
    - PPI was halved in 16/50
    - PPI continued at full dose in 7/50
  - Group B
    - No weight loss was seen
    - PPI was halved in 22/51
    - PPI was continued at full dose in 29/51
    - NO patients discontinued PPI therapy

Physical Medicine/OMT

- Study of 38 patients randomized to OMT of the diaphragmatic muscle vs sham technique
  - Esophageal manometry evaluated before and after treatment
  - Some parameters of the lower esophageal sphincter pressure improved after treatment
- Study on a single patient demonstrated improved GERD symptoms score over a series of four treatments


Physical Medicine/OMT

- Abdominal breathing exercise
  - Prospective randomized controlled study
  - At nine months patients who were taught breathing exercises
    - Sustained results
    - Improved quality of life scores
    - Decreased PPI use
  - While it may be difficult in a busy clinical practice, a holistic approach to reflux management would include physical medicine with the goal of reducing pharmacological therapy

Final Thought

- Proton pump inhibitors when used correctly are highly efficacious medications for the management of multiple acid peptic disorders.
- The art and science of osteopathic medicine requires that we:
  - Recognize patients at high risk for serious side effects of PPIs.
  - Recognize that some patients benefit greatly from PPIs.
  - Practice evidence-based guidelines and eliminate superfluous medications.
  - Reduce dosing amount and frequency whenever possible.
  - Use lifestyle modifications to eliminate medication dependency.

Thank-you for your attention.