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Pharmacy Pearls

June 2016

UR MEDICINE

ACCOUNTABLE HEALTH PARTNERS

Case Presentation

A 72 year old woman with HTN and osteoporosis presents for an annual wellness visit. Her most recent labs were remarkable for a GFR of 62, K 3.0, and Ca 8.1 which have been persistently low. Current meds include chlorthalidone 25 mg daily, omeprazole 40 mg daily, and alendronate 70 mg weekly. She begins the visit by telling you she tried to stop omeprazole because she heard it causes kidney failure, infections, and dementia but had to restart it because her symptoms returned after 2 days. How do you proceed?

What the Literature Says

- Up to 70% of patients receiving PPIs have no true indication for therapy
- Duration of PPI therapy frequently extends beyond the recommended 4 - 8 weeks for GERD & short-term treatment of PUD
- *"A large number of patients are taking PPIs for no clear reason - often remote symptoms of dyspepsia or 'heartburn' that have since resolved."* – JAMA Internal Med Feb 2016
- Though interpatient variability may exist, no PPI has definitively shown superior efficacy & comparative studies seldom used pharmacologically equivalent doses

Candidates for Cessation

- Asymptomatic patients with GERD or remote history of PUD without other indications for a PPI who have been maintained on long-term therapy.
- Those using PPIs on an as-needed basis. PPIs require at least 5 days of consecutive use to fully block parietal cells. Patients with intermittent symptoms may find better relief with an H2 blocker or antacid.

Proton Pump Inhibitors: Evidence Behind the Headlines

PPIs have consistently been among the most frequently prescribed medication classes in the United States. For decades, the medical community has been comfortable maintaining patients on these agents as they were believed to have a relatively benign safety profile. However, a growing body of literature has raised a number of safety concerns, particularly around long-term use. While the validity of these associations is variable, the overall compilation of evidence is suggesting these agents are not without risk. Increased attention in the general media and presents an opportunity to re-evaluate and discuss the necessity for continued therapy.

Addressing PPI Safety Concerns

- A compilation of observational trials suggest a small, but clinically significant, risk of renal damage including CKD, AKI, and AIN associated with PPIs. The results of the most recent study found treating 30 – 58 patients for 10 years may be expected to result in one additional case of CKD.
- The evidence suggesting an association with dementia is less compelling. These findings were based on prescriptions and medical claims data and the authors did not adjust for use of other medications with well-established risks of cognitive impairment.
- Hypomagnesemia is an under recognized adverse effects of chronic PPI therapy and often presents as refractory hypokalemia or hypocalcemia. Approximately 25% of cases are refractory to supplementation and resolve only with discontinuation.
- Long-term, high dose therapy has been associated with a slight increase in fracture risk. The results of a large cohort found treating 1960 patients for 8 years would result in one additional fracture.
- Patients receiving PPIs have been found to have 1.4 - 2.75 times the risk of *C.diff* infections relative to patients not receiving therapy. The FDA recommends considering *C.diff* as a potential cause in PPI users with persistent diarrhea.

Barriers to Successful Discontinuation

Patients who attempt to abruptly discontinue long-term PPI therapy often develop **rebound hypersecretion** thus reinforcing the need for continued used. This can be mitigated, though not necessarily eliminated, by using a gentle taper

- Reduce dose by 50% every 1 - 2 weeks until patient is at lowest available dose. Then reduce dose to every other day for 2 weeks, then stop.
- Inform patients that rebound hypersecretion may occur but should improve with time and advise use of an H2 blockers and/or antacids to manage symptoms.
- Encourage lifestyle modifications and use of H2 blockers and/or antacids for intermittent symptoms.
- If symptoms persist ≥3 months: consider 8 week retrial of PPI and/or EGD

Proposed Associations with PPI Use

	Summary Evidence
Renal Function Decline 1. Lazarus et al. JAMA Int Med Feb 2016 2. Antoniou et al. CMAJ Open April 2015	• NIH-funded cohort trial evaluating risk of new onset CKD in patients receiving PPIs relative to H2 blockers and no antisecretory therapy. Included>27,000 adults ages 45 - 64 and a baseline GFR >60 mg from two US databases.[1] • After adjusting for multiple factors including age, DM, HTN, diuretic and NSAID use, patients receiving PPIs were 20 - 50% more likely to develop CKD relative to patients receiving no antisecretory therapy. • The 10-year absolute risk difference of developing CKD on a PPI was estimated as 1.7% - 3.3%. (NNH: 30 - 58 patients treated for 10 years). • No significant increase in CKD was noted among patients receiving H2 blockers. • Consistent with previous literature, this trial showed an increased risk of AKI with PPI use.[2]
Dementia 3. Gomm et al. JAMA Neurology April 2016 4. Haenisch et al. Eur Arch Psych Clin Neurosci Aug 2015	• Review of German claims database. Included patients age ≥75 years with no prior diagnostic claims for dementia and regular prescription claims for a PPI during an 18 month period.[3] • After adjusting for age, gender, stroke, depression, and polypharmacy, frequent claims for a PPI was associated with a 44% increase risk of claims for dementia. While the use of claims data adds level of uncertainty, the results were consistent with the authors' previous findings.[4] • In a post-hoc analysis, claims for highly anticholinergic medications were associated with an 85% increased risk of dementia and no-adjustments were made for multiple other medication classes which could precipitate cognitive decline.
Hypomagnesemia 5. FDA Drug Safety Communication: http://www.fda.gov/Drugs/DrugSafety/ucm245011.htm	• FDA Drug Safety Communication, March 2011 based on cases reported to the organization as well as published reports.[5] • Time to onset ranged from 3 - 12 months, with most cases being reported after at least 1 year of use. There is an additive risk with concurrent use of thiazide or loop diuretics. • After discontinuation, median time to resolution is 7 days. Upon rechallenge, median time to recurrence is 2 weeks. • About 25% of cases are refractory to supplementation and require cessation of therapy. Case reports suggest effect is maintained despite substitution to another PPI.
Fractures 6. FDA Drug Safety Communication: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm213206.htm 7. Khalili et al. BMJ Jan 2012	• FDA Drug Safety Communication May 2010 based on multiple observational trials.[6] • Risk appears to be dose and duration dependent, begins to emerge after at least 1 year of use, and is believed to be greater among patients with other risk factors including age >50 years and smoking. • One of the largest trials reported an absolute risk difference of 0.051% (NNH 1960 patients treated for 8 years).[7]
C. Diff 8. FDA Drug Safety Communication: http://www.fda.gov/Drugs/DrugSafety/ucm290510.htm 9. Howell et al. Arch Int Med May 2010	• FDA Drug Safety Communication Feb 2012 based on multiple observational trials and meta-analyses.[8] • In trials, the magnitude of risk has varied (OR 1.4 - 2.75) and there is suggestion of higher risk with twice-daily therapy as well as additive risk among patients receiving antibiotics.[9]
Pneumonia 10. Eom et al. CMAJ Feb 2011 11. Filion et al. Gut April 2014	• Observational studies have yielded mixed results and interpretation is limited by the high potential for confounding. • One large meta-analysis found patients receiving PPIs or H2 blockers had a slight increase risk of pneumonia relative to those with no antisecretory therapy (OR 1.27 and 1.22, respectively).[10] • A second meta-analysis looking exclusively at PPIs for prophylaxis among new-start NSAID users found no association with PPIs or H2 blockers.[11]
B12 & Iron Malabsorption 12. Lam et al. JAMA Dec 2013	• PPIs have been shown to cause a slight reduction in B12 absorption and have been associated with an increased risk of deficiency. It is reasonable to consider PPIs as a potential cause of B12 deficiency in patient receiving long-term therapy[12] • The clinical relevance of reduced iron absorption is questionable and may be most applicable to patient receiving oral iron supplements.