WHAT’S NEW IN GERD
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Side Effects of PPIs Circa 2012
Potential side effects associated with PPI therapy include headache, diarrhea and dyspepsia in less than 2% of users. Switching to another PPI can be considered in these patients. Other much discussed associations are vitamin and mineral deficiencies, infections such as pneumonia and C. difficile, long bone fractures and cardiovascular events in patients using concomitant clopidogrel therapy. The FDA issued warnings regarding the potential for wrist, hip and spine fractures among PPI users in 2010 and warnings regarding potential for adverse cardiovascular events among clopidogrel users taking PPI therapy in 2009.

Two recent reviews demonstrated evidence that PPI therapy reduces the absorption of protein-bound vitamin B12, but not enough clinical evidence to document B12 deficiency in chronic PPI users or the need to check B12 levels. Recent studies have suggested that in elderly institutionalized long-term PPI users, B12 deficiency is more likely to develop and should be considered.

Gastric acid is needed to allow absorption of non-heme iron and also enhances iron salt dissociation from ingested food. Iron deficiency anemia has been reported in patients with atrophic gastritis, gastric resection, or vagotomy. To date, no data are available demonstrating the development of iron deficiency anemia in normal subjects on PPI therapy.

By their effects in increasing gastric pH levels, PPIs may encourage growth of gut microflora and increase susceptibility to organisms including Salmonella, Campylobacter jejuni, Escherichia coli, Clostridium difficile, Vibrio cholerae, and Listeria. An increased susceptibility in PPI users for Salmonella infections, Campylobacter and Clostridium difficile infections was found in a systematic review. Current recommendations are to carefully evaluate the need for PPI therapy in hospitalized patients who need intravenous antibiotics.

An increased risk for community-acquired pneumonia is difficult to demonstrate in association with PPI therapy. A meta-analysis showed that the overall risk of pneumonia was higher among people using proton pump inhibitors. If only randomized controlled trial data was analyzed, H2RAs were associated with an elevated risk of hospital-acquired pneumonia not PPIs. A more recent meta-analysis did find an increased risk of pneumonia associated with PPI usage, but the results were confounded by methodologic issues. Paradoxically, short duration of use was associated with an increased odds of community-acquired pneumonia but chronic use was not. No definite recommendation can be given.

Clinical studies in patients taking PPI therapy have shown mixed results regarding fracture. The study with the longest clinical follow-up matched cases with abnormal bone mineral density (osteoporosis) at the hip or lumbar vertebrae (T-score < or + = -2.5) to controls with normal bone mineral density (T-score > or – 1.0). PPI use was not associated with having osteoporosis at either the hip or the lumbar spine for PPI use >1500 doses over the previous 5 years. In the longitudinal study, no significant decrease was observed in bone mineral density at either site attributable to PPI use. This suggests the association between PPI use and hip fracture was probably related to factors independent of osteoporosis.

In a recent meta-analysis, the pooled odds ratio (OR) for fracture was 1.29 (95% confidence interval [CI], 1.18-1.41) with PPIs and 1.10 (95% CI, 0.99-1.23) with H2RA use compared to non-users. Another study showed that the hip fracture risk among PPI users was seen only in persons with at least one other fracture risk factor. A meta-analysis covering 1,521,062 patients showed significant risk for spine fractures (OR 1.50, 95% CI 1.32-1.72, p<0.001). For hip fractures, there was an increased risk of fractures with PPIs (OR 1.23, 95% CI 1.11-1.36, p<0.001). Overall an OR of 1.20 is seen for PPIs, and OR of 1.08 (95% CI 1.00-1.18, p=0.06) for H2RAs. Again, short duration of PPI use may be associated with increased risk of developing hip fracture (OR=1.24; 95% CI=1.19-1.28), however, not in long term PPI users (OR=1.30; 95% CI=0.98-1.70).

In 2009, the FDA issued a warning regarding potential for increased adverse cardiovascular events in concomitant users of PPI and clopidogrel therapy, particularly among users of omeprazole, lansoprazole, and esomeprazole. The concern arises from the fact that the antiplatelet activity of clopidogrel requires activation by CYP 2C19, the same pathway required for metabolism of some PPIs. In vitro studies have been conflicting. The newest data suggests that dexlansoprazole does not inhibit platelets in vitro to the same degree as the three former PPIs. Pantoprazole appears to have less inhibition as well. A recent meta-analysis (27 studies) focused on primary (myocardial infarction, stroke, stent occlusion or death) and secondary outcomes (re-hospitalization for cardiac symptoms or revascularization procedures). Outcomes from the two ran-
domized controlled trials did not show an increased risk for adverse outcomes. Meta-analysis of primary and secondary outcomes showed an increased risk difference for all studies. Essentially, the risk of adverse cardiac outcomes was 0% based on data from well controlled randomized trials. Data from retrospective studies and the addition of probable vascular events slightly but significantly increased the risk estimates, likely due to lack of adjustment for potential confounders.

Surgical Treatment

Potential non-medical options for GERD include laparoscopic fundoplication, bariatric surgery in the obese, the newest technique Linx®, and transoral intraluminal fundoplication (TIF). Ideal candidates for surgery are patients who have typical symptoms of heartburn and/or acid regurgitation, patients who no longer desire to take medical therapy, or have side effects to PPIs. Surgery can be considered for patients with large hiatal hernias, persistent non-acid reflux despite PPI therapy, or persistent symptoms with documented GERD. The highest surgical responses are seen in patients with heartburn (and/or regurgitation), a response to a PPI and an abnormal pH test. In patients with typical GERD who undergo fundoplication, long term remission rates can be expected to be comparable and in some cases statistically superior to medical therapy. In a long term follow-up of a VA cooperative randomized controlled trial comparing medical to surgical therapy for GERD, 92% of the patients in the medical arm were using medical therapy compared to 62% of the surgical cohort at 10 years. In a 12-year long term follow-up of patients randomized to fundoplication compared to omeprazole, 53% of the surgery cohort were in remission compared to 45% of the medically treated patients (p=0.02), although symptoms of gas bloat syndrome remained more common in the surgical cohort.

Patients with extra-esophageal symptoms appear to have decreased response to fundoplication. There is no experience with Linx® in these patients or good studies with TIF. In a Cochrane review, medical or surgical antireflux therapy was not associated with improvement in pulmonary function, asthma symptoms, or use of medication. While surgery can be effective in carefully selected patients with extraesophageal or atypical symptoms, response rates are lower than in patients with heartburn. It is particularly important to carefully evaluate patients with so-called laryngopharyngeal reflux before considering fundoplication. A response to PPI is critical. In the absence of a PPI response, surgery is not likely unlike to be effective even with an abnormal pH study.

A review assessed the efficacy for surgical therapies for obesity on gastroesophageal reflux. GERD symptoms improved after Roux-en-Y bypass surgery. Roux-en-Y was more effective than gastric banding in one study. Of the eight studies assessing vertical banded gastroplasty, one study showed improvement in GERD symptoms, but the other studies demonstrated no change or an increase in reflux symptoms.

Endoscopic therapies for GERD have been developed but have not demonstrated long-term efficacy. These therapies included radiofrequency ablation to the lower esophageal sphincter, silicone injection into the lower esophageal sphincter and endoscopic suturing of the LES. None of these therapies demonstrated substantial improvement in esophageal pH levels or ability for patients to stop antireflux therapy to recommend them.

SELECTED REFERENCES


