Adverse Effects of Long-Term Proton Pump Inhibitor Use: A Review for the Otolaryngologist

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Objective. Proton pump inhibitors (PPIs) are the mainstay of current medical management for laryngopharyngeal reflux, and treatment often involves long-term use of this class of medications. The long-term adverse effects of PPI use have not been studied extensively, but several analyses have demonstrated epidemiological links between PPI use and adverse outcomes. These include altered mineral and vitamin absorption, orthopedic injury, acute coronary syndromes (ACS), and infectious risks.

Study Design. A PubMed search was performed for subject headings, including PPIs and adverse outcomes. Relevant studies were included in this review. Studies were compiled, reviewed, and compared in a narrative form.

Results. Several epidemiological links between PPI use and metabolic, infectious, cardiac, and orthopedic adverse outcomes were found. No definite causal effects were identified.

Conclusion. Given these epidemiological patterns, we recommend that the clinician be aware of these possible unintended consequences. In addition, we recommend consideration of dual-energy X-ray absorptiometry (DEXA) bone density scans in at-risk patients who have not been previously tested. We recommend consideration of vitamin B₁₂ and iron levels in selected patients who are at high risk. We also recommend close communication with our cardiology colleagues, as we attempt to ascertain the relationship between clopidogrel and PPI use. We recommend caution in the use of omeprazole in patients undergoing active treatment for ACS. Finally, we recommend consideration of *Helicobacter pylori* or serum gastrin level testing in patients with known risk factors for gastric carcinoma.

Key Words: Reflux–Laryngopharyngeal reflux–Proton pump inhibitor–Antacid–Complications of proton pump inhibitor.

INTRODUCTION

Laryngopharyngeal reflux (LPR) has been well described in the literature as a causative agent in a multitude of otolaryngologic complaints, including hoarseness, globus pharyngeus, dysphagia, sore throat, chronic cough, and other airway disorders. It has been estimated that roughly 10% of patients presenting to an otolaryngologist have an upper aerodigestive tract complaint related to reflux. Although gastroesophageal reflux disease (GERD) and LPR have been clearly shown to have different disease patterns, they are often treated with a similar basic approach. The traditional approach to GERD treatment involves a combination of dietary/lifestyle modifications, acid suppression (via antacids, histamine 2 receptor-antagonists [H₂RAs], and/or proton pump inhibitors [PPIs]). Once-daily dosing of PPIs may be sufficient to treat GERD but fails to treat LPR in as many as 50% of LPR patients. As opposed to the physiological barriers of the esophagus, the tissues of the larynx and pharynx have little protection against gastric acid and pepsin exposure. This often necessitates around-the-clock aggressive PPI therapy for treatment of LPR. A 2002 position statement by the American Academy of Otolaryngology/Head and Neck Surgery recommended twice-daily dosing of PPIs for a minimum treatment period of 6 months for LPR. One dilemma is that PPIs were initially developed and marketed primarily for the GERD patient. Once Koufman and others brought LPR to our attention, this class of drugs was an obvious choice, given their high efficacy and long duration of action. Unfortunately, the long-term treatment and high dosing that usually accompanies LPR treatment with PPIs has not been extensively addressed, especially in the otolaryngology literature. From the gastroenterology, cardiology, and general medicine literature concerning epidemiological patterns associated with long-term PPI treatment emerged and received media attention. These include abnormalities in vitamin and mineral absorption, leading to increased risk factors for osteoporosis and fractures. Other concerning patterns suggest an interference with the function of platelet-inhibiting medications in cardiac patients, increased risk of infection, and possibly even risks of gastric carcinoma. This review article will attempt to bring some of these issues to light in the otolaryngology literature.

OVERVIEW OF PROTON PUMP INHIBITORS

H₂RAs have been suggested as one of the many first-line management options for mild LPR (those with symptoms that are noticeable but do not impair the patient’s daily life significantly). Although H₂RAs have been shown to effectively inhibit gastric acid production, they have unfortunately been shown to have two major limitations. This class of drugs has a relatively short duration of action, suppressing gastric acid for only 4–8 hours. Patients treated with this class of drugs have also been shown to develop increased tolerance to the drug within several weeks of treatment, decreasing their long-term efficacy.
As a class, PPIs are the most potent inhibitors of gastric acid production.\(^7\) Once absorbed systemically, the reactive species of PPIs irreversibly inhibits the H\(^+\)K\(^-\)ATPase facing the lumen of the secretory parietal cell in the gastric mucosa.\(^8\) Although other acid-suppressing medications have been shown to have decreased efficacy over time, PPI treatment is generally not limited by this, as they affect the final enzyme in the acid production pathway.

In general, PPIs are considered relatively safe when compared with many other prescription drugs. A recent study of the short-term adverse effect reports related to esomeprazole in the United Kingdom included almost 12,000 patients over a period of 8 months (average length of treatment: 26 weeks). During this time, 119 possible adverse effects were reported by the prescribing physician probably or possibly related to the medication. The most common adverse effects were nausea and/or vomiting, diarrhea, dizziness, and headache. There were few reported cases of hypersensitivity reaction, including three cases of angioedema and two cases of anaphylaxis, which were reported as possibly related to the medication.\(^9\) The goals and aims of this study were more geared toward short-term GERD treatment. With a mean treatment of 26 weeks, there were no data examining the possible long-term effects of PPI treatment.

**Proton pump inhibitors and calcium**
PPIs are believed to interfere with calcium absorption secondary to their induction of hypochlorhydria. Although most calcium absorption takes place in the small intestine, most dietary and supplementation forms of calcium must be dissolved and ionized from the food matrix or delivery form in the stomach. This process is facilitated by gastric acid. Calcium carbonate breakdown has been shown to decrease from 96% at a pH of 1 to 23% at a pH of 6.1.\(^10\)

O’Connell et al\(^11\) examined fractional calcium absorption in a small group of women aged 65 years or older. They studied the fractional absorption of radiolabeled calcium in 18 fasting women in a randomized, crossover fashion. When compared with placebo, omeprazole was found to decrease calcium absorption efficiency in elderly women by an average 41%.

In another study, Graziani et al\(^12\) examined the effects of omeprazole in calcium absorption in the short term. After completing a 7-day low-calcium diet, the patients ingested a test meal including 1 g of calcium. In patients taking a placebo, the postprandial calcium level rose significantly. In patients who had ingested omeprazole, there was no significant change in serum calcium levels. This would suggest that physiological alterations in gastric pH might indeed inhibit calcium absorption.

Elderly women are already more prone to osteoporosis, as the body’s ability to absorb calcium decreases with age. This physiological effect, combined with the possible contributions of hypocalcemia related to PPIs, has led to concerns regarding the adverse effects of osteoporosis, primarily hip fractures. One of the body’s physiological responses to decreased calcium absorption is to increase parathyroid hormone production (secondary hyperparathyroidism). This results in increased osteoclastic bone resorption, which would place the already “calcium-hungry” bones with even less structural support.

Hip fractures may be the most significant adverse outcome related to osteoporosis. It is estimated that in excess of 350,000 hip fractures occur in the United States each year. The mortality rate during the first year of life after a hip fracture is 24%. There is also significant comorbidity associated with hip fractures in the elderly, generally leading to a very poor functional status postfracture. Only 60% of those suffering a hip fracture will recover their prefracture walking ability by 6 months.\(^13\) Several recent population-based studies have evaluated hip fracture patients for an epidemiological link between hip fractures and PPI use.

Yang et al\(^14\) conducted a well-designed nested case-control study examining the risk of hip fractures related to the use of PPIs. The adjusted odds ratio (AOR) for hip fracture associated with more than 1 year of PPI use was 1.44. There was an even more impressive risk of hip fracture in patients with a history of long-term, high-dose PPI use (AOR: 2.65, 95% confidence interval (CI): 1.80–3.90; \(P < 0.001\)). The study also demonstrated a positive association with duration of therapy, as the strength of association increased from 1.22 at 1 year to 1.41 at 2 years, 1.54 at 3 years, and 1.59 at 4 years. Finally, the study found a significant difference \((P = 0.04)\) when comparing long-term, PPI therapy-associated risk of hip fracture in men versus women (odds ratio [OR]: 1.78 vs 1.36, respectively). Although this is counterintuitive, it may be secondary to one of the limitations of the study, which was a difficulty capturing the use of calcium supplementation (usually over the counter). One could surmise that many female patients may have been on long-term calcium supplementation that may have had a protective effect.

Although it is certainly impossible to exclude all confounding variables, Yang et al, showed a very convincing epidemiological link between PPI therapy and the risk of hip fractures. Further studies that clearly delineate causality are still needed.

Targownik et al\(^15\) performed a case-control study assessing cases of vertebral, wrist, or hip fractures in patients 50 years or older. They assessed yearly intervals (years 1–7) of exposure to PPI therapy and matched three age and comorbid controls for each case. Specifically, hip fractures were significantly associated with PPI use after 5 or more years of use (OR: 1.62, 95% CI: 1.02–2.58) and steadily increased with each additional year of use. With regard to all three fracture sites, a significant association was only shown in patients with 7 or more years of continuous exposure to PPI (OR: 1.92, 95% CI: 1.16–3.18). Again, causality was not shown, but this suggests an epidemiologic link. However, similar to the article by Yang et al, this study was limited by its ability to control for over-the-counter calcium and vitamin D supplementation.

**Proton pump inhibitors and vitamin B\(_{12}\) and iron**
Because PPIs alter gastric pH, they can theoretically alter absorption of certain nutrients. Dietary vitamin B\(_{12}\) requires both gastric acid and pepsin to initiate the absorption process. Valuck and Ruscin\(^16\) demonstrated a significant association between vitamin B\(_{12}\) deficiency and the use of an H\(_2\) receptor antagonist or PPI for 12 or more months (OR: 4.45, 95% CI:
Absorption of iron may also be altered by PPI use, as ferric iron is reduced to ferrous iron, which is more soluble.

Proton pump inhibitors and *Clostridium difficile*-associated diarrhea

Although nosocomial *Clostridium difficile*-associated diarrhea (CDAD) has been primarily linked with the use of antimicrobial agents, recent observational reports have suggested a link with the increased gastric pH caused by PPI therapy. It is believed that the inhibition of gastric acidity limits the body’s defense against ingested spores and bacteria. A 2008 study by Aseer et al. investigated the relationship between CDAD in hospitalized patients and PPI use. In a retrospective case-control study, the authors demonstrated CDAD associated with use of PPI in hospitalized patients based on an OR of 3.6 (95% CI: 1.7–8.3, P<0.001). The OR was also increased to 2.14 in patients using H₂ receptor antagonists but was not significant, likely because of the relatively small number of patients prescribed this class of medication. This study was carefully controlled for environmental factors (patient location in the hospital), antibiotic use, and other comorbidities.

Proton pump inhibitors and pneumonias

PPI use has been linked to an increased risk of community-acquired pneumonia (CAP). The proposed mechanism for this phenomenon, similar to that of CDAD, is increased pathogenic colonization of the upper aerodigestive tract because of less gastric acid suppression. Sarkar et al. conducted a nested case-control study using the United Kingdom’s well-established General Practice Research Database. The authors noted a strong association with PPI therapy and CAP in the short term (when PPI was started within 2, 7, or 14 days). Interestingly, there was no increased risk in patients on longer-term PPI therapy. These authors concluded that chronic PPI therapy is not likely to be associated with increased risk of CAP. Gulemez et al. found that recent (within 0–7 days) initiation of PPI treatment was associated with an odds ratio of 5.0 (95% CI: 2.1–11.7). They found the risk to decrease sharply with the duration of therapy, with the OR for patients treated more than 84 days to be 1.3 (95% CI: 1.2–1.4). They showed no association with H₂ receptor antagonists. Laheij et al. demonstrated an increased relative risk for CAP in patients currently being treated with PPIs, with an adjusted relative risk of 1.89 (95% CI: 1.36–2.62). Current users of H₂RAs also showed a 1.63-fold increased risk of pneumonia (95% CI: 1.08–2.48). There was a dose-related response in the PPI group, with current PPI users using more than one defined daily dose, showing a 2.3-fold increased risk of pneumonia compared with those with past use of PPI. This dose-response finding was not corroborated in the studies by Sarkar et al. or Gulemez et al.

Given the high prevalence of acid-suppressive medication use in the inpatient setting, Herzig et al. recently evaluated inpatients for a link between PPI use and hospital-acquired pneumonia (HAP). The authors studied all patients admitted to their tertiary care hospital for at least 3 days over a period of 3 years, excluding intensive care patients (to avoid inclusion of ventilator-acquired pneumonia patients). Out of almost 64,000 admissions and over 42,000 unique patients, there were 32,922 (52% of admissions) treated with acid-suppressive medication. Most of them received PPIs (83%, compared with 23% treated with H₂ receptor antagonists). The adjusted OR for the group exposed to acid-suppressive medications was 1.3 (95% CI: 1.1–1.4). Further breaking down the HAP group into aspiration pneumonia versus nonaspiration pneumonia, the OR remained significant for both groups but stronger for the aspiration pneumonia group (1.4 vs 1.2). Finally, a matched propensity score analysis was used to control for confounding variables. In this subset, only PPIs were associated with a significant risk of HAP, whereas the risk with H₂RAs was not significant.

When evaluating these studies, it is important to understand that PPI prescriptions are used as a surrogate for the presence of reflux disease. This may not be appropriate, because reflux disease that is asymptomatic or presents with atypical symptoms (such as cough) may not be treated. In other words, the presence or absence of reflux disease is not well controlled for in these studies. An improved evaluation would include controls that have documented reflux disease, untreated with PPIs. This would likely help delineate whether pneumonia is associated with untreated reflux or suppression of gastric acid by PPIs, or neither.

Proton pump inhibitors and clopidogrel

Several observational studies have suggested an interaction between omeprazole and clopidogrel, a platelet activation inhibitor used in acute coronary syndromes (ACS) and other ath erosclerotic disease processes. As clopidogrel often leads to gastrointestinal bleeding, many cardiac and stroke patients are placed on prophylactic PPI to reduce the risk of bleeding. Clopidogrel inhibits platelet activation induced by adenosine diphosphate (ADP). The prodrug of clopidogrel requires transformation via the cytochrome P-450 system. This activity directly parallels the dephosphorylation of intraplatelet vasodilator-stimulated phosphoprotein (VASP), making VASP levels an accurate predictor of clopidogrel activity. In a double-blind placebo-controlled trial, Gilard et al. examined 124 consecutive patients undergoing coronary artery stent implantation who were receiving aspirin and clopidogrel. Patients were randomized to receive either omeprazole 20 mg/d or placebo for 7 days. Clopidogrel effect was evaluated with phosphorylated VASP levels in the form of a platelet reactivity index (PRI). On day 7, patients in the PPI group had a significantly higher PRI (51.4% compared with 39.8% on placebo, P<0.0001). The authors hypothesized that PPIs reduce the biological action of clopidogrel, likely by competitive metabolic effects on Cytochrome P450 2C19. Obviously, in conditions, such as ACS, the goal is to have reduced platelet activity, which appears to be inhibited by omeprazole.

In another retrospective series, Pezalla et al. reviewed myocardial infarction (MI) patients younger than 65 years, who were determined to be adherent to clopidogrel therapy. They stratified patients based on adherence to PPI use, finding...
a difference in 1-year MI rates when comparing non-PPI users and high PPI-exposure patients (3.08% vs 5.03%, respectively, \(P < 0.05\)). After adjusting for comorbidities, they found the relative risk for MI in the high PPI use group to be 337% greater than that in the non-PPI group. This study was limited by confounding risk factors and a lack of breakdown, with regard to which specific PPIs were used.

Most recently, in a retrospective study of 8205 Veterans Affairs patients, a multivariate analysis suggested that simultaneous use of clopidogrel and PPIs has the potential for adverse cardiac effects. In this study, 63.9% of patients with ACS were found to have been prescribed PPIs at discharge from the hospital in addition to clopidogrel. Most patients were treated with omeprazole, with a smaller portion receiving rabeprazole. In their analysis, Ho et al.\(^\text{25}\) found that the use of clopidogrel + PPI was associated with an increased risk of death or rehospitalization for ACS compared with that of clopidogrel without PPI (AOR: 1.25, 95% CI: 1.11–1.41). Also, in patients taking clopidogrel after hospital discharge and prescribed PPI at any point during the follow-up period (3 years), a higher risk of death or rehospitalization for ACS was found during the use of PPI with clopidogrel (compared with that of clopidogrel without PPI, giving an adjusted hazard ratio of 1.27). When evaluating secondary outcomes, patients on PPI + clopidogrel were ultimately found to have a higher risk of requiring revascularization procedures compared with those taking clopidogrel alone (15.5% vs 11.9%, respectively). In a nested case-control design, patients were also found to have an increased risk of adverse outcomes when taking clopidogrel + PPI (AOR: 1.32). Finally, the authors showed that the use of PPI without clopidogrel was not associated with death or rehospitalization for ACS among patients not taking clopidogrel after discharge.

PPIs are metabolized by both CYP450 2C19 and 3A4, likely in different proportions based on their isomeric forms. The initial concern regarding the aforementioned studies was that the results suggested a class effect, or that all PPIs could alter clopidogrel metabolism. On the contrary, several studies have suggested that this is not likely to be an effect of the entire class of PPIs directly causing gastric enterochromaffin-like cell hyperplasia in both animal and human models. To date, no evidence of neoplasia or dysplasia has been noted in humans. However, the FDA states that “these studies are of insufficient duration and size to rule out the possible influence of long-term administration of omeprazole on the development of any premalignant or malignant conditions.”\(^\text{30}\)

Tamim et al.\(^\text{11}\) conducted a nested case-control study over a period of 8 years, examining patients with exposure to acid-suppressive drugs (either H2 receptor antagonists or PPIs) for long periods of time. Case patients were found to have a minor, yet significant, increased risk of gastric carcinoma compared with those not exposed to acid-suppressive drugs in the preceding 5 years. One limitation in this study was the fact that gastric carcinoma has a long latency period; hence, examining a longer period of time might be necessary to discern any relationship between acid suppression and gastric carcinoma.

A more recent study by Poulsen et al.\(^\text{12}\) evaluated the association between PPI use and gastric cancer in a large, population-based registry. The incidence rate ratios (IRR) of gastric cancer in patients taking either PPI or H2RA were 9.0 and 2.8, respectively. In an effort to prevent bias in the form of reverse causality, the authors further introduced a 1-year lag time for the date of diagnosis of gastric cancer. In this subset, both PPI and H2RA showed an IRR of 1.2 (95% CI: 0.8–2.0 and 0.8–1.8, respectively). Directly comparing PPI with H2RA, there was an overall IRR of 1.3 (95% CI: 0.7–2.3). There were also positive associations with longer follow-up and more prescriptions filled. By including the 1-year lag time, the study was able to restrict for many confounding variables. This study was limited by its ability to control for H. pylori infection as a confounding variable, as only certain patients had undergone eradication therapy.

**CONCLUSION**

PPIs are an integral treatment modality in the management of LPR, and therefore, the otolaryngologist must be aware of their potential acute and chronic side effects. With more work being published in both the general medical literature and the popular press, we must be knowledgeable of the issues and controversies surrounding these potentially life-threatening long-term side effects of PPI use. As much of the data presented in the review were epidemiological, there is little direct causal evidence linking PPIs to the unintended consequences. As the
body of scientific data regarding long-term use of PPIs continues to improve, we hope to either prove or disprove these possible links. Until then, we recommend that the clinician be acutely aware of these possibilities. In at-risk patients, it may be appropriate to consider dual-energy X-ray absorptiometry (DEXA) bone mineral density scans, vitamin B₁₂ levels, and iron levels. We also recommend close communication with our cardiology colleagues as we attempt to ascertain the relationship between clopidogrel and PPI use. In addition, we recommend caution in the use of omeprazole in patients undergoing active treatment for ACS. Finally, it may be prudent to include *H. pylori* testing in the workup of LPR. As otolaryngologists, we are prescribing PPIs to protect structures, such as the pharynx, larynx, and esophagus, but we must keep in mind that these medications have the potential for gastric effects, systemic side effects, and medication interactions.

**REFERENCES**


