



Indian Health Service
IHS National Pharmacy and Therapeutics Committee
Formulary Brief: Long-Term Use and Overuse of Proton
Pump Inhibitors
March 2014



Background:

The IHS National Pharmacy and Therapeutics (NPTC) reviewed the implications of long-term use and overuse of proton pump inhibitors at their February 2014 meeting. The NPTC modified the National Core Formulary to **remove** omeprazole as a named agent and **added** “proton pump inhibitor- any.” The NPTC also plans to engage in their first National Medication Utilization Evaluation (MUE) to investigate the way this class of agents is used within the Agency. This formulary brief is intended to review the most significant issues regarding long-term use and overuse of these agents.

Discussion:

The first proton pump inhibitor (PPI), omeprazole, was approved by the FDA in 1990 for the short-term treatment of GERD, active duodenal ulcer, severe erosive esophagitis, and pathological hypersecretory conditions. Since that time, this class has grown to include six different agents, with two available in over-the-counter preparations (omeprazole and lansoprazole). PPIs represent the third highest selling drug category in the US. Their mechanism of action is to bind the H⁺,K⁺-ATPase enzyme within parietal cells of the gastric mucosa, inhibiting the acid production by proton pumps in the secretory canalicular surface of the cell. Studies demonstrate that some patients remain on the agents for long periods of time, leading to increasing recognition of adverse impacts to the patient from long-term use and overuse of the products.

Enteric Infections

The less acidic gastric environment associated with PPI use is felt to lead to increased bacterial colonization. An association between PPI use and *Clostridium difficile* infection has been noted. Use of PPIs concomitantly with antibiotics is associated with a 1.96 times increased risk of *C. difficile* infection (95% CI: 1.42-2.72) compared to patients on antibiotics alone¹. Increasing levels of pharmacologic acid suppression are associated with increased risk of nosocomial *C difficile* infection. Patients on an H₂ receptor antagonist (H₂RA) showed a 1.53 times increased risk (95% CI= 1.12-2.10), compared to 1.74 times increase with daily PPI use (95% CI= 1.32-2.18) and 2.36 times increased risk with more frequent PPI use (95% CI= 1.79-3.11)². PPI use during incident *C. difficile* infection treatment was associated with a 42% increased risk of recurrence of the *C. difficile* infection [adjusted hazard ratio= 1.42 (95% CI= 1.11-1.82)]³.

Pneumonia (Community-acquired and Hospital-acquired)

Similar to issue with enteric infections, it is felt that acid suppression allows ingested pathogens to colonize the GI tract and relocate to the respiratory tract. Acid suppressing drug use was associated with a 30% increased odds of hospital-acquired pneumonia (4.9% vs. 2.0%, OR=2.6, 95% CI= 2.3-2.8), though statistical significance only seen with PPI use (OR: 1.3, 95% CI: 1.1-1.4)⁴. Acid suppressing drug use was also associated with a 33% increased likelihood of community-acquired pneumonia in patients ≥ 65 years who had a prior hospitalization for pneumonia (12% vs. 8%, aOR= 1.5, 95% CI= 1.1-2.1). All of the increased risk was seen in patients starting a PPI/H₂RA after initial pneumonia hospitalization (aOR= 2.1, 95% CI: 1.4-3.0)⁵.

Fractures

Long-term PPI therapy, particularly at high doses, is associated with an increased risk of hip fracture. Taking a PPI for > 1 year is associated with an adjusted odds ratio (aOR) of 1.44 for hip fracture (95% CI: 1.30-1.59). Taking a dose of PPI that was ≥ 1.75 times the average daily dose for > 1 year is associated with an aOR of 2.65 for hip fracture (95% CI: 1.80-3.90; P<0.001). The strength of the association increased with increasing duration of PPI therapy and increased dosage⁶. Patients with hip fractures are more likely than controls to have previously received a ≥ 2-year supply of PPIs (OR= 1.3, 95% CI= 1.21-1.39) or H₂RA (OR= 1.18, 95% CI= 1.08-

1.29). The risk was reduced after discontinuation. Excess risk was only seen in those patients with at least one fracture risk factor (alcohol abuse, arthritis, diabetes, kidney disease, or glucocorticoid use)⁷.

Rebound Acid Hypersecretion (RAH)

The low gastric acidity associated with PPI use leads to an increase in gastrin production by the G cells of the distal gastric mucosa. Gastrin stimulates histamine release by enterochromaffin-like cells (ECL). Although gastrin can directly stimulate parietal cells, histamine has the more potent effect through stimulating H₂ receptors on the parietal cell surface. In addition, gastrin has a trophic effect on both ECL and parietal cells, leading to cellular hyperplasia in the setting of hypergastrinemia. A systematic review in 2007 looked at eight studies evaluating this effect in trials with small numbers of patients, concluding there was no strong evidence for a clinically relevant increased acid production after withdrawal of proton pump inhibitor therapy⁸. However, a randomized, double-blind, placebo-controlled trial of 120 healthy volunteers in 2009, showed 44% of the PPI user group reported ≥ 1 relevant acid-related symptom in the first three weeks after 8 weeks of esomeprazole 40mg/d vs. 15% in the placebo group⁹. In another randomized, double-blind, placebo-controlled trial of 48 healthy, *H. pylori*-negative volunteers in 2010, 44% of the those on pantoprazole 40 mg/d for 28 days reported dyspepsia in the first week after treatment vs. 9% in the placebo group (P<0.01). The difference resolved by week three. Symptom scores during the first week after treatment correlated with basal (P<0.01) and meal-stimulated (P<0.01) gastrin levels at the end of treatment¹⁰. This increase in symptoms during the first weeks after cessation of PPI therapy may contribute to patients immediately restarting therapy due to lack of recognition of this short-term acid rebound effect.

Animal studies prior to the initial FDA approval of omeprazole had indicated an association with gastric carcinoid tumors, suspected to be associated with hypergastrinemia. This led to the initial approval for “short-term treatment”. In 2012, a case report from Norway described gastric carcinoids in two patients with a history of long-term PPI use. One was a 55 year-old male having a pre-operative EGD prior to antireflux surgery. He had been on lansoprazole 30 mg daily for 10 years, followed by esomeprazole 40 mg daily for 2 years. The second was a 68 year-old female having EGD due to dyspeptic symptoms. She had been treated with lansoprazole 30 mg daily for 10 years, followed by pantoprazole 40 mg daily for 3 years¹¹. These case reports suggest that the risk for gastric carcinoids may be more than theoretical.

Overuse of PPIs

Although PPIs are FDA approved for “short-term use”, many patients remain on these medications for long periods of time. Two recent studies from the VA looked at typical usage of PPIs. One study revealed that 90% of patients were inappropriately prescribed PPIs, the majority of which was attributed to lack of appropriate follow-up (35% with no documented follow-up after starting PPI therapy. For those with follow-up, the median time to first follow-up was 344 days)¹². The second showed that 65.8% of patients were given an initial prescription for ≥ 90-day supply with a mean number of annual refills of 2.9. Only 16.2% of patients received only the initial prescription without refills and only 3.3% of patients ever had step-down therapy in the 2 years of the study¹³.

Recommendations

A growing body of evidence demonstrates adverse effects associated with long-term use and overuse of PPIs for our patients. Because of rebound acid hypersecretion, some patients may mistakenly resume the medication after initial attempts to stop therapy, further contributing to misuse of these drugs. A 2001 study demonstrated an effective program for step-down management. In this program, the dose of the prescribed PPI was initially halved or stopped (if already on the lowest dose). Patients were reassessed in 2 weeks. If symptoms recurred, the prior dose was restarted. If the patient was asymptomatic, the therapy was stopped. The patients were followed up at 3 month intervals for 1 year. If symptoms recurred, they were treated with a stepwise addition of an H₂RA, a prokinetic agent, or resumption of a PPI at the lowest effective dose. Fifty-eight percent of patients were either asymptomatic off therapy or on a non-PPI therapy at the end of a year¹⁴. Although this study utilized a pharmacy-based GERD clinic, this could also be done through clinician office visits or a nursing-based case management program. Studies in patients with non-erosive reflux disease have shown

that on-demand therapy, averaging one dose of a PPI every 3-4 days can effectively control reflux symptoms, potentially decreasing the impact of long-term use of PPIs^{15, 16}. IHS clinicians should consider these approaches to reduce the negative impact of long-term use and overuse of PPIs in their patients and potentially reduce pharmacy expenditures.

If you have any questions regarding this document, please contact the NPTC at nptc1@ihs.gov.

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