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Clinical Considerations for Proton Pump Inhibitor (PPI) Use

Gregory W. Smith, PharmD, Clinical Coordinator
Drug Information Center, College of Pharmacy
The University of Louisiana at Monroe

Proton pump inhibitors are among the most frequently prescribed medications in the world, most likely due to their efficacy in reducing gastric acid and positive safety profile.¹ However, decisions to prescribe PPIs must include an assessment of patient-specific factors, such as concomitant medication use and the potential for adverse effects. Because proton pump inhibitors are used in long-term management for certain indications, these assessments become all the more important.

Interaction between Clopidogrel (Plavix®) and Proton Pump Inhibitors (PPIs)

- The prodrug, clopidogrel, is metabolized to a bioactive form by the cytochrome P450 (CYP2C19) isoenzyme. Studies have shown that patients with reduced activity of CYP2C19 due to loss-of-function polymorphism of the enzyme experience a diminished clinical effectiveness of clopidogrel.²⁻⁴
- In vitro studies have shown that the FDA-approved PPIs exhibit competitive inhibition for CYP2C19 at varying degrees of affinity by agent, which has led to the suspicion of an interaction between PPIs and clopidogrel.⁵
- The findings of several observational studies have supported the suspicion that the use of PPIs possibly alter clopidogrel's pharmacokinetics and potentially increase the risk of adverse cardiac outcomes.⁶⁻¹⁰
- Not all studies have been able to reproduce these findings as noted in an observational study by Simon, et al¹¹ and a nonrandomized study by Siller-Matual, et al.¹² Additionally, researchers that conducted a posthoc analysis of data from the PRINCIPLE-TIMI 44 and TRITON-TIMI 38 trials were not able to show that the use of PPIs is associated with increased risk of adverse clinical outcomes when used with clopidogrel or the new oral antiplatelet drug in these studies, prasugrel (Effient®).^{13,14} However, authors reported, "In our analysis, individual subgroups might have been underpowered to show an association between PPI use and risk of pharmacodynamic or clinical outcomes, if such a relation existed."¹⁵
- In a January 2009 Early Communication, the FDA recommended a thorough investigation of the potential interaction between clopidogrel and PPIs and asked healthcare providers to reevaluate the need of initiation or continuation of PPI treatment in patients taking clopidogrel.¹⁶
- In November 2009, the FDA issued a follow-up to its January Early Communication and required labeling revisions regarding the interaction. The follow-up is based on study results from the manufacturer of clopidogrel and advised prescribers AGAINST the concomitant use of clopidogrel with two specific PPIs, omeprazole and esomeprazole. According to the FDA, there is currently not enough information about drug interactions between clopidogrel and the other PPIs to advise against concomitant use.¹⁶⁻¹⁸

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- In addition to omeprazole and esomeprazole, the FDA advised AGAINST the co-administration of clopidogrel with other potent inhibitors of the CYP2C19 isoenzyme. These inhibitors include: cimetidine, fluconazole, ketoconazole, voriconazole, etravirine, felbamate, fluoxetine, fluvoxamine, and ticlopidine.¹⁷
- Figure 1 provides an excerpt from the FDA Postmarketing Drug Safety Information on the interaction.¹⁸ For the complete update, visit:
<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm190787.htm>

Figure 1. FDA Information for Healthcare Professionals: Clopidogrel-Omeprazole Interaction

Considerations for Healthcare Professionals

- The concomitant use of omeprazole and clopidogrel should be avoided because of the effect on clopidogrel's active metabolite levels and anti-clotting activity. Patients at risk for heart attacks or strokes, who are given clopidogrel to prevent blood clots, may not get the full protective anti-clotting effect if they also take prescription omeprazole or the OTC form (Prilosec OTC).
- Separating the dose of clopidogrel and omeprazole in time will not reduce this drug interaction.
- Other drugs that should be avoided in combination with clopidogrel because they may have a similar interaction include: esomeprazole (Nexium), cimetidine (which is available by prescription Tagamet and OTC as Tagamet HB), fluconazole (Diflucan), ketoconazole (Nizoral), voriconazole (VFEND), etravirine (Intelence), felbamate (Felbatol), fluoxetine (Prozac, Serafem, Symbyax), fluvoxamine (Luvox), and ticlopidine (Ticlid).
- At this time FDA does not have sufficient information about drug interactions between clopidogrel and PPIs other than omeprazole and esomeprazole to make specific recommendations about their co-administration. Healthcare professionals and patients should consider all treatment options carefully before beginning therapy.
- There is no evidence that other drugs that reduce stomach acid, such as most H2 blockers ranitidine (Zantac), famotidine (Pepcid), nizatidine (Axid), except cimetidine (Tagamet and Tagamet HB - a CYP2C19 inhibitor) or antacids interfere with the anti-clotting activity of clopidogrel. Ranitidine and famotidine are available by prescription and OTC to relieve and prevent heartburn and antacids are available OTC to relieve heartburn.
- Talk with your patients about the OTC medicines they take. Be aware that patients may be taking non prescription forms omeprazole and cimetidine.

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Possible Safety Issues Related to the Long-term Use of PPIs

For over a decade, concerns have been raised regarding the appropriateness of long-term antisecretory therapy (AST) for treatment of gastroesophageal reflux disease (GERD) symptoms, predominately with PPIs. According to studies, up to 70% of patients on chronic AST lack an indication verified endoscopically.^{19,20} Indications for long-term AST include symptomatic GERD, GI bleeding, erosive esophagitis, NSAID prophylaxis, and pathologic GI hypersecretory conditions (e.g., Zollinger-Ellison, multiple endocrine adenomas, systemic mastocytosis).²¹ Potential risks associated with prolonged and potentially imprudent use of PPIs have been investigated and are discussed below.

Nutritional Deficiency

- **Vitamin B-12:** Vitamin B-12 deficiency has been associated with PPI long-term use, yet no association has been determined between either past or short-term PPI use.²²⁻²⁴ Recent studies have produced mixed results.^{25,26} The overall body of evidence is based on case reports and small nonrandomized retrospective studies, which cannot firmly establish the association of PPI use with B-12 deficiency or the need for routine monitoring of B-12 levels.
- **Iron:** Several clinical studies have suggested that prolonged gastric acid hyposecretion might result in clinically significant iron malabsorption.^{27,28} Poor response to oral iron supplement absorption in 2 iron-deficient individuals improved after cessation of omeprazole in a published report.²⁹ One study showed that continuous treatment with omeprazole for 6 years did not cause decreased body iron stores or iron deficiency in patients with Zollinger-Ellison syndrome, suggesting that monitoring for iron deficiency is not necessary.³⁰ There is a need for long-term safety studies regarding iron deficiency in patients using PPIs for more general indications.
- **Calcium:** Increased risk of osteoporosis with AST has been speculated to be related to a reduction in absorption of calcium. However, the mechanism for increased fracture risk with AST has not been proven. Studies have demonstrated a reduction of calcium absorption with PPI use.^{31,32} Multiple studies have investigated the association between long-term PPI therapy and hip fracture, however, results are conflicting.³³⁻³⁶ Currently, there is not enough evidence to suggest all patients on long-term PPI therapy be screened for osteoporosis.³² However, there remains an urgent need to understand the effects of PPIs on calcium metabolism. It is recommended that these patients receive increased dietary calcium from food sources or calcium supplements. Supplements in the form of calcium citrate may allow greater bioavailability when acid-suppression therapy is being used and may be absorbed better than calcium carbonate regardless of whether co-administered with food. Calcium carbonate supplements taken with a meal may increase bioavailability.^{33, 37}

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Infectious Disease

- *Clostridium difficile*: There are data that link PPI use with an increase in *C. difficile* colitis³⁸⁻⁴¹ and bacterial gastroenteritis,⁴² but in each case the magnitude of risk is slight. The most recent evidence suggested only a slight association and concluded that "in settings with low rates of *C. difficile* infection (CDI), the benefit of PPI therapy outweighs the risk of developing CDI."⁴³
- Community-Acquired Pneumonia (CAP): Results from observational studies have suggested that PPI use is associated with an increased risk for developing CAP.⁴⁴⁻⁴⁶
 - The results of these studies demonstrated a temporal association between PPI use and risk for CAP, with risk being most pronounced among current users who initiated PPI therapy within the past 7⁴⁶ to 30^{44, 45} days. Of note, the study by Sarkar et al found that CAP risk was not associated with long-term PPI use.⁴⁵ Interestingly, Laheij et al observed a dose-response relationship among current users of PPIs such that persons using greater than 1 defined daily dose had a 2.3 times greater risk of CAP compared with past users of PPIs.⁴⁴ For this study, daily doses were defined as: omeprazole 20mg, esomeprazole 20mg, lansoprazole 30mg, pantoprazole 40mg, and rabeprazole 20mg.
 - "It should be considered that certain patients (e.g., those with pleuritic chest pain, hypothermia, systolic hypotension, tachypnea, diabetes mellitus, neoplastic disease, neurologic disease, bacteremia, leukopenia, multilobar pulmonary infiltrate) are at increased risk for developing infections and in these individuals community-acquired pneumonia may be associated with increased mortality."⁴⁷ Therefore, PPI use in these individuals and in other patient populations for whom pneumonia is often severe should be considered only when necessary and at the lowest effective dose.^{44,47}

Malignancy

- The risk of increased gastric and colon malignancy associated with long-term PPI use has been theorized due to results of animal studies, but has not been observed in humans.⁴⁸
- A study conducted by Jalving et al to determine whether PPI use contributed to fundic gland polyp development concluded the following: "Long-term (1-5 years) proton pump inhibitor use is associated with an up to fourfold increase in the risk of fundic gland polyps. Risk of dysplasia is negligible. Aetiologically, these polyps seem to arise because of parietal cell hyperplasia and parietal cell protrusions resulting from acid suppression."⁴⁹
- The FDA's Gastrointestinal Drugs Advisory Committee stated the following in the F-D-C Report ("*The Pink Sheet*"): "In the presence of [*Helicobacter pylori*] infection, data do not demonstrate that long-term antisecretory drug treatment increases the prevalence of atrophic gastritis, the prevalence of intestinal metaplasia, or the risk of developing gastric adenocarcinoma."⁵⁰ The committee also agreed that the evidence does not lead to the conclusion that "it is unsafe to treat *H. pylori*-positive patients with long-term antisecretory drugs."⁵⁰

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PPI Withdrawal

- Though past studies investigating rebound acid hypersecretion (RAHS) after cessation of PPI treatment have not provided strong supportive evidence for acid rebound,⁵¹⁻⁵³ data from a more recent, well-designed study suggested that discontinuation of PPI therapy results in acid-related symptoms.⁵⁴ This evidence raises a concern that if a patient who does not truly need a PPI reports withdrawal effects after discontinuation, the clinician might conclude that a relapse has occurred and resume PPI therapy unnecessarily.
- Future studies investigating how long RAHS symptoms persist may help guide decisions regarding the resumption of PPI therapy.
- Tapering of therapy over a 3-week period has not demonstrated an advantage over instant discontinuation for preventing RAHS.⁵⁵ Because studies have indicated that acid rebound may persist longer than 8 weeks, tapering over a longer period of time may be worthy of consideration.^{52,56}

Step-Down, Intermittent and On-Demand Therapy Strategies

- Concerns about cost, inconvenience, and/or potential adverse effects of continuous maintenance treatment using PPIs have led to the evaluation of various long-term strategies, including 'Step-Down,' 'Intermittent,' and 'On-Demand' therapy. These strategies are supported by clinical trials that have demonstrated efficacy, cost-effectiveness, and patient preference. According to a study conducted by Inadomi et al, almost 80% of patients taking a higher PPI dose could be reduced to a standard once daily dosing.⁵⁷
 - 'Step Down' therapy involves using a lower PPI dose or alternate day dosing, a less expensive PPI, or *stepping down* to an alternate therapy such as an H₂-receptor antagonist.⁵⁷ In GERD, patients taking more than once daily or high-dose PPI treatment, a *step down* to once daily or standard dose therapy should be attempted.⁵⁸
 - 'Intermittent' therapy uses repeated short courses (2-4 weeks) of AST to manage relapses. This method has been shown to be effective in about half of the patients in one study.⁵⁸
 - 'On-Demand' therapy is the administration of medication in response to symptoms followed by discontinuation after symptoms are alleviated. 'On-demand' PPI treatment may be appropriate in endoscopy-negative reflux disease.⁵⁸
- The best candidates for these strategies are patients with GERD symptoms that resolve with PPI treatment and that do not have complicated disease, such as those with esophageal stricture, Barrett's esophagus, extra-esophageal manifestations or diagnosed GERD.^{58,59}

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Conclusion

Patient safety is an important consideration in all prescribing decisions, including the potential for drug-drug interactions or the possibility of adverse effects associated with long-term treatment. These are important considerations, even for medications, such as PPIs, that are considered safe, very efficacious, and are frequently prescribed.

In light of current information, the FDA has advised against the co-administration of clopidogrel (Plavix®) and omeprazole (Prilosec®) or esomeprazole (Nexium®). Additionally, the FDA indicated that this interaction is not reduced by separation of doses. The FDA further recommended that clopidogrel and other potent CYP2C19 inhibitors should not be used together. Further studies are ongoing.

A variety of potential adverse effects related to long-term PPI use have been evaluated. While there is not sufficient evidence to establish a causal relationship, many of these observational studies have demonstrated an association between long-term PPI use and an increased risk for certain adverse effects. However, considering the number of patients using PPIs, these findings of possible risk for adverse effects warrant consideration in patient care.

PPIs are effective medications with a good safety profile; however, they should be prescribed only when clearly indicated, at the lowest effective dose, and for the shortest duration of treatment. Treatment decisions should be re-evaluated on a frequent basis. "After all, in the absence of benefit, a risk-benefit ratio is always unacceptable."³²

The Louisiana Drug Information Center (DIC) located at the University of Louisiana at Monroe (ULM) College of Pharmacy (COP) provides assistance with areas such as literature retrieval and evidence-based recommendations. The DIC provides a healthcare provider-focused service for the State of Louisiana that is also available to Medicaid providers through support from the Louisiana Medicaid Pharmacy Benefits Management Program. Healthcare providers can contact us at the following telephone number for drug information requests:

318-342-5501

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