Digesting the Complexity of PPI Management and Care

by Stuart A. Frank

The introduction of proton pump inhibitor (PPI) therapy in 1989 was a breakthrough, optimizing the pharmacotherapy of acid reflux disease. Not only are PPIs the most widely prescribed drug for acid reflux, they are also one of the top prescribed and dispensed drugs in the United States overall. Before PPIs were available, the mainstay of therapy for acid reflux was histamine-$_2$ receptor blockers (H_2-blockers). However, H_2-blockers only target histamine-$_2$ stimulated acid secretion, leaving other pathways available for continued acid secretion. PPIs are more effective and potent because they target the proton pumps, primary players in the final step of acid secretion in the body. PPIs inhibit meal stimulated acid secretion completely unlike H_2-blockers, which inhibit acid secretion approximately 30 percent.

As with all drug therapies, it is important to educate patients about how to appropriately use the prescribed therapy for optimal pharmacotherapy as well as optimal patient care. This editorial highlights key patient educational points, prescribing considerations with PPI therapy and acid reflux, and the latest technologies physicians rely on for patient care.

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MEDICATION COUNSELING

Whether initiating or managing a patient on PPI therapy, taking the time to educate and counsel patients will ensure necessary compliance to drug therapy and proper medication administration.

You want to assure patients that PPIs are very effective drugs; however, it is important that they be equally aware that it may take some time before they have symptomatic relief. Then, whether or not they experience immediate relief, this medication must be taken every day continuously and on a long-term basis in order for it to be effective. Taking PPIs on an as needed basis will not provide adequate acid inhibition in patients with more complex reflux, as PPIs do not permanently bind to proton pumps. Without routine use of the drugs, actions can be reversed by regulatory body mechanisms. Principally, glutathione reductase is responsible for reversal of acid inhibition by breaking the covalent bonds between the drug and the proton pumps. Additionally, PPIs only work on activated proton pumps. Because of the body's natural regulation process, inactivated ones will ultimately be activated, resuming acid secretion. Eventually, with continual and consistent use, maximal suppression of acid secretion can be achieved. Conversly, once PPIs have been discontinued, symptoms can return quickly, reinforcing that PPIs are not a cure for acid reflux. All these points cannot be emphasized enough to patients.

Next, it is prudent that patients understand the importance of taking PPIs properly. Patients should be

instructed to take PPIs in the morning, as this is when the amount of proton pumps located on the parietal cells is the greatest. PPIs should also be taken at least an hour before breakfast because they are absorbed in the small intestine, and it takes at least 30–40 minutes for the drug to empty out of the stomach and into the small intestine. Maximizing the absorption of the medication is the first step to ensuring optimal drug benefits. If a PPI is taken with food, complete absorption and subsequently, full drug effects, will be lost.

After the hour has passed, the type of meal eaten after taking a PPI is very important for maximizing the effectiveness of the medication. Patients should be informed that their first meal after a PPI should be a protein-rich meal (e.g., milk, cheese, yogurt). Protein stimulates the release of gastrin, the major hormone responsible for regulating acid secretion. Gastrin is located in the antrum and stimulates acid secretion through various mechanisms including direct stimulation of proton pumps on the parietal cells and enhancing histamine release.

Without sufficient protein in the meal following PPI intake, only about 10% of the proton pumps will be stimulated by the meal, and the other 90% of the pumps will remain inactive or "asleep." A protein-rich meal will better activate the release of gastrin to stimulate all available proton pumps, this ensures therapy is most effective, as PPIs can inhibit meal-stimulated acid secretion. I find that one of the best ways for patients to understand the repercussions is to talk in dollars and cents. They will only get 10 cents on every dollar if they do not eat enough protein after PPI intake.

Dose escalation may be necessary, so it is important patients try not to get discouraged with their therapy. Dosing is highly individualized, based on the level of inhibition required for each patient. Some patients will require twice a day dosing with PPIs due to severe reflux. For such patients, their first dose should be taken in the morning, an hour before breakfast, and their second dose should be taken in the evening, an hour before dinner. Patients should also be instructed to avoid taking their evening dose at bedtime.

An even smaller subset of patients will have nocturnal acid breakthrough (NAB), requiring an H_2-blocker at bedtime. Patients should be directed not to take H_2-blockers simultaneously with their PPI doses, or it may result in reduced efficacy on acid inhibition overall. Separating the evening PPI dose and bedtime H_2-blocker dose as much as possible will ensure optimal acid inhibition. Unfortunately, resistance to H_2-blockers may occur quickly. A 2002 study evaluated the combination of twice a day PPI therapy with bedtime H_2-blockers for patients with complicated gastroesophageal reflux disease. While results showed an 18% initial response rate, NAB resumed in 50% of those patients after one week and in 62% after one month. Hence, emphasizing the importance of continued use despite the lack of symptomatic relief becomes critical.

In general, PPIs are safe drugs with few serious adverse reactions and clinically significant drug-drug interactions. However, these possibilities should not be discounted, as PPIs may be associated with atrophic gastritis and an increased risk for enteric infections and nosocomial pneumonia. Physicians should always be aware of the potential consequences of any drug therapy they prescribe. Increase risk of *C. Difficile* diarrhea is reported as a risk with continued PPI therapy.

While the efficacy of PPIs may not frequently be compromised by other medications, drug-drug interactions can exist, particularly affecting the safety and efficacy of other pharmacotherapy. For example, concomitant administration of esomeprazole (Nexium®) with warfarin (Coumadin®) may increase INR levels and subsequently, the risk of bleeding. Another consideration is certain medications, such as iron salts, ketoconazole and aspirin, require the presence of acid for optimal absorption. Absorption of these drugs decreases at higher pH levels, which may lead to reduced efficacy. Whenever possible, if a patient is taking a drug dependent on the presence of acid, that drug should be taken in the morning before the PPI or at bedtime. Informing patients of the importance of the timing of medication administration, especially when they are on multiple medications, will help optimize pharmacotherapy.

PPIs are available in various dosage forms and strengths, offering patients more options for increased compliance. Liquid dosage forms are available for those unable to swallow pills or capsules. Additionally, capsule formulations may be opened, and the granules may be mixed with applesauce.

LIFESTYLE MODIFICATIONS

While pharmacotherapy plays a large role in the management of acid reflux, lifestyle modifications are just as important in controlling and relieving symptoms. It is crucial to stress lifestyle changes, as below, in patients suffering from acid reflux:

- Elevation at the head of bed to minimize reflux events, particularly helpful for patients with nocturnal symptoms
- Weight loss for obese patients to alleviate pressure on the esophageal sphincter
- Avoidance of supine position after meals to minimize reflux events
- Avoidance of tight and binding clothing to ease stress on the esophageal sphincter
- Avoidance of eating before bedtime to minimize acid secretion
- Avoidance of food that may aggravate reflux such as spicy foods, chocolate and peppermint, which act as calcium channel blocking agents and inhibits lower esophagus sphincter reflex which causes reflux
- Alcohol restriction, as excessive alcohol may worsen acid reflux
- Smoking cessation, as smoking reduces salivation, enhances acid secretion. Nicotine enhances acid secretion at lower doses and is dose dependent

Again, taking the time for proper patient education will help patients make these necessary behavioral changes. The combination of lifestyle modifications with appropriate drug therapy will provide good results for the majority of patients.

COMPLIANCE ASSESSMENT

Medication compliance with any chronic medication is important. To determine whether or not compliance is an issue, I recommend the following at every appointment:

- Ask patients if they remember to take their PPI every day
- Ask when and how they are taking their PPI
- Ask about changes and updates to their medications—in fact, have patients bring in all of their current medications, including their PPI, to every appointment
- Ask about lifestyle modifications

OTHER CONSIDERATIONS

Before determining whether or not a patient is a true non-responder to PPI therapy, several factors should be considered. Having patients bring in all of their medications to every appointment helps identify the potential for pill-induced esophagitis. Several medications and drug classes are known to cause esophageal mucosal injury, including aspirin, potassium supplements, quinidine preparations, tetracycline antibiotics, and bisphosphonates. Calcium channel blockers, widely prescribed medications for cardiovascular disease, can weaken esophageal sphincter pressure, resulting in heartburn symptoms. Whenever a patient is on a drug associated with acid reflux, just a change in medication can alleviate troublesome symptoms and more injury. The potential role of infections should also be considered when treating acid reflux. For instance, esophageal candidiasis is common in patients with diabetes mellitus. The presence of infection, in combination with existing acid reflux disease, may further exacerbate the patient's condition. Barrett's esophagus, a pre-malignant condition that affects one in 10 patients with reflux, should be ruled out. Those with Barrett's esophagus require a different therapeutic approach and typically higher PPI doses. Targeted individuals for endoscopies to rule out Barrett's esophagus are those with long-standing heartburn, white men >40 years old and smokers. Another important consideration is the presence of sleep apnea, especially in patients with NAB. Patients should be questioned on their sleep, with further workup possibly indicated in severe patients due to the prevalence of sleep apnea. Continuous positive airway pressure (CPAP) has been shown to be effective in patients with both sleep apnea and acid reflux. A 2003 study was conducted to evaluate the effect of CPAP on nocturnal reflux, and results showed a 48% improvement in patients compliant with CPAP. When all other possibilities have been ruled out, medications with off-label indications for reflux may be considered. Baclofen, a gamma amino butyric acid (GABA) agonist that is FDA-approved for the treatment of spasticity, has been used in patients with reflux refractory to PPIs. GABA-agonists are potent inhibitors of transient lower esophageal sphincter relaxation, but

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its use may be limited by intolerable adverse reactions in some patients.Surgery should be reserved for patients who have exhausted all other options, as there are advantages and disadvantages to surgery.

CLOSING REMARKS

In today's society, medical information is easily accessible on the Internet as well as on mobile devices. Particularly, mobile drug references, such as Epocrates Rx, have become invaluable for many practitioners, making pertinent drug information readily available. Providers can quickly look up safety information on their handheld devices and check for potential drug-drug interactions. Decision support tools can also be readily accessed for more complex patient scenarios to identify a differential diagnosis. Using a mobile device with clinical applications during a consultation may enhance the patient experience and trigger educational discussions.

In addition, the latest technologies have modernized the distribution of medical information, both for healthcare professionals and patients. While patients are engaged during the face-to-face consultation, they may forget some of the information after leaving the office. Supplementing the discussion with take-home educational materials can increase compliance and proper medication use. Many professional websites offer patient education materials that can be easily printed out in the office and handed directly to patients during their appointment. Other health websites geared towards the general public allow patients to do further research independently. However, practitioners should encourage patients to discuss any questions they may have to ensure accurate and relevant information with them. Employing available medical references (online or on a mobile device), in combination with direct patient counseling, will ultimately ensure optimal pharmacotherapy, patient safety and care for PPI patients and beyond. ■