

PHARMACIST *to* PHARMACIST

Clinical Care Review for the Pharmacist

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Beating Back GERD with PPIs

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Nearly 15 million Americans suffer daily from symptoms related to gastroesophageal reflux disease (GERD), and nearly 38 million people experience symptoms at least weekly.¹⁻³ A sedentary lifestyle contributes to the prevalence of the disease. Patients with GERD frequently are overweight, eat large high-fat meals, and drink caffeinated beverages—all of which increase the dilation of the lower esophageal sphincter and the subsequent reflux of acid into the lower esophagus (LE).⁴

Complications of acid reflux in the LE include varying degrees of erosive esophagitis (EE), stricture, bleeding, and anemia and may lead to Barrett's esophagus.⁵ Barrett's esophagus is thought to be a precursor to adenocarcinoma of the esophagus. The severity of EE often is classified by using the Los Angeles (LA) grading system, in which Grade A is mild disease and Grade D is severe disease complicated by ulcerations, significant inflammation, and in some cases stricture.²

Proton pump inhibitors (PPIs) are the most efficacious agents used in the treatment of EE.⁴ For mild-to-moderate disease (LA Grades A and B), all PPIs should result in greater than 90% healing rates. With more severe grades of EE, 70% and 80% healing rates are reported. Despite

the effective suppression of acid by PPIs, only about 70% of patients experience complete pain relief, and 40% to 70% of patients suffering from nocturnal GERD report sleep disturbances at least once per week.^{1,2,6}

Pharmacology

The PPIs are substituted benzimidazoles that covalently bind to the hydrogen-potassium adenosine triphosphatase (H^+/K^+ -ATPase) enzyme—thereby inhibiting the final step in gastric acid secretion in a dose-dependent manner.^{7,8} When exposed to acid in the canaliculus of a parietal cell, the PPI is converted to the active sulfonamide moiety, which binds to the various cysteine residue sites within the H^+/K^+ -ATPase proton pump, inhibiting the enzyme and acid secretion.⁸ Because PPIs block this final step, they are more potent than histamine receptor antagonists, which block only 1 pathway in acid secretion.

PPIs are acid-labile, in that exposure to acid prior to entry into the parietal cell will activate the molecule and cause binding to any H^+/K^+ -ATPase. Thus, most commercially marketed PPI capsules and tablets—omeprazole (Prilosec), esomeprazole (Nexium), rabeprazole (Aciphex), lansoprazole (Prevacid), pantoprazole (Protonix)—have an enteric coating to protect them from acid degradation

by gastric acid. All of these products are termed delayed-release PPIs (DR-PPIs).⁸

Immediate-release omeprazole/sodium bicarbonate (IR-OME; Zegerid) contains the antacid sodium bicarbonate to prevent omeprazole from degradation by gastric acid, making an enteric coating unnecessary.⁹ This drug is supplied to pharmacists as 20- and 40-mg capsules and as a powder for oral suspension in unit-dose packets. IR-OME is indicated for the short-term treatment of active duodenal ulcer or benign gastric ulcer; for symptomatic GERD; for the treatment and maintenance of healing therapy for EE; and for the reduction of risk of upper gastrointestinal bleeding in critically ill patients (IR-OME 40 mg/sodium bicarbonate powder for oral suspension).^{9,10}

A pharmacokinetic study comparing delayed-release omeprazole (DR-OME) capsules with IR-OME suspension demonstrated the time to mean peak plasma levels of IR-OME to be ~30 minutes on day 1, compared with 1.74 hours and 2.34 hours for DR-OME 20 and 40 mg, respectively.^{11,12} Extemporaneously compounded omeprazole in bicarbonate, generally referred to as *simplified omeprazole suspension*, should not be regarded as equivalent to IR-OME, because pharmaco-

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kinetic studies of this suspension have shown that it is similar to DR-OME capsules.^{12,13} There are no therapeutic equivalents for IR-OME, and, because of its unique absorption characteristics, IR-OME is not AB-rated, compared with DR-OME capsules or OTC omeprazole.¹⁴

Dosing and Administration

Depending on the indication, IR-OME is administered as 20 or 40 mg as a single dose daily. Titration to higher doses generally is not necessary in most patients. The American College of Gastroenterology recommends that PPIs be administered 30 minutes to 1 hour prior to a meal for optimal gastric acid suppression. Both the IR-OME capsule and the suspension should be administered on an empty stomach at least 1 hour before a meal for optimal acid suppression.^{9,15}

In an open-label, randomized, crossover trial of 36 patients with nocturnal GERD symptoms, IR-OME 40 mg dosed once daily at bedtime produced a significantly higher median gastric pH, achieved a greater percentage of time with gastric pH >4, and decreased the

proportion of patients with nocturnal acid breakthrough (NAB), compared with pantoprazole 40 mg dosed once daily before dinner.¹⁶ A primary end point in clinical studies is NAB (defined as gastric pH <4 for more than 1 hour during the nighttime). A study of 54 patients with nocturnal GERD symptoms compared IR-OME 40 mg, esomeprazole 40 mg, and lansoprazole 30 mg, all administered on an empty stomach 5 hours after dinner.¹⁷ Bedtime IR-OME produced a more rapid and sustained control of nighttime gastric pH and NAB, compared with both esomeprazole and lansoprazole. Bedtime administration of IR-OME may be an effective strategy in patients with NAB. Esomeprazole and lansoprazole, however, should be administered prior to a meal as instructed in their respective prescribing information.^{18,19}

Side Effects and Interactions

All PPIs generally are well-tolerated, with the most frequently reported adverse events being headache, diarrhea, and abdominal pain.¹⁵ Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated over a long term with omeprazole. Reaction to the sodium bicarbonate contained in IR-OME, including metabolic alkalosis, is possible in some patients.⁹

IR-OME powder for oral suspension contains 460 mg of sodium per dose in the form of sodium bicarbonate (1680 mg/20 mEq), and IR-OME capsules contain 300 mg of sodium per dose in the form of sodium bicarbonate (1100 mg/13 mEq). This quantity should be taken into consideration for patients on sodium-restricted diets.


PPI dosing generally does not require adjustment for renal impairment.⁸ Omeprazole dose adjustment should be considered, however, in patients with hepatic insufficiency and in Asians.^{9,20} Asians have

a decreased ability to metabolize omeprazole and have demonstrated a 4-fold increase in the area under the curve, compared with Caucasians.²⁰ Omeprazole has a Category C pregnancy rating. Omeprazole affects liver oxidation and may delay the clearance and enhance the pharmacodynamic actions of drugs eliminated by this route. These drugs may include diazepam, phenytoin, and warfarin.^{9,21} Patients should be monitored if these products are administered with omeprazole.

Clinical Outlook

IR-OME powder for oral suspension forms a homogeneous suspension that is FDA-approved for administration through naso- or orogastric tubes. Extemporaneously compounded PPI-bicarbonate products have limited shelf life and may clog tubes when administered. Crushing tablets is not recommended, and removal of the contents of capsules and delivering the drug through a tube may cause clogging.^{8,18,22-24} IR-OME suspension also is an alternative for patients who have difficulties swallowing solid dosage forms, such as capsules and tablets.

Patients with nocturnal GERD often report symptoms despite the once-daily administration of a PPI. Alternatives to reduce symptoms include twice-daily dosing and administration prior to the evening meal rather than before breakfast.¹⁵ The unique formulation of IR-OME and its ability to rapidly suppress gastric acid appear to be effective in controlling nocturnal gastric acidity. IR-OME dosing once daily at bedtime is more effective in controlling NAB than preprandial pantoprazole either once or twice daily or esomeprazole and lansoprazole administered orally at bedtime. **P**

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