Advances in Proton Pump Inhibitor Therapy: An Immediate-Release Formulation of Omeprazole

Ralph E. Small, PharmD

PROTON PUMP INHIBITORS: AN OVERVIEW

Acid-related disorders encompass a wide variety of diagnoses, including the extremely prevalent gastroesophageal reflux disease (GERD), which affects an estimated 25 million Americans,1 duodenal and gastric ulceration, stress-related mucosal disease, and acute upper gastrointestinal bleeding, a common medical emergency resulting in approximately 300,000 hospitalizations annually.2 During the last three decades, the management of these disorders has been revolutionized by the introduction of histamine-2 receptor antagonists (H2RAs) and proton pump inhibitors (PPIs).

Five available delayed-release PPIs include omeprazole (Prilosec®, AstraZeneca), lansoprazole (Prevacid®, TAP), pantoprazole (Protonix®, Wyeth), esomeprazole magnesium (Nexium®, AstraZeneca), and rabeprazole (AcipHex®, Eisai/Janssen). These drugs are highly effective, irreversible inhibitors of H+/K+-ATPase, the final step in gastric acid secretion.

Although these agents form the therapeutic cornerstone of management for a variety of acid-related disorders, there is still room for improvement in our armamentarium. For example, all PPI compounds are weak bases that are acid-labile and are rapidly degraded, usually within minutes, in the acidic environment of the stomach. Until the recent introduction of immediate-release omeprazole (IR-OME [Zegerid®, Santarus]), this pharmacological property required the active ingredient in all delayed-release oral PPI formulations to have an enteric coating. The coating protects the active ingredient from degradation by gastric acid, but it also delays absorption, so that the peak plasma concentration (Cmax) is not typically attained for up to five hours after oral administration of these formulations. In addition, patients must not chew or crush the tablets or the enteric-coated granules.

For patients who cannot swallow intact capsules or tablets or who have a nasogastric tube in place, various liquid formulations have been compounded ex-temporaneously from sodium bicarbonate solution, with omeprazole or lansoprazole granules, or crushed pantoprazole tablets.3,4 These formulations have a limited shelf life and may adhere to the syringe and the tubing used for administration, with the result that the tubing has the potential to become clogged.5 Limitations to enteric-coated PPI formulations also include the potential for nocturnal acid breakthrough (NAB), defined as an intragastric pH below 4 for at least one hour during the night with PPI therapy. NAB occurs in up to 70% of patients with GERD.6-9 Despite adequate therapeutic dosing (including twice-daily administration), patients taking enteric-coated, delayed-release PPIs may experience nocturnal gastric acidity, whether or not the agent is taken before breakfast, before dinner, or twice daily9-11 and may have nighttime symptoms of heartburn. Patients with nocturnal GERD may have a higher potential for severe reflux-induced complications such as esophagitis, Barrett’s esophagus, esophageal motility disorder, esophageal stricture formation, and esophageal adenocarcinoma.9,12-17 Individuals with nocturnal heartburn also report less satisfaction with PPIs and a diminished quality of life in terms of both mental and physical components, compared with GERD patients, who do not experience nocturnal heartburn.7,18

Strategies for managing nocturnal gastric acidity include increasing PPI administration from once to twice daily, increasing the dose, switching to another PPI, or adding an H2RA at bedtime.19-21 Although this last strategy may provide short-term efficacy, its clinical utility may be limited by the potential for the development of tolerance to H2RAs as well as by the additional cost of therapy.

Lapses in controlling gastric pH during PPI therapy may impair the ability of PPIs to adequately protect against stress-related intestinal mucosal disease, a significant clinical problem that occurs in 70% to 90% of critically ill patients22 and portends increased morbidity as well as extended hospital stays.23-28 Among patients who are not given prophylactic pharmacological therapy, overt upper gastrointestinal (GI) bleeding has been documented in 17% of critically ill patients.23

More than a decade ago, investigators found that various degrees of acid suppression produced different physiological effects in the gastric milieu.23 At a pH of 4.5 or above, pepsin begins to be inactivated; at a pH of 5 or above, it becomes completely inactivated; and at a pH of 7 or above, there is a potential for a decreased incidence of peptic ulcer rebleeding in patients who have already achieved hemostasis.23 Some investigators suggest that a gastric pH of 6.5 or higher is optimal for preventing stress ulceration; at this value, pepsin is inactivated and blood coag-
In an open-label, randomized, two-period crossover comparator trial with a 10- to 14-day washout period between treatments, IR-OME in strengths of 40 and 20 mg was compared with delayed-release 40- and 20-mg omeprazole capsules.35,41 During each treatment period, healthy subjects received seven consecutive single daily doses of each dosage strength one hour before they ate a standardized high-fat breakfast.

As illustrated in Figure 1, the T_{\text{max}} observed with each dosage strength of the IR formulation occurred much sooner (P < .001) (at approximately 30 minutes with each dose) than that of the respective dose of the enteric-coated formulation (at 1.8 and 1.4 hours, respectively) with delayed-release omeprazole 40 mg and 20 mg (Table 2).

The AUC of IR-OME 40 mg is about three-fold higher than that of the 20-mg dose, and repeated exposure to the IR form results in increased bioavailability. The observed increase in the AUC is almost doubled from a single dose, compared with the steady state (Table 2A).35 Because taking IR-OME one hour after a meal decreases the AUC by approximately 26% at steady state, optimal pharmacokinetic parameters are achieved when patients take this drug on an empty stomach. However, the AUC associated with a postprandial 40-mg dose of IR-OME is still substantial (3,862 ng • hour/ml) in the range associated with a 70% reduction in baseline gastric acidity.35

Approximately 95% of omeprazole is protein-bound. In healthy subjects, its plasma half-life is about one hour (range, 0.4–3.2 hours) and the plasma clearance averages between 500 and 600 ml/minute. Most of the omeprazole (77%) is excreted as metabolites in the urine, and the remainder is eliminated in the feces.35

**Elderly Populations**

Older age produces a slight decrease in the elimination rate of omeprazole and
increases its bioavailability. Compared with a bioavailability of 58% in younger subjects, the bioavailability of a single 40-mg dose of IR-OME in healthy older subjects was 76%. The extent of metabolite excretion in the urine (70%) was similar to that observed in younger subjects. The plasma half-life was also similar at approximately one hour.

**Hepatic Impairment**

In patients with chronic hepatic disease, the bioavailability of IR-OME increases, reflecting a decrease in first-pass metabolism. The plasma half-life increases to approximately three hours, and plasma clearance decreases to about 70 ml/minute.

**Renal Impairment**

In patients with chronic renal impairment (the creatinine clearance is between 10 and 62 ml/minute per 1.73 m²), the bioavailability of omeprazole is slightly increased and urinary elimination is decreased. The reduced elimination is related to the decrement in creatinine clearance.

**PHARMACODYNAMICS**

A gastric pH of greater than 4 has long been established as the target for effective mucosal healing. Studies in healthy subjects have found that once-daily dosing of 40 mg and 20 mg of IR-OME maintains the gastric pH above 4 for 77% and 51%, respectively, of a 24-hour period. In these two studies, IR-OME maintained a median gastric pH of 5.2 with the 40-mg dose and 4.2 with the 20-mg dose. The median 24-hour gastric pH exceeded 4 for 18.6 hours with 40 mg and 12.2 hours with 20 mg. The decrease from baseline for integrated gastric acidity (or total accumulated gastric acid) with IR-OME 40 mg was 84%; with 20 mg, the decrease was 82%.

Although no head-to-head studies have compared IR-OME with delayed-release esomeprazole, lansoprazole, or rabeprazole, the duration of time that IR-OME 40 mg and 20 mg maintain the gastric pH above 4 is slightly longer than the values reported in the product labeling for these delayed-release compounds (Table 3). In all cases, given the relatively short plasma half-lives of these medications (about one hour), the extended durations of antisecretory effects probably reflect the irreversible binding to the parietal cell H+/K+ ATPase enzyme by the PPIs.

**CLINICAL TRIALS**

**Efficacy**

**Nocturnal Acid Control**

One trial has confirmed the effectiveness of a bedtime dose of IR-OME in controlling nocturnal gastric acidity. Goldlust and colleagues presented data from an open-label study. IR-OME 20 mg
was administered once a day one hour before breakfast for seven days to 17 healthy subjects. On the eighth day, the participants received IR-OME 20 mg twice daily, one hour before breakfast and at bedtime (10 p.m., or 2200 hours). Twenty-four-hour gastric pH monitoring was performed on days seven and eight.

Figure 2 depicts the 24-hour median gastric pH profiles of patients taking IR-OME at the steady state with 40 mg once daily in the morning, 20 mg once daily in the morning, and 20 mg twice daily, in the morning and at bedtime. As shown in Figure 2C, the bedtime dose of IR-OME rapidly raised the gastric pH and sustained this effect for approximately eight hours. The median percentage of nighttime hours during which the gastric pH was above 4 was 87% with twice-daily dosing of 20 mg and 39% with once-daily morning dosing of 20 mg of IR-OME (P < .001).\(^4\) Twice-daily administration of 20 mg of IR-OME also significantly reduced the percentage of patients with NAB, compared with 20 mg administered once daily in the morning, namely, 29% (five of 17 patients) versus 76% (13 of 17 patients) (P = .005).\(^4\)

Castell and colleagues compared the nighttime gastric pH control of IR-OME suspension with that of delayed-release pantoprazole tablets.\(^4\) (Pantoprazole is currently the only PPI that is FDA-approved to treat nighttime symptoms of GERD.) In the first period of the open-label, two-period crossover trial, patients with a history of nocturnal GERD symptoms were randomly assigned to receive either IR-OME or pantoprazole. IR-OME 40 mg (n = 32) was taken at bedtime (10 p.m.) for six days. On day seven, 15 patients were randomly selected to receive IR-OME 20 mg twice daily, one hour before breakfast and at bedtime; 17 patients received IR-OME 40 mg twice daily, also one hour before breakfast and at bedtime.

Pantoprazole 40 mg was administered at 10 p.m. on day one and before dinner on days two through six. On day seven, this dose was given twice: one hour before breakfast and at bedtime. After a 10- to 14-day washout period, patients “crossed over” to the alternate treatment in the second period.

As illustrated in Figure 3, statistically significant differences (P < .001) were observed between the once-daily and twice-daily IR-OME suspensions and the comparative pantoprazole regimen in the median percentages of time that the gastric pH was maintained above 4 during the eight-hour nighttime interval (from 10 p.m. to 6 a.m.). For each paired comparison, the median values were as

---

**Table 3** Pharmacodynamic Parameters of Proton Pump Inhibitors by Product Labeling

<table>
<thead>
<tr>
<th></th>
<th>IR-OME (Zegerid(^ \circledR ))</th>
<th>Esomeprazole (Nexium(^ \circledR ))</th>
<th>Lansoprazole (Prevacid(^ \circledR ))</th>
<th>Rabeprazole (Aciphex(^ \circledR ))</th>
<th>Pantoprazole (Protonix(^ \circledR ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time gastric pH &gt; 4 (hours)</td>
<td>18.6 12.2</td>
<td>16.8 12.7</td>
<td>15.8 11.7</td>
<td>14.4 NA</td>
<td>14.4 NA</td>
</tr>
<tr>
<td>Percentage of time with gastric pH &gt; 4</td>
<td>77% 51%</td>
<td>70% 53%</td>
<td>66% 49%</td>
<td>60% NA</td>
<td>60% NA</td>
</tr>
<tr>
<td>Median gastric pH</td>
<td>5.2 4.2</td>
<td>4.9* 4.1*</td>
<td>4.9* 4.0*</td>
<td>3.5 3.8</td>
<td>3.8 2.9</td>
</tr>
</tbody>
</table>

IR-OME = immediate-release omeprazole; NA = not available.
* Mean.
Data from package inserts.\(^3\) 44–47

---

Figure 2 A, B. Twenty-four-hour gastric pH profiles of immediate-release omeprazole (IR-OME). Repeated administration of IR-OME in the morning produces a gastric acidity profile similar to other proton pump inhibitors (PPIs). C. Adding a second bedtime dose of IR-OME abruptly raises the gastric pH and sustains this level throughout the nighttime interval. HS = at bedtime. (From Goldlust B, Hepburn B, Hardiman Y. *Am J Gastroenterol* 2004;99:339.\(^4\))
shown in Figure 3.

The median nighttime gastric pH values were 4.7 with IR-OME 40 mg and 2 with pantoprazole 40 mg on day six ($P < .001$).

The percentage of patients who experienced NAB was also significantly smaller during IR-OME therapy than with pantoprazole on days six and seven ($P \leq .005$ for each comparison) (Figure 4). On day six, significantly fewer patients treated with IR-OME 40 mg (53.1%) experienced NAB than when they had used pantoprazole 40 mg (78.1%) ($P = .005$).

Twice-daily IR-OME produced a significantly higher median percentage of time during which the gastric pH was maintained above 4, compared with twice-daily pantoprazole during the 24-hour interval (10 p.m. to 10 p.m.). A median gastric pH level greater than 4 was maintained for 87.8% of the 24-hour interval with twice-daily IR-OME 40 mg, compared with 56.9% ($P < .001$) observed during twice-daily therapy with pantoprazole 40 mg.

At steady state, the median percentage of time with the gastric pH above 4 during the 24-hour interval was similar for paired patients taking once-daily IR-OME 40 mg and twice-daily pantoprazole 40 mg (Figure 5).

Reduction in Risk of Upper GI Bleeding in Critically Ill Patients

Conrad and colleagues established the efficacy of IR-OME in reducing the risk of upper GI bleeding in critically ill patients in a multicenter, randomized, double-blind, double-dummy, parallel-group study of 359 patients. These patients, who were undergoing mechanical ventilation in the intensive care unit (ICU) and had Acute Physiology and Chronic Health Evaluation II (APACHE II) scores of 11 or higher and one additional risk factor for upper GI bleeding, were enrolled at 47 sites in the U.S.

The patients were assigned to receive either IR-OME suspension via nasogastric or orogastric tube at a dose of 40 mg twice daily on day one (six to eight hours apart) and 40 mg once daily thereafter (and continuous intravenous [IV] placebo) or IV cimetidine (Tagamet® GlaxoSmithKline), given as a 300-mg bolus. This dose was followed by an infusion of 50 mg/hour thereafter (and placebo oral suspension). Each regimen was administered for up to 14 days.

Gastric aspirates were sampled for upper GI bleeding every two hours on the first and second days, then every six hours for the remaining study days. Gastric aspirates were also used to measure pH every two hours on the first and second days and immediately before and one hour after administration of the IR-OME suspension on days 3 to 14. The dose of IR-OME or cimetidine was doubled for patients with two successive gastric aspirates of a pH of 4 or less. A second daily dose of IR-OME 40 mg was administered to patients only on the day when they had two successive gastric aspirates of a pH of 4 or less, whereas the dose of cimetidine was doubled to 100 mg/hour for the duration of the study. Patients were permitted enteral feedings after the third day. Feedings were held for three hours before and for one hour after administration of the IR-OME suspension.

The primary efficacy endpoint of this non-inferiority study was the occurrence of clinically significant upper GI bleeding. This was defined as bright-red blood via a nasogastric or an orogastric tube that had not cleared after 5 to 10 minutes of lavage or as persistent Gastroccult®, positive coffee-ground material for at least eight consecutive hours on days one and two or for two to four hours on days...
whom were white, were treated for a mean of 6.8 days. Patient characteristics were similar between the treatment groups.49

The rates of clinically significant bleeding were 4.5% with IR-OME and 6.8% with cimetidine. These results satisfied the criteria for the non-inferiority of IR-OME in preventing upper GI bleeding in critically ill patients compared with IV cimetidine. IR-OME was more effective than IV cimetidine in maintaining a median gastric pH above 4.0 in critically ill patients.

The effects of IR-OME on gastric pH were consistent regardless of patients’ baseline pH values. Median gastric pH values greater than 6 were observed in almost all patients following the first dose of IR-OME. A median gastric pH above 6 was sustained on all days for patients receiving IR-OME but persisted on only 50% of the days for patients receiving cimetidine (Figure 6).

After three days of cimetidine administration, the median gastric pH began to decline, suggesting the development of tachyphylaxis. After day eight, at least 25% of the cimetidine patients had a median gastric pH below 4. During the entire trial, failure of pH control (two consecutive gastric aspirates of pH of 4 or below at least one hour apart on the same day) was observed in 58% of the cimetidine patients but in only 18% of the IR-OME patients ($P < .001$).

The incidence and type of adverse drug events (ADEs) reported with IR-OME and cimetidine were similar. For instance, nosocomial pneumonia occurred at a rate of 11.2% with IR-OME and at a rate of 9.4% with IV cimetidine ($P = .61$).49

All currently available PPIs, including IR-OME, are effective in relieving GERD symptoms, healing gastroduodenal ulcers, providing treatment of erosive esophagitis, and maintaining healing of lesions. Unlike the other PPIs, IR-OME may control nocturnal gastric acidity when it is given at bedtime.

IR-OME is the only PPI that has been subjected to clinical study and carries an FDA indication for reducing the risk of upper GI bleeding in critically ill patients.

Safety
Adverse Effects
In the U.S. trial of omeprazole, the most frequently reported ADEs in 465 patients that were considered possibly, probably, or definitely treatment-related were headache (in 2.4% of patients), diarrhea (in 1.9%), rash (in 1.1%), nausea (in 0.9%), constipation (in 0.9%), dizziness (in 0.6%), vomiting (in 0.4%), abdominal pain (in 0.4%), and asthenia (in 0.2%).

Occasional cases of atrophic gastritis have been noted in gastric corpus biopsies of patients receiving long-term omeprazole therapy.

A symptomatic response to omeprazole does not preclude the presence of gastric malignancy.35
Sodium Bicarbonate
Each 40-mg and 20-mg dose packet of IR-OME contains 460 mg of sodium in the form of sodium bicarbonate (1,680 mg, 20 mEq). This fact should be taken into consideration for patients who are following sodium-restricted diets. The use of IR-OME is contraindicated in patients with metabolic alkalosis and hypocalcemia. Sodium bicarbonate should also be used with caution in patients with Bartter’s syndrome, hypokalemia, respiratory alkalosis, and acid–base imbalances.

The long-term administration of sodium bicarbonate with calcium or milk can induce the milk-alkali syndrome.35

DRUG INTERACTIONS
Like the delayed-release, enteric-coated, oral PPI formulations, IR-OME may prolong the elimination of drugs that are metabolized by oxidation in the liver, such as diazepam (Valium®, Roche), warfarin (Coumadin®, Bristol-Myers Squibb), and phenytoin (Dilantin®, Pfizer). Increased International Normalized Ratios (INRs) and prothrombin times have been reported in patients receiving concomitant warfarin and omeprazole therapy. These increases may lead to abnormal bleeding and possibly death. Therefore, patients taking warfarin and omeprazole concomitantly should be monitored closely for INRs and prothrombin times.35

In studies of once-daily omeprazole 40 mg and clarithromycin (e.g., Biaxin®, Abbott) 500 mg every eight hours administered to healthy men, the steady-state plasma concentrations of omeprazole were increased: the Cmax by 30%, the AUC by 89%, and the half-life by 34%.35

INDICATIONS
As summarized in Table 1, IR-OME is indicated for the short-term treatment (four to eight weeks) of active duodenal ulcer, heartburn, and other symptoms associated with GERD; the short-term treatment of erosive esophagitis, as diagnosed by endoscopy; the maintenance of healing of erosive esophagitis (studies do not extend beyond 12 months); and the short-term treatment of active benign gastric ulcer.35 This is the only PPI to date that is indicated for lowering the risk of upper GI bleeding in critically ill patients and for nasogastric and/or orogastric tube administration.35

DOSEAGE AND ADMINISTRATION
The recommended dose of IR-OME is 40 mg or 20 mg, based upon the indication, to be taken once daily on an empty stomach at least one hour before a meal. When taken at bedtime, it reduces nocturnal gastric acidity to an extent that has not been observed with once-daily dosing of delayed-release PPIs.

Dosage modification is generally not needed in elderly patients or in those with mild-to-moderate renal or hepatic impairment.

The IR formulation is currently available as a peach-mint flavored powder for oral suspension in 40- and 20-mg packets. Because of this product’s unique pharmacokinetic profile, there are no therapeutically equivalent, and it is not AB-rated compared with delayed-release omeprazole (Prilosec®, Prilosec® OTC).50

The oral suspension offers an alternative for patients (e.g., elderly people and children) who require PPI therapy for acid-related conditions but who have difficulty swallowing tablets or capsules. Absorption is optimized when patients take this product on an empty stomach at least one hour before a meal. For the control of nighttime gastric acidity, however, the effect is greatest when it is taken at bedtime on an empty stomach.

Patients should be instructed to pour a packet of the powder for oral suspension into a small cup containing one to two tablespoons (15–30 ml) of water, to stir well, and to drink immediately. No other liquids or foods should be mixed with the powder. The cup should be refilled with an additional small amount of water, and this should also be consumed right away to ensure that a complete dose is ingested.35

For patients with nasogastric or orogastric tubes, the powder should be constituted with approximately 15 to 30 ml of water (0.5–1.0 fluid ounce). Other liquids or foods should not be used. The suspension should be stirred well and administered immediately, and a syringe of the appropriate size should be used to instill the suspension in the tube. The suspension should be washed through the tube with an additional 20 ml of water.35

The FDA is currently reviewing 40-mg and 20-mg IR-OME capsules and IR-OME chewable tablets.

CONCLUSION
The unique “non-enteric” formulation of IR-OME provides more rapid absorption and decreased time to peak plasma concentrations than do enteric-coated, delayed-release PPIs. These pharmacokinetic properties may confer advantages for patients with acid-related disorders, as suggested by emerging data about the product’s effectiveness in controlling nocturnal gastric pH in symptomatic GERD patients and its ability to control gastric acidity in critically ill patients.

Oral IR-OME, when taken on an empty stomach at bedtime, is effective in controlling nocturnal gastric acidity. It is an alternative to the use of IV acid-suppressant therapy for attaining and sustaining a gastric pH above 6 and for lowering the risk of upper GI bleeding in critically ill patients.

REFERENCES
9. Katz PO, Anderson C, Khoury R, Castell DO. Gastro-oesophageal reflux associated with nocturnal gastric acid break-


