

Immediate-Release Omeprazole for the Treatment of Nighttime GERD

A Review of Findings Presented at the
2006 Digestive Disease Week Meeting
May 20–25, 2006
Los Angeles, Calif.

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This review article contains certain information not included in the approved U.S. labeling for ZEGERID® (omeprazole/sodium bicarbonate), including alternate dosing schedules for treatment of GERD and suggestions of comparative efficacy to other PPIs. Please see ZEGERID package insert for complete prescribing information.

Special Considerations in Nighttime GERD Treatment

Gastroesophageal reflux disease (GERD) is a common health condition, with an estimated 15% of adults in the United States experiencing frequent reflux,^{1,2} and about 75% of these individuals having nocturnal symptoms. Nighttime GERD has significant effects, both immediate and long-term, including both physical and mental components. In a US telephone survey, individuals with nighttime GERD reported significantly poorer health-related quality of life compared with the general population. They reported levels of pain greater than individuals with hypertension and diabetes and similar to those with angina and congestive heart failure.¹ Moreover, 63% of individuals with nighttime GERD said that heartburn prevented them from sleeping well and 40% said that these sleep impairments affected their ability to function the next day.

Nocturnal GERD is associated with an increased risk of esophagitis and esophageal adenocarcinoma.³ In a population-based case-control study, persons with recurrent reflux, defined as having heartburn, regurgitation, or both at least weekly, had a 7.7-fold increased risk of esophageal adenocarcinoma compared with those without reflux; the relative risk increased to 10.8-fold among those with nocturnal symptoms.⁴

Transient lower esophageal sphincter relaxations have been identified as the primary mechanism of GERD but not the cause.⁵ The causes of nighttime GERD remain incompletely defined, and various factors, genetic and nongenetic, may be involved. Several characteristics are associated with an increased likelihood of having GERD, including respiratory conditions. In a population-based study of more than 65,000 persons in Norway, asthma

was associated with a 60% increase in the incidence of GERD after adjusting for use of asthma medication.⁶ Severity of reflux symptoms increased significantly with the degree of breathlessness. Body weight is also associated with the development of GERD—persons who are overweight or obese are at a significantly increased risk of having reflux symptoms. Even within the normal weight range, women who gain weight equivalent to a body-mass index increase of more than 3.5 are nearly three times as likely to have frequent reflux symptoms than are women who maintain their weight.⁷

Specific Risks of Nighttime GERD

The timing of GERD symptoms appears to significantly affect their severity. Although nocturnal reflux events occur less frequently than daytime events, they appear to be more severe. During the day, reflux generally occurs in short bursts after a meal, whereas nocturnal events, which are more prolonged, cause an increased duration of exposure to acid. Moreover, the body responds differently to esophageal acid exposure depending on when reflux occurs.^{8,9} During the day, the body responds by increasing salivary flow, increasing peristalsis, and inducing heartburn. These actions help clear the reflux and promote acid neutralization. During the night, however, these responses do not occur, leading to prolonged acid exposure.

Nighttime reflux appears to occur primarily in the early nighttime hours. Consecutive pH analyses of 59 patients with reflux, defined as having a pH below 4 at least 1.2% of the time while recumbent, showed that reflux was significantly more frequent during the first half

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of the recumbent period, with a median relative reflux time of 6.3% versus 0.3% during the second half of the period ($P < .001$).¹⁰

Treatments for Nighttime GERD

In 2006, Kaltenbach and colleagues¹¹ published a meta-analysis of 100 studies evaluating the impact of lifestyle modifications on GERD symptoms. Weight loss improved both esophageal pH profiles and GERD symptoms.

Over-the-counter medications represent a popular choice for patients. In the nationwide telephone survey, 71% of the 791 respondents with nighttime heartburn reported using over-the-counter treatments.² However, only 29% of respondents considered these treatments extremely effective. A total of 41% had used prescription medications for GERD and 49% considered this treatment strategy extremely effective. Apparently there is considerable room for improvement in the treatment of nighttime GERD.

Proton pump inhibitors (PPIs) have demonstrated considerable efficacy in the treatment of nighttime GERD. They suppress acid, minimize the effects of reflux on the esophageal mucosa, and decrease intragastric volume, thereby reducing the likelihood of reflux. H₂ receptor antagonists (H₂RAs) represent another treatment option, though PPIs offer more complete and faster symptom relief, according to a meta-analysis of 43 randomized studies involving 7,635 patients.¹² A number of PPIs have demonstrated efficacy in nighttime GERD, including esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole.

Importance of Dose Timing in Nighttime GERD Treatment

Dose timing of PPIs is important for maximizing efficacy. PPIs are generally taken in the morning, though different strategies have been evaluated in clinical trials. Pehlivanov and colleagues¹³ compared the efficacy of rabeprazole 20 mg administered either 30 minutes before breakfast or 30 minutes before the evening meal. Compared with morning administration, evening dosing significantly reduced nighttime supine esophageal acid exposure (0.2% vs 3.4%) and provided a significantly better reduction in mean nocturnal gastric acid breakthrough from baseline. In another study in which healthy volunteers (N=18) took omeprazole 40 mg before breakfast, 40 mg before dinner, or 20 mg before breakfast and dinner, nocturnal acid breakthrough occurred significantly more with the morning-only dose versus the evening dose or twice-daily dosing.¹⁴ The duration of gastric pH below 4 was also sig-

nificantly longer with the morning-only dose than with the other regimens.

These studies suggest that dose timing could significantly alter the ability of a treatment to minimize reflux and reduce symptoms. In addition to the time of day, the relation of dosing to meals may also be an important factor—taking PPIs before meals is thought to enhance treatment efficacy. However, many patients do not follow their prescribed dosing schedule. In fact, a study of 100 patients taking PPIs for persistent GERD symptoms showed that 54% of patients had suboptimal dosing habits, taking their PPI more than an hour before meals (39%), after meals (30%), at bedtime (28%), or as needed (4%).¹⁵ Only 12% of patients took their PPIs the recommended 15–30 minutes before meals.

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Immediate-Release Omeprazole for the Treatment of Nighttime GERD

A Review of: Nocturnal Gastric Acidity After Bedtime Dosing of Proton Pump Inhibitors in Patients With Nighttime GERD Symptoms

PO Katz, ED Ballard II, FK Koch, RG Bagin, and TC Gaultile

Presented at the 2006 Digestive Disease Week Meeting May 20–25, 2006 Los Angeles, Calif.

The recently introduced immediate-release omeprazole (Zegerid [omeprazole/sodium bicarbonate], Santarus, Inc.) may help control nighttime GERD while allowing patients to take the medication at bedtime. In an open-label crossover trial, Castell and colleagues¹ randomized 36 patients with nighttime GERD to either immediate-release omeprazole or delayed-release pantoprazole dosed either once or twice daily. Once-daily doses were taken in the evening, at bedtime for immediate-release omeprazole and either before dinner or at bedtime for pantoprazole. For the twice-daily regimens, a morning dose before breakfast was added to the bedtime dose. Patients randomized to once-daily immediate-release omeprazole had significantly better nocturnal gastric acid control than those randomized to once-daily pantoprazole or twice-daily pantoprazole. Observed benefits included a higher median gastric pH (4.7 vs 2.0 and 1.7, respectively), a higher proportion of time with a pH above 4 (55% vs 27% and 34%), and a lower proportion of patients experiencing nocturnal acid breakthrough (NAB; 53% vs 78% and 75%). Twice-daily immediate-release omeprazole 20 mg and 40 mg provided the greatest nocturnal acid control. Overall, 24-hour pH control was similar with once-daily immediate-release omeprazole 40 mg and twice-daily pantoprazole 40 mg.

In a study presented at the 2006 Digestive Disease Week Meeting, Katz and colleagues² compared gastric acid control obtained with once-daily bedtime dosing of immediate-release omeprazole 40 mg, lansoprazole 30 mg, or esomeprazole 40 mg. In this 3-period crossover trial, patients (N=54) were initially randomized to one of the three regimens. They received each regimen for 1 week, separated by 10-day washout periods. They took the study drug at bedtime on an empty stomach,

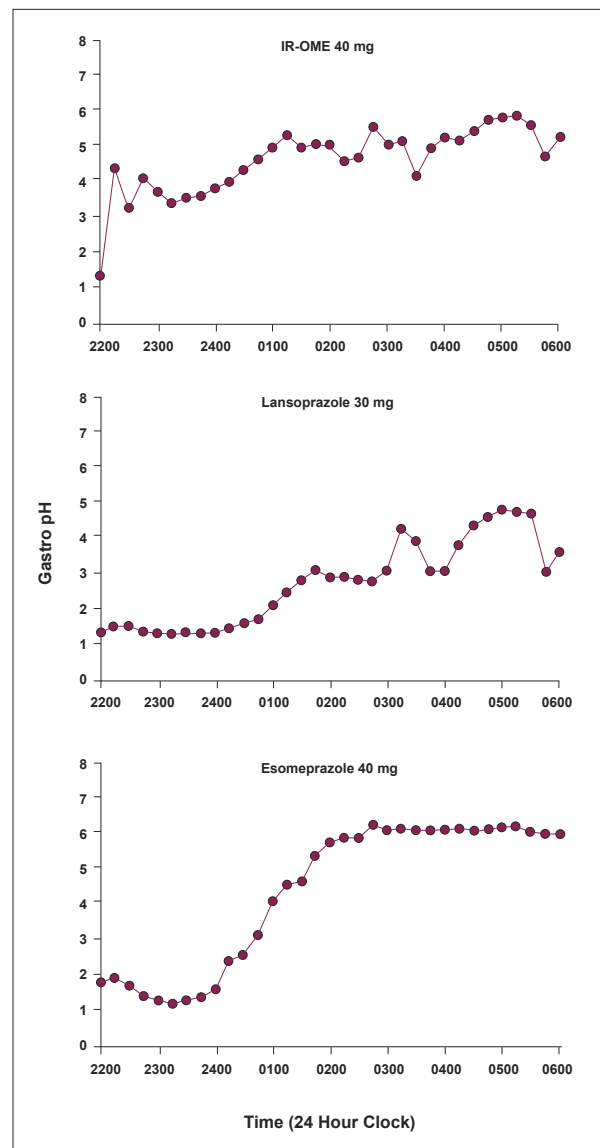


Figure 1. Once-daily bedtime dosing of immediate-release omeprazole vs lansoprazole vs esomeprazole: median gastric pH during the night on day 7.

IR-OME = immediate-release omeprazole/sodium bicarbonate suspension.

Table 1. Once-Daily Bedtime Dosing of Immediate-Release Omeprazole vs Lansoprazole vs Esomeprazole: Summary of Gastric Acidity After Bedtime Dosing on Day 7

Treatment	Nighttime Intervals			
	10 pm–12 am	10 pm–2 am	10 pm–4am	10 pm–6 am
<i>Immediate-Release Omeprazole/Sodium Bicarbonate Suspension (IR-OME) 40 mg</i>				
Percent time gastric pH >4	32.3 (6.6–94.1)	51.9 (16.8–88.7)	62.6 (26.0–88.1)	53.4 (31.3–90.3)
Median gastric pH	3.54 (1.88–5.14)	4.34 (2.27–5.57)	4.35 (2.63–6.13)	4.04 (3.04–6.13)
Integrated gastric acidity	10.9 (1.2–54.0)	14.1 (1.7–70.5)	27.6 (7.2–104.7)	35.4 (9.1–135.5)
<i>Lansoprazole 30 mg</i>				
Percent time gastric pH >4	0.0 (0.0–0.3)*	12.0 (0.0–32.1)*	26.6 (2.8–43.9)*	34.2 (13.3–52.2)*
Median gastric pH	1.25 (1.01–2.39)*	1.51 (1.10–2.64)*	1.76 (1.31–3.32)*	2.09 (1.46–4.75)*
Integrated gastric acidity	120.9 (39.5–193.6)*	182.0 (67.9–320.2)*	215.1 (81.7–397.8)*	242.2 (107.1–443.4)*
<i>Esomeprazole 40 mg</i>				
Percent time gastric pH >4	0.1 (0.0–14.8)*	30.1 (5.1–48.6)*	46.5 (29.5–64.1)	54.9 (38.2–68.6)
Median gastric pH	1.43 (1.17–2.95)*	2.37 (1.49–3.92)*	3.49 (2.11–5.91)	4.85 (3.27–6.06)
Integrated gastric acidity	85.5 (28.4–141.4)*	103.9 (55.6–161.2)*	134.6 (55.6–176.2)*	135.0 (58.6–186.4)†

Medians and (25th and 75th percentiles) presented throughout

* $P < .001$; † $P = .008$, when compared with IR-OME when using the Wilcoxon signed-rank test.

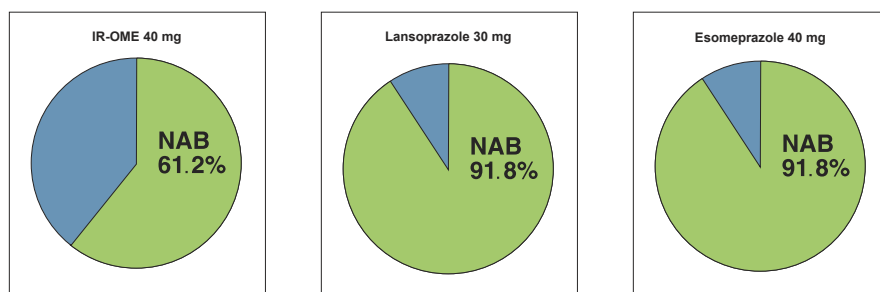


Figure 2. Percentage of patients with nocturnal acid breakthrough on day 7. $P < .001$ for both comparisons.

IR-OME = immediate-release omeprazole/sodium bicarbonate suspension; NAB = nocturnal acid breakthrough.

approximately 5 hours after dinner. Beginning at 7 am on day 7 of each study period, patients underwent 24-hour gastric pH monitoring. The primary endpoint was NAB, defined as having a gastric pH above 4 for longer than one continuous hour between 10 pm and 6 am.

The bedtime dose of immediate-release omeprazole was associated with a rapid increase in gastric pH that was not observed with lansoprazole or esomeprazole. Immediate-release omeprazole provided significantly greater gastric acid control than lansoprazole in terms of the proportion of time with gastric pH above 4 (53.4% vs 34.2%; $P < .001$) and median gastric pH (4.04 vs 2.09; $P < .001$). Overall, gastric pH-related outcomes achieved with esomeprazole were similar to those observed with immediate-release omeprazole (Figure 1, Table 1). However, a breakdown of gastric acidity by time period showed that immediate-release omeprazole provided significantly better acid control than lansoprazole or esomeprazole in the first half of the night according to percent time with gastric pH above 4 and median gastric pH. This early benefit is important, given that most reflux occurs during the first half of the night.³

Immediate-release omeprazole was also associated with significantly lower integrated gastric acidity than lansoprazole or esomeprazole in the first half of the night and during the 8-hour period from 10 pm to 6 am. Moreover, NAB occurred in significantly fewer patients taking immediate-release omeprazole (61.2%) versus lansoprazole (91.8%) or esomeprazole (91.8%) ($P < .001$ for both comparisons; Figure 2).

In summary, these recent studies indicate that immediate-release omeprazole provides effective, sustained control of gastric acidity while allowing convenient once-daily bedtime dosing.

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Commentary

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It was in the late 1990s that Castell, Katz, and associates completed their early work on the phenomenon of nighttime gastric acid breakthrough. They observed that in both gastroesophageal reflux disease (GERD) patients and healthy individuals, twice daily dosing with a proton pump inhibitor (PPI) taken before breakfast and before dinner did not provide complete 24-hour inhibition of production of gastric acid. Instead, with this regimen, in the early morning hours between midnight and 2 or 3 am, most patients and healthy individuals resume the ability to secrete gastric acid. The investigators added a third dose of PPI, and found that administering a PPI at breakfast, at dinner, and at bedtime still did not inhibit the previously observed nocturnal acid breakthrough. Later it was demonstrated that dosing with an H₂ receptor antagonist (H₂RA) at bedtime, along with the two doses of PPIs before breakfast and dinner, was more effective than a third PPI dose at inhibiting nocturnal acid production.

At this point clinicians and researchers were aware of the issue of nighttime acid breakthrough as a normal physiologic and pharmacologic observation. In the long term, H₂RAs are relatively ineffective in preventing nocturnal acid breakthrough due to issues of potency and tolerance that develop in some patients. Further, a recent meta-analysis of lifestyle modification recommendations (eg, nighttime dietary restrictions, head-of-the-bed elevation) has shown them to be relatively ineffective in controlling symptoms of GERD both during the day and nocturnally. This observation is likely due to the fact that patients experience reflux due to transient sphincter relaxation, which is a neuromuscular abnormality of the lower esophageal sphincter, or because of an incompetent sphincter, phenomena that cannot be addressed adequately by lifestyle modification.

Thus, without the tools to control nighttime gastric acid breakthrough, research continued to focus on daytime dosing, symptom control, and the healing of esophagitis that can be achieved with traditional delayed-release PPIs. The problem of nighttime GERD symptoms was understudied and incompletely understood. It is only recently that the prevalence of these symptoms and their impact on patient quality of life, most likely due to sleep disturbance, has been more fully recognized. With the

introduction of a new, immediate-release formulation of the PPI omeprazole (Zegerid [omeprazole/sodium bicarbonate], Santarus, Inc.), which seems uniquely able to inhibit nighttime gastric acid breakthrough, new interest is being generated in this arena.

The study presented at the 2006 Digestive Disease Week in Los Angeles by Katz and associates is definitive in showing the substantially greater efficacy of immediate-release omeprazole versus two delayed-release formulations of PPIs in controlling gastric acid breakthrough in the most vulnerable nighttime hours of midnight to 2 am. Further, these results replicate and reinforce those of an earlier study comparing immediate-release omeprazole with a third delayed-release formulation of PPI, thus demonstrating a consistent pharmacologic effect between these PPI formulations.

The study design has been deemed controversial and has been criticized by some researchers because delayed-release PPI formulations are designed to be taken before stimulating the gastric pumps (ie, before a meal). In order to optimize the pharmacologic effect of these agents, they should be dosed before breakfast or dinner, not at bedtime as dosed in this study. However, other researchers commend the study design because it replicates the way that patients take their medicine in the real world. Although patients are advised to take medication before a meal, those with nighttime symptoms often, if not usually, will take it at bedtime, regardless of physician instruction. Thus the study design reproduces actual clinical experience and gives all three comparative treatments the same ground rules and the same hurdles to overcome in terms of patient compliance. As a physician, I believe that this real-world study design may be more valuable than carefully controlled experimental studies that may not have clinical relevance.

It should be noted that none of the studies comparing immediate- versus delayed-release PPI formulations for nighttime gastric acid breakthrough have examined patient quality of life or nocturnal symptom relief during the course of the study. Although it is likely, and clearly a valid hypothesis, that immediate-release omeprazole is the more effective agent in this regard, this specific outcome has not been studied and clinicians should be careful when making decisions and recommendations based on pharmacodynamic data alone. Further clinical studies specifically examining symptomatic outcomes will be required before we can adopt a dogmatic stance of bedtime dosing with immediate-release omeprazole for nighttime heartburn symptoms. There are plans for studies to support this concept but it remains speculative at this time.

Along with studies of nighttime symptom relief, other trials are also planned to examine the speed of

symptom relief with the immediate-release formulation. Another novel attribute of this product is its fast onset of action in controlling gastric pH. This is a critically important area of study in that there has been a shift in philosophy over the past 5 years that recognizes GERD as a symptom-driven disease. Historically, success of GERD therapy has focused on the healing of erosive esophagitis, which is an excellent objective measure but not one of concern to most GERD patients. Disease complications are unusual in patients effectively medicated to control their symptoms and there are now at least five randomized controlled trials showing that delayed-release PPIs, taken intermittently to control symptoms rather than daily as prescribed, are effective in maintaining patient quality of life. There are also data showing that most patients use PPIs intermittently to control symptoms, despite their once-daily prescription.

With this in mind, if patients are going to utilize “on-demand” therapy and data are available showing that on-demand therapy is effective, it then follows that the best formulation would be the one that works most quickly.

If PPI dosing is triggered by the experience of symptoms, then patients should not need to wait 1–2 days for the therapy to become effective. Immediate-release omeprazole has a pharmacologic profile that suggests an ability to provide immediate yet sustained symptom relief. Again, clinical studies must be completed to prove this hypothesis. If studies do confirm this hypothesis, this formulation will prove to be a better agent for patients utilizing PPI therapy on an on-demand basis.

Suggested Readings

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1-ZEG06230