Donald O. Castell, M.D., Series Editor

Immediate-release Omeprazole Powder: An Effective Alternative Approach to Refractory GERD

by Vishal Jain, Inder Mainie, Wojciech Blonski, Raj Sharma, and Donald O. Castell

Background: **Refractory GERD, defined as symptoms unresponsive to twice daily PPIs after four-to-eight weeks of therapy, occurs in 25%–42% of patients. Causes of refractory GERD include non-compliance, improper timing of dose, nocturnal acid breakthrough (NAB) and non-acid reflux. There is evidence that immediate-release omeprazole powder (IR-OME) could be effective in the management of patients with nocturnal reflux on PPIs.** ***Aim:*** **To identify if refractory GERD patients have symptom improvement with the addition or substitution of IR-OME.** ***Methods:*** **Records of 55 patients who were prescribed IR-OME with a bedtime dose for symptomatic GERD on daily PPIs were reviewed. During a phone interview patients were asked a five item questionnaire, which included overall assessment of symptoms, night-time symptoms, sleep disturbance, duration and frequency of therapy.** ***Results:*** **Of the 55 patients, 38 (25 female; mean age 52 years) completed the questionnaire (11 never took the medication and six could not be contacted). The majority of respondents had taken IR-OME for more than a month (32/38), with 66% (25/38) using it twice daily. The addition of IR-OME led to an improvement in overall symptoms in 57% (22/38) of patients, improvement in night-time reflux symptoms in 55% (21/38) and improvement of GERD associated sleep disturbance in 42% (16/38) of the patients.** ***Conclusion:*** **Our results suggest that bedtime IR-OME offers a potential advantage in refractory GERD patients, since symptom relief was obtained in the majority of these patients.**

INTRODUCTION

Gastroesophageal reflux disease (GERD), with its cardinal symptoms of heartburn and regurgitation, is the most common disorder of the esophagus (1). A Gallup survey reported that 14% of the general population has frequent GERD symptoms. Reporting data from a national survey, Shaker, et al showed that nighttime heartburn was an under-appreciated clinical problem (2). They reported that 79% of the respondents had experienced heartburn at night with the more troublesome finding of high prevalence of sleep disturbances attributed to nighttime heartburn and a negative impact on their next day function (3).

Single daily doses of proton-pump inhibitors (PPIs) provide marked suppression of gastric acid, resulting in effective treatment of symptoms of GERD in many patients and healing of esophagitis in 80%-90% of patients with typical GERD (4,5). However, for a subset of patients, a greater level of acid control

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is required not only for acceptable symptom relief but also for mucosal healing and prevention of complications (6). This group of patients often exhibits a higher grade of esophagitis and frequent extra-esophageal symptoms (7–9). Complete gastric acid control is often not attainable even with twice daily dosing of these medications due to a phenomenon called nocturnal acid breakthrough (NAB), defined by recovery of gastric acidity to a pH <4 for at least one continuous hour on a PPI taken twice daily. It is a common pharmacodynamic event, observed in approximately 70% of both healthy subjects and GERD patients treated with twice daily administration of delayed-release PPIs, regardless of whether the PPI is administered in the morning, prior to dinner, or at bedtime (10–12).

Various approaches to treating nighttime reflux have been proposed including lifestyle modifications (13), evening dose PPI (14), and adding a bedtime H_2RA (15). Initial studies with Immediate-release omeprazole powder (IR-OME), a compound in which omeprazole powder is combined with bicarbonate, suggest that there may be an advantage to bedtime administration of this agent over traditional PPIs in control of NAB (16).

DESIGN AND METHODS

The aim of this study was to evaluate whether refractory GERD patients show symptom improvement with the use of IR-OME powder. A retrospective review was conducted of records of patients referred to the esophageal clinic at the Medical University of South Carolina between October of 2004 and October 2006. Patients with persistent GERD symptoms on daily PPI, who were prescribed IR-OME, were selected for this study. The drug was either added to or substituted for the existing regimen with at least one dose taken at bedtime. The diagnosis of GERD was made by either an abnormal 24 hr pH study, abnormal multichannel intraluminal impedance pH (MII-pH) study off therapy, or esophagitis on endoscopy. All patients were contacted by phone by the same physician. Questions on the survey were designed to assess the efficacy of adding or substituting IR-OME to their current regimen for reflux symptom control. Patients were asked if they were prescribed and took IR-OME. If they

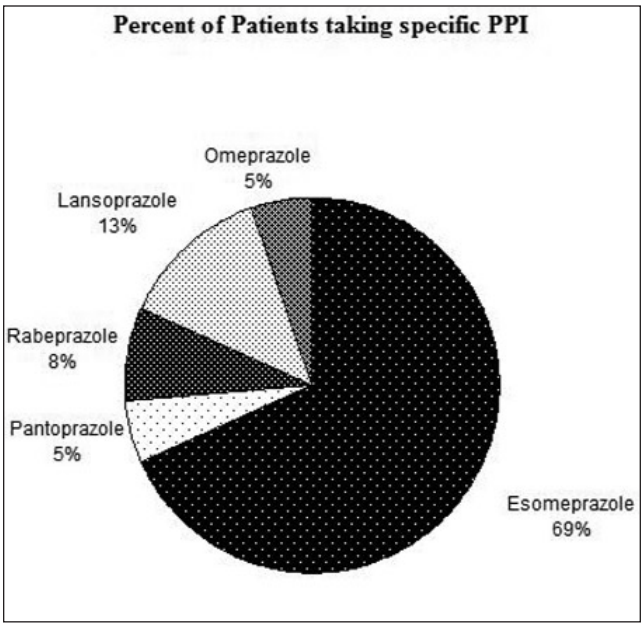

Figure 1. Percent of Patients taking specific PPI.

responded yes, five questions were asked verbatim and objectively. These included an assessment of overall symptoms, nighttime symptoms and sleep disturbance rated on a five point scale:

1. Much worse
2. Slightly worse
3. Same
4. Slightly better
5. Much better

In addition they were asked about frequency and duration of IR-OME use. Patients reported IR-OME therapy frequency as "once a day," "twice a day" or "more than twice a day". Duration of IR-OME therapy was categorized as "less than one month," "one to six months" or "greater than six months."

RESULTS

A total of 55 patients were identified with a diagnosis of refractory GERD who were prescribed IR-OME. Forty-nine (89%) were successfully contacted by phone and of these 11 never took the prescribed medication. All 38 patients who took the medication (25

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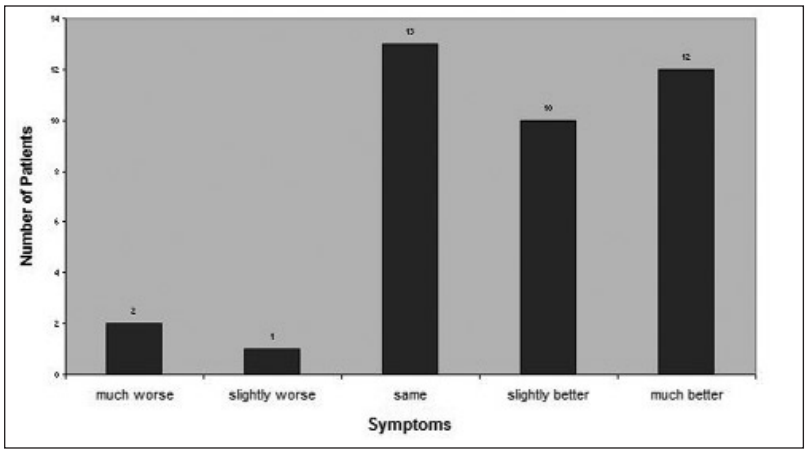

Figure 2. Overall symptom response with IR-OME.

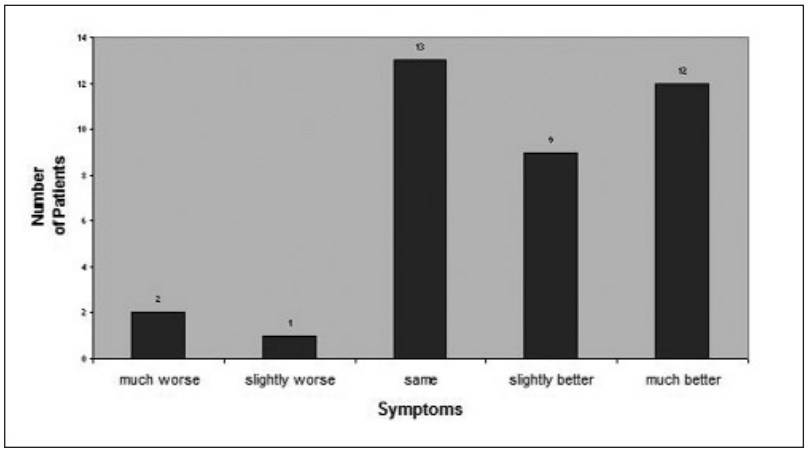

Figure 3. Nighttime symptom response.

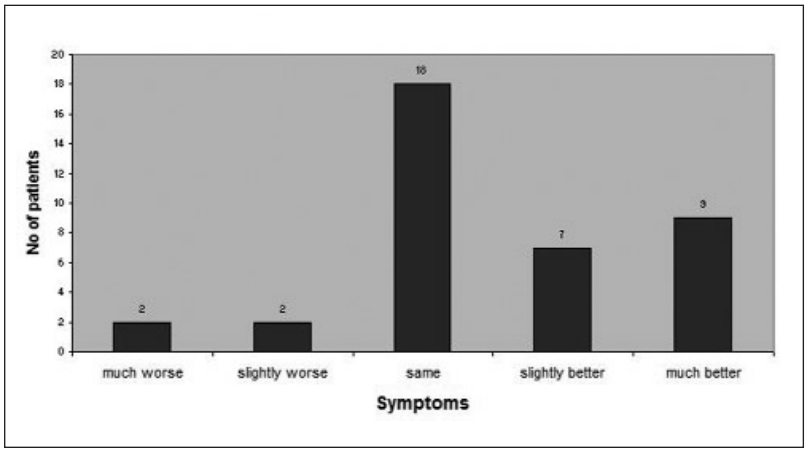

Figure 4. Sleep disturbance response.

female; mean age 52 yrs) had a diagnosis of GERD by MII-pH study, conventional pH study or endoscopy. Ninety-five percent (36/38) of the patients with persistent symptoms were on twice daily PPI. Specific PPI therapy is shown in Figure 1.

Some overall symptom improvement (either slightly better or much better) was perceived by 57% (22/38) of patients after addition/substitution of bedtime IR-OME while 34% (13/38) remained the same (Figure 2). A total of 21 patients (55%) reported at least some improvement in their nighttime symptoms (Figure 3) and 42% of the patients (16/38) said that they had a decrease in their sleep disturbances while on IR-OME (Figure 4).

The majority of patients (32/38: 84%) had been taking the IR-0ME for more than a month, the longest being on it for more than a year (Figure 5). The frequency of IR-OME use was varied. Sixty-five percent (25/38) took it twice daily with a nighttime dose and 10% (4/38) used it more than twice a day (Figure 6).

DISCUSSION

Patients with refractory GERD, defined as symptoms unresponsive to twice daily PPIs after four-to-eight weeks of treatment, should first undergo upper endoscopy to exclude complications (17). The next step in dealing with a patient who has continued nocturnal gastric acid production, esophageal reflux, and symptoms is to maximize the efficacy of the PPI. This is done by addressing the issue of dose timing. A careful history will often reveal that the evening PPI dose is being taken at bedtime rather than before dinner, thus minimizing the effect of the PPI on overnight pH control (18).

Nocturnal acid breakthrough occurring in approximately 70% of patients has been identified as one of the causes of refractory GERD. H_2-receptor antagonists (H_2-RAs)

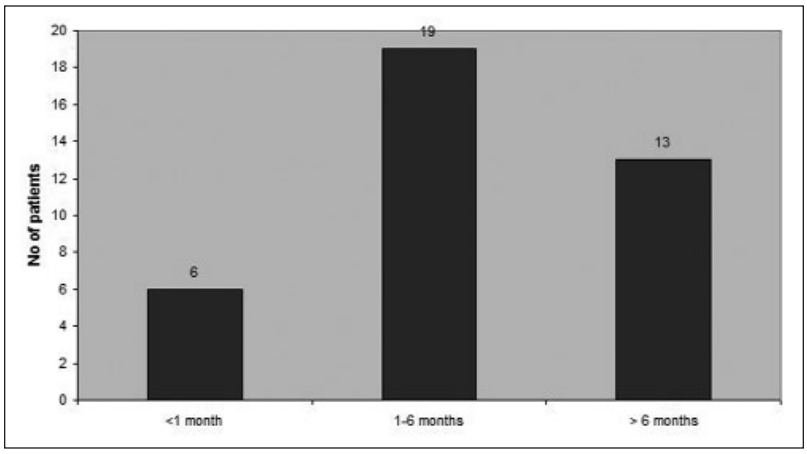

Figure 5. Duration of IR-OME use.

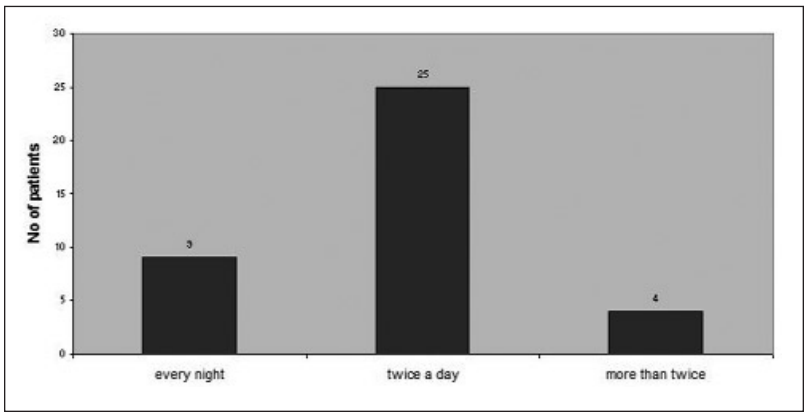

Figure 6. Frequency of IR-OME use.

at bedtime have been shown to successfully eliminate NAB in healthy volunteers. However, concerns about tolerance with usage over one week have been raised (19). Another alternative is to add IR-OME taken at bedtime as was done in our study. IR-OME is unique among PPI formulations in that it has no enteric coating. It is associated with rapid absorption of OME and rapid onset of increased intragastric pH due to the bicarbonate. Because IR-OME provides a better control of NAB than twice daily regimens of most delayed-release PPIs (16), and is not likely associated with the tachyphylaxis possible with long term use of H_2-RAs (20,21), chronic nighttime dosing with IR-OME may be a good long-term treatment option.

Our study shows that IR-OME with a bedtime dose improved overall symptoms in more than 55% of our patients with refractory GERD on daily delayed-release PPI. Furthermore, similar results were seen with nighttime symptoms and sleep disturbance. More than 54% reported improved nighttime symptoms with the addition of a nighttime dose of IR-OME. These observations suggest that there is a potential indication for nighttime IR-OME in refractory GERD patients, particularly those with troublesome nighttime symptoms. The explanation for the observation may lie in the requirement for gastric proton pumps to be in an active state in order to be maximally inhibited by a PPI. Delayed-release PPIs are often administered in conjunction with a meal to take advantage of the active pump status achieved by the meal itself (22), and they may be less effective given at bedtime since that stimulus is not present. It would appear that the rapid neutralization of the gastric acid contents by the sodium bicarbonate in the IR-OME formulation is sufficient to activate the proton pumps, rendering them more susceptible to the substantial plasma concentrations of omeprazole achieved within minutes of acid neutralization by the sodium bicarbonate. Also, IR-OME has a higher mean peak plasma omeprazole concentration (C_{max}) and a significantly shorter mean time to reach C_{max} (t_{max}) than delayed-release omeprazole (23). Bedtime dosing with 40 mg of IR-OME suspension provides better control of nocturnal gastric acidity than once daily dosing with delayed-release PPIs (16).

The results of our study have inherent limitations. Phone administered surveys are subject to observational bias while retrospective questions are subject to recall bias. Based on the current results, we believe that a prospective collection of similar data using a blinded, randomized, placebo-controlled design is warranted.

Because IR-OME provides better control of NAB than twice daily regimens of most delayed-release PPIs, and is not associated with the tachyphylaxis pos-

sible with long term use of H_2-RAs (19), chronic nighttime dosing with IR-OME may be a good long-term treatment option for patients with refractory GERD symptoms possibly related to nocturnal acid breakthrough. ■

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