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Editorial

Can Nocturnal Acid-breakthrough Be Reduced by Long-acting Proton Pump Inhibitors?

Hye Kyung Jeon and Gwang Ha Kim*

Department of Internal Medicine, Pusan National University School of Medicine, and Biomedical Research Institute, Pusan National University Hospital, Busan, Korea

Article: Esophageal acidification during nocturnal acid-breakthrough with ilaprazole versus omeprazole in gastroesophageal reflux disease
Karyampudi A, Ghoshal UC, Singh R, Verma A, Misra A, Saraswat VA
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Gastroesophageal reflux disease (GERD) is a condition characterized by reflux of the gastric contents causing troublesome symptoms and complications.[1] Proton pump inhibitors (PPIs) are the mainstay of treatment for GERD and significantly decrease gastric acid secretion. In spite of their potent acid suppression, PPIs cannot eliminate intragastric acidity, particularly during the night. PPIs have a relatively short plasma half-life and all proton pumps are not active at the same time. Therefore, during the night, the morning dosed PPIs are no longer effective on acid suppression of newly activated proton pumps. During the night, there is no gravity-mediated drainage and significant reduction in swallows; thus, reflux episodes are of longer duration.[2] Based on these circumstances, nocturnal acid-breakthrough (NAB) has been the subject of attention to describe refractory GERD. NAB was first described as a decrease in gastric pH less than 4 for at least 60 consecutive minutes in the overnight period in patients on twice-daily PPIs treatment.[3]

Originally, the rationale behind measuring intragastric pH and presence of NAB was that the stomach is the source of acid in the refluxate; suppression of gastric acid may reduce the injurious effect of the refluxate in GERD. To overcome short plasma half-life of PPIs, several pharmacological attempts have been made to control NAB with different regimens and doses of PPIs. In addition, investigators have also attempted to eliminate NAB by targeting the night time histamine surge, with administration of histamine H2 receptor antagonists (H2RA) (Table).[2,4-12]

What is the treatment effect of PPIs, which are known to have a longer plasma half-life on NAB? In this issue of the *Journal of Neurogastroenterology and Motility*, Karyampudi et al[13] evaluated esophageal acidification during NAB with ilaprazole, versus omeprazole in patients with uncomplicated GERD, in a prospective manner. A total of 58 patients with GERD prescribed 10 mg of ilaprazole or 20 mg of omeprazole once daily for more than 1 month were enrolled in this study, and underwent 24-hour impedance-pH monitoring. A total of 72.4% of patients had NAB. Despite the long-action of ilaprazole, its frequency, duration, and mean intra-gastric pH during NAB, as well as nocturnal esophageal acidification and nocturnal symptoms were comparable between the

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*Correspondence: Gwang Ha Kim, MD, PhD
Department of Internal Medicine, Pusan National University School of Medicine, and Biomedical Research Institute, Pusan National University Hospital, 179, Gudeok-ro, Seo-gu, Busan 49241, Korea
Tel: +82-51-240-7869, Fax: +82-51-244-8180, E-mail: doc0224@pusan.ac.kr

Table. Summary of Published Studies About Management of Nocturnal Acid-breakthrough in Gastroesophageal Reflux Disease

Authors	Year	Study design	Results
Hatlebakk et al[2]	1998	Volunteers (n = 18) 1) OME 40 mg qAM 2) OME 40 mg qPM 3) OME 20 mg bid	Split dosing was superior.
Khoury et al[4]	1999	Volunteers (n = 21) 1) OME 20 mg AM + OME 20 mg PM + placebo HS 2) OME 20 mg AM + placebo PM + H2RA HS	Bedtime H2RA did not replace an evening dose of PPI in patients requiring more than a single daily dose of PPI.
Xue et al[5]	2001	GERD patients 1) PPI bid (n = 60) 2) PPI bid + H2RAs HS (n = 45) 3) Both regimen (n = 11)	A bedtime H2RA enhanced nocturnal gastric pH control and decreased esophageal acid exposure during NAB.
Fackler et al[6]	2002	Volunteers (n = 18), GERD patients (n = 16) OME bid for 2 wk → OME bid + H2RA 300 mg HS for 28 day	Combination of H2RA and PPI reduced NAB only with introduction of therapy (due to H2RA tolerance).
Orr et al[7]	2003	Symptomatic GERD patients (n = 19) OME 20 mg bid for 1 wk + H2RA or placebo HS + nighttime provocative reflux meal	In spite of reduction of intragastric acidity, H2RA had no effect on the occurrence of gastroesophageal reflux during sleep.
Adachi et al[8]	2003	Volunteers without *H. pylori* (n = 10) 1) RAB 20 mg qAM 2) RAB 20 mg qAM + H2RA HS (last day only) 3) RAB 20 mg qAM + continuous H2RA HS 4) RAB 10 mg bid	Split dosing was better in gastric acid suppression. Continuous H2RA was less effective.
Shimatani et al[9]	2004	Volunteers without *H. pylori* (n = 18) 1) RAB 10 mg qAM 2) RAB 20 mg qAM 3) RAB 10 mg bid	Split dosing was more potent and long-lasting acid suppression.
Hammer et al[10]	2004	Volunteer (n = 13) 1) ESM 20 mg bid 2) ESM 40 mg qAM	Split dosing improved nighttime acid suppression.
Katz et al[11]	2007	Nocturnal GERD patients (n = 54) 1) IR-OME 40 mg HS 2) LPZ 30 mg HS 3) ESM 40 mg HS	Bedtime dosing with IR-OME was effective with night-time heartburn.
Mainie et al[12]	2008	GERD patients (n = 100) 1) PPI bid (n = 58) 2) PPI bid + H2RA HS (n = 42)	A bedtime H2RA reduced the percentage time of the intragastric pH < 4 and also NAB.

OME, omeprazole; qAM, once daily before breakfast; qPM, once daily before dinner; bid, twice a day; HS, at bed time; H2RA, histamine H2 receptor antagonist; PPI, proton pump inhibitor; GERD, gastroesophageal reflux disease; NAB, nocturnal acid-breakthrough; *H. pylori*, *Helicobacter pylori*; RAB, rabeprazole; ESM, esomeprazole; IR-OME, immediate release omeprazole; LPZ, lansoprazole.

ilaprazole and omeprazole groups. Among those who had NAB, a lesser number of NAB episodes occurred in the ilaprazole group compared to the omeprazole group ($P = 0.010$). On the contrary, a previous study showed that 20 mg of ilaprazole provided significantly higher mean 24-hour intragastric pH than the same dose of omeprazole and that low-dose ilaprazole (5 mg and 10 mg) offered a gastric acid inhibition comparable to a routine dose of omeprazole.[14] In another study, 10 mg or higher of ilaprazole may provide better control of NAB, nocturnal esophageal acidification, and nocturnal symptoms.[13]

Another important thing in this study was that the authors evaluated the clinical significance of NAB. The frequency and duration of nocturnal esophageal acidification and nocturnal symptoms were comparable with or without NAB. Regarding specific conditions

such as Barrett's esophagus, ineffective esophageal motility, and complicated GERD including high-grade erosive reflux disease, NAB has been reported to be more likely accompanied by esophageal reflux.[15-19] Therefore, if patients with these conditions show resistance to PPI treatment, the existence of NAB with nocturnal acid reflux should be considered. Otherwise, several previous studies suggested that NAB did not correlate well with esophageal acid exposure or nocturnal reflux symptom.[20-22] Ours et al[22] reported that all subjects, whether treated with a PPI or a PPI plus H2RA, and regardless of drug schedule, were asymptomatic after treatment despite the presence of NAB; they concluded that NAB is a purely gastric phenomenon with no correlation to esophageal acid levels or symptom improvement.

In regards to uncomplicated GERD patients who have particularly normal esophageal clearance mechanisms, the clinical importance of NAB is likely to be little. NAB is common during administration of PPIs, and identification of esophageal acidification and nocturnal symptoms are essential to evaluate the "real" clinical effect of PPIs on GERD, not intragastric pH.

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