EVIDENCE-BASED GI
AN ACG PUBLICATION

Addition of Bedtime Lafutidine Inhibits Nocturnal Acid-Breakthrough and Improves Sleep Quality in GERD Patients on

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This article reviews Wang D, He R, Zhang X, Duan C, Bai T, Xu J, Xiang X, Hou X. Addition of bedtime lafutidine inhibits nocturnal acid-breakthrough and improves sleep quality in gastroesophageal reflux disease patients on esomeprazole: A randomized controlled trial. Sci Rep. 2025 Jul 2;15(1):23286.

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Keywords: lafutidine, GERD, NERD, RCT.

STRUCTURED ABSTRACT

Question: Is the addition of bedtime lafutidine 10 mg (a new generation histamine 2-receptor antagonist) to esomeprazole 20 mg twice daily effective in inhibiting acid and improving the clinical patient's gastroesophageal reflux disease (GERD) symptoms?

Design: Single-center, observer-blinded, placebo-controlled, randomized trial.

Setting: A single center in China.

Patients: Patients had to meet all of the inclusion criteria for enrollment: 1) aged between 18 and 65-years old; 2) GERD-Q score≥8 with nocturnal symptoms (regurgitation

or heartburn); 3) completed upper endoscopy within the past year; 4) willingness to take part in this study. Patients with any of the following conditions were excluded: 1) there are contraindications to esophageal high-resolution esophageal manometry and 24-h pH monitoring, such as cardiopulmonary dysfunction, esophageal stenosis, or varices; 2) pregnant or lactating women; 3) participating in other clinical studies; 4) taking gastric acid-inhibiting drugs within 1 week.

Interventions/Exposure: The duration of treatment was 1 week. Patients were randomly assigned to either the treatment group (lafutidine+esomeprazole) or the control group (placebo + esomeprazole). Baseline information, symptom evaluation, and sleep quality were assessed at enrollment and upon completion of treatment. High-resolution esophageal manometry and 24-hour multichannel intraluminal impedance monitoring were performed on the last day of the treatment.

Outcome: The primary outcome was the intragastric pH metrics assessed after 1 week of treatment, including the nocturnal acid breakthrough rate and the gastric pH>4 holding time ratio (pH 4 HTR). The secondary outcomes include esophageal pH metrics, changes in symptom scores, and changes in sleep quality scores.

Data Analysis: The authors hypothesized that the incidence of nocturnal acid breakthrough would be 20% in the esomeprazole + lafutidine group and 60% in the esomeprazole + placebo group. A 10% difference between the 2 groups was determined to be clinically significant. Assuming a dropout rate of 10%, for 80% power at an alpha level of 0.05 with a 2-sided test, the required number of 2each group was 30. An interim analysis was conducted when enrollment reached 80% of the calculated sample size. The clinical trial was terminated early due to the demonstration of significant efficacy of the primary outcomes. The primary outcome analysis was conducted in the intention-to-treat (ITT) population, comprising all patients who received at least 1 dose of study medication. Multiple imputations were performed to address missing data for primary outcomes. All outcome analyses were further evaluated in the per-protocol (PP) population, which included patients who adhered to their assigned treatment regimen and completed the 1-week follow-up questionnaire and esophageal measurements.

Funding: National Natural Science Foundation of China and the Natural Science Foundation of Hubei Province, China.

Results: A total of 48 subjects were included from 59 enrolled participants (24 in each arm). The cohort was predominantly male sex (58.3% in both arms). Of the 59 participants, 8 were not willing to participate, 2 had low symptom scores, and 1 person was pregnant.

The addition of bedtime lafutidine to esomeprazole significantly increased nocturnal intragastric pH>4 holding time ratios and decreased the occurrence of nocturnal acid breakthrough (NAB). GERD patients who added lafutidine experienced a more pronounced improvement in sleep quality, and correlated with NAB reduction.

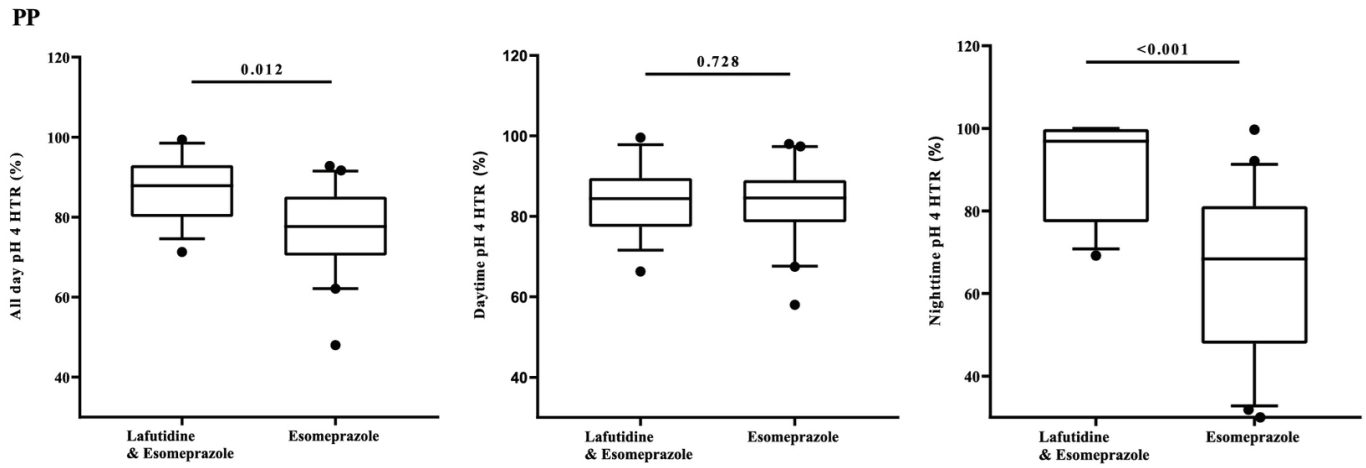

Figure 1. The intragastric 24-h pH parameters of participants of 2 groups. Left: All-day intragastric pH 4 HTR by PP analysis. Middle: Daytime intragastric pH 4 HTR by PP analysis. Right: Nighttime intragastric pH 4 HTR by PP analysis. *Image originally appeared as Figure 2d-f from Wang et al. Reproduced under CCBY-NC-ND 4.0.*

COMMENTARY

Why Is This Important?

The family of illnesses termed "gastroesophageal reflux disease" includes a range of conditions from erosive esophagitis to non-erosive reflux disease (NERD) to reflux hypersensitivity and functional heartburn. The former 2 conditions are marked by acid-related changes to the esophagus, and the latter 2 disorders are thought to be more representative of a nerve hypersensitivity state, including potentially disordered gut-brain interaction (DGBI). It is a common practice to add bedtime/nighttime histamine 2 receptor antagonists when escalation of proton pump inhibitor

therapy to twice daily dosing is not effective.

Through the 2020s, most acid suppression guidelines for the treatment of GERD spectrum complaints center on the penultimately developed treatment class, proton pump inhibitors (PPIs). There was a recognition that histamine 2 receptor antagonists (H2RA) could play an adjunctive role in refractory cases. The American College of Gastroenterology's 2022 GERD guidelines[1] "use of a bedtime H2RA may be beneficial if dosed on an as-needed basis for patients with nocturnal symptoms and for patients with objective evidence of nocturnal acid reflux on pH monitoring despite PPI treatment." Lafutidine is thought to have additional benefits over other H2RAs like famotidine.[2] These include possible benefits to mucosal blood flow, with reports of increased plasma concentrations of the calcitonin gene-related peptide and somatostatin. This could offer a more effective treatment compared to older H2Ras.

Key Study Findings

The addition of bedtime lafutidine 10 mg to esomeprazole 20 mg twice daily significantly increased nocturnal intragastric pH >4 holding time ratios and decreased the occurrence of nocturnal acid breakthrough. GERD patients who added lafutidine experienced a more pronounced improvement in sleep quality, correlated with a reduction in nocturnal acid breakthrough. This bolsters existing ACG clinical guidelines for newer-generation H2RAs.

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Caution

The major strength of this article is the use of objective assessment of acid exposure time, which has been a significant limitation in other acid reflux spectrum treatments, such as potassium-competitive acid blockers. The caution, paradoxically, can come from this strength – in the community, adding on lafutidine empirically without verified acid exposure status, and potentially missing out on GERD-spectrum conditions like reflux hypersensitivity and functional heartburn that could benefit from central neuromodulation. Rarely do I find patients who fit into a binary classification of "total treatment response" and "total treatment failure." Namely, functional heartburn criteria include the presence of "no" symptom

relief of heartburn symptoms despite optimal use of acid-suppressing therapy. In my clinical practice, at least, rarely does someone describe a total lack of symptom relief from acid suppression therapy, but rather a less-than-expected benefit. I hope those who begin to use lafutidine in their practice keep in mind that there may still be a need to offer pH monitoring[3] (when available) to distinguish among the various GERD-spectrum disorders. Additionally, with the advent of potassium-competitive acid blockers (PCABs), which are potent and independent of meal-based dosing, is there really a market for another H2RA?

My Practice

Based on this trial, I will be on the lookout for lafutidine should it be approved by United States regulatory authorities. The reality is that, despite my pronouncements above, people tend to avoid pH testing unless it is necessary. Often in my very tertiary practice (not reflective of the typical gastroenterologist's practice), they have already tried adding an H2RA to twice-daily PPI; they would not be in my clinic if they had not. In this instance, I have a greater ability to insist on pH testing. Even so, it is often a hard sell – catheter-based testing is uncomfortable, wireless testing involves endoscopy and anesthesia. But patients are generally willing to consider such testing if they have maximized their acid suppression without significant improvement in symptoms. Perhaps acid-based testing can be delayed a little longer, should another tool be available to fight against the GERD burden.

For Future Research

Now that potassium-competitive acid blockers are playing a growing role in the management of GERD, it would be useful to compare PPI + H2RA with PCAB to determine whether one therapy is superior to the other. Another potential avenue is to determine whether this new generation H2RA is effective as needed for the DGBI-spectrum conditions that can be confused with GERD, such as functional heartburn and reflux hypersensitivity. People tend to have concerns about the central neuromodulator agents, given their use in other mental health conditions. Perhaps offering these patients additional pharmacotherapy, such as new-generation acid antagonists, may be effective.

Conflict of Interest

Dr. Vélez has received funding from Ironwood Pharmaceuticals, which has tested and/or offers non-PCAB GERD therapeutics.

Abbreviations

DGBI, disordered gut-brain interaction; GERD, gastroesophageal reflux disease; NAB, nocturnal acid breakthrough; NERD, non-erosive reflux disease; PPI, proton pump inhibitor.

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