Effects of Esomeprazole on Sleep in Patients with Gastroesophageal Reflux Disease as Assessed on Actigraphy

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Abstract

Objective Gastroesophageal reflux disease (GERD) is strongly associated with sleep disturbances. Although treatment with proton pump inhibitors (PPIs) helps to improve GERD symptoms and subjective sleep parameters, the effects of PPI therapy on objective sleep parameters are conflicting. The aim of this study was to examine the effects of esomeprazole treatment on GERD symptoms and sleep parameters assessed using actigraphs and questionnaires.

Methods Thirteen patients with GERD received 20 mg of esomeprazole once daily for two weeks. The patients wore actigraphs from three days before the initiation of PPI treatment to the end of therapy. They were also asked to answer the following self-reported questionnaires: Frequency Scale for the Symptoms of GERD (FSSG), Pittsburg Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS). Objective sleep parameters were evaluated using actigraphy.

Results Treatment with esomeprazole significantly decreased the total FSSG score, including the scores for reflux and dysmotility, as well as the ESS score, although it had no effect on the PSQI score. After the second week of treatment, esomeprazole significantly decreased the wake time (from 47.5±39.6 min to 36.0±27.1 min) and sleep latency period (from 19.5±19.8 min to 9.9±10.2 min) and increased the percentage of sleep time (from 89.1±8.8% to 91.9±6.3%); however, improvements were not noted in all objective parameters.

Conclusion Esomeprazole treatment significantly improves various objective sleep parameters in Japanese patients with GERD. Further placebo-controlled randomized trials are needed to obtain detailed results.

Key words: gastroesophageal reflux disease, sleep, esomeprazole, actigraph

(Intern Med 54: 559-565, 2015)
(DOI: 10.2169/internalmedicine.54.3718)

Introduction

The prevalence of gastroesophageal reflux disease (GERD) in Japan has been increasing since the 1990’s, and approximately 10-20% of the adult population in Japan currently complains of GERD symptoms, such as heartburn and acid regurgitation (1). The goal of GERD treatment is to alleviate impairments related to various aspects of the quality of life, e.g., eating habits, work and daily activities and sleep conditions (2, 3). GERD is strongly associated with sleep disturbances via a bidirectional relationship (4). Several Japanese epidemiological studies have shown that approximately 50% of patients with GERD experience sleep problems, including difficulty falling asleep, arousal during sleep and poor sleep quality (5, 6). In particular, patients

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Received for publication July 22, 2014; Accepted for publication August 21, 2014
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with non-erosive reflux disease are highly affected by sleep disturbances in Japan (6-8).

Therapy involving proton pump inhibitors (PPIs) is the mainstay of treatment for controlling GERD symptoms, such as heartburn and acid regurgitation. Johnson et al. conducted a large placebo-controlled study involving 642 patients with GERD and found that treatment with esomeprazole significantly improved GERD symptoms as well as subjective sleep parameters, as assessed according to the Pittsburg Sleep Quality Index (PSQI) and a work productivity evaluation (9). Two other large randomized controlled trials also demonstrated similar results with respect to improvements in subjective sleep parameters (10, 11). However, the effects of PPI therapy on the objective sleep parameters in GERD patients are controversial and have not been elucidated in Japanese patients with GERD.

The aim of the present study was to determine the effects of once daily esomeprazole treatment on subjective sleep parameters and GERD symptoms, as well as objective sleep parameters as assessed on actigraphy, in Japanese patients with GERD.

Materials and Methods

Patients

A total of 13 adult patients from three hospitals were enrolled in this study between June 2012 and March 2013. Only outpatients ≥20 years of age with non-treated GERD were eligible for inclusion. The diagnosis of GERD was confirmed when, in addition to complaints of GERD symptoms, such as heartburn and acid regurgitation, an endoscopic examination revealed the presence of reflux esophagitis according to the modified Los Angeles Classification. Hiatal hernia was diagnosed according to Makuuchi’s classification (12). Patients with a history of upper gastrointestinal surgery or having to work night shifts were excluded. The disease-related exclusion criteria were severe disease of any major body system, malignant disease of any kind, depression or any other severe psychiatric disease and/or severe sleep disorders. Patients were also excluded if they had received acid-suppressive drugs continuously within the two weeks prior to the start of the study. The study protocol was approved by the Osaka City University Ethics Committee and the respective Ethics Review Boards of each participating hospital. Written informed consent was obtained from all participants.

Study protocol

All patients were asked to wear an actigraph in order to obtain objective measurements of the duration of sleep for a period of three days before and during the two weeks of treatment with esomeprazole at a dose of 20 mg once daily. The subjects were asked to wear the actigraph when they went to bed at night and take it off only once they woke up in the morning. In addition, the participants were asked to complete three questionnaires, the Frequency Scale for the Symptoms of GERD (FSSG), Epworth Sleepiness Scale (ESS) and PSQI, three days before and after two weeks of esomeprazole treatment.

Actigraphy

Actigraphs, a watch-like device worn on the nondominant wrist, record motions through accelerometers stored digitally in the device (Ambulatory Monitoring, Ardley, USA) with the ability to collect data continuously over an extended period. The stored digital information can then be downloaded using ActMillenium (3.58.0.2) (Ambulatory Monitoring) and analyzed with a proprietary software program (AW2 version 2.6) (Ambulatory Monitoring) to identify periods of quiescence that can be inferred as times of sleep (13). We analyzed the total minutes scored as awake (wake time) and asleep (sleep time), percent minutes scored as sleep time (% sleep), wake after sleep onset (WASO), defined as the wake time between the onset of a 20-minute block of sleep and the offset of sleep, sleep efficiency, defined as the sleep time divided by the WASO, sleep latency, defined as the number of minutes to the start of the first 20-minute block of sleep (with >19 min of sleep), number of wake episodes, mean duration of wake episodes, number of long wake episodes, defined as wake episodes lasting longer than five minutes, and the duration of the longest wake episode. The data acquired three days before treatment and at the first and second weeks of treatment are expressed as the mean and standard deviation (SD).

FSSG

The FSSG is a simplified questionnaire used to evaluate symptoms of GERD and is employed to objectively assess the symptoms experienced by patients with GERD. The questionnaire consists of 12 items scored between 0 and 4, where the score corresponds to the frequency of the symptom (0= never, 1= occasionally, 2= sometimes, 3= often and 4= always). In the present study, the FSSG was evaluated using the total score, which is divided into scores for each of the seven questions concerning acid reflux-related symptoms (reflux score) and five questions concerning dyspeptic symptoms (dysmotility score) (14).

PSQI

The PSQI is a standardized rating scale in which 18 individual items generate seven component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications and daytime dysfunction. Each dimension is rated on a four-point scale, and the sum of the scores for the seven components yields a single global score. A high score indicates that the subject is more disturbed during sleep (15, 16).

ESS

The ESS measures a subject’s general level of daytime sleepiness. This scale consists of eight self-rated items,
Effects of esomeprazole on GERD symptoms

Esomeprazole treatment significantly decreased the total FSSG score from 7.8±2.8 before treatment to 4.9±2.2 after the first week of treatment and 3.7±1.7 after the second week of treatment (Fig. 1A) and significantly reduced the reflux and dysmotility scores at both the first and second weeks of treatment (Fig. 1B, C). These data suggest that esomeprazole significantly alleviated the subjects’ GERD symptoms.

Effects of esomeprazole on the PSQI and ESS scores

Esomeprazole did not affect the total PSQI score (Fig. 2A); however, the ESS score significantly decreased from 4.8±1.1 before treatment to 3.8±1.0 after treatment (Fig. 2B), suggesting that two weeks of treatment with esomeprazole had little effect on the subjective sleep parameters.

Effects of esomeprazole on objective sleep parameters

Esomeprazole treatment significantly decreased the total wake time (Fig. 3A) but did not affect the number of awake episodes (Fig. 3B). The percentage of sleep after the first and second week of esomeprazole treatment was found to be significantly higher than that before treatment (Fig. 4A), especially among the patients whose % sleep values exhib-
Figure 2. Effects of esomeprazole on the subjective sleep parameters. A: PSQI total score. B: ESS score. Esomeprazole significantly improved the ESS score but did not affect the PSQI score after treatment. PSQI: Pittsburg Sleep Quality Index, ESS: Epworth sleepiness score. *p < 0.05 versus before treatment.

Figure 3. Effects of esomeprazole on the wake time and number of awake episodes. A: Total wake time. B: Number of awake episodes. Esomeprazole significantly decreased the total wake time but did not affect the number of awake episodes. *p < 0.05 versus before treatment.

Discussion

This study showed that once daily treatment with esomeprazole for two weeks significantly decreased the FSSG...
Figure 4. Effects of esomeprazole on the percentage of sleep and sleep latency. A: Percentage of sleep B: Sleep latency. Esomeprazole significantly increased the percentage of sleep time at both the first and second weeks after treatment and reduced the sleep latency at the second week after treatment.

Table. Effects of Esomeprazole on the Objective Sleep Parameters Assessed on Actigraphy

<table>
<thead>
<tr>
<th></th>
<th>Before treatment</th>
<th>After the first week of treatment</th>
<th>After the second week of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep time (min)</td>
<td>386.2 ± 76.0</td>
<td>409.4 ± 80.1</td>
<td>408.3 ± 78.7</td>
</tr>
<tr>
<td>Number of sleep episodes</td>
<td>7.7 ± 3.4</td>
<td>7.8 ± 3.6</td>
<td>7.6 ± 3.3</td>
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<tr>
<td>Mean sleep episodes (min)</td>
<td>78.2 ± 62.4</td>
<td>97.2 ± 65.6</td>
<td>98.9 ± 56.7</td>
</tr>
<tr>
<td>Number of long sleep episodes</td>
<td>5.8 ± 2.4</td>
<td>5.7 ± 2.3</td>
<td>5.5 ± 2.2</td>
</tr>
<tr>
<td>Longest sleep time (min)</td>
<td>186.8 ± 74.6</td>
<td>206.5 ± 73.1</td>
<td>209.1 ± 62.7</td>
</tr>
<tr>
<td>Wake time (min)</td>
<td>47.5 ± 39.6</td>
<td>37.3 ± 26.4</td>
<td>36.0 ± 27.1</td>
</tr>
<tr>
<td>Number of wake episodes</td>
<td>7.7 ± 3.4</td>
<td>7.7 ± 3.8</td>
<td>7.3 ± 3.3</td>
</tr>
<tr>
<td>Mean wake episodes (min)</td>
<td>6.0 ± 4.4</td>
<td>5.0 ± 2.2</td>
<td>4.8 ± 2.5</td>
</tr>
<tr>
<td>Number of long wake episodes</td>
<td>2.4 ± 1.3</td>
<td>2.3 ± 1.4</td>
<td>2.1 ± 1.4</td>
</tr>
<tr>
<td>Longest wake time (min)</td>
<td>20.6 ± 16.0</td>
<td>16.0 ± 9.4</td>
<td>15.3 ± 10.7</td>
</tr>
<tr>
<td>Sleep latency (min)</td>
<td>19.5 ± 19.8</td>
<td>9.6 ± 8.7</td>
<td>9.9 ± 10.2</td>
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<tr>
<td>Wake time after sleep onset (min)</td>
<td>27.0 ± 23.1</td>
<td>27.0 ± 19.8</td>
<td>24.7 ± 17.6</td>
</tr>
<tr>
<td>% Sleep</td>
<td>89.1 ± 8.8</td>
<td>91.6 ± 6.1</td>
<td>91.9 ± 6.3</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>91.1 ± 6.0</td>
<td>93.8 ± 4.8</td>
<td>94.1 ± 4.4</td>
</tr>
</tbody>
</table>

The data are expressed as the mean ± SD. *p < 0.05 versus before treatment.

scores, including those for reflux, dysmotility and ESS, whereas no changes were noted in the PSQI scores. In addition, the esomeprazole therapy significantly increased the percentage of sleep time and decreased the wake time and sleep latency time, although it did not affect the total sleep time, number of wake events or sleep efficiency. These results indicate that esomeprazole treatment improves GERD symptoms as well as various objective sleep parameters in Japanese patients with GERD.

Few studies in the literature have examined the effects of PPIs on objective sleep parameters. For example, Orr et al. performed polysomnography to examine the effects of rabeprazole treatment (20 mg bid, for one week) in 28 patients with GERD and found no differences in the percentage of sleep efficiency, percentage of slow-wave sleep (non-rapid eye movement sleep stages 3 and 4), percentage of rapid eye movement sleep and number of arousals during sleep between the subjects treated with rabeprazole and those given a placebo; however, the visual analogue scale findings showed that rabeprazole improved sleep quality (18). Another study demonstrated no differences in total sleep time, percentage of sleep efficiency or sleep onset latency among 15 patients with GERD receiving treatment with esomeprazole at a dose of 40 mg bid or a placebo for
one week (19). These results suggest that, compared to a placebo, treatment with PPIs does not improve objective sleep parameters assessed on polysomnography in patients with GERD. On the other hand, Dimario et al. evaluated 16 patients with or without GERD with polysomnography and pH monitoring and found that omeprazole treatment reduced the number of acid reflux-associated arousals and increased the total sleep time, rapid eye movement sleep time and sleep efficiency (20). The reasons for the discrepancies among the findings of these and the present study are unknown. Although polysomnography is the gold standard for assessing sleep parameters, it requires hospitalization. The actigraph device used in this study was able to record continuous data regarding sleep parameters in the patient’s own bed. These differences in modality may be associated with the discrepancies observed in the effects of PPIs on objective sleep parameters. Meanwhile, Chand et al. reported that treatment with esomeprazole at a dose of 40 mg for eight weeks significantly improved subjective sleep parameters, although it did not affect sleep efficiency, the immobile time or total activity score assessed on actigraphy (21).

In the present study, esomeprazole improved the percentage of sleep and sleep latency but not the number of awake episodes. Although the exact reasons for these findings are unknown, our observations may be related to the phenomenon of transient lower esophageal sphincter relaxation (TLESR), which plays a central role in gastroesophageal reflux (22). Dent et al. demonstrated that TLESR after short arousals is always responsible for nighttime reflux during sleep in healthy subjects (23). This finding may explain why PPI therapy did not affect the number of awake episodes in this study, although other mechanisms, such as free reflux and strain reflux, are in part associated with nighttime reflux in GERD patients (24).

In our study population, PPI treatment improved the objective sleep parameters and ESS scores; however, it did not affect the total PSQI score, which is commonly used to assess subjective sleep disturbances, likely due to the short duration of treatment and characteristics the study subjects. Previous large clinical trials have demonstrated significant improvements in the PSQI scores after treatment for four weeks (9-11). Therefore, a longer duration of therapy may be required to elicit improvements in subjective sleep scores. In the current study, we enrolled non-treated patients with GERD, irrespective of sleep disturbances or nighttime heartburn, and the lower PSQI scores observed before treatment may have affected the statistical significance of our findings. Poh et al. showed that nighttime reflux is seldom symptomatic (25), suggesting that GERD induces sleep disturbances through arousals due to nighttime heartburn during sleep as well as sleep fragmentation and other complex mechanisms (4). Further studies involving patients with sleep disturbances confirmed based on assessments of objective sleep parameters are thus needed.

Several clinical studies have been conducted to evaluate the effects of PPI treatment on subjective sleep disturbances among Japanese patients with GERD. For example, Fujisawa et al. examined the effects of rabeprazole at a dose of 10 mg for eight weeks on sleep disturbances in 134 patients with GERD who subsequently completed the PSQI. The authors found that 52% of the patients with GERD had sleep disturbances and that PPI treatment significantly improved the PSQI scores (6). Another study showed that twice daily treatment with rabeprazole for four to eight weeks significantly reduced the frequency of nighttime reflux symptoms, arousals due to nighttime reflux symptoms during sleep, daytime sleepiness and poor sleep quality in patients refractory to once daily standard PPI treatment (26). In addition, Aimi et al. conducted a placebo-controlled randomized trial of 171 patients with insomnia, of whom 69 had typical reflux symptoms, and found that therapy with omeprazole at a dose of 20 mg for two weeks was effective in alleviating insomnia, as assessed with the PSQI (27). Although these studies demonstrated the efficacy of PPI therapy in improving subjective sleep disturbances, the present study is the first to show the effectiveness of PPI treatment in ameliorating objective sleep parameters in Japanese patients with GERD.

The present study is associated with some limitations. First, the number of study subjects was small, and we did not include a control group treated with a placebo. Therefore, a large randomized placebo-controlled study is needed to confirm the present results. Second, a recent investigation showed that, compared with nocturnal sleep, napping is significantly associated with esophageal acid exposure and GERD symptoms (28). Hence, further studies focusing on the effects of naps are needed in the future.

In conclusion, esomeprazole treatment significantly improves GERD symptoms and various objective sleep parameters in Japanese patients with GERD. Our results suggest that PPI therapy is useful for treating reflux symptoms as well as sleep disturbances in Japanese patients with GERD.

Author’s disclosure of potential Conflicts of Interest (COI).
Tetsuo Arakawa: Honoraria, Otsuka Pharmaceutical and Eisai; Research funding, Otsuka Pharmaceutical and Eisai.

Financial Support
This study was supported, in part, by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

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