

学位論文の要旨

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学位論文名 Effects of Omeprazole on Sleep Disturbance: Randomized Multicenter Double-Blind Placebo-Controlled Trial

発表雑誌名 Clinical Translational Gastroenterology (5: e57, 2014)
(巻, 初頁~終頁, 年)

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論文内容の要旨

INTRODUCTION

Sleep disturbance is an important extraesophageal complication in patients with gastroesophageal reflux disease (GERD) and a close association between them has recently been reported. Several clinical investigations have indicated that proton pump inhibitor (PPI) administration can improve sleep disorders associated with GERD, though the presented evidence is inadequate because of small sample sizes or inappropriate study design.

GERD without typical reflux symptoms may have some role in sleep disturbance, as affected individuals often have endoscopy-proven asymptomatic reflux esophagitis. Silent GERD patients also frequently develop sleep disturbance, thus PPIs may improve that in those with and without reflux symptoms. We examined whether PPI administration has a therapeutic effect for improving insomnia in patients without reflux symptoms in the same manner as those with reflux symptoms.

MATERIALS AND METHODS

This multicenter randomized double-blind placebo-controlled prospective study of patients with sleep disturbance was conducted from 2010 to 2012 at Shimane University Hospital, and 13 affiliated hospitals and clinics. Patients who visited outpatient clinics for management of primary insomnia were enrolled. Those who took hypnotics, PPIs, and/or histamine H₂ receptor antagonists within 2 weeks before enrollment, with a history of treatment for mental disorders or with serious underlying diseases that may influence sleep quality were excluded. Women who were pregnant or had a high possibility of pregnancy, and patients allergic to omeprazole were also excluded. Background and clinical factors such as age, gender, height, body weight, body mass index, drinking, smoking, presence of typical GERD symptoms (heartburn, acid regurgitation), throat discomfort, cough, chest pain, otalgia, and asthma were recorded at the time of enrollment. The subjects were randomly assigned to 2 groups according to a prefixed order; with 1 receiving omeprazole (20 mg) and the other an indistinguishable placebo 30 minutes before dinner daily for 2 weeks. Four self-reporting questionnaires, QOLRAD-J (Japanese translation of Quality of Life in Reflux and Dyspepsia), Pittsburg Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), and a sleep diary, were used to evaluate GERD-related quality of life (QOL) and sleep disturbance. The study protocol was approved by the Ethics Committee of Shimane University and written informed consent was obtained from all subjects.

RESULTS AND DISCUSSION

A total of 176 patients were initially enrolled, with 171 analyzed after withdrawals for enrollment criteria violations and dropout during treatment. We investigated the prevalence of reflux symptoms in these subjects with insomnia and found that as many as 40% (69/171) had typical reflux symptoms, indicating an important role for GERD as a possible pathogenetic factor in sleep disturbance.

In patients with reflux symptoms, omeprazole significantly improved GERD-related

(QOLRAD-J, total) and sleep-related (QOLRAD-J, sleep-related) QOL from 30.8 ± 0.7 to 33.0 ± 0.5 and 6.0 ± 0.2 to 6.6 ± 0.1 , respectively (both $P < 0.01$). Omeprazole also statistically significantly improved sleep quality (PSQI 15.1%, ESS 15.9%, diary record 14.3% improvement), whereas administration of the placebo had no significant therapeutic effect (3.4%, 7.7%, and 0% respectively). Several double-blind randomized studies have investigated the effectiveness of PPIs for treatment of sleep disturbance in patients with symptomatic GERD and all concluded that they improved sleep quality for such patients. The results of our study confirmed that PPI administration is effective for insomnia in patients with reflux symptoms.

In contrast, in patients without reflux symptoms, there was no difference between omeprazole and the placebo for improvement in sleep quality (PSQI 19.8% vs. 22.4%, ESS 7.7% vs. 17.3%, diary record 13.6% vs. 9.5%). The effect of the placebo on sleep quality was especially large in this group, and both that and omeprazole significantly improved sleep quality in subjects without reflux symptoms. We consider that the lack of effect from PPI administration for improving sleep disturbance in cases without typical reflux symptoms is an interesting finding of the present study. Based on this result, we concluded that silent gastroesophageal reflux is not a major factor causing sleep disturbance, in contrast to reflux symptoms. Furthermore, the presence of reflux symptoms may be a good indicator for predicting a good therapeutic effect from PPI administration for sleep disturbance.

CONCLUSION

Approximately 40% of our clinical patients with insomnia had typical reflux symptoms. Their condition was effectively improved by omeprazole, whereas patients without reflux symptoms were not improved by PPI administration.