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ORIGINAL ARTICLE

Effectiveness of the leukotriene receptor antagonist pranlukast hydrate for the treatment of sleep disorder in patients with perennial allergic rhinitis

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Abstract

Conclusion: We found that addition of pranlukast to the conventional treatment for perennial allergic rhinitis may contribute to improvements in sleep disorder symptoms through a decrease in nasal congestion. **Objective:** We aimed to determine whether the leukotriene receptor antagonist pranlukast hydrate is effective in treating sleep disorder in patients with perennial allergic rhinitis. **Methods:** We conducted a questionnaire survey to determine the symptoms of rhinitis and sleep disturbances in 48 adult patients with perennial allergic rhinitis who visited the outpatient otolaryngology departments in hospitals in Yamaguchi Prefecture, Japan. The subjects presented with nasal symptoms and symptoms of sleep disorder during the last 2 weeks of treatment for allergic rhinitis that lasted for at least 1 month. A questionnaire based on the Pittsburgh Sleep Quality Index and Athens Insomnia Scale with some modifications was administered before and 4 weeks after the addition of pranlukast to the conventional treatment. **Results:** Addition of pranlukast improved the symptoms of perennial allergic rhinitis, with responses to all items of the questionnaire administered 4 weeks after pranlukast addition indicating significant improvements. Furthermore, the improvement in sleep disorder symptoms significantly correlated with improvement in nasal congestion, but not with improvements in sneezing and nasal discharge.

Keywords: *Nasal congestion, questionnaire survey*

Introduction

Sleep disorders can lead to daytime somnolence, lack of attentiveness, low motivation, and emotional disorders, resulting in reduced productivity/operating efficiency in daily work and study. These effects of sleep disorders may increase the incidence of accidents, including traffic accidents; hence, sleep disorders represent a serious medical issue as well as a social challenge. Although various factors may induce sleep disturbances, allergic rhinitis is a particularly important underlying physical cause [1–6]. Allergic rhinitis is a disease that can significantly decrease the quality of life (QOL) of patients. Therefore, a precise, efficacious treatment is required. The treatment of allergic rhinitis includes antigen

avoidance/elimination, drug therapy, specific immunotherapy, physical therapy, and surgical treatment. Among these treatments, drug therapy has been used most widely, and various drugs have been developed for specific stages of the disease.

Pranlukast hydrate (trade name Onon Capsule, hereinafter referred to as pranlukast), a leukotriene receptor antagonist, is one of the drugs used to treat allergic rhinitis. The drug can improve the three major symptoms of allergic rhinitis: sneezing, nasal discharge, and nasal congestion. Pranlukast is more efficacious than second-generation antihistamines, particularly for treating nasal congestion [7]. In our previous study in patients with perennial allergic rhinitis, we used the Japan Rhinoconjunctivitis Quality of Life Questionnaire (JRQLQ), which is a

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standard Japanese questionnaire for allergic rhinitis. We found that pranlukast improved not only sneezing, nasal discharge, and nasal congestion, but also all the QOL-related items listed in the JRQLQ, in addition to significantly improving sleep disorder symptoms [8].

In the present study, we administered a questionnaire survey to confirm the symptoms of rhinitis and determine the quality of sleep in adult patients with perennial allergic rhinitis who visited the outpatient otolaryngology departments of hospitals in Yamaguchi Prefecture. In addition, we administered pranlukast to patients with sleep disorders and nasal symptoms to examine whether the drug improved the symptoms of rhinitis and of sleep disorder. Herein, we report the results of the study.

Material and methods

We administered a questionnaire survey to adult patients who had undergone treatment for perennial allergic rhinitis for 1 month or longer at 28 medical facilities in Yamaguchi Prefecture after obtaining written informed consent from each of the patients. We selected 48 patients from among the patients who complained of nasal symptoms and sleep disorder within 1–2 weeks before administration of our survey. The subjects included 33 male and 15 female patients, and their mean age was 48.2 ± 19.4 years. Each patient provided written informed consent to undergo additional treatment with pranlukast.

Pranlukast at a dose of two capsules twice a day (after breakfast and dinner) was added to conventional treatments for 4 weeks. Patients' symptoms of rhinitis and sleep disorder were evaluated for 1–2 weeks immediately before and after pranlukast administration. To evaluate nasal symptoms and sleep quality, we compared patient responses before and after drug administration by using a questionnaire prepared in

accordance with the Pittsburgh Sleep Quality Index (PSQI) [9] and Athens Insomnia Scale (AIS) [10] (Figures 1 and 2). The rhinitis symptoms were evaluated on a scale of 0 to 4 points (0, none; 4, extremely severe), while sleep disorder-related symptoms were assessed on a scale of 0 to 3 points (0, no problems; 3, serious problems). Data analysis was performed using IBM SPSS Statistics version 20.0 (IBM Inc., Armonk, NY, USA). For statistical analyses, the Wilcoxon signed-rank test was used to compare the points before and after drug administration. Pearson's correlation coefficient was calculated to determine whether the improvement in each of the three individual rhinitis symptom scores correlated with the improvement in the total sleep disorder score.

The survey was administered from July to December 2007 to minimize the influence of seasonal allergic rhinitis, especially that of pollinosis from cedar. In this study, the conventional treatments undergone by the subjects were as follows: 38 patients were treated with antihistamine and 23 patients used the intranasal corticosteroid. Three patients used topical nasal decongestant. Sixteen patients used both the antihistamine and intranasal corticosteroid. Those conventional treatments continued in this study with pranlukast. Oral steroid was not added in the present study. The following patients were excluded from our survey: those who were treated with leukotriene receptor antagonists, thromboxane A_2 receptor antagonists, or oral steroids; those who were receiving immune tolerance therapy; those with the complication of nasal polyps; and those with asthma.

The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 1983. The study protocol was approved by the local ethics committee (Yamaguchi Society for Allergic Disease in Otolaryngology, Ube, Japan).

Questionnaire sheet					
Evaluation of nasal symptoms					
Instructions: Please answer the following questions regarding conditions that developed within 1–2 weeks by circling the appropriate number. Thank you very much.					
Nasal symptoms	None	Mild	Moderate	Severe	Extremely
					severe
Sneezing	0	1	2	3	4
Nasal discharge	0	1	2	3	4
Nasal congestion	0	1	2	3	4

Figure 1. Questionnaire sheet for evaluation of nasal symptoms. Symptoms were graded on a scale of 0 to 4 points (0, no symptoms; 4, serious symptoms).

Results

The symptoms of rhinitis – nasal congestion, nasal discharge, and sneezing, which were observed 1–2 weeks before the administration of pranlukast, were confirmed in 47, 34, and 31 subjects, respectively. The highest score (2.71) was for nasal congestion (Table I). Regarding the indices of sleep disorder reported 1–2 weeks before pranlukast administration, ‘insufficient overall quality of sleep’ and ‘daytime sleepiness’ were confirmed in 40 subjects and ‘arousal during sleep’ was confirmed in 39 subjects. The scores for arousal during

sleep and for insufficient overall quality of sleep were the highest (1.15) (Table I).

After the 4-week administration of pranlukast, significant improvement was confirmed for all the three major symptoms of rhinitis. The score for nasal congestion, which was the highest before pranlukast administration, improved from 2.71 to 1.31, while the scores for sneezing and nasal discharge improved from 1.17 to 0.69 and from 1.31 to 0.92, respectively (Table II). Furthermore, significant improvement was also observed for each symptom of sleep disorder compared with the data obtained before pranlukast administration (Table III).

Questionnaire sheet	
Evaluation of sleep quality	
Instructions: Do you experience any sleep-related problems due to rhinitis symptoms?	
Please circle all that apply below if you have experienced problems sleeping for at least three times a week within the last 1 month. Thank you.	
Time required from going to bed to falling asleep (Sleep-onset insomnia)	
Always fall asleep easily	0
Took more time than usual	1
Took a long time	2
Took an extremely long time, or no sleep	3
Waking up during night-time (Arousal during sleep)	
No problem	0
Slightly problematic	1
Extremely problematic	2
Serious situation, or no sleep	3
Waking up earlier than scheduled, and cannot sleep any more (Early arousal)	
None	0
Slightly early	1
Fairly early	2
Extremely early, or no sleep	3
Total sleep duration	
Sufficient	0
Slightly insufficient	1
Fairly insufficient	2
Extremely insufficient, or no sleep	3
Overall quality of sleep: regardless of sleep duration	
Satisfied	0
Slightly dissatisfied	1
Fairly dissatisfied	2
Extremely dissatisfied, or no sleep	3
Daytime sleepiness	
None	0
Slightly sleepy	1
Frequently sleepy	2
Always sleepy	3

Figure 2. Questionnaire sheet for evaluation of sleep quality. Sleep quality was graded on a scale of 0 to 3 points (0, no problem; 3, serious problems).

The total score for the six symptoms related to sleep disorder significantly improved from 6.38 before pranlukast administration to 2.71 after pranlukast administration (Table IV).

Figure 3 shows the correlations for the improvement in each of the three individual rhinitis symptom scores with the improvement in the total sleep disorder score. We found that the decrease in the total

sleep disorder score was significantly correlated only with the improved nasal congestion score, but not with the scores for sneezing and nasal discharge.

Discussion

Patients with perennial allergic rhinitis experience symptoms throughout the year, and severe symptoms

Table I. Symptoms of rhinitis and sleep disorder before administration of pranlukast ($n = 48$).

Symptoms of rhinitis and sleep disorder	No. of subjects (prevalence)	Score (mean $\pm$ SD)
Sneezing	31 (64.6%)	1.17 $\pm$ 1.10
Nasal discharge	34 (70.8%)	1.31 $\pm$ 1.15
Nasal congestion	47 (97.9%)	2.71 $\pm$ 0.92
Sleep-onset insomnia	33 (68.8%)	1.06 $\pm$ 0.93
Arousal during sleep	39 (81.3%)	1.15 $\pm$ 0.80
Early arousal	35 (72.9%)	1.02 $\pm$ 0.81
Reduction of total sleep duration	37 (77.1%)	1.00 $\pm$ 0.71
Insufficient overall quality of sleep	40 (83.3%)	1.15 $\pm$ 0.74
Daytime sleepiness	40 (83.3%)	1.00 $\pm$ 0.58

Table II. Changes in rhinitis symptoms before and after administration of pranlukast ($n = 48$).

Rhinitis symptoms	Score before administration (mean $\pm$ SD)	Score after administration (mean $\pm$ SD)	p value*
Sneezing	1.17 $\pm$ 1.10	0.69 $\pm$ 0.78	< 0.001
Nasal discharge	1.31 $\pm$ 1.15	0.92 $\pm$ 0.92	< 0.001
Nasal congestion	2.71 $\pm$ 0.92	1.31 $\pm$ 0.80	< 0.001

*Wilcoxon test.

Table III. Changes in sleep disorder score before and after administration of pranlukast ($n = 48$).

Symptoms of sleep disorder	Score before administration (mean $\pm$ SD)	Score after administration (mean $\pm$ SD)	p value*
Sleep-onset insomnia	1.06 $\pm$ 0.93	0.42 $\pm$ 0.58	< 0.001
Arousal during sleep	1.15 $\pm$ 0.80	0.35 $\pm$ 0.53	< 0.001
Early arousal	1.02 $\pm$ 0.81	0.46 $\pm$ 0.62	< 0.001
Reduction of total sleep duration	1.00 $\pm$ 0.71	0.44 $\pm$ 0.54	< 0.001
Unsatisfactory overall sleep quality	1.15 $\pm$ 0.74	0.44 $\pm$ 0.54	< 0.001
Daytime sleepiness	1.00 $\pm$ 0.58	0.60 $\pm$ 0.57	< 0.001

*Wilcoxon test.

Table IV. Changes in total sleep disorder score before and after the administration of pranlukast ($n = 48$).

Clinical features	Total score before administration (mean $\pm$ SD)	Total score after administration (mean $\pm$ SD)	p value*
Allergic rhinitis symptoms	5.19 $\pm$ 3.17	2.92 $\pm$ 2.50	< 0.001
Overall sleep disorder	6.38 $\pm$ 3.49	2.71 $\pm$ 2.13	< 0.001

*Wilcoxon test.

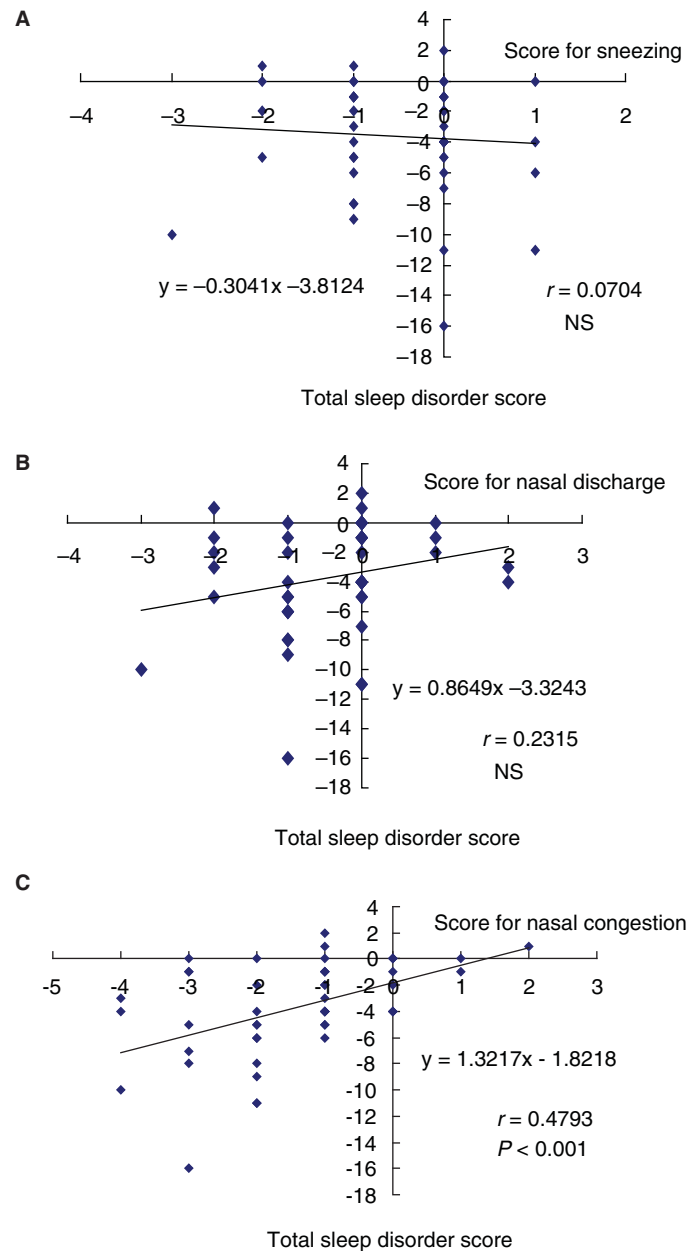


Figure 3. The correlation between improvement in individual rhinitis symptom scores and the total sleep disorder score. Both individual rhinitis symptom scores and the total sleep disorder score decreased after administration of pranlukast. The decrease in total sleep disorder score correlated significantly with the decrease in the score for nasal congestion (c) but not with the decrease in the scores for sneezing (a) or nasal discharge (b). r = Pearson's correlation coefficient.

decrease the QOL for such patients [11]. In Japan, a study of patients with perennial allergic rhinitis performed using the JRQLQ showed disturbance of daily life activities [12]. Perennial allergic rhinitis often causes sleep disturbances and is associated with daytime somnolence, which results in a poor QOL. Various clinical interventions in patients with sleep disorder seek to improve symptoms and QOL. Léger et al. reported that all dimensions of sleep were impaired by allergic rhinitis, particularly by

the severe type, and sleep was significantly more impaired in patients with severe allergic rhinitis than in those with mild allergic rhinitis [3]. They concluded that their data underscored the close relationship between allergic rhinitis and sleep and highlighted the need for clinicians, particularly general practitioners, to be attentive to this relationship.

The drugs for allergic rhinitis may be roughly divided into compounds that decrease the liberation of chemical mediators, antagonists of chemical-mediated receptors,

topical steroids, and autonomic drugs. Chemical-mediated receptor antagonists may be classified into first/second-generation antihistamines, antileukotrienes, and antiprostaglandin D₂/thromboxane A₂ drugs, all of which exhibit specific clinical effects.

Previous studies have suggested a relationship between nasal congestion and sleep disorder [1,13,14]. Udaoka et al. reported that chronic nasal obstruction causes daytime sleepiness and decreases the QOL even in the absence of snoring [13]. Stull et al. reported that nasal congestion alone had only a slightly smaller negative impact on sleep adequacy relative to allergic rhinitis symptoms, but that congestion increased the likelihood of sleep problems, fatigue, shortness of breath, headache, and daytime somnolence [14]. However, only a few reports have suggested that effective treatment against nasal congestion improves the quality of sleep [15,16]. Hughes et al. reported that compared with placebo, the topical nasal corticosteroid budesonide significantly improved daytime fatigue ($p = 0.03$), somnolence ($p = 0.02$), and quality of sleep ($p = 0.05$) in patients with perennial allergic rhinitis. They concluded that budesonide improved congestion, sleep, and daytime somnolence [15]. In a study conducted by Santos et al. in a small cohort of subjects ($n = 31$), compared with placebo, the leukotriene receptor antagonist montelukast improved the symptoms of perennial allergic rhinitis and reduced daytime fatigue and daytime somnolence in patients with perennial allergic rhinitis [16].

Pranlukast is a leukotriene receptor antagonist that can improve the three major symptoms of allergic rhinitis and is more efficacious than second-generation antihistamines, particularly for nasal congestion [7]. On examining the effect of pranlukast with regard to improvement in the QOL of perennial allergic rhinitis patients with nasal congestion symptoms, we found that nasal congestion improved in 73.7% of patients after 4 weeks, and scores for all of the QOL-related items in the JRQLQ improved. Interestingly, sleep was scored as the most impaired item before pranlukast administration, but after pranlukast administration, the score for sleep was the same as those achieved for the other QOL items. The effects of pranlukast on the symptoms of rhinitis and sleep disorder have not been examined previously. Therefore, we performed a prospective study to examine whether this drug could improve the symptoms of rhinitis and/or sleep disorder.

We found that the symptoms of rhinitis and sleep disorder improved after pranlukast administration in patients who were also treated with conventional therapy. Since pranlukast has no antihistaminic effects to induce sleepiness, the improvement in sleep disorder was possibly caused by an improvement in the

symptoms of rhinitis. In addition, the total sleep disorder score correlated only with the improvement in the score for nasal congestion, among the rhinitis symptoms, indicating that improvement in nasal congestion is important for improvement in sleep disorder in patients with perennial allergic rhinitis.

In conclusion, the results of this study suggest that pranlukast improves sleep disorder symptoms in patients with perennial allergic rhinitis by improving nasal congestion.

There are several limitations of this study. First, according to Table I, the average scores for sneezing and nasal discharge were between mild and moderate, but the average score for nasal congestion was close to severe; therefore we speculated that the previous treatments did improve sneezing and nasal discharge to some extent but did not improve nasal congestion in these selected patients. Therefore, patients may not be satisfied with the previous treatments, and it can be speculated that the patients had a bias that might have affected the effectiveness of pranlukast. To investigate the direct effect of pranlukast, the patients should have been treated with pranlukast alone after washing out the effects of previous treatment or the effectiveness should be compared with a placebo group. Regrettably, we were unable to do the experimentation in this study. We are now considering the idea of investigating this point in a future study. Second, the study was based on a questionnaire, and the physical findings of patients were not clinically verified. To further evaluate the effectiveness of pranlukast for treating sleep disorder symptoms as well as for improving the physical condition of patients with perennial allergic rhinitis, studies will be performed combining rhinoscopic examination with polysomnography.

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