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Effectiveness of Second-Generation Antihistamine for the Treatment of Morning Symptoms Observed in Patients with Perennial Allergic Rhinitis: Comparison Study of Bepotastine Besilate versus Olopatadine Hydrochloride

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Abstract

Objective: The aim of the present study was to examine circadian rhythm-based treatment strategies with the intension of improving the pharmacotherapy for morning symptoms with perennial allergic rhinitis. We investigated the effects of two second generation antihistamines, with different pharmacokinetic parameters, bepotastine besilate and olopatadine hydrochloride, for the treatment of morning symptoms.

Methods: Twenty-four subjects with perennial allergic rhinitis were recruited for this study. They were randomly allocated to either a bepotastine group (n=10) or an olopatadine group (n=14). During the 1-hour period after waking up in the morning, the patients counted and recorded the number of sneezes and nose blowing. PNIF was also measured. The study participants took the allocated medicine twice a day. They continued recording their nasal symptoms and PNIF after awakening for 10 to 14 days.

Results: In both group, taking bepotastine and olopatadine, the mean sneezing count and the mean nose blowing count were well suppressed. However, a significant change in the nasal congestion score was not observed throughout the study. Especially in olopatadine group, PNIF increased from day 2 onward and a significant increase was observed for the following 10 days.

Conclusion: The worsening of nasal symptoms after awakening that is associated with perennial allergic rhinitis has a significant impact on the quality of life of patients. Two second-generation antihistamines, bepotastine besilate and olopatadine hydrochloride, were effective for the treatment of these morning symptoms. The measurement of Peak Nasal Inspiratory Flow (PNIF) value might lead to a favorable self-evaluation of nasal symptom and treatment effects. Some guidance regarding the taking of medicine from Powered by Editorial Manager® and ProduXion Manager® from Aries Systems Corporation the viewpoint of chronotherapy might improve the satisfaction of patients with the results of pharmacotherapy.

Keywords: Gastrointestinal tract; Antihistamine; Pharmacotherapy

Introduction

Chronobiology is the science of biological rhythms and the bioclocks that drive them. Circadian rhythms influence disease symptomatology and affect the pharmacokinetics and pharmacodynamics of many drug classes. Therefore, these phenomena sometimes have important implications for the treatment of allergic rhinitis. The circadian rhythms that influence the gastrointestinal tract, liver, and kidney affect the absorption, distribution, and elimination of medications [1-4]. Thus, the effects of medications can differ depending on whether they are administered during the evening or morning [5].

Bronchial asthma tends to worsen or to occur mainly at night. The chronobiology and chronotherapy of asthma are important subjects of investigation. Circadian rhythms influencing the autonomic nervous system, endocrine function, and airway inflammation can contribute to the pathogenesis of bronchial asthma [6,7]. The symptoms of allergic rhinitis are also affected by these phenomena and other circadian functions [8]. In patients with allergic rhinitis, a worsening of nasal symptoms after waking up is often observed [9]. This phenomenon is known as a "morning attack". In allergic rhinitis, the intensities of nasal congestion, rhinorrhea, and sneezing are greatest early in the morning in approximately 70% of patients [3]. One or more of the following factors may contribute to the occurrence of maximum nasal congestion in the morning: nasal congestion is worse when the subject is in a recumbent position; secretions accumulate overnight; allergen exposure to mites, mold, or dander may occur while sleeping; cortisol levels are lowest at night (increasing the levels of inflammatory mediators); and autonomic nervous system activity at night promotes vagal tone, favoring vasodilatation [4,8].

The aim of the present study was to examine circadian rhythm-based treatment strategies with the intention of improving pharmacotherapy for allergic rhinitis. In the present study, we focused on the treatment of morning symptoms. We investigated the effects of two second-generation antihistamines, with different pharmacokinetic

parameters, bepotastine besilate and olopatadine hydrochloride, for the treatment of morning symptoms.

Method

Study subjects

Twenty-four subjects were recruited for this study. All the subjects were patients with perennial allergic rhinitis associated with a house dust mite allergy (19 women, 5 men; 32 ± 5 years old). Some of the patients had seasonal Japanese cedar pollinosis, but this study was not performed during the season for pollinosis. All the patients with allergic rhinitis had tested positive for mite nasal allergy, as diagnosed based on a clinical history of moderate to severe rhinosinusitis, a rhinoscopic examination, a nasal smear for eosinophilia, and an intradermal test or the determination of specific IgE antibodies using a capsulated hydrophobic carrier polymer radioallergosorbent test (CAP-RAST). The inclusion criteria for allergic rhinitis were a positive CAP-RAST result (score of 2 or greater) or a positive skin prick test (wheal >5 mm) for house dust or mites. The protocol was approved by the ethics committees of Tokyo Woman's Medical University and the Nippon Medical School, Musashikosugi Hospital. Written informed consent was obtained from each of the participating patients before the start of the study.

Study design

A 2-week washout period was scheduled before the present study during which none of the subjects received anti-allergic medicines, such as antihistamines or intra-nasal corticosteroids. During the 1-hour period after waking up in the morning, the patients counted and recorded the number of sneezes and the number of times they blowed their noses using a self-check sheet. Nasal congestion was evaluated using a 5-point scale (0-4), according to the classification of symptom severity used by the Japanese guidelines for allergic rhinitis [10]. The Peak Nasal Inspiratory Flow (PNIF) was also measured using a portable inspiratory flow meter (In-checkTM; Clement Clarke International Limited, Harlow, UK) with an anesthetic mask for the evaluation of nasal congestion (Figure 1).

Figure 1: The Peak Nasal Inspiratory Flow (PNIF) was measured using a portable inspiratory flow meter (In-checkTM, Clement Clarke International Limited, Harlow, UK) with an anesthetic mask for the evaluation of nasal congestion.

The PNIF was measured while the subject was in a seated position. A good seal was ensured, and each of the patients was instructed to make a maximal inspiratory effort with his or her mouth closed. The best result of three attempts was used after appropriate training had been performed. Three days before the start of treatment, the subjects were asked to begin recording their nasal symptoms and PNIF values during the 1-hour period after awakening. The averages of these counts and data obtained during the 3-day period were used as control values.

We conducted this clinical study to evaluate the inhibitory effects of two second-generation anti-histamines, bepotastine besilate (10 mg) and olopatadine hydrochloride (5 mg), on the morning nasal symptoms of patients with allergic rhinitis. The study participants took the allocated medicine twice a day (after breakfast and before bed). They continued recording their nasal symptoms and PNIF after awakening for 10 to 14 days. Twenty-four subjects who provided their informed consent were randomly allocated to either a bepotastine group (B group; n=10) or an olopatadine group (O group; n=14).

Statistical analysis

Data were expressed as the mean ± standard error of the mean. The nasal symptoms and PNIF values at each measurement point were compared with those observed before drug administration. The Wilcoxon signed-rank test was used for the statistical analysis. Differences with P values of less than 0.05 were considered significant.

Results

The average compliance rate was approximately 92%.

A) Nasal symptoms during 1 hour after awakening

1) Sneezing

The mean ± SEM sneezing count before the study was 1.43 ± 0.45 for group B and 2.64 ± 1.00 for group O. In group B, the mean sneezing count was significantly lower on day 3, 7, 10, and 13. In group O, it was significantly lower on day 2 and was well suppressed for the following 10 days (Figure 2).

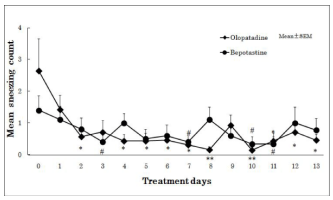

Figure 2: Changes of the mean ± SEM sneezing count throughout the study. They were followed during 2 weeks using second-generation antihistamines. Especially in group O (olopatadine hydrochloride), it was well suppressed.

*p<0.05 Group O vs before administration

**p<0.01 Group O vs before administration

#p<0.05 Group B (bepotastine besilate) vs before administration

2) Rhinorrhea

The mean nose blowing count before the study was 2.30 ± 0.5 for group B and 2.71 ± 0.45 for group O. In group B, the mean nose blowing count was significantly lower on day 2. Thereafter, the count varied day by day, but it was reduced on day 11 and day 14. In group

O, it was significantly lower from day 2 onwards, and this symptom was well suppressed for the following 10 days (Figure 3).

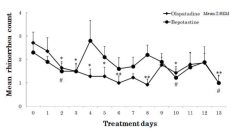

Figure 3: Changes of the mean nose blowing count throughout the study. Especially in group O, it was well suppressed.

*p<0.05 Group O vs before administration

**p<0.01 Group O vs before administration

#p<0.05 Group B vs before administration

3) Nasal congestion

The mean nasal congestion scores using a 5-point scale before the study were 1.70 ± 0.26 in group B and 1.86 ± 0.21 in group O. In both groups, a significant change in the nasal congestion score was not observed throughout the study (Figure 4).

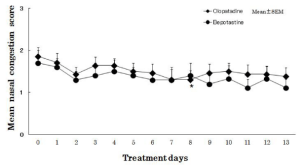

Figure 4: Changes of the mean nasal congestion score throughout the study

In comparison with other scores, a significant change was not observed in both groups.

*p<0.05 Group O vs before administration

B) PNIF measured within 1 hour after awakening

The mean ± SEM of the PNIF value measured before the study was 73.5 ± 3.80 for group B group and 72.9 ± 7.00 for group O. In group B, the PNIF increased during the study, but the change was statistically significant only on day 11. In group O, the PNIF increased from day 2 onwards, and a significant increase was observed for the following 10 days (Figure 5).

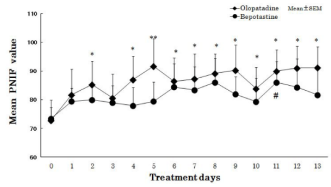

Figure 5: Changes in the mean ± SEM value of PNIF throughout the study

Especially in group O, significant increase of PNIF was observed.

*p<0.05 Group O vs before administration

**p<0.01 Group O vs before administration

#p<0.05 Group B vs before administration

Discussion

The maximum drug concentration time (Tmax) and the half-life period (t 1/2) of bepotastine besilate were 1.2 and 2.4 hours, respectively, while the Tmax and t 1/2 of olopatadine hydrochloride were 1.0 and 8.8 hours, respectively. We hypothesized that a medicine with a long t 1/2 and a short Tmax might be useful for controlling the morning symptoms of allergic rhinitis if it was taken before bed and after breakfast. The results of the present study indicated that the second-generation antihistamines bepotastine and olopatadine were useful for relieving the morning symptoms of allergic rhinitis. Especially, in olopatadine group, PNIF increased from day 2 onward and a significant increase was observed for the following 10 days. The t 1/2 of olopatadine is 8.8 hours, which is longer than that of bepotastine. Therefore, the effects of olopatadine taken the night before were more likely to persist and be more prominent than those of bepotastine. On the other hand, morning dosing with a quick-acting medicine can control morning suffering. The Tmax of these two medicines is 1.0 to 1.2 hours. Thus, to some extent, these medicines can be expected to act quickly from a clinical perspective. Although anti-leukotrienes are also useful for the treatment of allergic rhinitis, their pharmacokinetic parameters are different from anti-histamines. The Tmax and the t 1/2 of montelukast sodium are 3.9 and 4.6 hours, respectively, while the Tmax and t 1/2 of pranlukast hydrate are 5.2 and 1.2 hours, respectively. We hypothesized that their Tmax is too long to control the morning symptoms of allergic rhinitis if it was taken after breakfast. The t 1/2 of montelukast sodium is 4.6 hours and the effects of montelukast taken the night before may persist until next morning. The comparison study using anti-leukotriene is our concern.

In this study, we recruited patients who worked regular hours at the same workplace. Many of them were staff members at our hospital and were women. Therefore, the sex ratio was not well balanced in this study (5 men and 19 women). Morning attacks of allergic rhinitis are thought to occur regardless of sex or age [11]. Although the number of participants was not very large, we analyzed the subjects regardless of these patient characteristics.

Sneezing and rhinorrhea decreased significantly 2 days after the start of treatment. Concerning nasal congestion, we used a 5-point scale for evaluation, but we could not detect any significant changes, probably because this evaluation was performed during the first hour after awakening. According to the Japanese guidelines for allergic rhinitis, the degree of nasal congestion should be evaluated according to the presence or absence of mouth breathing throughout the day, and an evaluation performed within a 1-hour period, as in the present study, might not be appropriate [10]. All the patients selected 1 point or 2 points to represent their daily nasal congestion, but we could not detect any significant changes.

As this result was anticipated, we also used the PNIF to evaluate nasal congestion, and this method seemed suitable for our purposes. The peak expiratory flow is often used as a measure in the management of lower airway diseases, such as bronchial asthma. On the other hand, the PNIF is not broadly used in clinical fields for diseases of the upper airways. The clinical use of PNIF for the evaluation of nasal congestion was recommended in ARIA, and some

studies have demonstrated the usefulness of PNIF [12-14]. In the present study, we used a portable inspiratory flow meter (In-checkTM) originally used for the management of bronchial asthma. Using the facemask attached to this device, it can be adapted for the evaluation of nasal congestion. PNIF can be used to evaluate nasal congestion objectively and is useful for the self-evaluation of nasal congestion. Moreover, the results of the self-evaluation encouraged the subjects to continue their treatments. We concluded that PNIF is a useful tool for evaluating the therapeutic effects of treatment for allergic rhinitis.

At the beginning of this study, we performed a medical interview and confirmed that the patients' morning nasal symptoms had worsened. However, none of the subjects had previously heard of a doctor mentioning the "morning attack" phenomenon. This study dealt with perennial allergic rhinitis, but many patients also suffer from morning attacks of seasonal allergic rhinitis in their daily lives [9]. When second-generation antihistamines are used daily, we usually recommend that patients take them after breakfast or before bed and do not clearly explain the difference in the clinical effects of these strategies. Chronotherapy should be performed on a case-by-case basis after considering the Tmax of the medicine and the patient's lifestyle and situation.

A previous study examining chronotherapy using the antihistamine meqitazine has been reported [5]. Meqitazine (7.5 mg) was more useful when administered once after supper for the management of morning attacks of perennial allergic rhinitis. Bepotastine besilate and olopatadine hydrochloride are typically administrated twice daily, but considering their Tmax and T1/2 values, they are suitable for managing morning attacks and are effective against nasal congestion. While our study examined chronotherapy using antihistamines, it is important to note that the medicines were administered twice daily, and the study was not a comparison of the effects of these medicines when administered according to an evening versus morning dosing schedule. Thus, strict chronotherapeutic comparisons and assessments cannot be made.

The results of a survey of 770 patients showed that morning attacks occur in 66% of perennial allergic patients and 56% of seasonal allergic rhinitis patients [9]. Another study, which investigated 756 patients with perennial allergic rhinitis, demonstrated that sneezing, rhinorrhea, and nasal congestion were most severe after awakening [11]. In the present study, it was impossible to ask the participants to record their nasal symptoms for 24 hours because of their jobs. Therefore, our study investigated only morning symptoms, and not morning attacks in the strictest definition; nevertheless, the goal of our study was achieved.

In recent years, the relationship between allergic rhinitis and sleep disturbance has become a concern [15]. Treatments with intra-nasal corticosteroids and/or leukotriene receptor antagonists reduce nighttime nasal congestion and, as a result, improve the quality of sleep [16-18]. First-generation antihistamines are not effective for nasal congestion and worsen daytime somnolence [19]. On the other hand, second-generation antihistamines have been shown to relieve nasal congestion. However, the nighttime effects of second-generation antihistamines have not been fully investigated [4,20]. Although sleep disturbance itself and daytime symptoms were not evaluated in our study, chronotherapeutic dosing should contribute to the alleviation of nasal congestion during sleeping.

An Internet survey in Japanese regarding seasonal allergic rhinitis reported that only 35% of patients were satisfied with the first antihistamine that was prescribed to them [21]. Until now, chronotherapy for allergic rhinitis has not been widely considered. Some guidance regarding the taking of medicine from the viewpoint of chronotherapy could improve the satisfaction of patients with pharmacotherapy. The measurement of PNIF values might also lead to a favorable self-evaluation of nasal symptoms and treatment effects. Suggestions regarding chronotherapy and self-evaluations could greatly improve the satisfaction of patients with the results of therapy.

Conclusions

The worsening of nasal symptoms after awakening that is associated with perennial allergic rhinitis has a significant impact on the quality of life of patients. Two second-generation antihistamines, bepotastine besilate and olopatadine hydrochloride, were effective for the treatment of these morning symptoms. The evaluation of nasal congestion using subjective scores is not appropriate for short observation periods, such as 1 hour. The PNIF was useful for self-evaluations of nasal congestion and the effects of therapy. Some guidance regarding the taking of medicine from the viewpoint of chronotherapy might improve the satisfaction of patients with the results of pharmacotherapy.

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