

Expert Opinion

1. Introduction
2. Methods
3. Results
4. Discussion

Bepotastine besilate OD tablets suppress nasal symptoms caused by Japanese cedar pollen exposure in an artificial exposure chamber (OHIO Chamber)

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Objective: To investigate the efficacy and safety of bepotastine, we conducted a randomized, investigator-blind, placebo-controlled and parallel study to evaluate the allergic symptoms and the cognitive function of the subjects with Japanese cedar (JC) pollinosis in response to JC pollen exposure in an artificial exposure chamber. **Methods:** Twenty-four volunteers with JC pollinosis were enrolled in this study. The subjects were randomly divided into two groups: a bepotastine group and a placebo group (12 subjects each). Subjects received either a 10-mg bepotastine OD (orally disintegrating) tablet or a placebo 10 min before entering the chamber for a 3-h exposure. The nasal and ocular symptoms were evaluated by each patient at regular intervals. The amount of nasal discharge was measured and the number of sneezes recorded. To evaluate the cognitive function, a digit cancellation test (D-CAT), in which the subjects have to eliminate certain numbers within a fixed time, was conducted. **Results:** Twelve subjects in the placebo group developed nasal and/or ocular symptoms, whereas six subjects in the bepotastine group showed none of the symptoms during exposure. Mean secretion weights and number of sneezes were significantly lower in the bepotastine group than in the placebo group. In D-CAT, no deterioration of work performance was observed in the bepotastine group. No adverse effects were observed in either group. **Conclusion:** Bepotastine treatment is effective and well tolerated in patients with allergen-induced symptoms exposed to JC pollen in an exposure chamber.

Keywords: bepotastine besilate, cognitive function, environmental exposure chamber, Japanese cedar pollinosis

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1. Introduction

Japanese cedar (JC) pollinosis is a seasonal allergic rhinitis mainly with nasal and ocular symptoms, caused by JC pollen dispersed usually between February and April in Japan. On average, approximately 13% of the Japanese population suffers from the allergy and in some regions more than 30% of people are affected [1]. The number of people suffering from allergic rhinitis is on the rise worldwide. Recently revised in 2008, ARIA (allergic rhinitis and its impact on asthma) is used as an international guideline for allergic rhinitis (AR) [2]. In this guideline, new classifications have been introduced according to the AR symptomatic period (intermittent or persistent) and impairment of the daily activities, or severity (mild, moderate or severe). On the other hand, there is a

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widely used guideline in Japan for AR, developed by Japanese AR experts [3], which discusses various diagnostic methods and recommended treatment plans for patients with JC pollinosis in consideration of Japanese circumstances. Since we have diagnosed pollinosis patients according to this guideline for years, we will regard JC pollinosis as seasonal allergic rhinitis (SAR), which is the conventional classification, in this paper.

Bepotastine besilate OD tablet is a second-generation antihistamine agent, which has recently become available for use in the clinical field as an orally disintegrating formulation containing menthol. Along with its strong antihistaminic action, this drug suppresses eosinophilic migration to nasal mucosa at a clinical dose. A double-blind comparative study demonstrated that bepotastine is significantly superior to terfenadine in the treatment of patients with perennial allergic rhinitis (PAR) [4]. Other clinical studies have demonstrated not only the effectiveness of bepotastine in the treatment of allergic rhinitis but also its safety [5,6].

The purpose of this study was to investigate the efficacy of a single administration of a bepotastine OD tablet (10 mg) in the treatment of SAR patients exposed to JC pollen. To achieve a stable environment, since the amount of dispersed pollen grains and climate cannot be controlled in the natural environment, we conducted this study in a recently built (Tokyo, 2005) pollen exposure chamber (OHIO chamber) [7]. The OHIO chamber has the following features:

1. Cedar pollen concentration in the room is spatially uniform at a certain temperature/humidity.
2. The direct response to only pollen exposure can be obtained in a clean air environment in the absence of hazardous materials such as volatile organic compounds (VOCs).
3. An automatic cleaning system thoroughly removes pollen in the room to prevent fungus growth.

The biggest advantage using this chamber is that the drug efficacy can be tested during the non-cedar pollen dispersing season.

2. Methods

2.1 Subjects

The subjects in this study were adult patients with JC pollinosis. The inclusion criteria were: allergic symptoms during the pollen season for at least 2 years, with scores of 2 or more for JC pollen and a score of 1 or less for house dust and mites on the CAP radioallergosorbent test (CAP-RAST; Phadia AB, Sweden), which is the most popular test to measure allergen specific IgE levels in sera. The results of the CAP-RAST test are reported as scores ranging from 0 to 6; scores of 2 or more are judged as positive for the corresponding allergen. The exclusion criteria include: presence of nasal diseases (deviated nasal

septum or nasal polyp) and upper airway disorders (acute rhinitis, chronic rhinitis, congestive rhinitis, atrophic rhinitis, chronic rhinosinusitis, purulent mucus and flu-associated sinusitis) affecting the study outcomes or evaluation; presence of systemic diseases including asthma, hypertension, and diabetes mellitus; history of treatment with steroid injections within 6 months before entry into the chamber; history of treatment with oral, inhalational or topical steroid therapy and/or antihistamines within 4 weeks before entry into the chamber; and pregnant or breast-feeding women, and women trying to conceive. People who were deemed ineligible by the physicians in charge were eliminated as well.

The study was conducted in June, which is not a JC pollen-dispersing season, and in accordance with GCP guidelines and the declaration of Helsinki. The study protocol was reviewed and approved by the IRB of Shinanozaka clinic. Informed consent was obtained from all subjects.

2.2 Study design

This was a randomized, investigator-blinded, placebo-controlled, parallel study, conducted in June, which is a non-pollen-dispersing season. The subjects were randomized to receive a 10-mg bepotastine OD tablet or a placebo tablet 10 min before entering the OHIO chamber. Owing to the nature of this orally disintegrating tablet, blindness could not be maintained by the subjects. Therefore, the study was conducted as a single-blind study for the physicians in charge. The study schedule is shown in Figure 1. The predetermined JC pollen concentration was 8000 grains/m³, an amount equivalent to the number of pollen grains dispersed annually in the suburban districts of Tokyo. The pollen count was measured by a laser particle counter (KC-20, Rion Co., Tokyo, Japan), and was computerized to be stable in the chamber. The temperature inside the chamber was set at 22°C, and the humidity to 45%. A maximum of 12 people could enter the OHIO chamber at a time. The subjects were exposed to JC pollen for 3 h and were informed to leave the chamber whenever they became uncomfortable.

2.3 Assessment

Each subject was instructed to grade and record the severity of their nasal symptoms (sneezing, nasal discharge, nasal obstruction, and itchy nose) and ocular symptoms (itchy eyes and tears) every 15 min according to the following five-point scale: 0 = none (no symptoms); 1 = mild (symptoms present but easily tolerated); 2 = moderate (awareness of symptoms; bothersome, but tolerable); 3 = severe (definite awareness of symptoms; difficult to tolerate, but does not interfere with the activities of daily living); 4 = very severe (difficult to tolerate and interferes with the activities of daily living). The total nasal symptom score (TNSS) and total non-nasal symptom score (TNNSS) are the mean sums of

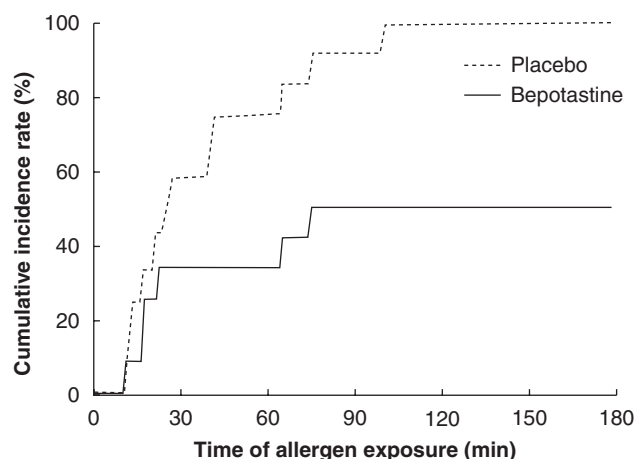


Figure 1. Comparison of the time to occurrence of the symptoms between bepotastine group (solid line) and placebo (dotted line) using Kaplan-Meier's method.

A significant difference is observed between the two groups. Log rank test: $p = 0.012$.

Table 1. Patient demographics.

	Bepotastine group	Placebo group	Total
Age (years)			
Mean $\pm$ SD	42.9 $\pm$ 9.8	35.3 $\pm$ 9.3	39.1 $\pm$ 10.1
Range	29 – 57	23 – 50	23 – 57
Gender			
Male, n (%)	2 (16.7)	4 (33.3)	6 (25.0)
Female, n (%)	10 (83.3)	8 (66.7)	18 (75.0)
Duration of SAR			
Mean $\pm$ SD	19.1 $\pm$ 8.4	15.7 $\pm$ 10.2	17.4 $\pm$ 9.3
Range	6 – 32	4 – 35	4 – 35
Presence of RAR			
Yes, n (%)	6 (50)	5 (41.7)	11 (45.8)
No, n (%)	6 (50)	7 (58.3)	13 (54.2)

SAR: Seasonal allergic rhinitis; PAR: Perennial allergic rhinitis.

Bepotastine group (n = 12): Subjects received 10-mg bepotastine OD tablet before entering the OHIO Chamber.

Placebo group (n = 12): Subjects received placebo before entering the OHIO Chamber.

Significant differences were not found between Bepotastine group and placebo group in the patients' background.

the four nasal symptoms and the two ocular symptoms, respectively. The total symptom score (TSS) is the sum of TNSS and TNNSS.

The interval from the time of entry of a subject into the chamber to the occurrence of the first nasal symptom (any of 4 nasal symptoms) or the first ocular symptom

was designated 'time to occurrence of symptoms', which is one of the end points, and the time was recorded for each subject.

Regarding the objective signs, the amount of nasal discharge and the number of sneezes were recorded every hour. The subjects were instructed to use tissue distributed to each subject to blow their noses. At every fixed time point (every 30 min), the used tissue was collected in a plastic bag. The weight difference between the tissue before and after use was considered the amount of nasal discharge. The number of sneezes was counted by each subject and reported at a fixed time point.

To determine impaired performance due to drug administration, digit cancellation test (D-CAT), a screening test for assessment of cognitive function [8], was conducted before the pollen exposure, and at 1, 2 and 3 h after the start of exposure. In this test, the subjects were asked to eliminate certain numbers out of 600 randomly arranged digits (0 to 9), with 50 numbers per line, within 1 min [8]. Impaired performance was evaluated as change in work performance and change in elimination error at each measuring point.

2.4 Statistical analysis

Fisher's direct test and the Student's t-test were used to analyze the sex ratio and age in the background factors of the subjects in the two groups, and the Wilcoxon rank sum test was used to analyze the comparison of disease duration and the serum IgE antibody titers for JC pollen.

The log rank test was used to analyze the time to develop the symptoms and the total number of subjects with the symptoms. The TSS, TNSS and TNNSS in each group were expressed as the changes from the scores before JC pollen exposure. And the amount of change in weight of nasal discharge, number of sneezes in each time period and the work performance test in each group was analyzed using the Wilcoxon rank sum test. The paired t-test was used to analyze the results of the work performance test in each group. We used SAS for Windows Version 9.1.3 (SAS Institute, Inc. Cary, NC, USA) for data analysis; $p < 0.05$ was considered statistically significant.

3. Results

3.1 Demography of the subjects

A total of 24 subjects (6 men and 18 women) who satisfied the inclusion criteria and did not have exclusion criteria were enrolled in this study. The subjects were randomly divided into two groups, a bepotastine group and a placebo group (12 subjects each). There were no significant differences in baseline scores of TSS, TNSS, TNNSS and individual symptom scores of the subjects in the two groups. The detailed patient backgrounds are shown in Table 1. This study was conducted two times, in the morning and the afternoon, on the same day. There were no

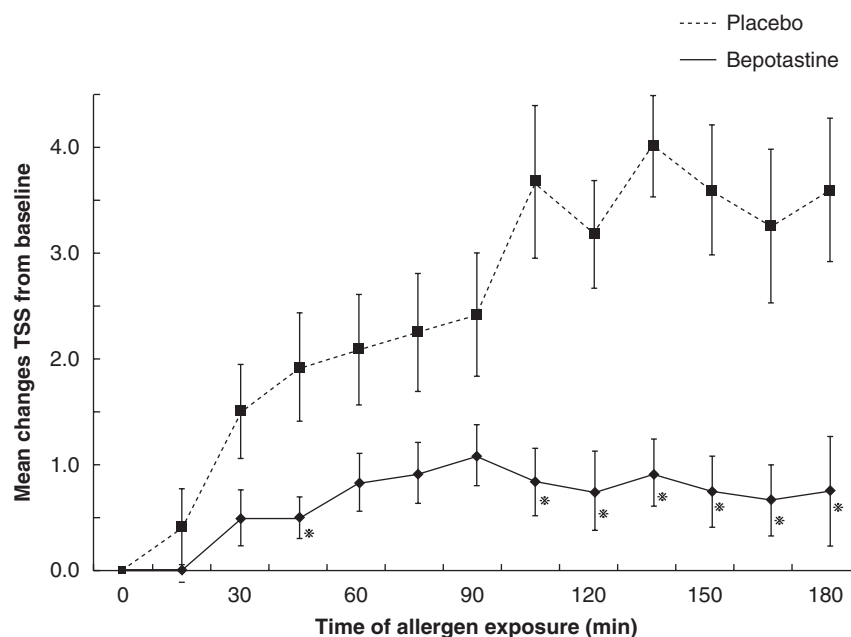


Figure 2. Mean changes in total symptom scores in questionnaire from baseline in response to Japanese cedar pollen exposure.

Error bars are $\pm$ SD. A significant difference was found between bepotastine and placebo group at 45 min and from 105 min to the end of pollen exposure. Wilcoxon rank sum test: $p < 0.05$.

statistical differences in patient background between them (data not shown).

3.2 Time to develop the symptoms

Figure 1 shows the chronological changes in the total number of subjects who developed symptoms in the bepotastine group and the placebo group. In the placebo group, all subjects developed nasal and/or ocular symptoms due to pollen exposure after approximately 100 min of dispersing pollen. By contrast, only six subjects developed the symptoms in the bepotastine group. When we statistically analyzed the time to develop the symptoms and the total number of subjects with symptoms, the bepotastine group was significantly superior to the placebo group (log rank test: $p < 0.012$).

3.3 Symptoms induced by pollen exposure

Compared with the placebo group, the bepotastine group showed a lower TSS during pollen exposure (Figure 2). The TSS score was significantly lower at 45 min and from 105 min after the exposure to the end of exposure (Wilcoxon rank sum test: $p < 0.05$).

Regarding the individual symptoms of sneezing, nasal discharge and nasal obstruction, the bepotastine group showed a lower score than the placebo group (Figure 3A – C).

The ocular symptoms seemed to be relieved in the bepotastine group, but there were no significant differences between the two groups (data not shown). Considering the

number of sneezing and the amount of nasal discharge, the bepotastine group showed lower values in both measurements, and there were significant differences in the number of sneezing after 61 – 120 min and after 121 – 180 min and in the amount of discharge after 121 – 180 min (Table 2).

3.4 Results of the work performance test

D-CAT was conducted before entering the chamber, and at 1, 2 and 3 h after JC exposure. Work performance increased gradually from 878.0 ± 156.1 to 914.0 ± 132.5 , 936.7 ± 153.7 and 965.8 ± 119.5 , respectively, in the bepotastine group. A significant difference was observed in work performance between before entering the room and at 3 h after exposure (paired t-test: $p < 0.05$). By contrast, the results of the work performance test were 860.5 ± 78.6 , 853.5 ± 83.1 , 829.8 ± 67.4 and 858.3 ± 106.6 , respectively, in the placebo group. There were no significant differences between the observed points. Regarding the changes in work performance at each measuring point, the changes in the bepotastine group were higher at all of the measuring points compared with the placebo group, and there were significant differences at 2 and 3 h after exposure (Wilcoxon rank sum test: $p < 0.05$) (Figure 4A). In addition, in terms of the changes in elimination error rate at each measuring point, both groups showed a tendency to decrease, but there were no significant differences between the two groups (Figure 4B).

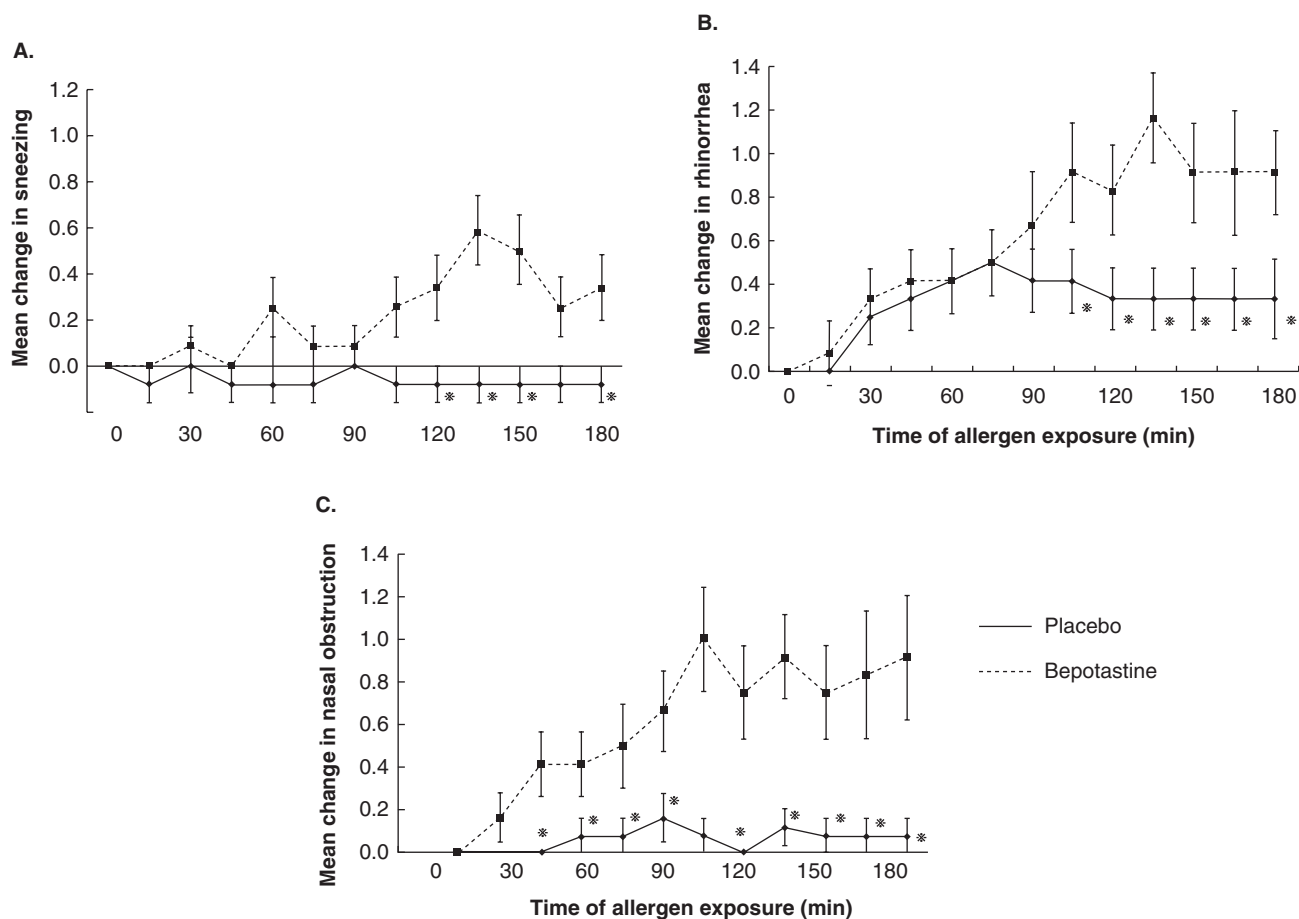


Figure 3. Mean changes in the individual symptom score for (A) sneezing, (B) rhinorrhea, and (C) nasal obstruction from baseline in response to Japanese cedar pollen exposure in bepotastine and placebo groups.

Error bars are $\pm$ SD. Wilcoxon rank sum test: $p < 0.05$.

Table 2. Results of nasal secretion weight and number of sneezes.

	Bepotastine group	Placebo group	p value
Nasal secretion weight (g)			
0 – 60 min	0.5	0.5	NS
61 – 120 min	0.6	1.7	NS
121 – 180 min	0.4	1.9	$p < 0.05$
No. of sneezes			
0 – 60 min	0.1	0.5	NS
61 – 120 min	0.2	2.0	$p < 0.05$
121 – 180 min	0.0	2.3	$p < 0.05$

Data are given as mean.

3.5 Safety

Neither group developed any serious side effects while staying in the exposure room or on the next day.

4. Discussion

Our study demonstrated that administration of a 10-mg bepotastine OD tablet before pollen exposure reduces the development of symptoms in patients with JC pollinosis. In this study, a pollen exposure chamber (OHIO Chamber) was used, which can accommodate up to 12 people at a time to be exposed to a certain concentration of cedar pollen in a fixed, stable environment [7]. Changes in subjective symptoms and objective signs, and the level of impaired performance due to administration of antihistamine drug after exposure can be measured.

In the bepotastine group, the development of overall nasal symptoms was significantly suppressed compared with the

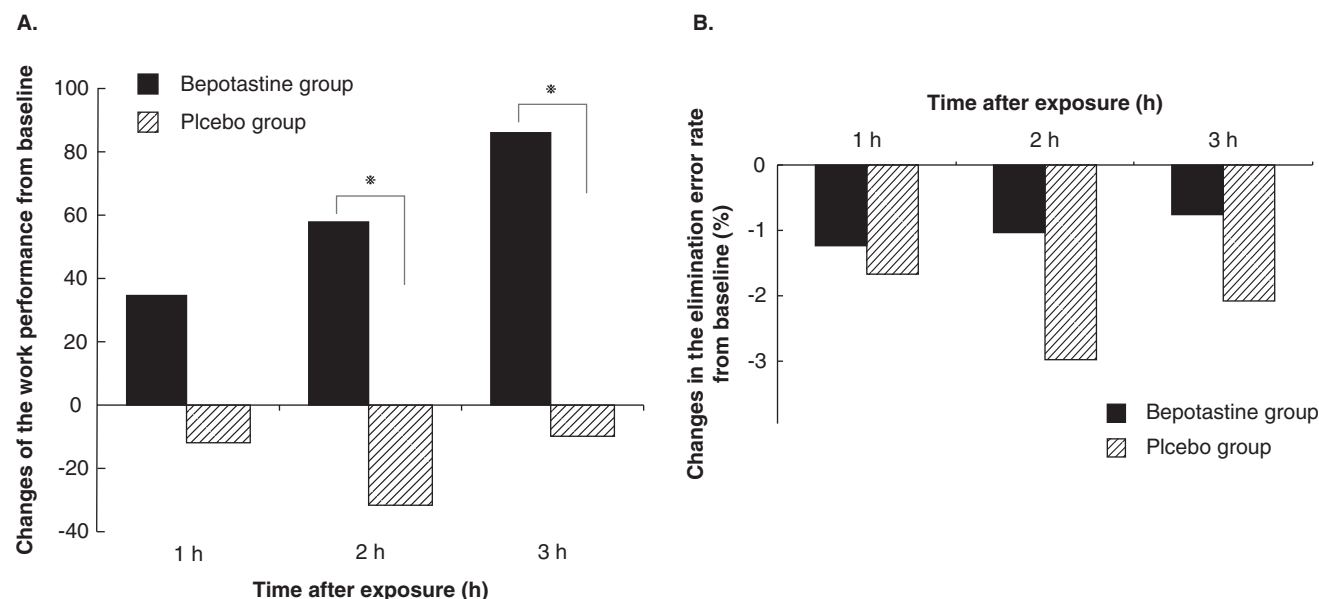


Figure 4. Changes in (A) work performance from baseline in D-CAT and (B) elimination error rate from baseline in D-CAT.

A significant difference was not found between bepotastine and placebo group. *Wilcoxon rank sum test: $p < 0.01$.

placebo group. Interestingly, the development of nasal obstruction was suppressed during pollen exposure in the bepotastine group. In general, it has been considered that antihistamine drugs are highly effective for suppressing histamine-induced sneezing and nasal discharge, but not for nasal obstruction [2]. However, bepotastine treatment showed a significant difference in the final overall improvement score in a double-blind study conducted on PAR patients in a natural environment while using terfenadine as a control [4]. In addition, this study also showed the drug efficacy for nasal obstruction.

The bepotastine OD tablets contain menthol, which has no effect on nasal obstruction in objective methods. Inhalation of menthol, however, caused a subjective nasal decongestant effect without any change in nasal airway resistance [9]. This drug has not only a strong antihistamine action but also anti-allergic actions to suppress IL-5 production and suppress eosinophilic invasion at a clinical dose [10]. These facts could explain why this drug is effective in relieving nasal obstruction.

Enomoto *et al.* [11] investigated the effects of cetirizine hydrochloride on nasal symptoms using a placebo as a control in Wakayama environmental exposure unit (Wakayama EEU), which was the first facility capable of conducting a cedar pollen exposure study. Similar to our results, effects of the active drug on nasal obstruction were observed, although they used a visual analog scale (VAS) to evaluate the drug effects. The efficacy of second-generation antihistamine drugs on nasal obstruction have not been well documented; however, our results point towards the potential activities on nasal congestion of bepotastine OD

and the need for further investigation on this drug as well as on other antihistamines.

The bepotastine OD tablet reaches its maximum blood concentration in an hour after administration [12], indicating its fast action on nasal symptoms. In the present study, the tablet was administered only once before the JC pollen exposure. Only six out of 12 subjects showed symptoms in the bepotastine group, whereas all of the subjects showed symptoms in the placebo group, indicating the possibility of using bepotastine as a prophylaxis to relieve the symptoms by administering this drug in advance of the JC pollen dispersion.

Pollinosis is known to undermine daily quality of life and lower work performance, and its economical damage has become a social problem [13]. In the present study, a performance test using the D-CAT was conducted to assess cognitive function. In the placebo group, cognitive level did not change significantly during exposure, whereas in the bepotastine group the cognitive level ameliorated over time. We could not clearly demonstrate a tendency of decreasing work performance in the untreated pollinosis patients. However, that lower work performance in the treated group was not observed in this study indicates that bepotastine did not induce impaired performance.

Bepotastine is known to maintain brain penetration at a low level as a substrate for P-glycoprotein [14]. In addition, Tashiro *et al.* classified bepotastine as a 'non-sedating' antihistamine drug based on the brain penetration study using PET [15]. Our results also supported these characteristics.

Bepotastine besilate OD tablet is classified as a new second-generation and non-sedating antihistamine with an

anti-allergic action to suppress IL-5 production and eosinophilic invasion at a clinical dose, characterized by the rapid onset of action [16]. In this study, using an OHIO chamber, which allows dispersion of a fixed amount of pollen under stable conditions, we demonstrated that administration of a 10-mg bepotastine OD tablet to patients with JC pollinosis relieves the nasal symptoms induced by JC pollen exposure and maintains work performance compared with placebo. In addition, we demonstrated that bepotastine OD tablet is fast-acting and safe. It could be possible to use bepotastine as a prophylaxis to relieve symptoms by administering it in advance of pollen

dispersion, although a prophylactic use of antihistamine in SAR patients has not been approved. We believe that bepotastine OD is highly effective and well tolerated for the treatment of JC pollinosis.

Declaration of interest

This study was supported by a grant from Public Health Research Foundation, Tokyo Japan. None of the authors has any financial interest in the subject materials, materials or equipments and report no conflict of interest.

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