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BRIEF REPORT

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Histamine antagonist Bepotastine suppresses nasal symptoms caused by Japanese cedar and cypress pollen exposure

Sho Kanzaki[a], Kazuhiro Hashiguchi[b], Ken-ichiro Wakabayashi[c], Kiyochika Suematsu[b] and Kimihiro Okubo[d]

[a]Department of Otorhinolaryngology, Keio University School of Medicine, Tokyo, Japan; [b]Otorhinolaryngology, Futaba Clinic, Tokyo, Japan; [c]Department of Otorhinolaryngology, Kitasato Institute Hospital, Tokyo, Japan; [d]Department of Otorhinolaryngology, Nippon Medical School, Tokyo, Japan

ABSTRACT

Objective: To determine the efficacy of the antihistamine bepotastine on treating nasal symptoms in patients with Japanese cedar and cypress pollinosis, based on two previous studies that looked at bepotastine OD's inhibitory effect on symptom onset after exposure.

Design and methods: Randomized double-blind placebo controlled, parallel study. Twenty-eight volunteers with Japanese cedar and cypress pollinosis were randomly assigned into two experimental groups: a bepotastine-treated or a placebo control group. Subjects received either 10 mg bepotastine tablets or placebo tablets 1 day before entering an artificial exposure pollen chamber (OHIO Chamber) and also for three or more consecutive days. They were exposed to Japanese cedar and cypress pollen for 3 h per day for 2 days. Nasal and ocular symptoms were self-rated by each patient at regular intervals in addition to being objectively measured. Possible cognitive impairment was assessed by using the digit cancellation test (D-CAT).

Results: In Study 1, under controlled conditions, there were no significant differences ($p > .05$) between subjects exposed to Japanese cedar pollen and those exposed to cypress pollen in terms of total nasal symptom score (TNSS).

In Study 2, in the placebo group, the amount of nasal discharge and the number of sneezes did not diminish before cypress pollen exposure on the second day ($p < .05$). This suggests that an antihistamine can suppress the symptoms of hang over. No deterioration of work performance was observed in the bepotastine group after pollen exposure for 2 days, as measured by D-CAT ($p > .05$).

Conclusion: We conclude that bepotastine can suppress allergy-related symptoms without impairing work performance in subjects with seasonal allergic rhinitis caused by Japanese cedar pollen or cypress pollen.

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Japanese cedar pollinosis; cypress pollinosis; artificial exposure chamber; antihistamine

Introduction

This report was based on two Japanese papers that looked at bepotastine OD's inhibitory effect on symptom onset after exposure.[1,2] The number of people suffering from allergic rhinitis (AR) has become a global health care problem that greatly affects daily activity, work productivity, learning, sleep, and quality of life.[3–5]

In Japan, the prevalence of AR has continued to rise over the past decade, with rates increasing from 29.8% in 1998 to 39.4% in 2008.[6] In some regions more than 30% of the people are affected. The main symptoms are sneezing, nasal discharge, and nasal obstruction, which are not life threatening but it can be difficult to tolerate when it is more severe. The major AR phenotype in Japan is Japanese cedar-cypress pollinosis (JCCP), which has a prevalence of 26.5%.[6] JCCP is mainly due to exposure to Japanese cedar (*Cryptomeria japonica*) and Japanese cypress (*Chamaecyparis obtuse*) pollen.[6] During spring, the dispersal of cypress pollen typically occurs between April and May after the dispersal of cedar pollen, which typically occurs between February and April. Although the peak levels for these two types of pollen occur at separate times, AR pollinosis-related symptoms can last for as long as 4 months, from February until early May, because cedar pollen and cypress pollen contain several cross-reactive components.[7,8]

These conditions lead to allergen and non-specific irritant hypersensitivities, which contribute to the onset of AR.

The Practical Guideline for the Management of Allergic Rhinitis in Japan (PG-MARJ) recommends that patients who annually experience substantial symptoms of pollinosis should receive early prophylactic treatment, starting immediately after pollen release or at the onset of symptoms.[6]

The PG-MARJ recommends that physicians determine the drug regimen for each patient individually based on the amount of anticipated pollen release during the current

CONTACT Sho Kanzaki, M.D., Ph.D. skan@a7.keio.jp Department of Otorhinolaryngology, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan

www.informahealthcare.com/jda

season and the type and severity of symptoms that each patient has experienced in the past during the peak pollen season. Treatments should be selected from among the chromones, second-generation H1-receptor antagonists (H1RA) and anti-leukotorien, PGD2/TXA2, and Th2-related cytokines inhibitor.

Initial dispersion of the pollen can have a priming effect and cause minimal persistent inflammation (MPI) characterized by an influx of inflammatory cells such as eosinophils into the nasal mucosa. Thus, to decrease the incidence of MPI, early interventional treatment or pre-seasonal treatment can be considered for pollinosis patients.

Bepotastine besilate is a second-generation antihistamine that has recently become available for clinical use as an orally disintegrating (OD) formulation that contains menthol. Along with its strong antihistamine action, this drug suppresses eosinophilic migration to nasal mucosa at clinical doses.[9,10]

A double-blind comparative study demonstrated that bepotastine is significantly superior to terfenadine in the treatment of patients with perennial allergic rhinitis (PAR).[9] Other clinical studies have demonstrated not only the effectiveness of bepotastine in the treatment of AR, but also its safety.[12]

However, some questions remain. The purpose of this study was to investigate the efficacy of a single dose of bepotastine (10 mg bepotastine OD tablet) in the treatment of allergic rhinitis patients exposed to Japanese cedar and cypress pollen. Climate and the amount of dispersed pollen grains cannot be controlled in the natural environment. Thus, to achieve a stable, controlled environment, we conducted this study using a pollen exposure chamber (OHIO chamber).[11] Subjects are exposed to controlled amounts of Japanese cedar and cypress pollen in this way.

Subjects and methods

Subjects

There are 47 subjects in study 1 and 28 subjects in study 2. The subjects were adult patients with Japanese cedar and cypress pollinosis. They ranged in age from 20 to 65 years. The inclusion criteria were as follows: candidate subjects had to experience allergic symptoms during the pollen season for at least 2 years of the previous years and have a current allergy score of 2 or more on the CAP-radioallergosorbent test (CAP-RAST) specific for Japanese cedar pollen and score of 1 or more specific for cypress pollen. They also had to have an allergy score of 2 or less on a CAP-RAST specific for house dust and mites.

The exclusion criteria were as follows: candidate subjects having a nasal disease (e.g. deviated nasal septum or nasal polyp) or an upper airway disorder (e.g. acute rhinitis, chronic rhinitis, congestive rhinitis, atrophic rhinitis, chronic rhinosinusitis, purulent mucus, or flu-associated sinusitis); the presence of systemic disease, including asthma, hypertension, and diabetes mellitus; history of treatment with steroid injections 6 months or less before the start of the study; history of treatment with oral inhalational or topical steroid therapy and/or antihistamine therapy 4 weeks or less before the start of the study; or female candidates that were pregnant or breast feeding; or women trying to conceive a child. The presence of any of these could confound the study outcomes or evaluation. People who were deemed ineligible by the physicians in charge were also excluded.

These studies were conducted in July, which is not the pollen-dispersing season for Japanese cedar and cypress. However, this was done for experimental control (see Study Design subsection).

The study was conducted in accordance with Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki. The Institutional Review Board (IRB) of Shinanozaka Clinic reviewed and approved the study protocol. We registered this study in the University Hospital Medical Information Network (UMIN ID 000005659). Informed consent was obtained from all subjects.

OHIO chamber

The subjects were exposed to pollen in an apparatus called the OHIO chamber, which we have already reported.[11,12] Its square measure is 25 m^2, the height is 2.5 m, and have a capacity of 15 subjects. Compressed air transfers pollen grains from an outside dust feeder into the operation room where it is mixed with conditioned air inside the pollen diffuser after which the mixed air jets out upward from the diffuser.

The chamber has several features that make it useful for studying AR at different times of the year. Pollen concentration in the chamber is spatially uniform at certain temperatures and humidity, thereby ensuring that the exposure is uniform throughout the test period. Pollen count is monitored and maintained with a computerized laser particle counter (KC-20; Rion Co., Tokyo, Japan). Direct responses to only pollen exposure can be obtained, because the chamber environment is void of hazardous materials, such as volatile organic compounds. The chamber also has an automatic monitoring system that thoroughly removes pollen in the chamber to prevent fungal growth. The biggest advantage of using this chamber is that drug efficacy testing can be performed during non-cedar-pollen dispersing seasons.[11,12]

Study design

Brief overview

We performed two clinical studies, the first of which was a pilot study. In this preliminary trial (study 1), we compared the symptom scores of subjects: patients exposed to Japanese cedar pollen and cypress pollen (Tables 1 and 2).

Table 1. Characteristics of subjects participating in study 1.

Total		47
Gender	Male	22
	Female	25
Age (year)	Average ± SD	35.3 ± 9.2
Illness history(year)	Average ± SD	14.4 ± 7.2

The interval between these two pollen exposures was 1 week, which is enough in study 1. We confirmed the patients had nasal and eye symptoms if they were exposed to cypress pollen.

In study 2, we compared the symptoms of patients treated with a placebo and another group treated with bepotastine OD tablets. Both groups of patients in study 2 were exposed to Japanese cedar pollen on day 1 of the study, followed by cypress pollen on day 2.

Details of the two studies

The experiment was conducted in an OHIO chamber (see below). The predetermined concentration we used for Japanese cedar and cypress pollen in the chamber was 8000 grains/m^3, an optimal number of pollen grain to yield nasal and ocular symptoms in the subjects with Japanese cedar and cypress pollinosis.[9]

The pollen count was measured with a computerized laser particle counter (KC-20; Rion Co., Tokyo, Japan) that was mounted in the chamber. The temperature inside the chamber was set to 22 °C, and the humidity was 45%. The OHIO chamber can hold a maximum of 15 people at one time.

Table 2. CAP RAST score of subjects participating in study 1.

cypress \ ceder				
	0	0	1	1
	0	4	9	1
	11	15	4	1

Table 3. Characteristics of subjects participating in study 2.

			Bepotastine	Placebo
Total			14	14
Gender	Male		4	5
	Female		10	9
Age (years)	Average ± SD		44.6 ± 9.4	42.4 ± 5.7
Illness history	Average ± SD		20.4 ± 9.0	18.1 ± 9.7
IgE score	Japanese cedar	3	8	5
		4	5	4
		5	1	5
	Japanese cypress	1	12	12
		2	2	2
	Mites	1	5	5
		2	2	2
	House dust	0	1	1
		1	4	4
		2	2	2

They were informed that they could leave the chamber if they became uncomfortable. The details for assessing subject symptoms are described below in a separate section (see Assessment).

In study 1, the subjects were exposed to either Japanese cedar pollen or cypress pollen for 2 h. The subjects were exposed to Japanese cedar pollen and exposed to cypress pollen 1 week after that.

Study 2 was a randomized investigator-blinded, placebo controlled, parallel study. The study was conducted in July. Subjects were randomly assigned to receive either a 10 mg bepotastine OD tablet or a placebo tablet 1 day before exposure to pollen and a second tablet 10 min before entering the OHIO chamber (Table 3). There, they were exposed to pollen (8000 grains/m^3) 3 h per day on two separate days. Since the bepotastine OD tablet has specific physical characteristics that could not be mimicked in the placebo tablet, the subjects could not be blinded to the treatment. Therefore, the study was conducted as a single-blind study for the physicians in charge. Chamber conditions were the same as those described above for study 1.

The schedule for study 2 is outlined in Table 4. The subjects were exposed to Japanese cedar and cypress pollen for 3 h. They were informed that they could leave the chamber if they became uncomfortable. The details for assessing subject symptoms are described in a separate section (see Assessment)

Assessment

Each subject was instructed to rate and record the severity of their nasal symptoms (sneezing, nasal discharge, nasal obstruction, nasal itching) 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 (aware of symptoms, bothersome but tolerable); 3, severe (definitely aware of symptoms, difficult to tolerate but does not interfere with activities of daily living); 4, very severe (difficult to tolerate, interferes with activities of daily living). For each subject, we calculated a TNSS, which was the mean sum of scores for the four nasal symptoms. We also calculated a total symptom score (TSS), which was the mean sum of scores for the four nasal symptoms and ocular symptoms.

We also measured symptoms objectively. The amount of nasal discharge and the number of sneezes of each subject were measured every hour. The subjects were instructed to use a clean tissue to blow their noses each time. Every 30 min, the used tissues were collected in a plastic bag, labeled, and

Table 4. Schedule for study 2.

	Seven days before exposure	One day before exposure	Day 1 exposure	Day 2 exposure
Examination	•		•	•
CAP-RAST				
Pollen exposure(Chamber)			• (Japanese cedar)	• (Japanese cypress)
Medication		• •	• •	• •
Allergy diary				
Check the side effects	•		•	•

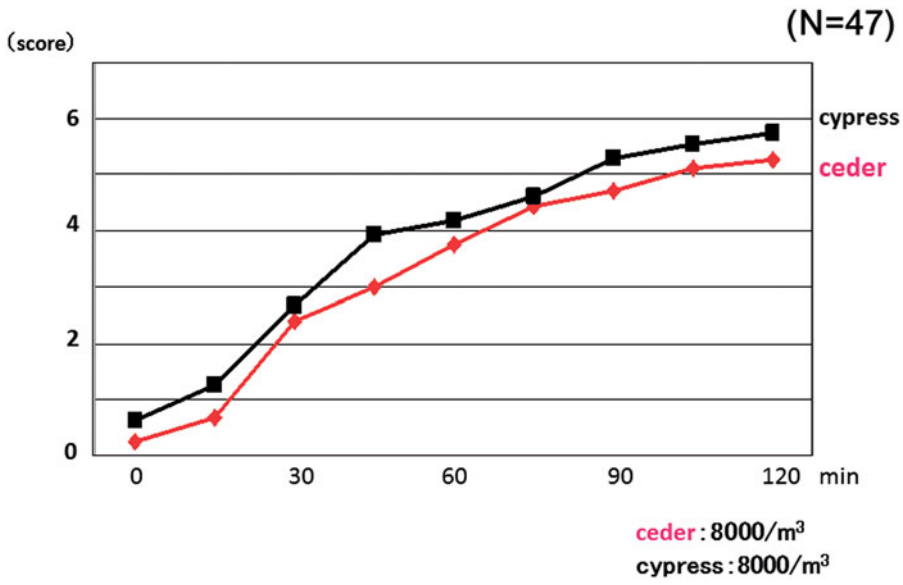

Figure 1. TSS (nasal and ocular symptoms) of subjects ($N = 47$) in study 1 over time after exposure to Japanese cedar and cypress pollen under controlled conditions in an OHIO chamber.

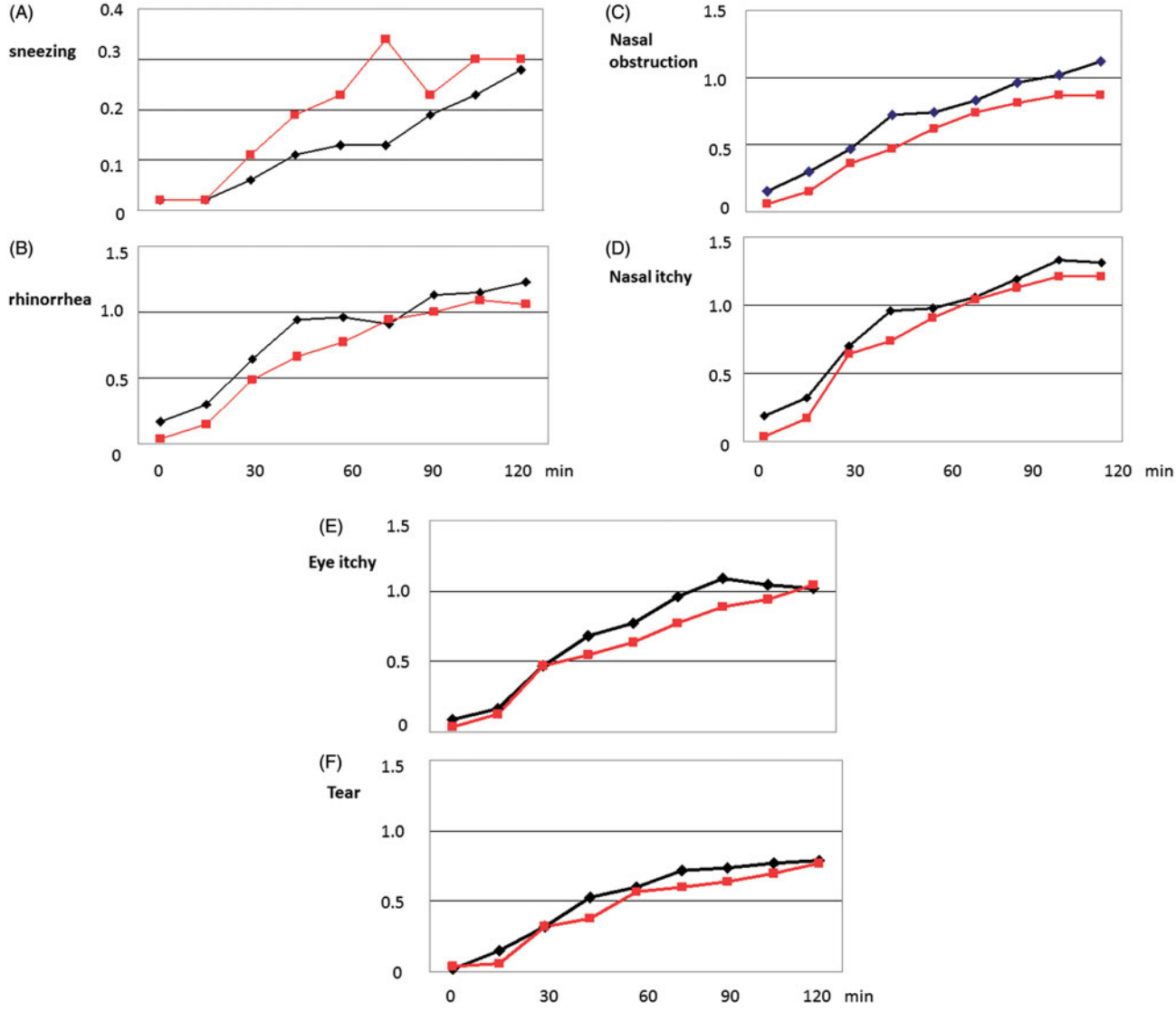

Figure 2. Time course of development of nasal and eye symptoms scores for subjects in study 1 after exposure to Japanese cedar and cypress pollen. TNSS are plotted over time after controlled pollen exposure in an OHIO chamber. (A) Sneezing, (B) Rhinorrhea, (C) Nasal obstruction, (D) Nasal itchiness, (E) Eye itchiness, (F) Tearing.

weighed immediately after the end of exposure. The difference between the tissues' weight before and after use was estimated to be the amount of nasal discharge. In addition, each subject was instructed to count and record the number of times they sneezed every 30 min. To determine whether drug administration might impair the subjects' work performance, we assessed cognition by using the digit cancellation test (D-CAT), a screening test that assesses cognitive function.[9]

The D-CAT was administered before pollen exposure and 1, 2, and 3 h after the start of exposure. In this test, the subjects are asked to mark out certain predetermined numbers in an array of 600 randomly arranged digits (0–9) within 1 min. A same D-CAT was tested at every time point.

Impaired performance on the D-CAT was taken as a change in work performance and a change in elimination error at each measuring point. We expected that the learning curve could have occurred in both the groups, however, the learning curve in the bepotastine group is better than in the placebo group.

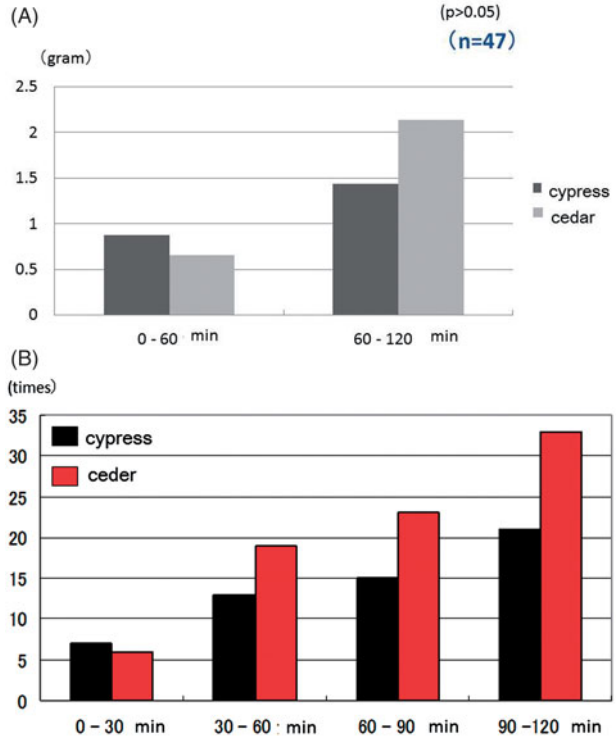

Figure 3. Rhinorrhea and sneezing in subjects exposed to Japanese cedar and cypress pollen in study 1. (A) Average amount of rhinorrhea (grams). (B) Average number of sneezes.

Statistical analysis

Fisher's direct test and Student's *t*-test were used to analyze the gender composition ratio and age of the subjects in the two groups. The Wilcoxon rank sum test was used to analyze disease duration differences and the serum IgE antibody titers for Japanese cedar and cypress pollen in the two groups. The symptom scores of each group were expressed as changes from the scores before Japanese cedar and cypress pollen exposure. The amount of change in the weight of nasal discharge, the number of sneezes for each time period, and the D-CAT for each group was analyzed using the Wilcoxon rank sum test. A paired *t*-test was used to analyze the results of the work performance test for each group. We used SAS for Windows Version 9.1.3 (SAS Institute, Inc. Cary, NC). Test values that were at $p < .05$ were considered statistically significant.

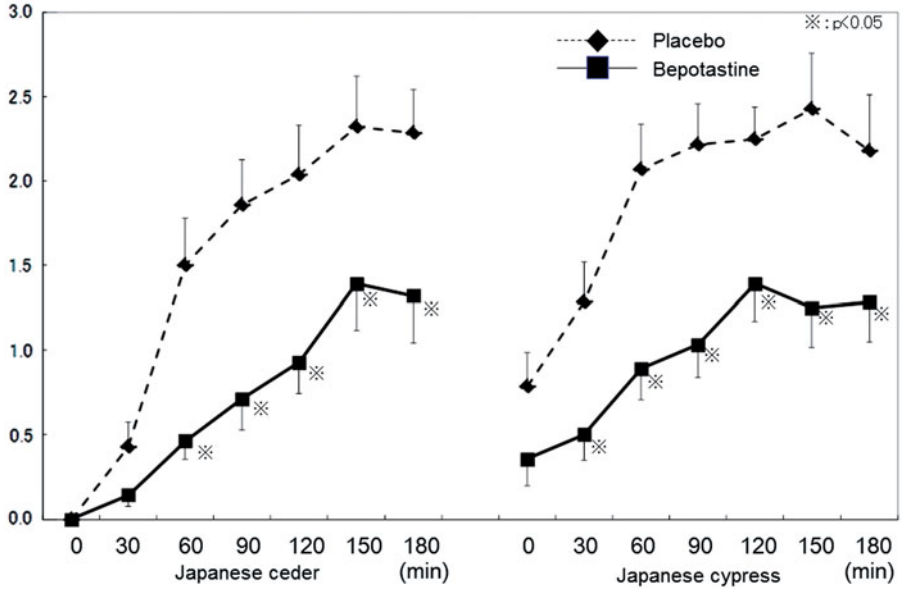

Figure 4. Group comparisons of mean changes in total symptom scores from baseline in response to Japanese cedar and cypress pollen exposure in study 2. Error bars are ± SD. A significant difference was found between the bepotastine and placebo groups from 30 min to 180 min after pollen exposure ($p < .05$).

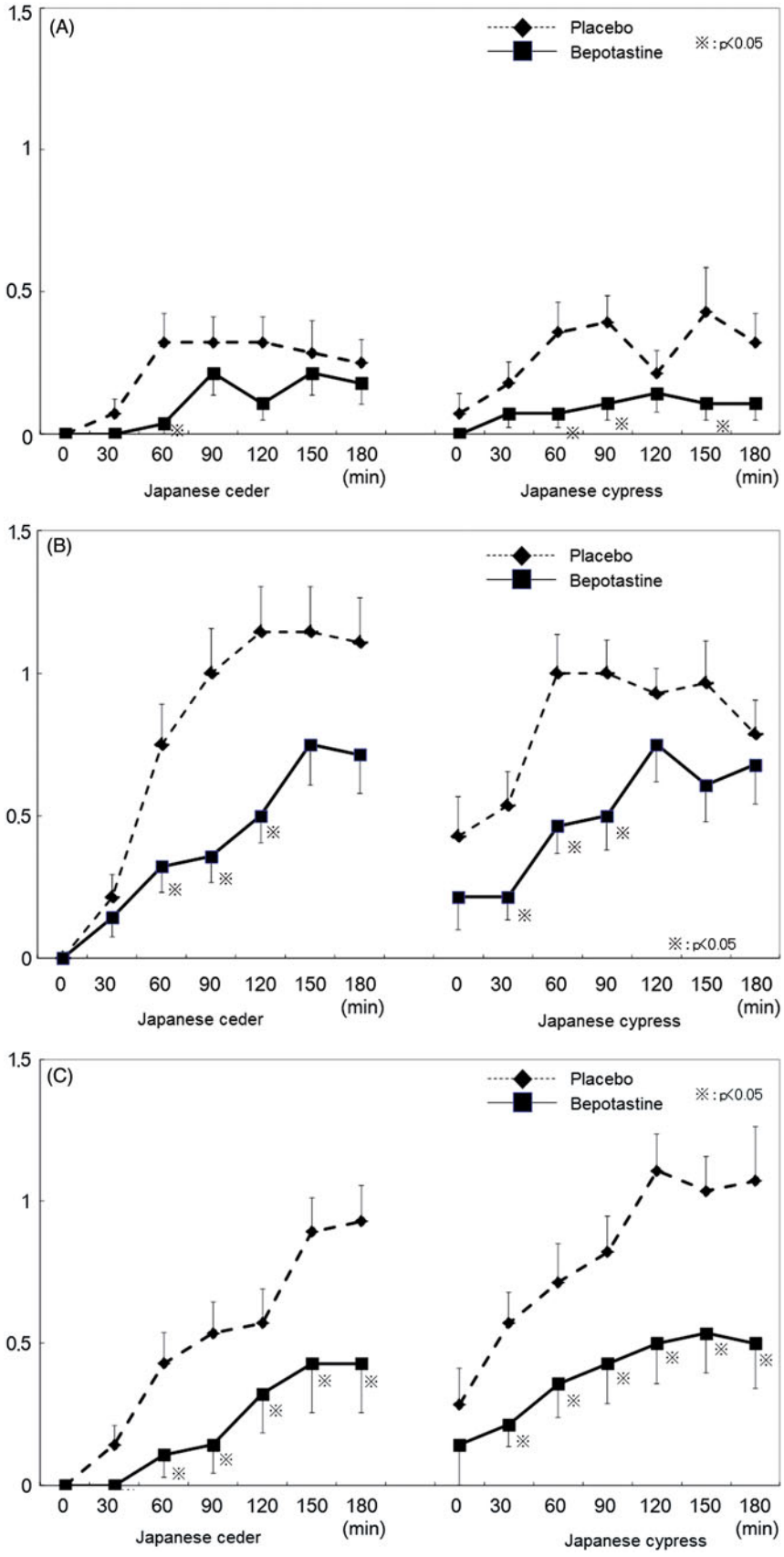

Figure 5. Mean changes in the individual symptom scores of the bepotastine and placebo groups for (A) sneezing, (B) rhinorrhea, and (C) nasal obstruction compared to baseline in response to Japanese cedar pollen exposure in study 2.; $^{*}p < .05$.

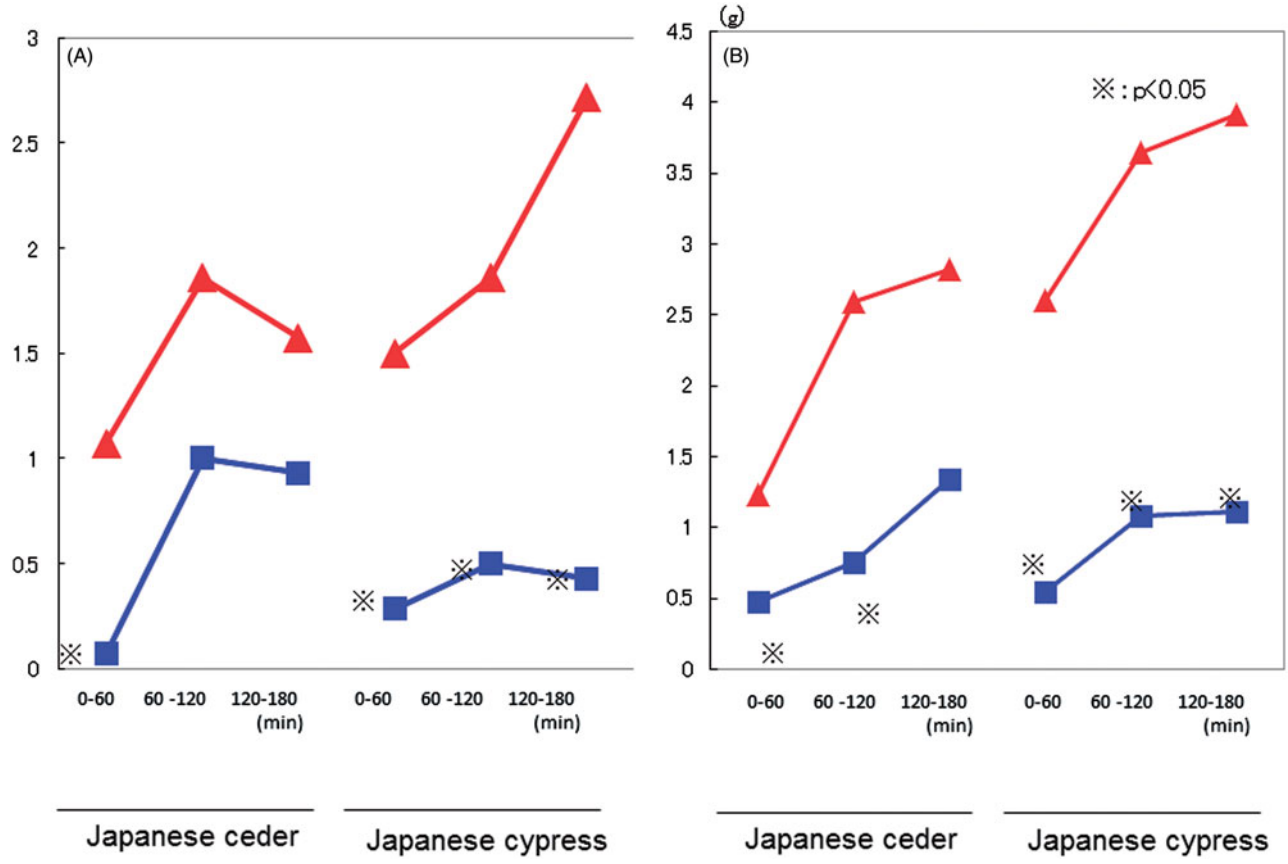

Figure 6. Mean changes in (A) the number of sneezes and in (B) the amount of rhinorrhea in study 2.

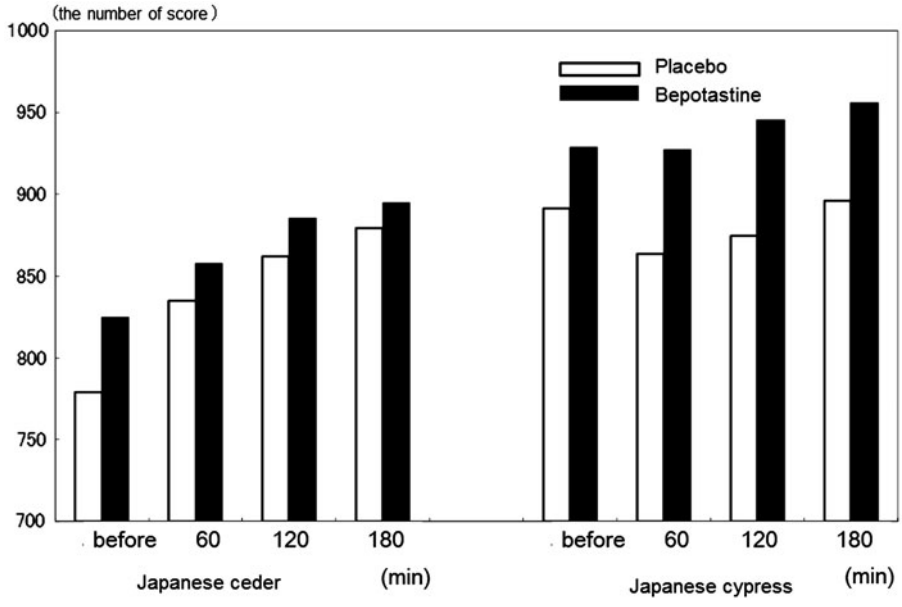

Figure 7. Changes in work performance from baseline as assessed with the D-CAT in study 2.

Results

Study 1

Comparison of Japanese cedar and cypress pollen symptoms

Forty-seven subjects participated in Study 1. Under controlled conditions there were no significant differences ($p > .05$) between subjects exposed to Japanese cedar pollen and those exposed to cypress pollen in terms of TNSS and sneezing, rhinorrhea, nasal obstruction, nasal itching, and eye symptoms (Figures 1–3).

Study 2

Figure 4 shows the changes over time in the TSS values of subjects in the bepotastine group and the placebo group

after controlled exposure to Japanese cedar and cypress pollen. There are significant differences between treatment and the placebo group. In the bepotastine group, subjects developed nasal and/or ocular symptoms reliably 60–180 min after exposure to Japanese cedar pollen on day 1 and 30–180 min after Japanese cypress pollen exposure on day 2.

Statistical analyses of the total number of subjects with symptoms demonstrated that bepotastine was significantly superior in delaying the appearance of allergy symptoms compared to the placebo.

Symptoms induced by pollen exposure

Compared with the placebo group, the bepotastine group had lower scores for each allergy-associated symptom during pollen exposure (Figure 5(A–C)). In the bepotastine group, all the symptoms excluding sneezing scores were significantly lower 60 min after exposure on day 1 and 30 min after exposure on day 2 compared to those of the placebo group (Wilcoxon's rank sum test: $p < .05$). Indeed, subjects in the bepotastine group experienced less sneezing, nasal discharge, and nasal obstruction symptoms than the placebo group did overall. The bepotastine group had a significantly fewer number of sneezes during the first 30 min of pollen exposure on day 1, and during the first 180 min of exposure on day 2 than the placebo group (Figure 6(A)). Moreover, the bepotastine group produced significantly less nasal discharge than the placebo group (Figure 6(B)). Although bepotastine seemed to relieve ocular symptoms as well, this difference was not statistically significant (data not shown). We asked whether the patients had adverse effects.

Cognitive assessment – work performance test (D-CAT)

D-CAT was conducted before the subjects entered the chamber and 1, 2, and 3 h after pollen exposure. In the bepotastine group, work performance increased gradually through the 2 days in the chamber. However, in the placebo group, work performance increased only on the first day of pollen exposure. It did not increase on the second day (Figure 4).

Safety

Neither group developed any serious side effects from pollen exposure while in the OHIO chamber or on the day after leaving the chamber.

Discussion

In these two studies, an OHIO Chamber was used to expose subjects to a fixed concentration of pollen in a stable environment.[1,2]

Our study demonstrated that there was no significant difference in the allergy-associated symptoms elicited by Japanese cedar pollen and cypress pollen under controlled conditions of dispersal (study 1).

Administration of a 10 mg bepotastine OD tablet before pollen exposure reduced the development of symptoms in patients with Japanese cedar pollinosis. In subjects treated with bepotastine, the development of nasal symptoms was significantly suppressed compared with the placebo group in the earlier time periods, suggesting that bepotastine is useful for early intervention of AR symptoms due to Japanese cedar pollinosis.

On day 2, allergy-related symptoms of subjects receiving placebo were similar to that of a hangover. These symptoms worsened due to exposure to cypress pollen on day 2. Therefore, continuous administration of bepotastine can also prevent hangover symptoms.

Pollinosis is known to undermine daily quality of life and to impair work performance, and its economic impact has become a social problem. In the present study, we assessed the subjects' cognitive function using a performance test called the D-CAT. The cognitive level of the subjects in the placebo group did not change significantly during pollen exposure, whereas those in the bepotastine group improved over time.[12] Interestingly, work performance of the placebo group did not increase on day 2, indicating that continuous exposure to pollen impaired performance. In the bepotastine group, work performance increased, indicating that bepotastine did not impair performance. From this point of view, continuous administration of antihistamine is critical.

Bepotastine distribution to the brain occurs at a low level, because it is a substrate of P-glycoprotein, which limits its distribution to the brain.[13] Bepotastine is classified as a new second-generation, "non-sedating" antihistamine drug based on a brain penetration study using PET.[13] Our results show that bepotastine does not impair cognition, as demonstrated with the D-CAT, are consistent with these pharmacological characteristics.

Conclusion

We conclude that bepotastine can suppress allergy-related symptoms, while leaving work performance unaffected in subjects with seasonal AR caused by Japanese cedar pollen or cypress pollen.

Transparency

Declaration of funding

This study was supported by a grant from the Public Health Research Foundation, Tokyo, Japan.

Declaration of financial/other interests

None of the authors has any financial interest in the subjects, materials, and equipment. The authors report no conflict of interest. JDA Peer Reviewers on this manuscript have no relevant financial relationships to disclose.

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References

[1] Kanzaki S, Hashiguchi K, Wakabayashi K, et al. Artificial exposure chamber (OHIO) trial inhibitory effect of bepotastine – OD for nasal allergy II (ACTION II study). J New Rem & Clin. 2011;60:30(2216)–43(2229) (in Japanese).

2 Kanzaki S, Hashiguchi K, Takeshi J, et al. Artificial exposure chamber (OHIO) trial inhibitory effect of bepotastine – OD for nasal allergy III(ACTION III study). J New Rem & Clin. 2012; 61∼24(2208)–32(2016) (in Japanese)

3 Okuda M. Epidemiology of Japanese cedar pollinosis throughout Japan. Ann Allergy Asthma Immunol. 2003;91:288–296

4 Bousquet J, Khaltaev N, Cruz AA, et al. Allergic rhinitis and its impact on asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy. 2008;63:8–160

5 Kanzaki S, Ogawa H, Ikeda M, et al. Quality of life of Japanese seasonal allergic rhinitis patients is related to timing of pollen dispersal – multicenter analysis. Acta oto-laryngologica. 2011;131:290–297

6 Committee of Practical Guideline for Management of Allergic Rhinitis. Practical guideline for the management of allergic rhinitis in Japan (in Japanese). Tokyo Japan: Tokyo Life Science Publishing Co. Ltd; 2016.

7 Sone T, Dairiki K, Morikubo K, et al. Identification of human T cell epitopes in Japanese cypress pollen allergen, Cha o 1, elucidates the intrinsic mechanism of cross-allergenicity between Cha o 1 and Cry j 1, the major allergen of Japanese cedar pollen, at the T cell level. Clin exp allergy. 2005;35:664–671

8 Sone T, Dairiki K, Morikubo K, et al. Recognition of T cell epitopes unique to Cha o 2, the major allergen in Japanese cypress pollen, in allergic patients cross-reactive to Japanese cedar and Japanese cypress pollen. Allergol Int. 2009; 58:237–245

9 Baba S, Takasaka T, Baba K. Clinical trial of TAU-284 (bepotastine besilate) on perennial allergic rhinitis – a double-blind study in comparison with terfenadine (in Japanese). J Clin Ther Med. 1997;13:1307–1335.

10 Kaminuma O, Ogawa K, Kikkawa H, et al. A novel anti-allergic drug, betotastine besilate, suppresses interleukin-5 production by human peripheral blood mononuclear cells. Biol Pharm Bull. 1998;21:411–413

11 Hashiguchi K, Tang H, Fujita T, et al. Preliminary study on Japanese cedar pollinosis in an artificial exposure chamber (OHIO Chamber). Allergology international : official journal of the Japanese Society of Allergology. 2007;56:125–130.

12 Hashiguchi K, Tang H, Fujita T, et al. Validation study of the OHIO Chamber in patients with Japanese cedar pollinosis. International archives of allergy and immunology. 2009;149:141–14

13 Hashiguchi K, Tang H, Fujita T, et al. Bepotastine besilate OD tablets suppress nasal symptoms caused by Japanese cedar pollen exposure in an artificial exposure chamber (OHIO Chamber). Expert Opin Pharmacother. 2009;10:523–529.