

Evaluation of the Efficacy and Safety of Olopatadine and Fexofenadine Compared With Placebo in Japanese Cedar Pollinosis Using an Environmental Exposure Unit

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■ Abstract

Background: Second-generation oral H₁-antihistamines have become a mainstay of treatment for the symptoms of seasonal allergic rhinitis; however, the effect of olopatadine has not been widely reported to date.

Objectives: To evaluate the efficacy of 2 oral H₁-antihistamines, olopatadine and fexofenadine, in the treatment of the nasal symptoms of Japanese cedar pollinosis and their possible side effects.

Methods: This was a randomized, double-blind, placebo-controlled, crossover study conducted in an environmental exposure unit (EEU). Twenty volunteers suffering from Japanese cedar pollinosis were randomly divided into 3 groups and exposed to cedar pollen in the EEU with oral administration of olopatadine hydrochloride (5 mg), fexofenadine hydrochloride (60 mg), or placebo 1 hour prior to pollen exposure. Nasal symptoms, activity impairment, and subjective sleepiness were self-assessed during the study period. Attention was measured using the digit cancellation test. The trial was repeated after 4 and 7 weeks.

Results: Compared with placebo, olopatadine significantly improved nasal symptoms and activity impairment during pollen exposure ($P < .05$). There was no significant relief of nasal discharge or nasal congestion with fexofenadine throughout the 5-hour exposure to cedar pollen. Furthermore, olopatadine significantly reduced nasal congestion during the first 2 hours, as well as sneezing and nasal discharge 4 hours after admission to the EEU compared with fexofenadine ($P < .05$). There was no significant difference in the effect on subjective sleepiness among the 3 groups, and all 3 agents had little effect on attention.

Conclusions: These findings suggest that olopatadine is more effective than placebo and fexofenadine in improving nasal symptoms of Japanese cedar pollinosis.

Key words: H₁-antihistamines. Olopatadine. Fexofenadine. Allergic rhinitis. Japanese cedar pollinosis. Environmental exposure unit. Randomized controlled trial.

■ Resumen

Antecedente: La segunda generación de antihistamínicos orales se ha convertido en un pilar principal en el tratamiento de los síntomas de la rinitis alérgica estacional; sin embargo, no se ha informado ampliamente del efecto de la olopatadina hasta la fecha.

Objetivos: Evaluar la eficacia de 2 antihistamínicos H₁ orales, olopatadina y fexofenadina, en el tratamiento de los síntomas nasales de la polinosis por cedro japonés y sus posibles efectos secundarios.

Métodos: Éste fue un estudio transversal aleatorizado, doble ciego, controlado con placebo, realizado en una unidad de exposición ambiental (UEA). Se aleatorizaron 20 voluntarios afectados de polinosis por cedro japonés en 3 grupos y se expusieron a polen de cedro en una UEA con administración de clorhidrato de olopatadina (5 mg), clorhidrato de fexofenadina (60 mg), o placebo 1 hora antes de la exposición al polen. Se autoevaluaron los síntomas nasales, la afectación de la actividad, y la somnolencia subjetiva durante el período de estudio. La atención se evaluó empleando el test de cancelación de dígitos. El ensayo se repitió tras 4 y 7 semanas.

Resultados: Comparado con placebo, la olopatadina mejoró significativamente los síntomas nasales y la afectación de la actividad durante la exposición al polen ($P < 0,05$). No hubo un alivio significativo de la destilación o congestión nasal con fexofenadina a lo largo de las 5 horas de exposición al polen de cedro. En oposición, la olopatadina redujo significativamente la congestión durante las primeras 2 horas, así como los estornudos y la destilación nasal a las 4 horas tras la admisión en la UEA comparados con fexofenadina ($P < 0,05$). No había diferencias significativas en el efecto sobre la somnolencia subjetiva entre los tres grupos, y en los 3 hubo discretos efectos en la atención.

Conclusiones: Estos hallazgos sugieren que la olopatadina es más eficaz que el placebo y la fexofenadina en mejorar los síntomas nasales de la polinosis por cedro japonés.

Palabras clave: Antihistamínicos H₁. Olopatadina. Fexofenadina. Rinitis alérgica. Polinosis por cedro japonés. Unidad de exposición ambiental. Ensayo controlado aleatorizado.

Introduction

The treatment of seasonal allergic rhinitis is based on drug therapy, mainly second-generation oral H₁-antihistamines, whose efficacy and safety have been well documented [1,2]. Cedar pollinosis, which is the most common type of seasonal allergic rhinitis in Japan, is estimated to affect 16.2% of the Japanese population [3]. It attracts so much public attention that it is often referred to as the “Japanese national disease.” Yet, very few studies assess the usefulness of drugs for patients with pollen allergy in Japan. Some outdoor studies have evaluated drugs in the same environment [4-6], although they were limited by drawbacks such as difficulty in maintaining constant exposure to a fixed amount of pollen, dependence on weather conditions, and feasibility of studies limited to the pollen season. In order to resolve these problems and reproduce natural allergic reactions in a room, allergen challenge chambers have been developed in the US and Europe. Several well-designed studies have used such facilities to assess the onset or duration of action, and other variables [7-15].

Olopatadine hydrochloride is a second-generation H₁-antihistamine, whose rapid and potent effect has been confirmed [16-19]. Furthermore, the efficacy and safety of olopatadine nasal spray have recently been analyzed [20-24]. However, few solid conclusions have been reached about the use of oral olopatadine in allergic rhinitis.

In 2004, the Japan Health Promotion Supporting Network (JHPSN), a nonprofit organization, established Japan's first environmental exposure unit (EEU) in the Wakayama Prefecture [3]. Free from the many limitations of conventional approaches, the EEU enables a variety of studies to be performed. In this randomized, double-blind, placebo-controlled, crossover study in the Wakayama EEU, we evaluated the efficacy of olopatadine and fexofenadine on the nasal symptoms of Japanese cedar pollinosis and their possible side effects, including sedation.

Materials and Methods

Patients

According to our previous design, a sample size of 20 cases was considered appropriate for study [3]. This sample comprised 20 volunteers with Japanese cedar pollinosis (8 men, 12 women; mean age, 38.2 y [range, 25-51 y]) as shown in Table 1. All patients had allergic manifestations during the cedar pollen season, and showed positive allergen-specific IgE against cedar

Table 1. Patient Characteristics

No.	Age, y	Gender	Cedar pollen RAST class
1	41	F	4
2	45	F	4
3	41	F	6
4	41	M	2
5	25	F	3
6	45	F	3
7	36	F	3
8	39	F	3
9	39	F	5
10	41	F	3
11	27	M	3
12	28	M	5
13	34	F	3
14	48	M	3
15	31	M	3
16	36	F	3
17	45	M	2
18	51	M	3
19	33	M	3
20	38	F	3

Abbreviations: F, female; M, male; RAST, radioallergosorbent tests.

pollen in sera (CAP-radioallergosorbent test [RAST], class 2 to 6). No patient had other inhalant allergies that could have affected the symptoms at the time of the study. The exclusion criteria were as follows: nasal diseases that could interfere with the results; severe concomitant illness of the liver, kidney, heart, or other organs; pregnancy, possible pregnancy, or lactation; and patients considered by the investigator to be unsuitable for the study for any reason. Patients with typical allergic symptoms before the cedar pollen season were also excluded.

Before being allowed to participate, all patients were shown to have no current health or sleep problems by means of an interview and questionnaire. Their rest conditions before the test had been the usual ones for them. The study was performed under the approval of the JHPSN ethics committee, and each patient signed an informed consent form.

Study Design

Each patient was challenged with cedar pollen (*Cryptomeria japonica*) in the Wakayama EEU 3 times in a crossover design, with washout periods of 3 or 4 weeks between sessions, during September and October 2005 (outside the cedar pollen season). They were randomly divided into 3 groups (Table 2), and received oral olopatadine hydrochloride (5 mg), fexofenadine hydrochloride (60 mg), or placebo (vitamin B₂ preparation) in the predetermined sequence. The study medications were administered before exposure to pollen.

In order to ensure that patients and investigators were blinded to treatment assignment, each dose was put in an opaque capsule without being milled, and taken immediately at

9 AM (baseline) on the day of the allergen challenge. The volunteer was admitted to the EEU at 10 AM and exposed to cedar pollen for 5 hours till discharge at 3 PM (Figure 1). The pollen level in the air was set at approximately 8000 grains/m³, which was much higher than the usual outdoor level, and sufficient to induce nasal symptoms as indicated by our preliminary studies [3,15]. As the effectiveness of olopatadine and fexofendaine disappear after 2 and 11 days, respectively, the washout period was set at 2 weeks.

Before and after dosing, all patients recorded their nasal symptoms, activity impairment, subjective sleepiness, and attention. At the same time, patients reported that they had not taken any medication that might affect the evaluation of sleepiness and attention. The first allergen challenge was conducted on September 11, 2005, the second challenge 4 weeks later, and the third challenge 3 weeks after the second challenge. Each participant attended 3 challenge sessions at the Wakayama EEU.

Assessments

Nasal symptoms and activity impairment: Sneezing, nasal discharge, nasal congestion, and activity impairment were assessed at baseline and every hour after admission to the EEU (5 time points in total) by the patients themselves. Sneezing was assessed based on the frequency of episodes. Nasal discharge was measured by how often the patient blew his/her nose. Nasal congestion and activity impairment in the EEU were rated on a 10-cm visual analog scale (VAS), with 0 representing no problems and 10 representing intolerable conditions.

Table 2. Overview of the Study

	Challenge	Washout Session 1	Challenge	Washout Session 2	Challenge Session 3
Group A	Olopatadine	4 weeks	Placebo	3 weeks	Fexofenadine
Group B	Fexofenadine	4 weeks	Olopatadine	3 weeks	Placebo
Group C	Placebo	4 weeks	Fexofenadine	3 weeks	Olopatadine

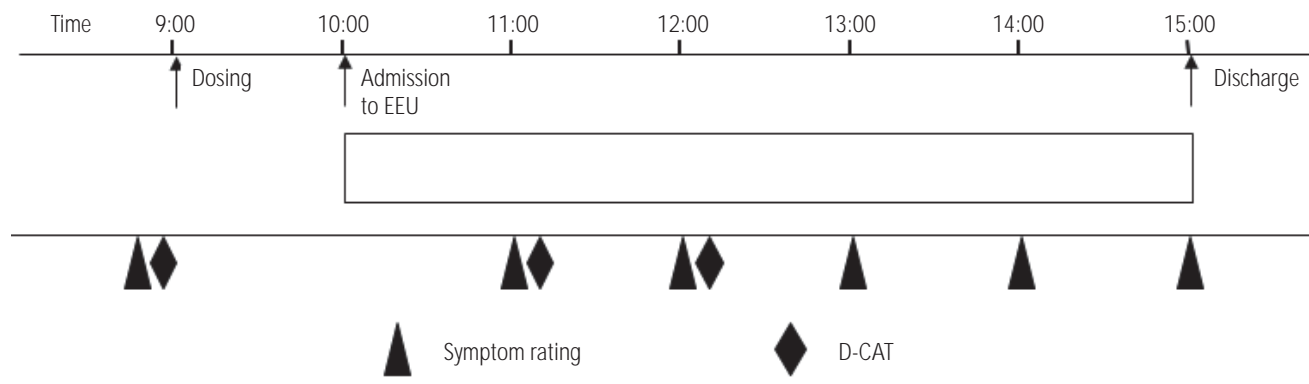


Figure 1. Study schedule. D-CAT indicates digit cancellation test; EEU, environmental exposure unit.

Subjective sleepiness and attention: Subjective sleepiness was assessed at baseline and every hour after admission to the EEU (5 time points in total). Patients rated how sleepy they were on a 10-cm VAS (0 [not sleepy at all] to 10 [intolerable]) and recorded the results. The digit cancellation test (D-CAT) [25] was conducted to measure attention at baseline, and 1 and 2 hours after admission. This test uses a sheet containing a total of 600 numbers ranging from 0 to 9 and randomly arranged in rows of 50 each, and requires the participant to cross out as many digits as possible that are equal to the specified number(s) within a minute. Three sheets with differently arranged digits were used in each trial. The quantity of work was expressed as the total number of digits crossed out in the test. The failure rate was the ratio of the number of digits not crossed out to the number of digits that should be crossed out. Changes in attention were assessed using both parameters.

Statistical Analysis

In a generalized linear mixed model, data were analyzed using SAS 9.1, with an adjustment for multiple testing at each time point. *P* values less than 5% (2-tailed) were considered statistically significant.

Results

Nasal Symptoms and Activity Impairment

Changes in sneezing, nasal discharge, nasal congestion, and activity impairment during the 5-hour exposure to cedar pollen in the EEU are presented in Figure 2.

Sneezing: Olopatadine significantly reduced sneezing compared with placebo throughout the 5-hour exposure ($P < .01$), and compared with fexofenadine at 4 hours after admission to the EEU ($P < .05$). During the last 2 hours, no significant differences were found between patients receiving fexofenadine and those receiving placebo ($P > .05$).

Nasal discharge: Olopatadine significantly reduced the frequency of nose blowing compared with placebo at 4 of the 5 assessment times ($P < .05$ at 11 AM and 3 PM, and $< .01$ at midday and 2 PM), and compared with fexofenadine at 4 hours after admission ($P < .05$). There was no significant difference between fexofenadine and placebo groups at any time point ($P > .05$).

Nasal congestion: Olopatadine significantly reduced nasal congestion compared with placebo throughout the 5-hour exposure ($P < .01$ at 11 am and midday, and $< .05$ at other time points), and compared with fexofenadine during

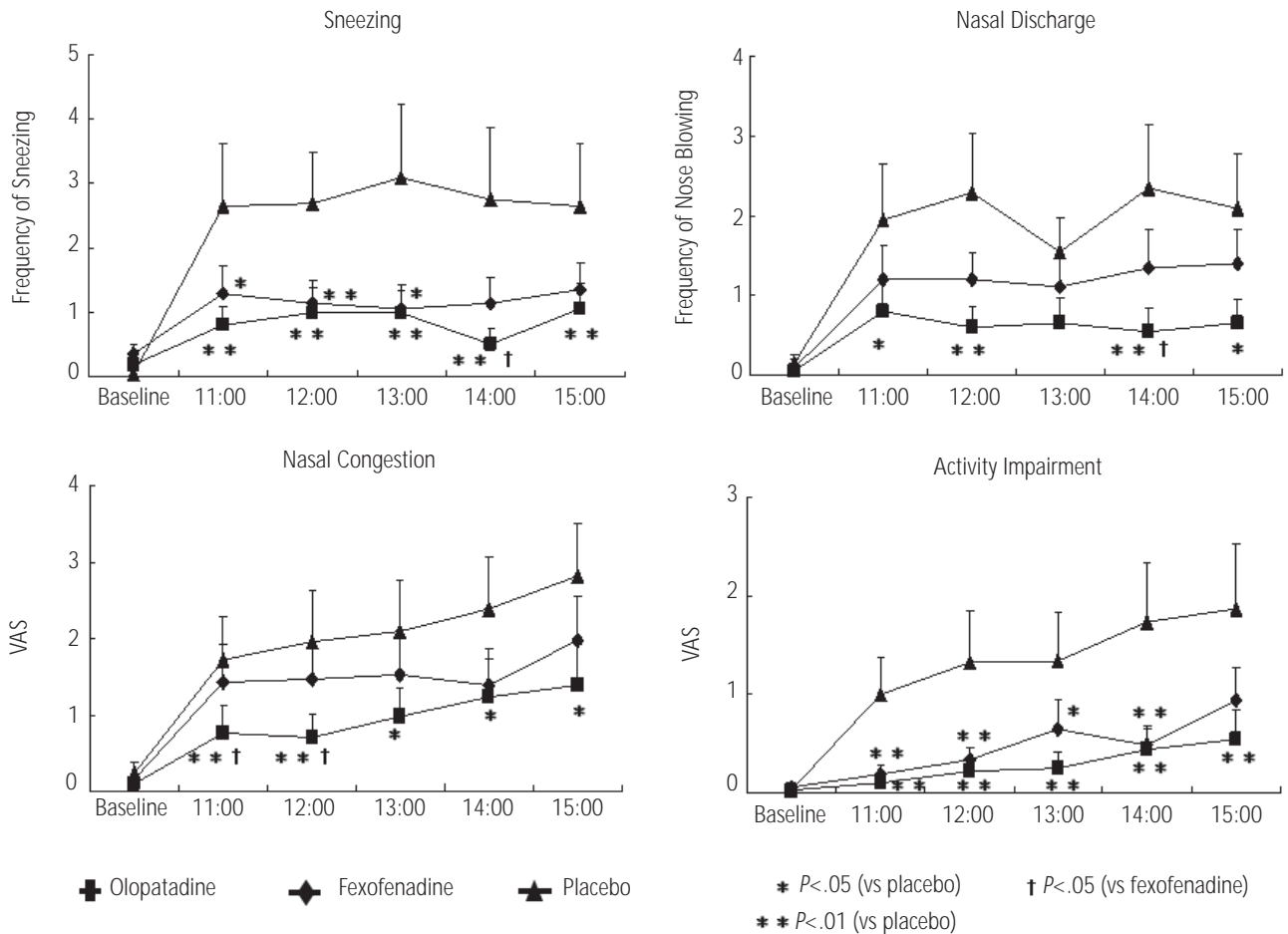


Figure 2. Changes in nasal symptoms and activity impairment in the environmental exposure unit. VAS indicates visual analogue scale.

the first 2 hours ($P < .05$). However, fexofenadine provided no significant change compared with placebo at any time point ($P > .05$).

Activity impairment: Compared with placebo, olopatadine significantly reduced activity impairment (eg, reading) throughout the 5-hour exposure ($P < .01$), whilst fexofenadine significantly reduced activity impairment except during the last hour ($P < .01$ at 11 AM, midday, as well as 2 PM, and $< .05$ at 1 PM). There was no significant difference between the olopatadine and fexofenadine groups at any time point ($P > .05$).

Subjective Sleepiness and Attention

Subjective sleepiness: Changes in subjective sleepiness at baseline and after admission to the EEU are shown in Figure 3. The 3 groups presented a similar pattern with VAS scores increasing over time; however, the difference was not statistically significant between groups ($P > .05$).

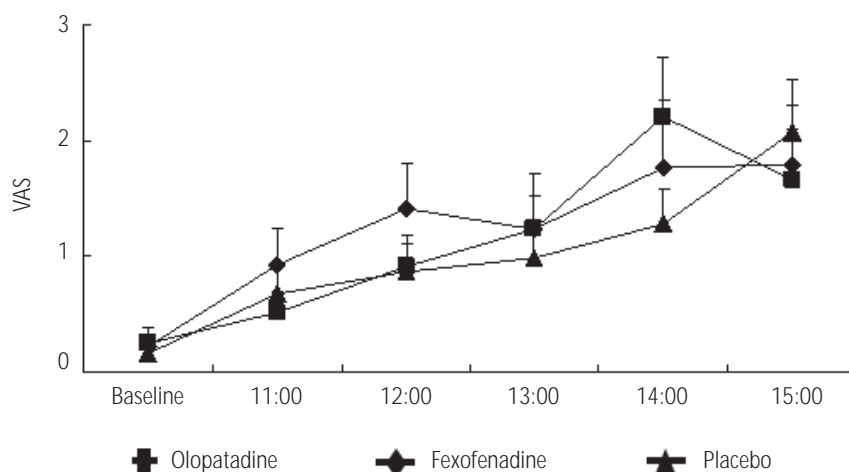


Figure 3. Changes in sleepiness assessed by the VAS in the environmental exposure unit. VAS indicates visual analog scale.

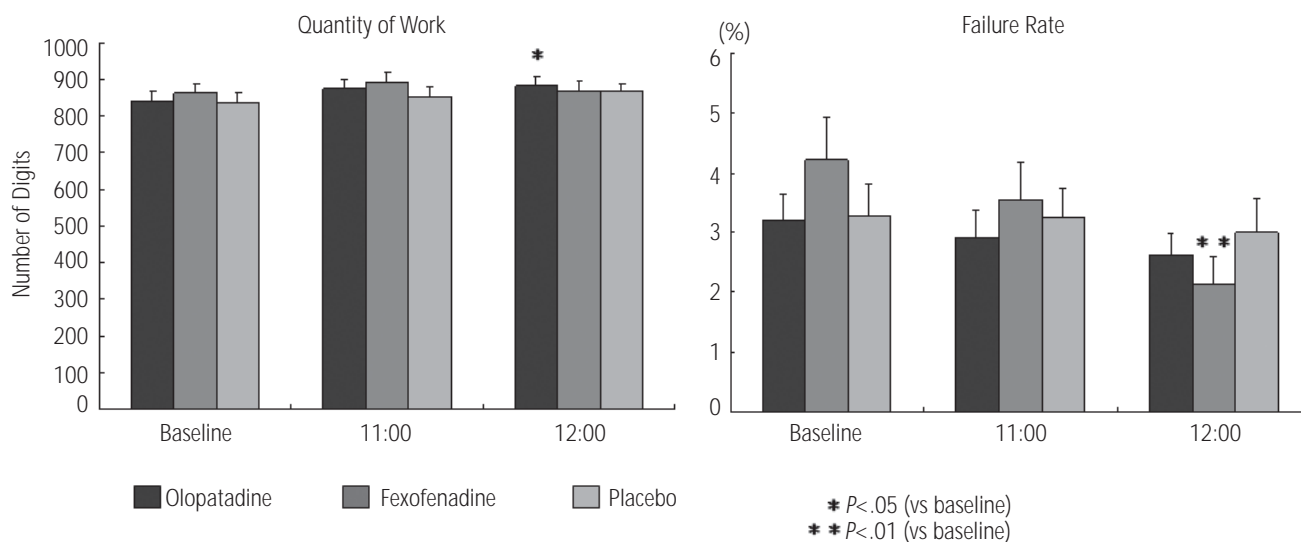


Figure 4. Effects on attention measured by digit cancellation test in the environmental exposure unit.

Attention: The effect of treatment on attention as measured by D-CAT is shown in Figure 4. The quantity of work increased over time in patients receiving olopatadine or placebo, whereas the failure rate tended to decrease over time in all 3 groups. At 2 hours after admission to the EEU, olopatadine significantly increased the quantity of work ($P < .05$), while fexofenadine provided a significant reduction in failure rate ($P < .01$).

Discussion

The EEU is useful to compare the efficacy of different antiallergic drugs [26]. We conducted a pollen challenge study using Japan's first EEU to confirm the efficacy and safety of 2 second-generation oral H_1 -antihistamines that are widely used to treat cedar pollinosis, a common seasonal allergic rhinitis in Japan. To ensure fairness in the evaluation of therapeutic

benefit, olopatadine hydrochloride and fexofenadine hydrochloride (the most commonly used twice-daily drugs in Japan) were selected and compared in a randomized, double-blind, placebo-controlled, crossover study. Patients with Japanese cedar pollinosis were exposed to pollen outside the pollen season in the Wakayama EEU, in which cedar pollen was dispersed evenly and at much higher levels than during the pollen season. Patients took either of the drugs 1 hour before exposure, and changes in symptoms were monitored. Those patients who received placebo experienced sneezing, nasal discharge, and nasal congestion within an hour after admission, and this persisted throughout the 5-hour exposure. In this study, there was a greater reduction in sneezing, nasal discharge, and nasal congestion with olopatadine than with placebo at almost all time points.

Fexofenadine significantly reduced sneezing compared with placebo during the first 3 hours, but presented no significant change in nasal discharge or nasal congestion throughout the 5-hour exposure to cedar pollen. Interestingly, there was significant relief of nasal congestion with olopatadine compared with fexofenadine during the first 2 hours of pollen exposure. A previous study in Japan involving patients with perennial allergic rhinitis showed that the beneficial effect on nasal congestion occurred approximately 50 minutes after oral administration of olopatadine [27]. Our results and those of other authors also suggest that olopatadine has a rapid onset of action [16,20-24].

The mechanism by which olopatadine relieves nasal congestion is uncertain. Olopatadine is a novel selective histamine H₁-receptor antagonist that inhibits the release of inflammatory lipid mediators such as leukotriene and thromboxane from human polymorphonuclear leukocytes and eosinophils [28]; hence its beneficial effects on nasal congestion. Clinical trials conducted during the developmental phase of olopatadine in patients with perennial allergic rhinitis demonstrated that it was very effective at relieving sneezing, nasal discharge, and nasal congestion [29]. In the present study, it markedly reduced the nasal symptoms of Japanese cedar pollinosis in patients evaluated in the EEU.

The VAS for sleepiness increased with time regardless of treatment, although the difference was not significant between the groups. The increased VAS was attributed not only to the treatment, but also to the possible contribution of lunch during the challenge session. The results of the D-CAT, which was used to detect the effect of treatment on attention [25], showed that all groups generally experienced an increase in the quantity of work and a decrease in failure rate after admission to the EEU. These findings were contrary to our expectations that the aggravation of symptoms caused by pollen exposure would decrease the quantity of work and increase the failure rate. This may be because D-CAT was a simple test that had been conducted 3 times during 1 session. Presumably, repeating the test in a short period of time improved the results. Further investigation is necessary in this respect.

Recent clinical trials have demonstrated that the safety profile of olopatadine nasal spray is comparable to that of placebo in the treatment of seasonal allergic rhinitis [20,21]. In healthy participants, there were no significant differences in subjective drowsiness and objective cognitive function

between oral olopatadine and placebo [19]. However, the sedative effect of olopatadine on psychomotor performance has also been reported to be more significant than that of fexofenadine [17,18]. Our data suggest that oral olopatadine is also safe, and that the effect on sleepiness and attention is similar to that produced by fexofenadine and placebo. Nevertheless, our small sample size means that safety should be discussed in further studies. In addition, ours was a single-dose study; therefore, the safety information was limited to some extent. Moreover, the small sample size could imply a certain element of bias.

In conclusion, olopatadine hydrochloride provided greater reduction in nasal symptoms of Japanese cedar pollinosis than placebo and fexofenadine hydrochloride, with a more effective relief of nasal congestion.

The authors declare no conflicts of interest.

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