

Comparison of nasal steroid with antihistamine in prophylactic treatment against pollinosis using an environmental challenge chamber

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ABSTRACT

Environmental challenge chambers (ECC) have been used to expose people to pollen allergens within a stable atmosphere and to examine the efficacy of treatment. Although pollinosis is one of the typical IgE-mediated type I allergic diseases, allergic inflammation is thought to contribute to the fundamental pathogenesis and prophylactic treatment may reduce exacerbations of pollinosis. The purpose of this study was to compare the efficacy of prophylactic treatment with nasal steroid (mometasone furoate nasal spray) or an antihistamine (fexofenadine) in the control of cedar pollinosis using the ECC. In a randomized, double-blind two-way crossover study, 48 patients received nasal steroid or antihistamine for 7 consecutive days (days 1–7). On day 8, patients were exposed to cedar pollen (8000 grains/m³) in the ECC for 3 hours. Nasal symptoms induced by pollen exposure were assessed. Total nasal symptom scores (TNSSs) during the exposure in the ECC were not significantly different between the antihistamine and the nasal steroid groups. Nasal symptoms induced by pollen exposure using the ECC persisted for up to 3 days. TNSSs after pollen exposure on days 8–11 were significantly lower in the nasal steroid group compared with the antihistamine group. Prophylactic treatment with nasal steroid is more effective than antihistamine against pollinosis, particularly in the late phase. Clinical trial registration JAPIC CTI 101182 (www.clinicaltrials.jp/user/ctiMain_e.jsp).

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Recently, allergen challenge testing using an environmental challenge chamber (ECC) has been widely used to examine the efficacy of various treatments.^{1–6} The ECC can be used to induce symptoms in patients with allergic rhinitis and asthma under well-controlled stable conditions and is expected to offer consistent results.

However, the differences in the symptoms of pollinosis induced by pollen exposure in the ECC versus conventional provocation tests, *i.e.*, using a disk coated with pollen allergen extract or a spray of the extract, and those observed during the natural pollen season have not been well clarified. Hohlfed *et al.* reported the reproducibility of total nasal symptom scores (TNSSs) during natural seasonal exposure and found that the restricted reproducibility was caused by differences in the dispersion of pollen in the natural environment.⁷ Although the levels of pollen exposure varies among individuals by season, local regional differences of the

residence and the lifestyle of each subject could also significantly influence the symptoms and severity. Therefore, evaluation of the treatment should be performed carefully and a large number of subjects must be enrolled in a clinical study during the natural pollen dispersal season. However, pollen exposure investigations using the ECC have a significant advantage in this regard.

Arboreal pollen, Japanese cedar (*Cryptomeria japonica*) pollen, in particular, is the most common allergen in Japan.^{8,9} Enormous amounts of Japanese cedar pollen are produced every year, with large annual variations occurring due to climate changes. Distinct from grass pollen, which can be dispersed <100 m, cedar pollen can travel >100 km, thus causing widespread pollinosis.¹⁰ Repeated exposure to pollen induces allergic inflammation and hypersensitivity of the nasal mucosa, and early intervention against mild pollinosis, just after the start of the pollen dispersal season, may have a significant effect on the severity of symptoms when pollen dispersal reaches its peak.^{11–13} During drug treatment, antihistamines, in particular, the second-generation antihistamines, are among the most widely prescribed in Japan, owing to their early onset of action and safety.¹⁴ Although randomized controlled studies have suggested that antihistamines are less effective than nasal steroids,¹⁵ recent *in vitro* studies have suggested that antihistamines work as inverse agonists against the H₁-receptor and that con-

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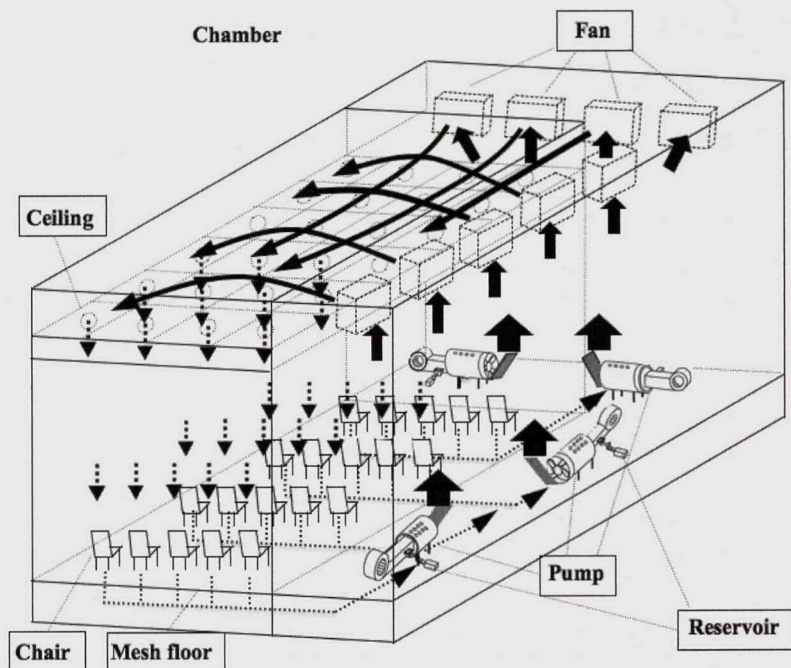


Figure 1. Chamber. The chamber can accommodate up to 50 subjects. Pollen is supplied from a reservoir using a piston pump and is discharged from the holes in the ceiling into the chamber room. The pollen is collected from underneath the mesh floor and circulated back into the chamber through the ceiling to maintain pollen dispersal throughout the chamber and avoid accumulation on the floor.

tinuous administration increases the efficacy and works effectively in prophylactic treatment.¹⁶

Most of the patients who are exposed to Japanese cedar pollen for only a limited number of hours in the ECC, outside of the pollen season, usually exhibit symptoms both during the pollen exposure in the chamber and after they have left the chamber, *i.e.*, a late-phase reaction. In conventional provocation studies, the symptoms are usually mild and, in particular, nasal secretion and sneezing are rarely observed in the late phase. The symptoms induced by continuous pollen exposure in the ECC more precisely reflect the symptoms observed with natural pollen exposure. Although it is difficult to evaluate the acute and late-phase reaction separately during the natural pollen season, only a few ECC studies have evaluated the late-phase symptoms. In this study, we examined the efficacy of nasal steroid and antihistamine on the symptoms of the acute-phase reaction in the ECC and of the late-phase reaction after leaving the ECC in a double-blind crossover study of patients with Japanese cedar pollinosis. We evaluated the characteristics of these drugs and determined the effectiveness of medications for relieving the symptoms during natural pollen dispersal.

METHODS

The ECC (α -Chamber)

The chamber, which was built at Chiba University in 2008, has an area and ceiling height of 71.8 m² and 2.6 m, respectively, and can accommodate up to 50 subjects who are under constant supervision by medical staff. The chamber unit is controlled at a constant

temperature and relative humidity. Pollen is supplied from a reservoir using a piston pump and discharged from the holes in the ceiling into the chamber room. Any pollen that falls through the mesh floor into a catchment area is circulated back into the chamber to maintain pollen dispersal throughout the chamber and to avoid the accumulation of pollen on the floor (Fig. 1). The pollen level is monitored during the exposure at 56 points (on the back of each chair) within the chamber using automatic pollen counters (online supplement Fig. E1 *a*), to maintain the pollen at constant levels (500–16,000 grains/m³).

Each patient records the frequencies of induced sneezing and rhinorrhea and subjectively assesses symptoms using mobile communication devices that allow their precise evaluation (online supplement Fig. E1 *b*). In the chamber, patients wear clean disposable clothes, including hair caps and shoe covers, to avoid transport of any pollen out of the chamber unit after the exposure (online supplement Fig. E1 *c*).

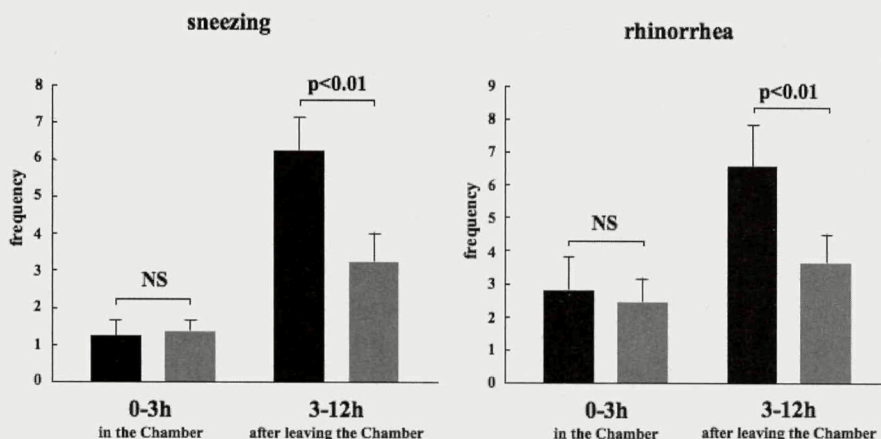
Subjects

The study population consisted of patients with Japanese cedar pollinosis who lived in Chiba City. Their ages ranged from 18 to 64 years and subjects met the following inclusion criteria: a positive allergen-specific intradermal skin test result (wheal diameter ≥ 10 mm) to a standardized cedar pollen extract (Torii Pharmaceutical Co., Ltd., Tokyo, Japan) and serum cedar pollen-specific IgE level score of ≥ 2 by the CAP radioallergosorbent test (CAP-RAST; SRL, Tokyo, Japan). The exclusion criteria included complication of moderate/severe perennial allergic rhinitis that required treat-

Frequency of sneezing and rhinorrhea on day 8

■ fexofenadine
■ MFNS

Figure 2. Frequency of sneezing and rhinorrhea on day 8. There were no significant differences in the average number of sneezing and rhinorrhea episodes during the exposure in the environmental challenge chamber (ECC) (0–3 hours) between the nasal steroid and antihistamine groups. Sneezing and rhinorrhea were observed in all subjects after leaving the chamber (3–12 hours). However, the average incidences of both symptoms were significantly reduced in the nasal steroid group. Data are expressed as the mean $\pm$ SD.



ment, a history of severe asthma, use of antiallergic drugs within 4 weeks, and a prior history of any allergen-specific immunotherapy, pregnant women, or women of childbearing potential.

The study was conducted at a university hospital in compliance with the Ethical Guidelines for Clinical Studies¹⁷ and Good Clinical Practice¹⁸ and the Declaration of Helsinki (2000 revision).¹⁹ The protocol was approved by the Ethics Committee of Chiba University and Chiba University Hospital Clinical Research Center. Each of the subjects received a detailed explanation of the study and of the possible side effects and written informed consent was obtained before participation in the study.

Study Protocol

This randomized double-blind study used a two-way crossover double-dummy design to compare the efficacy of prophylactic treatment with nasal steroid (mometasone furoate nasal spray [MFNS]) and antihistamine (fexofenadine). The study was performed outside of the pollen season with enrollment and allocation by the Chiba University Hospital Clinical Research Center from July to August 2010. In 2010, the cedar pollen season was from January to April. A treatment allocation number was given to each subject. This information was closely guarded by the controller and by one member of the ethical committee who was not directly involved with the study. The study schedule is shown in online supplement Fig. E2. Before the study, subjects were interviewed regarding their medical history and underwent a CAP-RAST and an allergen-specific intradermal skin test, to measure specific serum antibodies against cedar pollen, and were preliminarily exposed to cedar pollen (8000 grains/m³) in the chamber to confirm the elicitation of an allergic response.

Subjects were randomized to receive either treatment A (MFNS at 200 μ g and placebo capsule) or treatment B (nasal placebo spray and fexofenadine at 120 mg) for 7 consecutive days (days 1–7) in a random order using a two-way crossover design, with a washout period of 14 days between drugs. The MFNS and nasal placebo spray were placed inside opaque containers and the fexofenadine and placebo tablets were placed inside opaque capsules that were identical in shape, size, color, and smell to allow the double-blind administration. On day 8, subjects were exposed to cedar pollen (8000 grains/m³) in the chamber for 3 hours (online supplement Fig. E2).

The subjects recorded the frequencies of sneezing and rhinorrhea using mobile communication devices and medical staff checked these symptoms during the 3 hours of cedar pollen exposure in the ECC. Subjective assessment of the severity of nasal congestion was conducted just before the subject entered the chamber and then every 30 minutes during the 3 hours of cedar pollen exposure.

For examination of nasal symptoms after the pollen exposure, subjects were asked to record the symptoms using an allergy diary for 5 days (days 8–12) after leaving the chamber.

Nasal Symptom Scores in the Chamber and after Leaving the Chamber

The TNSS was the sum of the three major nasal symptoms based on both records (*i.e.*, mobile communication device and daily nasal allergy diary) according to the following criteria.

For nasal symptoms, the severity of sneezing (number of sneezes per day), rhinorrhea (number of times the subjects blew their nose per day), and nasal congestion were evaluated on a 5-point scale (0–4), based on the Clinical Guidelines for the Management of Al-

lergic Rhinitis in Japan, as follows: 0, no sensation; 1, mild; 2, moderate; 3, severe; and 4, extremely severe. Episodes of sneezing and rhinorrhea per day were rated from 0 to 4 as follows: 0, none; 1, 1–5 episodes; 2, 6–10 episodes; 3, 11–20 episodes; and 4, >21 episodes. The TNSS system is different from that used in United State rhinitis trials, which is a 0- to 3-point scale including four nasal symptoms (sneezing, rhinorrhea, nasal congestion, and itchy nose).

Primary Efficacy Variables

The primary efficacy variables were the mean TNSS for 0–12 hours on day 8. We investigated the efficacy of prophylactic treatment with nasal steroid or antihistamine on both the early and the late-phase reaction.

Secondary Efficacy Variables

Secondary efficacy variables included the mean TNSS in the chamber, the number of sneezing and rhinorrhea episodes in the chamber (0–3 hours) and after leaving the chamber (3–12 hours) on day 8, and the mean TNSS on days 9–12.

We investigated the efficacy of prophylactic treatment with nasal steroid or an antihistamine on both the early and the late-phase reaction separately.

Sample Size

Forty-four subjects were needed to detect an effect size of 0.6 TNSS with MFNS compared with fexofenadine on day 8, with a power of 80% and using a 5% two-tailed test. Therefore, we planned to recruit 48 subjects in anticipation of dropouts.

Statistics

The subjects on whom analyses were conducted represented an intention-to-treat population. Data analysis was performed with two-tailed tests at a significance level of 5%, using paired *t*-tests in SAS Version 9.1.3 (Cary, NC). Paired sample *t*-tests were used to compare symptom scores, *i.e.*, the number of sneezing and rhinorrhea episodes. The primary variables were analyzed using an ANOVA model adapted for the crossover design with the baseline score as a covariate.

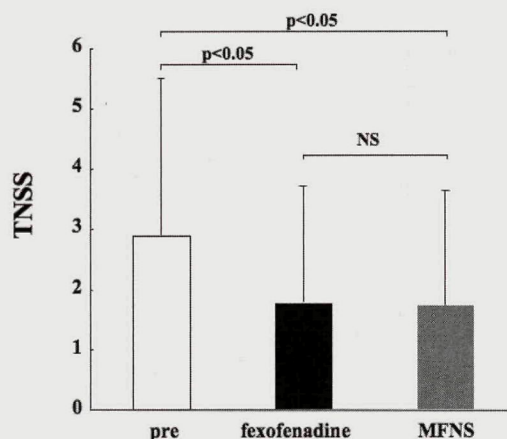
RESULTS

Environmental Challenge Chamber

The pollen concentration was set to 8000 grains/m³ because all of the subjects exhibited nasal symptoms in the preliminary study, as described previously. Furthermore, this pollen concentration has been used previously in other chamber studies with Japanese cedar pollen.²⁰

After the initiation of the pollen spread, the pollen concentration in the chamber reached 8000 grains/m³

Total nasal symptom score in the chamber (0–3 hours)



** $p < 0.05$

Figure 3. Total nasal symptom scores (TNSSs) in the chamber (0–3 hours). The mean TNSS after 0–3 hours in the chamber was not significantly different between the nasal steroid and antihistamine groups. However, when compared with the preliminary exposure at the beginning of the study, the mean TNSS observed in the chamber improved in both the nasal steroid and the antihistamine groups. Data are expressed as the mean $\pm$ SD.

within 15 minutes. The concentration of pollen was affected by the movement of the patients in the chamber but was maintained at constant levels within an error range of 10%.

The Subjects

Forty-eight subjects were enrolled in the study, and none dropped out or failed to record the data. The mean age of the subjects was 37.4 ± 11.8 years, and 29 (59.2%) were women. The mean cedar-specific IgE level was 23.3 ± 27.4 UA/mL (cedar pollen RAST score; class 2, 7 subjects; class 3, 24 subjects; class 4, 12 subjects; class 5, 2 subjects; class 6, 3 subjects).

All subjects underwent 3-hour exposure to cedar pollen on day 8, after receiving either treatment A (MFNS at 200 μ g and placebo capsule) or treatment B (nasal placebo spray and fexofenadine at 120 mg) for 7 consecutive days (days 1–7) in a random order, using a two-way crossover design.

Number of Sneezing and Rhinorrhea Episodes and Nasal Symptom Scores during and after the Chamber Exposure

The number of sneezing and rhinorrhea episodes increased with time and all of the subjects exhibited sneezing and rhinorrhea that reached a plateau after 2 hours during the exposure in the ECC in the preliminary pollen exposure. Of the subjects, 67% exhibited nasal congestion. These symptoms continued after leaving the chamber in all subjects. The peak of sneez-

Nasal symptom score on day 8 (0-12hours)

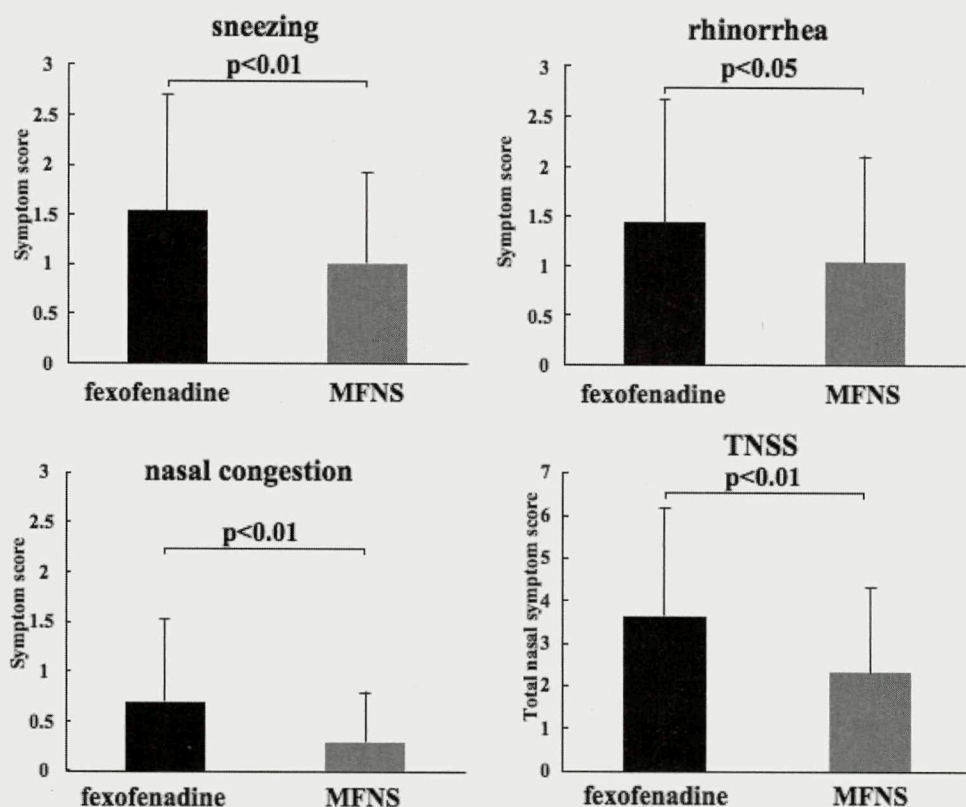


Figure 4. Nasal symptom scores on day 8 (0–12 hours). The symptom scores for sneezing, rhinorrhea, and nasal congestion in the nasal steroid group were significantly lower than those in the antihistamine group. The score of nasal congestion was also lower in the nasal steroid group. The mean total nasal symptom score (TNSS) for 0–12 hours postexposure on day 8 was decreased significantly in the nasal steroid group compared with that in the antihistamine group. Data are expressed as the mean $\pm$ SD.

ing and rhinorrhea was between 3 and 9 hours after leaving the chamber, although there was significant variation among the subjects. The nasal congestion was evaluated subjectively and also continued after leaving the chamber; however, its severity decreased gradually.

There were no significant differences between the nasal steroid and antihistamine groups in the average number of sneezing and rhinorrhea episodes (Fig. 2), the subjective severity of nasal congestion (data not shown), or TNSS (Fig. 3) during the exposure in the ECC chamber (0–3 hours). Sneezing and rhinorrhea were observed in all subjects after leaving the chamber (3–12 hours). However, the average incidences of both symptoms were significantly reduced in the nasal steroid group (Fig. 2).

On day 8 (0–12 hours), the symptom scores for sneezing, rhinorrhea, and nasal congestion in the nasal steroid group were significantly lower than those in the antihistamine group (Fig. 4). The score of nasal congestion was also lower in the nasal steroid group. The mean TNSS for the first 0–12 hours postexposure on day 8 was decreased significantly in the nasal steroid group compared with that in the antihistamine group (Fig. 4).

The lower TNSS in the nasal steroid group lasted from days 9 to 11 (Fig. 5).

Carryover or period effects were analyzed by testing the interaction terms between the intervention type and the date of intervention. No carryover effect was anticipated because of the use of a sufficient washout time between treatment periods, during which the subjects received no medication or pollen exposure (online supplement Fig. E3). The 2-week washout period was considered to be sufficient.

DISCUSSION

The aim of this study was to compare the efficacy of prophylactic treatment with MFNS or fexofenadine in the control of cedar pollinosis using the ECC. In other studies using the ECC, only nasal symptoms during the exposure have been examined^{3,4} and those occurring after the subjects left the ECC have rarely been reported.⁷ In this study, after leaving the pollen exposure chamber, all of the subjects exhibited nasal symptoms, including sneezing and rhinorrhea. These symptoms continued for around 3 days after a single session of pollen exposure for only 3 hours. The severity of the symptoms in the late phase did not correlate with the severity of those in the chamber. Because the patients were clothed in disposable overalls, including hair caps and shoe covers, it is not likely that they carried the pollen outside the chamber.

Total nasal symptom score (TNSS) on day 9 - 12

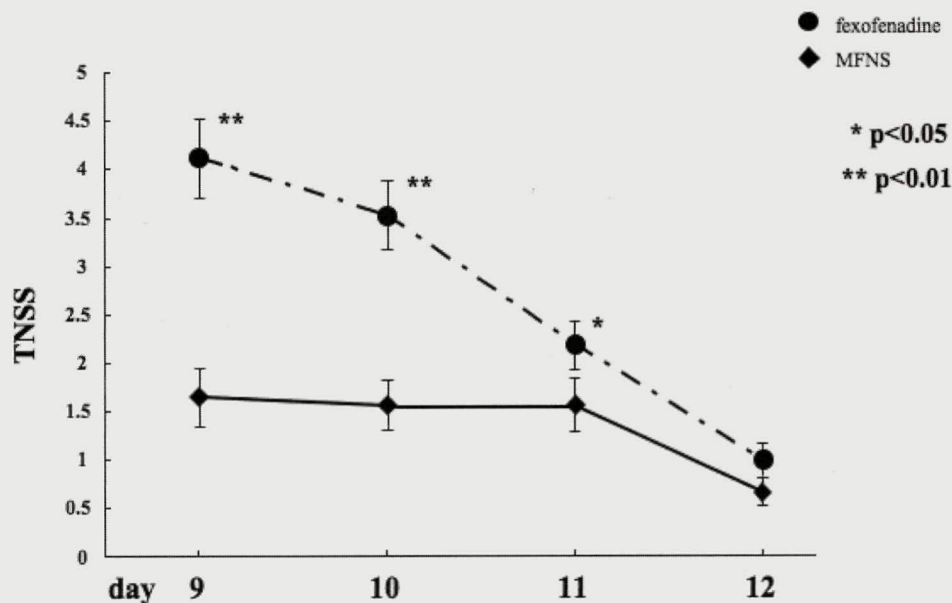


Figure 5. Total nasal symptom scores (TNSSs) on days 9–12. TNSSs on days 9–12 in fexofenadine (●) and mometasone furoate nasal spray (MFNS; ◆) groups. The lower TNSS in the nasal steroid group lasted from days 9 to 11. Data are expressed as the mean $\pm$ SE. * $p < 0.05$; ** $p < 0.01$.

The pollen exposure in the chamber might result in enhanced expression of adhesion molecules, increased infiltration of the nasal mucosa by inflammatory cells, hyperpermeability of epithelial cells, and increased neural sensory response. The nasal allergic inflammation and increased sensitivity are believed to contribute independently to the induction of symptoms, including sneezing and rhinorrhea during the late phase after an acute phase reaction to specific pollen allergens.^{21,22} Examination of the inflammatory mediators in this study was difficult because the nasal washing procedure might influence the nasal symptoms and interfere with the precise evaluation of the treatment. In our previous study using eight volunteers with Japanese cedar pollinosis, increased concentrations of IL-4, IL-5, IL-13, IL-33, eotaxin, leukotrienes, and eosinophilic cationic protein, as well as the numbers of eosinophils and basophils were observed in the nasal washings collected 6 hours after pollen exposure in the chamber compared with those collected immediately before the pollen exposure. Thus, the mechanisms underlying the late-phase response need to be elucidated in further study.

No significant differences were observed in the symptoms in the exposure chamber between the antihistamine and the nasal steroid treatment groups. Compared with the symptoms observed during the preliminary exposure at the beginning of the study, the antihistamine improved the sneezing and rhinorrhea, as well as nasal congestion. However, each symptom was significantly reduced in the nasal steroid treatment group compared with that in the antihistamine group in the late phase. The symptoms in the late phase observed in the antihistamine group were not

different from those observed during the preliminary exposure and the improving effect of the antihistamine treatment was not clear. The antihistamine, fexofenadine, is effective for at least 12 hours, which is shorter than MFNS. However, the symptoms observed up to 12 hours postexposure were significantly less in the nasal steroid group, after taking the drugs immediately before pollen exposure.

During the natural pollen season, pollen dispersal is known to increase with temperature and to be much greater in the daytime than at night.^{14,23} However, many patients with pollinosis suffer from the symptoms at night and experience sleep problems.^{24,25} It is impossible to distinguish between the early and late-phase reactions under the conditions of natural pollen dispersal. We can not ignore the direct contribution of the transport of some pollen into the house, but the late-phase reaction could play a major role in the onset of these symptoms either indoors or at night.

Repeated exposure to pollen induces allergic inflammation and hypersensitivity of the nasal mucosa, and early intervention against mild pollinosis immediately after the start of the pollen dispersal season could have a significant effect on the severity of symptoms during peak pollen dispersal.^{11–13}

Histamine plays an important role in the induction of acute-phase symptoms and antihistamines have been known to exhibit rapid efficacy and improve sneezing and rhinorrhea as well as some degree of nasal congestion,^{26–29} as observed in this study. However, to more effectively control the symptoms of the late-phase reaction, the inclusion of anti-inflammatory medications in the treatment is necessary. Additional studies that include immunologic parameters are

needed to elucidate the detailed mechanisms of the late-phase response to improve the control of these symptoms.

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