

Inhibition of the Antigen Provoked Nasal Reaction by Second-generation Antihistamines in Patients with Japanese Cedar Pollinosis

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ABSTRACT

Background: Epinastine hydrochloride and fexofenadine hydrochloride, the second-generation antihistamines, are largely used in the indication of allergic rhinitis in Japan. The purpose of this study was to compare the protective efficacy of epinastine hydrochloride or fexofenadine hydrochloride using a nasal provocation test with Japanese cedar pollen allergen.

Methods: A single-dose, placebo-controlled, single-blind crossover clinical study was conducted in patients with Japanese cedar pollinosis. The pollen exposure was done by the antigen provocation by disc method and involved repeated provocation five times per day.

Results: Among the active agents studied—epinastine hydrochloride and fexofenadine hydrochloride—epinastine hydrochloride significantly decreased the number of sneezing attacks and the quantity of nasal discharge for 3 hours after drug administration compared with placebo, a finding supported by the quantity of nasal discharge in the nasal findings. In this study, fexofenadine hydrochloride showed no significant difference compared with placebo.

Conclusions: This study demonstrates better protection with epinastine hydrochloride than with fexofenadine hydrochloride or placebo in a nasal provocation test with Japanese cedar pollen allergen.

KEY WORDS

allergic rhinitis, epinastine hydrochloride, fexofenadine hydrochloride, nasal provocation, rhinoscopy

INTRODUCTION

Pollinosis is seasonal allergic rhinitis due to pollen antigens, and its prevalence is high enough to be called a national disease in Japan. Among the many pollen antigens, Japanese cedar pollinosis is the most common.¹ Government policies after World War II led to the planting of Japanese cedar trees, and the area planted with Japanese cedar trees began to increase in the late 1960's. In the early 1970's, the number of patients increased rapidly, and currently 10–20% of the Japanese population suffers from Japanese cedar pollinosis, as has been reported in several studies.²

In the treatment of pollinosis, second-generation antihistamines are used as initial therapy to inhibit the hypersensitivity reaction caused by repeated antigen exposure.³ The Practical Guideline for Management of Allergic Rhinitis states that these agents are the first-line agents of choice for the treatment after onset of symptoms such as sneezing and rhinorrhea, and thus are an essential component of pollinosis therapy.⁴ Presently, several second-generation antihistamines are marketed with the allergic rhinitis indication. To provide objective information concerning drug selection, various studies to evaluate efficacy are being conducted in the form of clinical studies in the field,⁵ studies in environmental exposure units,⁶ anti-

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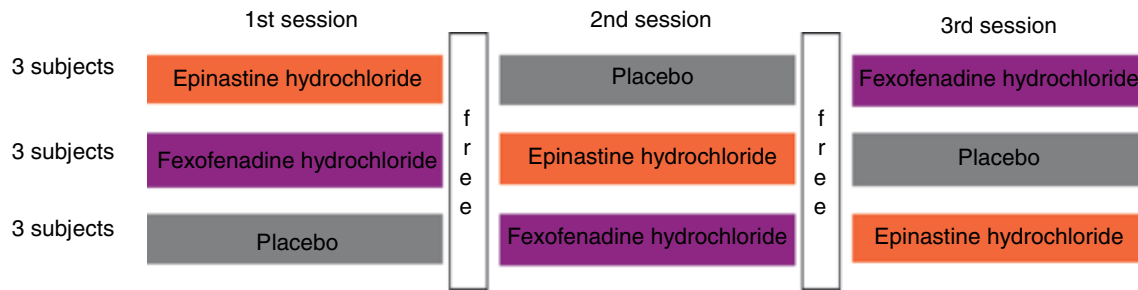


Fig. 1 Study design

Table 1 Nasal finding score

Nasal Findings	Score			
	3	2	1	0
Inferior nasal turbinate mucosal swelling	Middle turbinate not seen	Intermediate between (3) and (1)	To centre of middle turbinate	None
Nasal discharge	Filled	Intermediate between (3) and (1)	Small amount adhered to the skin	None

gen provocation tests,⁷ and QOL surveys.⁸ The antigen nasal provocation test is a test in which the antigen is applied directly to the nasal mucosa to elicit nasal symptoms from such a stimulation.⁹ Since this is a quantitative clinical study, where a fixed amount of antigen is applied, it is possible to reproducibly elicit the allergy reactions and allows the evaluation of drugs for their treatment effect of nasal symptoms.

In this study, we examined patients with Japanese cedar pollinosis using Japanese cedar antigen discs to conduct the nasal provocation test and evaluated two second-generation antihistamines, epinastine hydrochloride tablets and fexofenadine hydrochloride tablets, for efficacy compared with placebo in a crossover clinical study.

METHODS

SUBJECTS

This study was conducted between August 14 and October 2, 2004. The subjects were male and female volunteers with Japanese cedar pollinosis who were 20 years old or older. The inclusion criteria required that the subjects have a CAP-RAST score for Japanese cedar of 2 or greater, show a positive nasal provocation reaction to the Japanese cedar antigen disc (more than two symptoms by the nasal provocation test from among nasal itching, sneezing, rhinorrhea and nasal congestion), and provide written consent to participate in this study.¹⁰

The following subjects were excluded.

* Subjects with a history of hypersensitivity to the components of the study drugs

* Subjects who were unable to stop smoking on the days of the clinical study

* Subjects who had used steroids within one month of the start day of the clinical study

* Subjects who within one week of the start day of the clinical study used drugs that may affect the results of the clinical study (antihistamines, antiallergic drugs, vasoconstrictors)

* Subjects undergoing desensitization therapy

* Subjects with nasal diseases that affect the assessment of the nasal provocation reaction, such as acute/chronic rhinitis, nasal polyps, hypertrophic rhinitis, deviated septum or sinusitis

* Subjects who were reactive to multiple antigens including pollens other than Japanese cedar (ragweed, mugwort), and had worsening of nasal symptoms when the nasal provocation test was conducted during the season of dispersion of the pollen

STUDY DRUGS, STUDY DESIGN

Study drugs were epinastine hydrochloride 20 mg tablets (epinastine), fexofenadine hydrochloride 60 mg tablets (fexofenadine), and placebo indistinguishable from epinastine (provided by Nippon Boehringer Ingelheim Co., Ltd., Hyogo, Japan with fees paid).

The clinical study consisted of four visits. Visit 1 consisted of screening tests, and visits 2, 3 and 4 involved nasal provocation tests using Japanese cedar antigen discs.

In the study design, the three study drugs were administered to subjects as a single dose on the days of the three nasal provocation tests in an open 3-way crossover method in the order assigned by the randomization (Fig. 1). A study drug administrator who was neither the physician nor the clinical study collaborator conducted the randomization, and the study

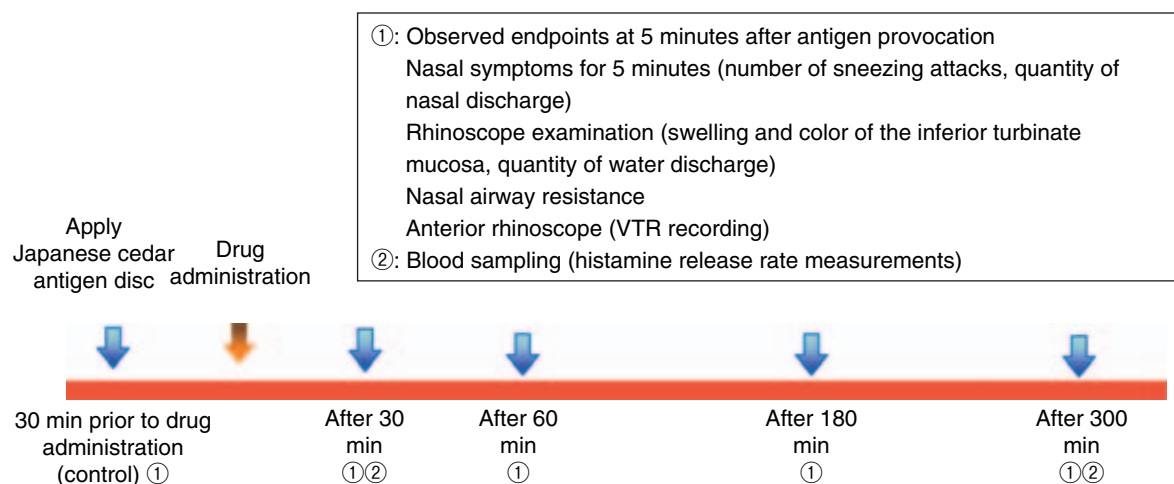


Fig. 2 Observed endpoints

Table 2 Characteristics of subjects

Sex	male	5
	female	4
Age (years)	mean $\pm$ S.E.	23.56 $\pm$ 0.57
Age at onset (years)	mean $\pm$ S.E.	16.67 $\pm$ 1.16
Disease type	sneezing, rhinorrhea	8
	nasal airway closure	1
CAP-RAST (score)	house dust	2.22 $\pm$ 0.82
	mites	2.33 $\pm$ 0.89
	Japanese cedar	3.22 $\pm$ 0.31
	mugwort	0.44 $\pm$ 0.38
	ragweed	0.56 $\pm$ 0.43
Co-existing illnesses	no	1
	yes	8
	chronic allergic rhinitis	5
	seasonal allergic conjunctivitis	2
	allergic conjunctivitis	2
Allergy prior history	no	9
	yes	0
Prior therapy (desensitization, surgery)	no	9
	yes	0

drug administrator performed the drug administration in a way that could not be identified by the physician nor the clinical study collaborator.

OBSERVED ENDPOINTS

Efficacy

During the 5 minutes after provocation, the nasal symptoms were observed, including the number of sneezing attacks and quantity of nasal discharge (weight of tissues used).

At 5 minutes after provocation, a rhinoscope exami-

nation was conducted to examine and rate the swelling and color of the mucosa of the inferior nasal turbinates and nasal discharge. The rating was conducted according to the nasal finding classification of The Practical Guideline for Management of Allergic Rhinitis.⁴ The extent of the inferior nasal turbinate mucosal swelling and nasal discharge were scored (3 points, 2 points, 1 point, none; Table 1), and the changes in the nasal finding score over time were determined for each drug.¹⁰

In addition, nasal airway resistance measurements,

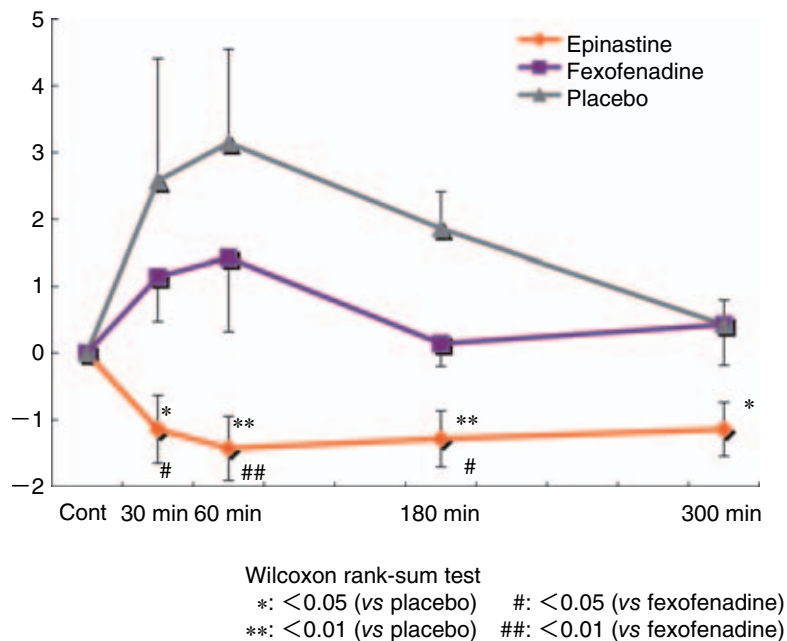


Fig. 3 Change in the number of sneezing attacks

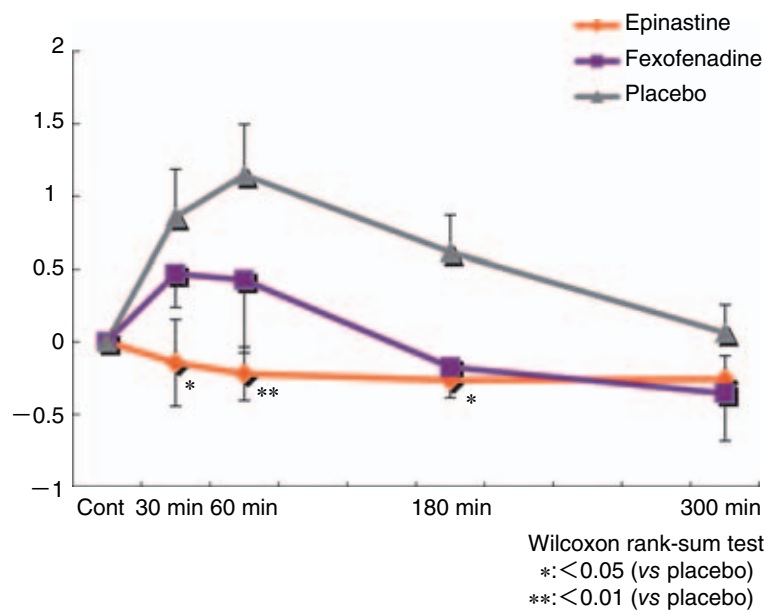


Fig. 4 Change in the quantity of nasal discharge (weight of tissues used)

VTR recording by anterior rhinoscopy for a one-minute period immediately after provocation and for a one-minute period beginning at 5 minutes after provocation, and histamine release rate (HRT Shionogi, Osaka, Japan) after first nasal provocation (30 minutes before drug administration) and at the end of the last nasal provocation (300 minutes after drug administration) were also observed.

Safety

At each visit, the physician conducted an examination at 30 minutes prior to drug administration before the nasal provocation and at 300 minutes after drug administration after the completion of the nasal provocation.

Patient-reported Evaluation

After completion of all clinical studies, subjects were

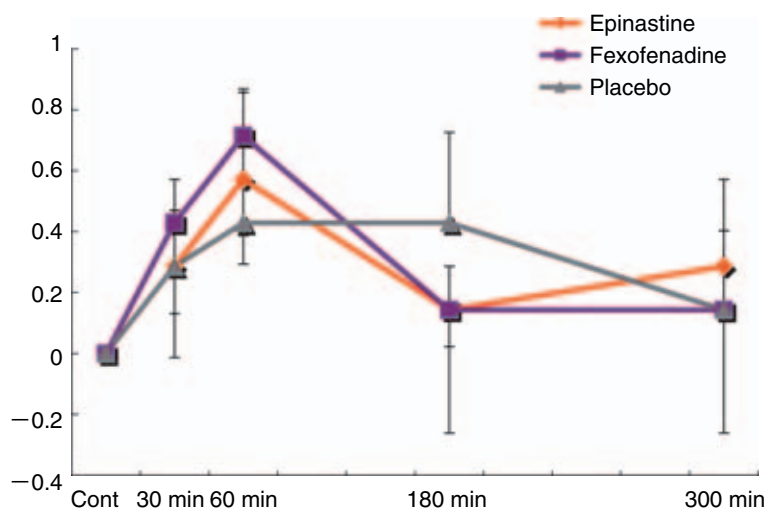
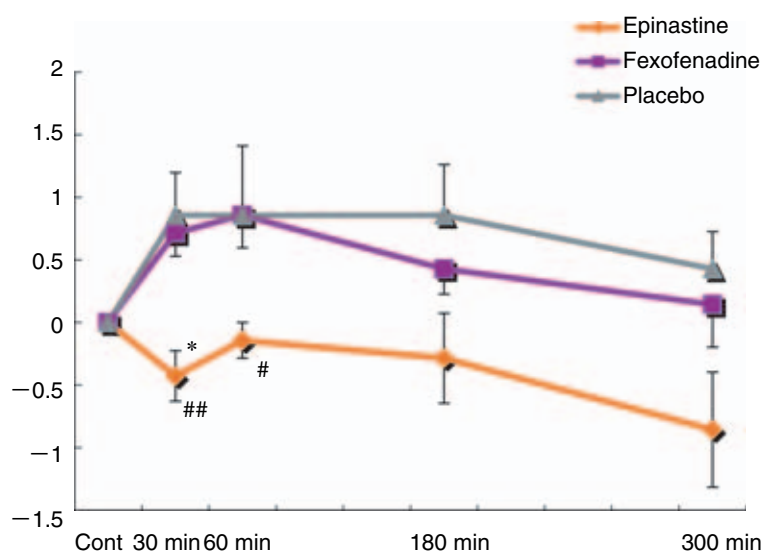


Fig. 5 Change in the inferior nasal turbinate mucosal swelling (nasal finding score)



Wilcoxon rank-sum test

*: <0.05 (vs placebo)

#: <0.05 (vs fexofenadine)

##: <0.01 (vs fexofenadine)

Fig. 6 Change in the nasal discharge (nasal finding score)

surveyed using questionnaires for their impressions on the efficacy of the study drugs to determine patients' opinions.

STUDY METHODS

The nasal provocation was done using Japanese cedar antigen discs containing 50 ng of Cry j1 (kindly provided by National Hospital Organization Sagami-hara National Hospital, Kanagawa, Japan), and were applied to the anterior portion of both inferior nasal turbinates for 5 minutes. The procedures for each ob-

servation day are indicated below.

Day of Screening Tests (Visit 1)

Subjects were given an explanation regarding their participation in this clinical study and provided written consent.

The subjects underwent a physical examination, laboratory tests (hematology, blood chemistry, urinalysis) and the nasal provocation test. The subject's background, past medical history and co-existing illnesses, and concomitant drugs were surveyed to con-

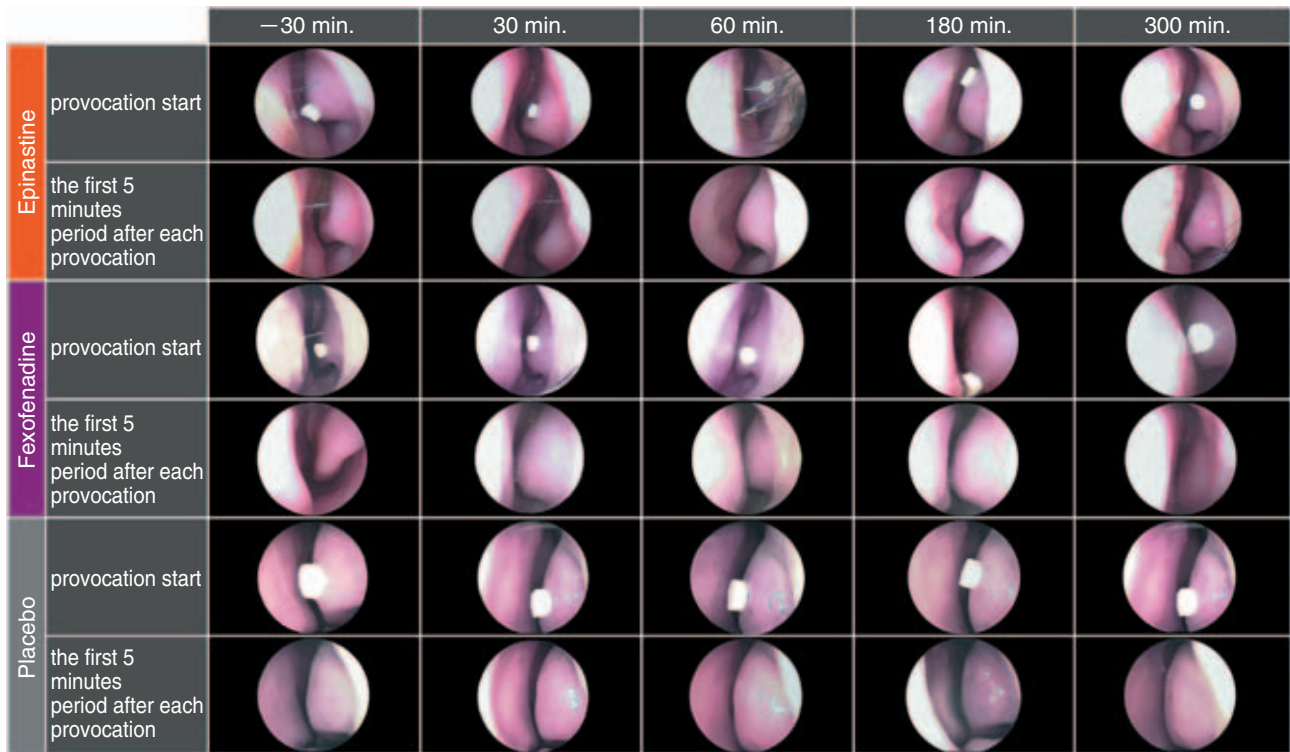


Fig. 7 The appearance of nasal mucosa by rhinoscope

firm inclusion criteria and exclusion criteria.

Days of Nasal Provocation Tests (Visits 2, 3, 4; Fig. 2)

The study drugs were administered at the three visits, and at each visit, a study drug was given as a single dose. There was a drug-free period of 14 days between visits.

The first nasal provocation was conducted at 30 minutes prior to any study drug administration, after which the study drug was administered. Then, subsequent nasal provocation was conducted at 30 minutes, 60 minutes, 180 minutes, and 300 minutes after drug administration (a total of five times). At each time point, the respective observations were conducted.

Statistical Analysis

The results were evaluated as the rate of change in the value after antigen provocation prior to drug administration compared with those after drug administration, and the value was expressed as a mean $\pm$ standard error. Comparison between study drugs was performed using the Wilcoxon rank-sum test.

This clinical study was conducted at the Tokyo Clinical Research Organization for Medicine Clinic (ToCROM). Prior to conducting the study, the study was reviewed by the Independent Ethics Committee of the Osaka Pharmacology Research Clinic and was approved by the clinic director.

RESULTS

There were nine subjects (5 men, 4 women), mean age 23.56 ± 0.57 years. The details of subjects' demographics are in Table 2. None of the subjects experienced safety problems during the study. One subject did not return for visits 3 and 4, while one subject did not return for visit 3. Thus, 7 subjects received all study drugs.

EFFICACY

Nasal Symptoms

Changes in the number of sneezing attacks and changes in the quantity of nasal discharge (weight of tissues used) are shown in Figures 3, 4. The number of sneezing attacks was maintained below baseline for up to 300 minutes after administration of epinastine. On the other hand, with fexofenadine and with placebo, the number of sneezing attacks increased during the 60 minutes after study drug administration, followed by a decrease. However, the number of attacks did not drop below baseline. Epinastine showed a significant difference against placebo from 30 minutes to 300 minutes after drug administration and against fexofenadine from 30 minutes to 180 minutes after drug administration.

The changes in the quantity of nasal discharge showed a trend that was similar to that of the number of sneezing attacks. Epinastine showed values below

Table 3 Subject impressions

	effective		neither effective nor ineffective		ineffective
Epinastine	3	42.86%	2	28.57%	2
Fexofenadine	2	28.57%	4	57.14%	1
Placebo	0	0.00%	3	42.86%	4

baseline continuously to 300 minutes after administration. The changes in the quantity of nasal discharge increased for 30 minutes after administration of fexofenadine and for 60 minutes after the administration of placebo, followed by a decrease. Epinastine showed significant differences in the changes in the quantity of nasal discharge compared with placebo from 30 minutes to 180 minutes after administration.

Nasal Findings

Figures 5, 6 show the changes over time in the swelling of the inferior nasal turbinate mucosa and nasal discharge expressed as the nasal finding score. The nasal finding score for swelling increased for 60 minutes after drug administration for all three study drugs. There were no significant differences among the study drugs.

The nasal finding score for the nasal discharge increased for 60 minutes after the administration of fexofenadine and placebo and was higher than baseline to 300 minutes after administration, while at no time point did epinastine show values above baseline. Epinastine showed significant differences compared with placebo at 30 minutes after administration and with fexofenadine at 30 minutes and 60 minutes after administration.

Nasal Airway Resistance

There were no significant differences among the study drugs.

VTR Recording By Anterior Rhinoscopy

Figure 7 shows examples of intranasal images at each measurement time point before and after nasal provocation.

The swelling of the inferior nasal turbinate mucosa was inhibited from 30 minutes after administration of epinastine and from 180 minutes after administration of fexofenadine.

Histamine Release Rates

The mean $\pm$ standard error at 30 minutes before and 300 minutes after administration were $53.24 \pm 15.67\%$ and $50.16 \pm 9.24\%$ for epinastine, $43.00 \pm 11.01\%$ and $40.17 \pm 10.25\%$ for fexofenadine, and $49.56 \pm 14.24\%$ and $35.44 \pm 11.06\%$ for placebo, respectively, showing decreases with all three study drugs. There were no significant differences among the study drugs.

SAFETY

None of the subjects experienced any adverse events.

PATIENT-REPORTED EVALUATION

Table 3 shows the subjects' impressions concerning the study drugs after the completion of the clinical study. 3 of 7 subjects given epinastine (42.86%), 2 of 7 subjects given fexofenadine (28.57%) and 0 of 7 subjects given placebo reported that the "study drug was effective."

DISCUSSION

The nasal provocation test exposes a fixed amount of the antigen directly to the nasal mucosa and determines the changes in the extent of nasal allergy symptoms. Thus, it is a simple method for objectively evaluating the efficacy and duration of effect of antiallergic agents.^{7,9,11} Usui *et al.* have studied the efficacy of Ketotifen oral agent and nasal agent by the nasal provocation test using house dust antigens.¹² Konno and Yoshida *et al.* have also repeated antigen nasal provocation using the Japanese cedar antigen and have reported that even during non-dispersion seasons, nasal symptoms seen in the field can be reproduced.^{13,14} When there is no pollen dispersion, the specific IgE in the nasal mucosa is decreased, but when antigen in an amount sufficient to elicit the development of allergic symptoms is applied, then the disease becomes apparent. In recent years, many studies have also been conducted to observe nasal allergy symptoms and conduct drug efficacy evaluation in pollen (antigen) exposure chambers,⁶ but from the standpoint of being able to expose all subjects to a fixed amount of antigen, the antigen provocation test is superior for evaluation of nasal symptoms. On the other hand, in terms of being able to reproduce symptoms of pollinosis during a pollen-dispersion season, exposure tests in pollen exposure chambers are superior to the antigen provocation test. This is because exposure chambers are closer to the exposure to pollen in the field and can elicit symptoms that do not arise in antigen provocation tests, such as symptoms in the eye and throat. However, studies like the present clinical study involving a small number of subjects, particularly studies that include detailed assessments such as rhinoscope examination, require exposure to a fixed amount of antigen. Thus, we adopted the antigen provocation test. In addition, repeated provocation reaction was used to reproduce repeated antigen exposure similar to the repeated ex-

posure in the field occurring during a pollen-dispersion season. In a simple one-time antigen exposure, the pollen is in a non-dispersion state and the allergy reaction that occurs is the pure immediate phase reaction followed by the late phase reaction.⁷ However, in the actual clinical setting, since there is repeated exposure to large quantities of dispersed pollen, it may be important to determine the efficacy of drugs under conditions with immediate phase and late phase occurring simultaneously.

It was thought that repeated antigen provocation reactions can lead to better reproduction of the actual pollinosis symptoms, and that increasing the number of exposures may lead to an increase in reactivity. However, the reaction including nasal mucosal swelling after placebo administration increased to a certain point after antigen provocation but showed a trend towards a decrease beyond one hour, and by 5 hours the reactivity was at the level prior to drug administration with the first provocation. This may be because the current clinical study was started in a pollen-free state. Specific IgE in the nasal mucosa begins to increase at the time of the year when the pollen dispersion is starting,¹⁵ and it has been shown in clinical studies in Japanese cedar pollinosis in Japan that at that time of the year, the hypersensitivity increases gradually.^{13,14} For this reason, in this clinical study, the hypersensitivity becomes apparent for a short period of time, and thereafter, possibly because of the low level of specific IgE, the decreased reactivity of mast cells results in decreased production and release of histamine and decreased nasal discharge after four or five antigen provocation reactions.

The study drugs used here, epinastine hydrochloride and fexofenadine hydrochloride, are popular second-generation antihistamines in Japan. Fexofenadine hydrochloride in the pollen-dispersion season showed clinical efficacy starting around day 2 of administration, and improved QOL early in treatment.⁸ There are no similar data for epinastine hydrochloride, but a rapid response has been reported in a clinical study involving the skin.¹⁶ In this study, a comparison of these two agents and placebo was conducted under conditions close to pollen exposure in the field using repeated antigen provocations. The results indicated that epinastine hydrochloride showed the features characteristic of second-generation antihistamines, in which the number of sneezing attacks and quantity of nasal discharge decreased after antigen provocation at 30 minutes after administration. The single dose administration inhibited these symptoms for at least 3 hours, while the number of sneezing attacks was inhibited for 5 hours. Fexofenadine hydrochloride also showed a trend towards inhibition of these symptoms, but the effect was not significantly different from placebo. There are actual efficacy data for fexofenadine hydrochloride with respect to QOL in pollinosis,⁸ and it is expected that the dif-

ferences would become significant with a larger sample size, but no significant difference was observed in this study, possibly because the dose in this clinical study of once a day differs from the usual dosage used in clinical practice. The anti-histamine effect was not caused by only a single dose, but also by one-day dosage. If we add the second tablets of fexofenadine hydrochloride, the result of 300 minutes would be changed. Further work in the future is needed to determine whether significant differences can be seen using identical experimental methods in a larger number of subjects. On the other hand, it was evident that epinastine hydrochloride showed significant differences, and thus its rapid efficacy and usefulness need to be confirmed.

The observation that neither of the drugs showed significant differences compared with placebo with respect to efficacy measures such as the inferior nasal turbinate mucosal swelling score and nasal airway resistance may be explained by the fact that this study involved a single dose administration. The histamine release assay results may also be explained by this observation.

Based on the results of this clinical study, the efficacy of epinastine hydrochloride in the early phase of pollinosis treatment was demonstrated by the observation that a single dose administration led to the suppression of the nasal mucosal reaction elicited by repeated provocation. One may consider these data to be one line of evidence for pollinosis treatment in the early phase of pollen dispersion or when there is rapid increase in the quantity of pollen dispersed.

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