

Effects of Pranlukast Hydrate on Airway Hyperresponsiveness in Non-Asthmatic Patients with Japanese Cedar Pollinosis

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ABSTRACT

Background: Recent studies have suggested that allergic rhinitis is closely related to bronchial asthma, reflecting the “one airway-one disease” hypothesis. It is unclear if the effects of pranlukast, a leukotriene-receptor antagonist, are consistent with this hypothesis.

Objective: The goal of the study was to determine if pranlukast has effects on the upper and lower airways through a comparison of the effects of fexofenadine and pranlukast on airway hyperresponsiveness in non-asthmatic patients with cedar pollinosis before the Japanese cedar pollen season and during the peak pollen season.

Methods: Patients received fexofenadine hydrochloride plus oral mequitazine (fexofenadine group) or pranlukast hydrate plus oral mequitazine (pranlukast group) as an initial treatment. Subsequent changes in airway responsiveness to acetylcholine were measured.

Results: Among patients in whom coughing developed during the peak pollen season, airway responsiveness significantly increased in the fexofenadine group. In the pranlukast group, airway responsiveness did not increase significantly, regardless of the presence or absence of coughing.

Conclusions: The results indicate that pranlukast hydrate inhibits airway hyperresponsiveness in non-asthmatic patients with Japanese cedar pollinosis. In turn, this suggests that cysteinyl leukotrienes have a role in increased airway responsiveness.

KEY WORDS

airway responsiveness, allergic rhinitis, leukotriene, one airway-one disease, pranlukast hydrate

INTRODUCTION

The concept of “one airway-one disease” proposed by Grossman suggests that allergic rhinitis and bronchial asthma are closely related allergic diseases that involve the entire airway, rather than separate diseases of the upper or lower respiratory tract.¹ International guidelines for the treatment of allergic rhinitis have been proposed in the World Health Organization Initiative on Allergic Rhinitis and its Impact on Asthma (ARIA).² These guidelines also emphasize involvement of the upper and lower airways in allergic

rhinitis, again suggesting an interaction between allergic rhinitis and bronchial asthma.

The upper airway has an influence on the lower airway, since the severity of rhinitis correlates positively with clinical symptoms of asthma and increased severity of rhinitis is associated with asthma exacerbation.³ In non-asthmatic patients with allergic rhinitis, bronchial mucosa eosinophil counts are often higher than in healthy subjects, although not as high as those for asthmatic patients.⁴ Airway responsiveness in non-asthmatic patients with allergic rhinitis also falls between those for asthmatic patients and healthy

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Table 1 Subject characteristics

	Fexofenadine group	Pranlukast group	P value
Age (year)	35.9 ± 2.5	35.5 ± 2.7	N.S. ¹⁾
Sex (M/F)	5/13	6/10	N.S. ²⁾
Height (cm)	159.7 ± 1.6	163.3 ± 1.8	N.S. ¹⁾
Atopy family history (+/-)	12/6	12/4	N.S. ²⁾
Onset (years)	12.8 ± 1.7	10.9 ± 1.1	N.S. ¹⁾
Total IgE (IU/ml)	188.5 ± 39.9	200.7 ± 51.8	N.S. ¹⁾
Specific IgE (CAP score) cedar	3.7 ± 0.2	4.2 ± 0.3	N.S. ³⁾
PC ₂₀ Ach (mg/ml)	19120 ± 880.0	17900 ± 1179.9	N.S. ¹⁾
Peripheral blood eosinophils (cell/ml)	241.7 ± 36.9	294.2 ± 65.9	N.S. ¹⁾

Data are shown as means ± S.E.; N.S.: Not significant; 1) Student's t test, 2) χ^2 test, 3) Mann-Whitney U test; groups: fexofenadine + mequitazine, pranlukast + mequitazine.

subjects, but is considered to be increased.⁵

Therapeutic agents for allergic rhinitis include nasal steroid sprays, chemical mediator release inhibitors, antihistamines, leukotriene-receptor antagonists (LTRAs), antiprostaglandin D₂, and antithromboxane A₂. Cysteinyl leukotrienes are inflammatory mediators that have a common causative role in the pathogenesis of allergic diseases in both the upper and lower airways,⁶ and LTRAs are effective for both bronchial asthma and allergic rhinitis.⁷⁻¹⁰ Thus, LTRAs appear to inhibit allergic inflammation in both airways. To examine this hypothesis, we compared the effects on airway responsiveness of an LTRA with those of a second-generation antihistamine during the peak cedar pollen season in non-asthmatic patients with Japanese cedar pollinosis.

METHODS

SUBJECTS

The study included 34 non-asthmatic patients with a diagnosis of Japanese cedar pollinosis according to diagnostic guidelines for nasal allergy (2002).¹¹ The patients visited our clinic before the cedar pollen season from January 24 to February 19 in 2005 and received a thorough explanation of the study protocol. All subjects gave informed consent, and they were re-examined after cedar pollen shedding (February 22) especially during the peak pollen season from March 7 to April 9 in 2005.

DRUG ADMINISTRATION

Patients received fexofenadine hydrochloride (120 mg/day, one 60-mg tablet twice daily) plus oral mequitazine (6 mg/day, one 3-mg tablet twice daily)

(fexofenadine group) or pranlukast hydrate (450 mg/day, two 112.5-mg capsules twice daily) plus oral mequitazine (6 mg/day, one 3-mg tablet twice daily) (pranlukast group). The groups were established based on the order of patient visits before the cedar pollen season (January 24 to February 19). Use of nasal steroid sprays was avoided whenever possible, and levocabastine hydrochloride eye drops and nasal drops were permitted only on exacerbation of symptoms.

AIRWAY RESPONSIVENESS TO ACETYLCHOLINE

Acetylcholine was inhaled before the pollen season (January 24 to February 19) and during the peak pollen season (March 7 to April 9) according to the standard method of Makino *et al.*¹² Sensitivity to acetylcholine (PC₂₀Ach) was defined as the concentration of acetylcholine that provoked a 20% or more reduction in the forced expiratory volume in 1 second (FEV_{1.0}) after inhalation, compared with the baseline value.

PULMONARY FUNCTION AND PERIPHERAL BLOOD EOSINOPHIL COUNT

Pulmonary function tests were performed on a spirometer (HI-801, CHEST M.I., Tokyo, Japan). FEV_{1.0} (AS-7, MINATO, Osaka, Japan) and peripheral blood eosinophil counts were measured before the pollen season and during the peak pollen season.

SYMPTOMS AND DAILY ACTIVITIES

Symptoms were assessed based on self-administered questionnaires during the peak pollen season. Variables included nasal and ocular symptoms, the degree of impairment of daily activities, and the frequency and severity of coughing. Briefly, the frequency of coughing was graded according to the evaluation method proposed by Nishi *et al.*¹⁴: 0 indicating none (never); 1 indicating infrequent (5 times or less); 2 indicating somewhat frequent (6 to 10 times); 3 indicating frequent (11 to 20 times); and 4 indicating very frequent (21 times or more). The severity of coughing was graded as follows: 0 indicating none; 1 indicating mild, 2 indicating moderate; 3 indicating severe; and 4 indicating very severe. Next, nasal and ocular symptoms, such as rhinorrhea, sneezing, nasal congestion, nasal itching, itching of the eyes, and watery eyes, were graded according to the Japan Allergic Rhinitis Standard Quality-of-Life Questionnaire (JRQLQ No. 1)¹³: 0 indicating none; 1 indicating mild; 2 indicating moderate; 3 indicating severe; and 4 indicating very severe. The degree of impairment of daily activities was graded according to the 2002 diagnostic guidelines for nasal allergy: 1 indicating unable to work or study; 2 indicating difficulty in starting to work or study; 3 indicating intermediate between 2 and 4; 4 indicating almost no prob-

Table 2 Clinical characteristics of 18 cedar pollinosis subjects treated with fexofenadine and mequitazine

Subject No.	Age (year)	Sex	Height (cm)	Atopy family history	Onset (years)	Total IgE (IU/ml)	Specific IgE (CAP score)						
							Cedar	Cypress	Dacylis	Ambrosia	Artemisia	HD	Mite
1	48	M	170	(+)	12	108	3	0	0	1	0	3	2
2	26	F	167	(+)	7	210	4	3	0	0	0	3	3
3	34	F	153	(-)	3	63	4	3	0	0	0	0	0
4	27	F	153	(-)	10	49	4	2	0	0	0	2	1
5	34	F	153	(-)	20	677	4	2	3	0	0	3	3
6	43	F	162	(+)	18	54	3	1	0	0	0	2	2
7	31	F	158	(+)	15	250	5	3	0	0	0	3	4
8	23	F	153	(+)	10	ND	4	0	0	0	0	0	0
9	38	M	169	(+)	3	250	3	2	0	0	0	3	3
10	46	F	158	(-)	14	213	3	0	0	0	0	0	0
11	52	M	166	(+)	25	193	4	2	0	0	0	0	0
12	59	M	164	(+)	26	119	3	0	0	0	0	0	0
13	45	F	155	(-)	20	200	4	2	4	0	3	1	2
14	26	F	158	(+)	15	231	4	0	0	0	0	3	3
15	34	M	172	(-)	10	ND	3	2	3	2	0	0	0
16	28	F	153	(+)	3	164	3	2	2	0	0	2	2
17	27	F	155	(+)	12	46	3	0	0	0	0	0	0
18	25	F	155	(+)	8	ND	5	3	0	2	0	0	0

ND: Not detected.

Table 3 Clinical characteristics of 16 cedar pollinosis subjects treated with pranlukast and mequitazine

Subject No.	Age (year)	Sex	Height (cm)	Atopy family history	Onset (years)	Total IgE (IU/ml)	Specific IgE (CAP score)						
							Cedar	Cypress	Dacylis	Ambrosia	Artemisia	HD	Mite
1	39	M	173	(+)	15	200	6	3	0	0	0	2	2
2	37	M	168	(+)	9	740	5	2	0	2	0	2	2
3	60	F	164	(-)	12	300	3	2	0	0	1	0	0
4	26	F	156	(+)	15	69	6	3	2	0	0	0	0
5	45	M	173	(+)	10	66	3	2	0	0	0	0	0
6	36	F	159	(+)	16	156	6	3	3	0	6	6	6
7	30	F	156	(-)	9	103	3	2	0	0	0	0	0
8	42	F	153	(+)	20	166	5	3	3	2	2	2	2
9	27	M	173	(+)	10	469	4	3	0	0	0	3	3
10	23	M	164	(-)	3	93	3	0	4	0	0	0	0
11	34	F	158	(+)	8	ND	5	3	2	2	2	4	4
12	22	F	157	(-)	5	51	4	3	0	0	0	0	0
13	30	F	163	(+)	9	25	4	3	2	0	0	0	0
14	40	F	160	(+)	13	22	4	3	0	0	0	0	0
15	25	F	161	(+)	6	154	3	0	0	0	0	4	4
16	52	M	174	(+)	15	410	3	0	0	0	0	3	3

ND: Not detected.

lems with working or studying; and 5 indicating no problems.

STATISTICAL ANALYSIS

Data are expressed as means $\pm$ SD. Demographic characteristics were compared between groups by

the chi-square test, Student t test, and Mann-Whitney U test. Airway responsiveness, peripheral blood eosinophil counts, and FEV_{1.0} were compared within groups by paired t-test and between groups by the Student t-test. Symptoms and daily activities were compared within groups by the Mann-Whitney U

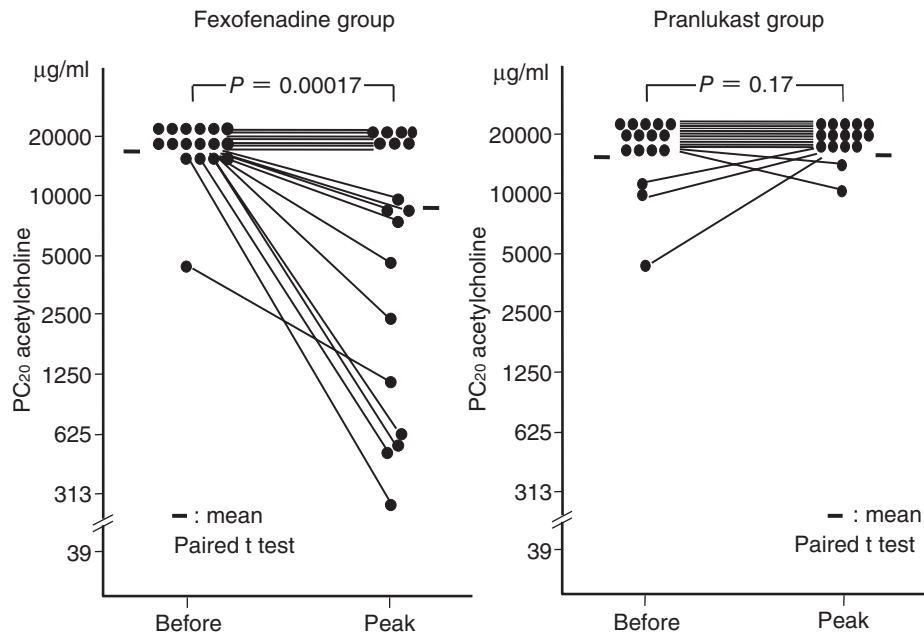


Fig. 1 Airway responsiveness to acetylcholine (ACh). Seasonal variation of PC₂₀ACh values in non-asthmatic subjects with Japanese cedar pollinosis. In the fexofenadine group, airway responsiveness to acetylcholine increased significantly during the peak pollen season compared with before the pollen season. However, airway responsiveness did not increase significantly in the pranlukast group.

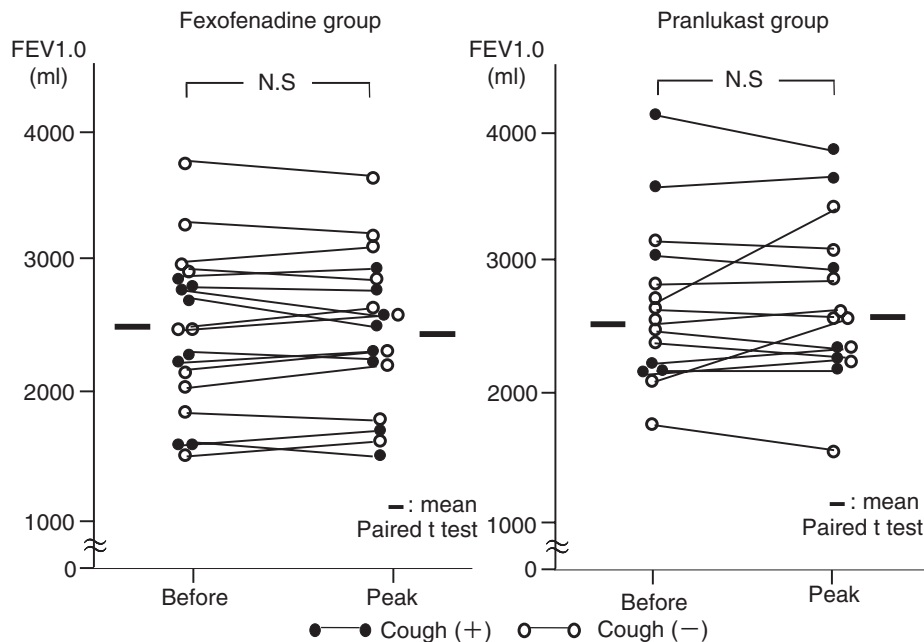


Fig. 2 Respiratory function. Seasonal variation of FEV1.0 in non-asthmatic subjects with Japanese cedar pollinosis. No significant difference in FEV1.0 was observed before and during the peak pollen season.

test. Multiple linear regression analysis was used to compare the correlations among sensitivity to acetylcholine (PC₂₀ACh) and symptom score. All P values are two-tailed and $P < 0.05$ was considered to indicate

statistical significance.

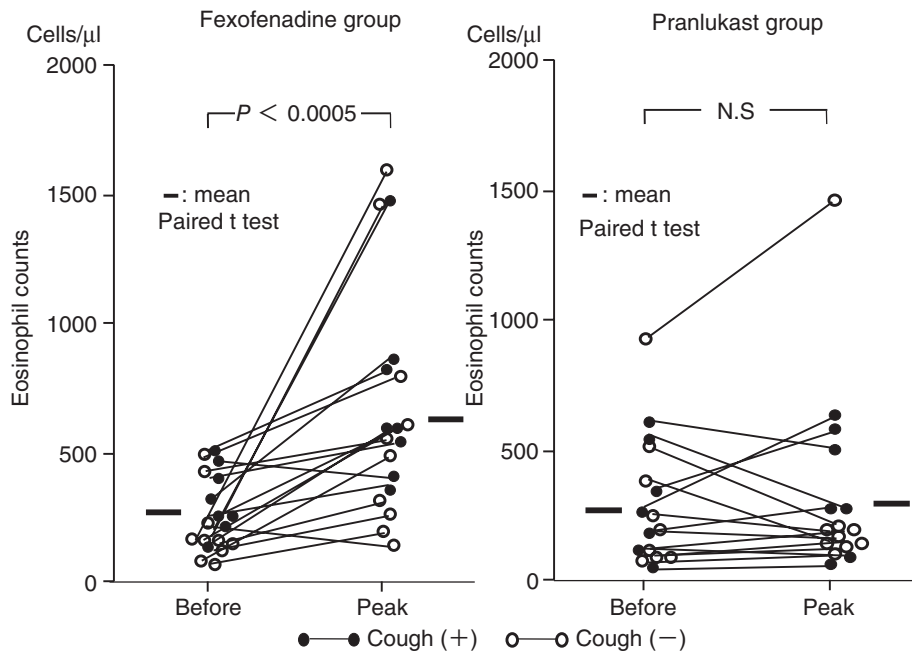


Fig. 3 Peripheral blood eosinophil. Seasonal comparison of eosinophil counts in peripheral blood. Eosinophil counts increased significantly during the peak pollen season compared with before the pollen season in the Fexofenadine group. No significant difference in eosinophil counts was observed before and during the peak pollen season in the Pranlukast group.

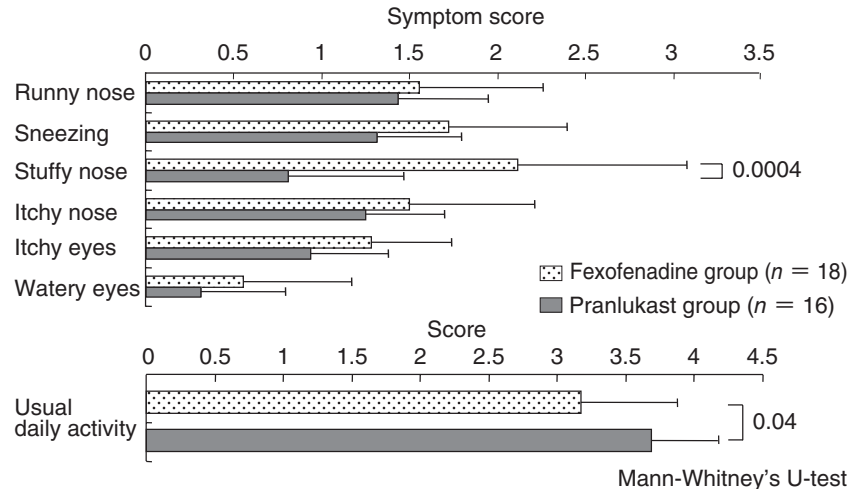


Fig. 4 Score of nasal symptoms, ocular symptoms and daily life activity during the peak pollen season. There was a significant difference in stuffy nose and daily life in the Pranlukast group compared with the Fexofenadine group. Data are presented as means $\pm$ SD.

RESULTS

DEMOGRAPHIC CHARACTERISTICS

The mean demographic characteristics of each group are shown in Table 1, and the characteristics for individual patients are shown in Table 2, 3. Of the 34 patients in the study, 18 received fexofenadine hydro-

chloride plus oral mequitazine (5 men and 13 women; mean age, 35.9 ± 2.5 years [mean $\pm$ standard error]) and 16 received pranlukast hydrate plus oral mequitazine (6 men and 10 women; mean age, 35.5 ± 2.7 years). All patients tested positive for Japanese cedar pollen antigen, and many patients also tested positive for hinoki (*Chamaecyparis obtusa*), house dust, and

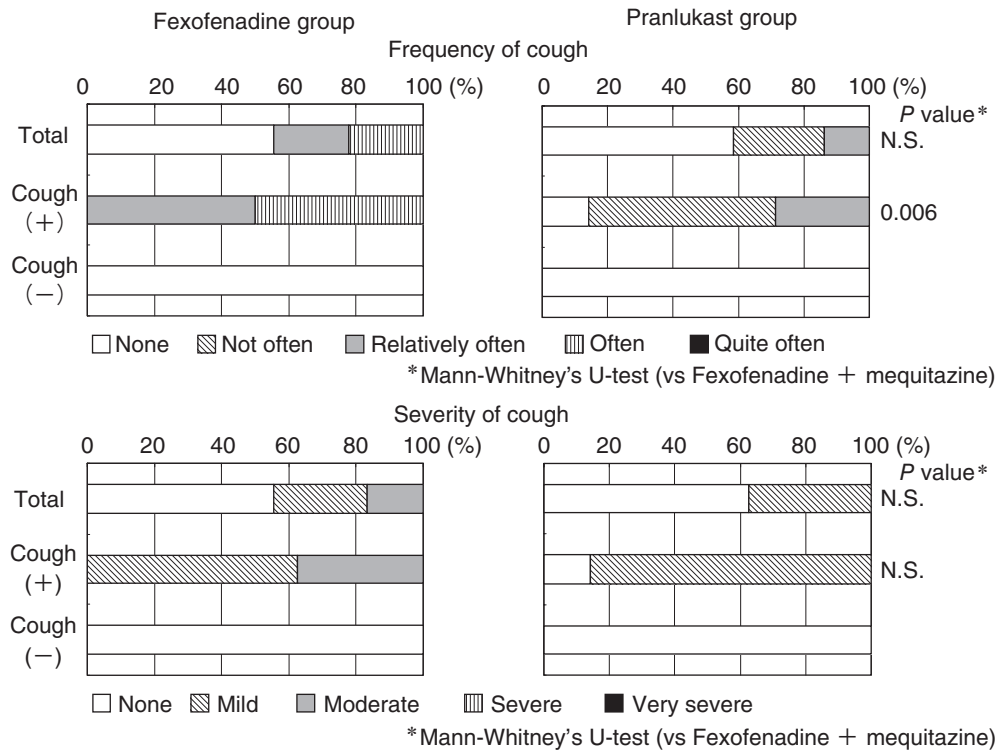


Fig. 5 Frequency and severity of cough during the peak pollen season. The frequency of coughing in subjects with cough in the pranlukast group was significantly lower than that of subjects with cough in the fexofenadine group.

house-dust mite antigens. There were no significant differences in age, sex ratio, height, family history of atopic disease, duration of disease, serum IgE levels, Japanese cedar-specific IgE (CAP score), airway hyperresponsiveness before the pollen season, and peripheral blood eosinophil counts between the groups.

AIRWAY RESPONSIVENESS

PC₂₀Ach levels were compared before the pollen season and during the peak pollen season. In the fexofenadine group the PC₂₀Ach level decreased significantly during the peak pollen season ($p < 0.001$), but in the pranlukast group the PC₂₀Ach level did not decrease significantly. PC₂₀Ach levels during the peak pollen season were significantly lower in the fexofenadine group than in the pranlukast group ($p < 0.001$) (Fig. 1).

PULMONARY FUNCTION

FEV_{1.0} before the pollen season did not differ significantly from that during the peak pollen season in either group (Fig. 2). The same results were indicated in some to very frequent (6 times or over) cough group (cough [+]), and none or infrequent (5 times or less) cough group (cough [-]), respectively.

PERIPHERAL BLOOD EOSINOPHIL COUNT

Eosinophil counts in the fexofenadine group were

significantly higher during the peak pollen season compared to before the pollen season ($p < 0.001$), but eosinophil counts in the pranlukast group before the pollen season did not differ significantly from those during the peak pollen season (Fig. 3).

SYMPTOMS

The severity of nasal and ocular symptoms, particularly nasal congestion, during the peak pollen season was significantly milder in the pranlukast group than in the fexofenadine group ($p < 0.001$), and the degree of impairment in daily activities during the peak pollen season was significantly lower in the pranlukast group than in the fexofenadine group ($p = 0.04$) (Fig. 4). The frequency of coughing during the pollen season did not differ between the fexofenadine group (8/18) and the pranlukast group (7/16), but among the patients with coughing, the frequency of coughing was significantly lower in the pranlukast group compared to the fexofenadine group ($p = 0.006$) (Fig. 5).

RELATIONSHIP BETWEEN AIRWAY RESPONSIVENESS AND SYMPTOMS

We examined whether the severity of nasal and ocular symptoms and the severity and frequency of coughing during the peak pollen season differed between patients with increased (PC₂₀Ach $< 20,000$ $\mu\text{g}/\text{mL}$) and normal airway responsiveness (PC₂₀Ach $\geq$

LTRA Regulates Airway Responsiveness

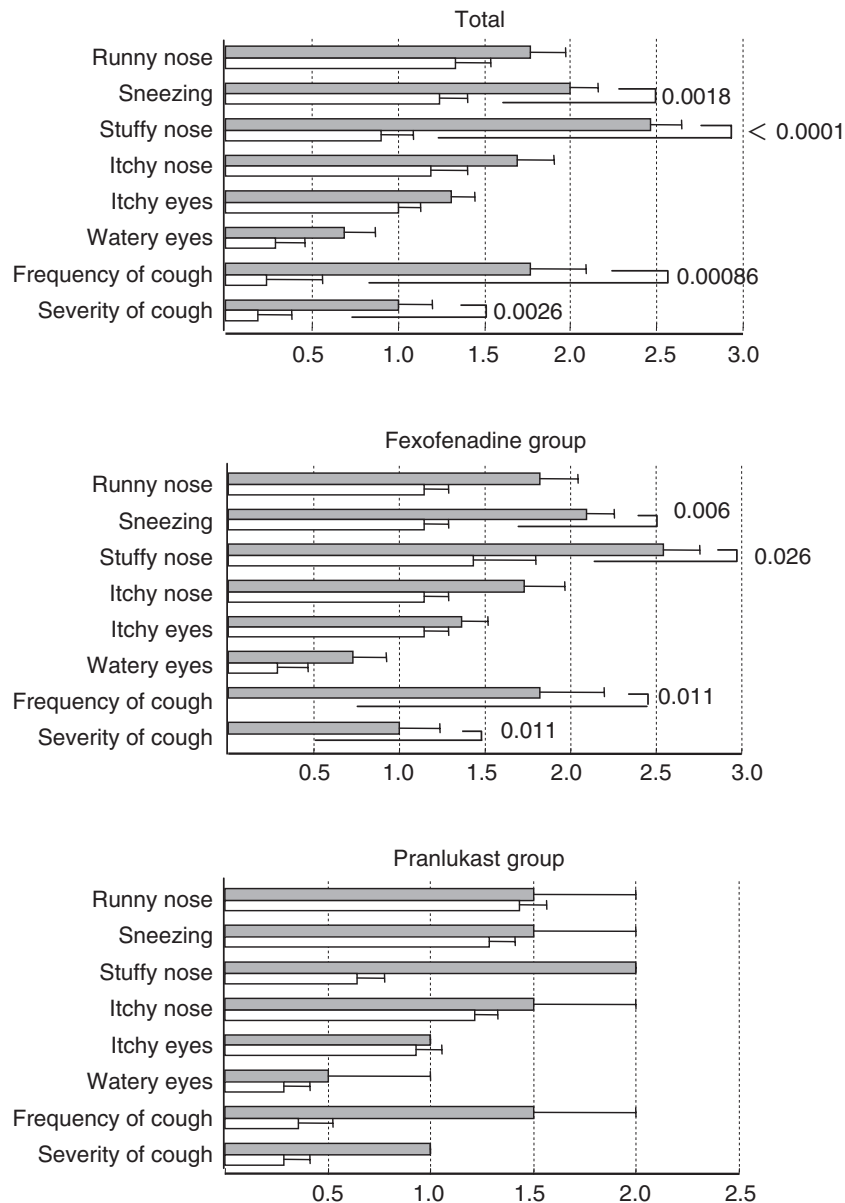


Fig. 6 Relationship between airway responsiveness to acetylcholine (Ach) and symptom scores during the peak pollen season in patients treated with fexofenadine. *P* values were calculated using the Mann-Whitney U test. Closed bars: PC₂₀Ach < 20,000 mg/ml; open bars: PC₂₀Ach ≥ 20,000 mg/ml; error bars show S.D. In the pranlukast group, *p* values were not calculated due to the small number of subjects.

20,000 µg/mL). Overall, the mean scores for sneezing and nasal congestion and the frequency and severity of coughing were significantly higher in patients with increased airway responsiveness. Patients in each treatment group were similarly classified into two subgroups based on airway responsiveness. In both treatment groups, the frequency and severity of sneezing, nasal congestion, and coughing were significantly higher in patients with increased airway responsiveness. In the pranlukast group, the frequency

and severity of nasal congestion and coughing were also high, but statistical analysis was not performed because of the small number of patients (Fig. 6). There was a strong correlation between airway hyperresponsiveness and nasal symptom score, such as the scores for runny nose, sneezing, nasal congestion, and frequency or severity score of cough (Fig. 7).

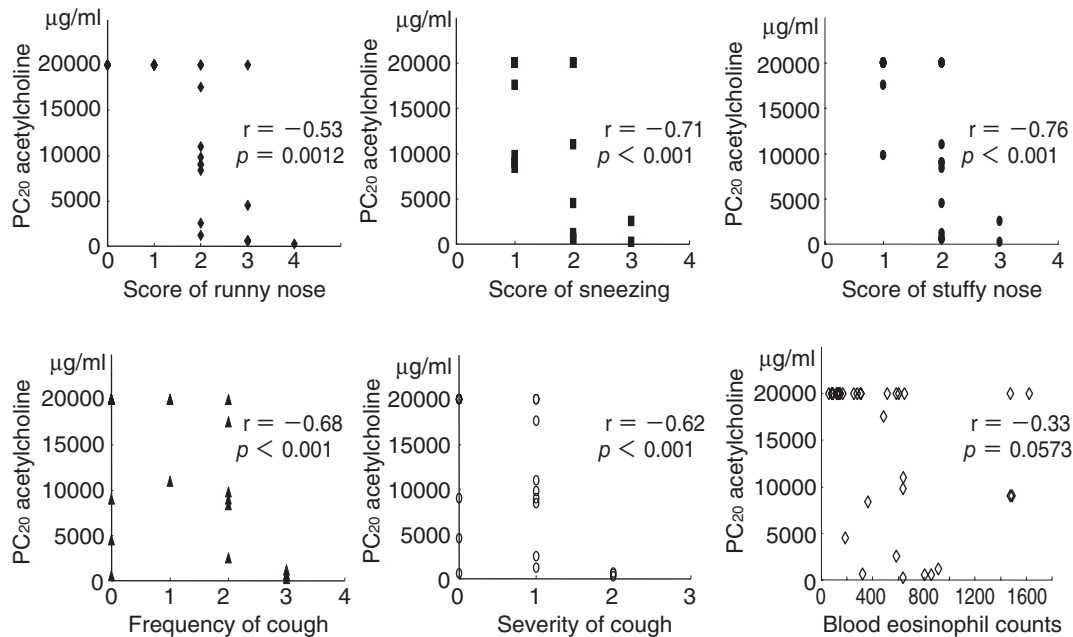


Fig. 7 Factors influencing airway hyperresponsiveness. The data shows the correlation of airway responsiveness to acetylcholine (PC₂₀Ach) with the runny nose score, sneezing score, stuffy nose score, frequency of cough, severity of cough, and peripheral blood eosinophil counts during the peak pollen season in all patients ($n = 34$). These correlations were evaluated by using pearson's correlation coefficient test.

Table 4 Multiple linear regression analysis of airway hyperresponsiveness including nasal/ocular symptoms, cough, daily activities, and eosinophil counts during the peak pollen season in all patients ($n = 34$)

	Coefficients	Standard error	P value
Runny nose	1486.18	2981.92	0.622938
Sneezing	-4827.33	3139.27	0.137761
Stuffy nose	-2775.12	1317.44	0.046281
Itchy nose	-627.114	3458.65	0.857707
Itchy eyes	-413.431	2349.52	0.861862
Watery nose	-986.674	2385.82	0.683028
Cough (frequency)	-4475.87	2385.94	0.073414
Cough (severity)	3651.79	3867.30	0.354844
Daily activity	-851.327	2983.23	0.777914
Eosinophil counts	0.198604	2.45659	0.936264

MULTIPLE LINEAR REGRESSION ANALYSIS OF AIRWAY RESPONSIVENESS INCLUDING NASAL/OCULAR SYMPTOM SCORE

The results of multiple linear regression analysis included the nasal/ocular symptom score, frequency or severity score of cough, daily activity score, and eosinophil counts. As shown in Table 4, only the score of stuffy nose was correlated with airway responsiveness.

RELATIONSHIP BETWEEN COUGHING AND AIRWAY RESPONSIVENESS

We also examined the effects of treatment on airway

responsiveness in each group according to the presence or absence of coughing during the pollen season. In the fexofenadine group, the AC₂₀Ach level decreased significantly during the peak pollen season, compared with the value before the pollen season, regardless of the presence or absence of coughing (Fig. 8). In particular, airway responsiveness increased in all patients with coughing, whereas AC₂₀Ach levels during the peak pollen season decreased significantly in patients without coughing ($p = 0.002$). In the pranlukast group, the AC₂₀Ach level did not decrease significantly during the peak pollen season, compared with the value before the pollen season, regardless of the presence or absence of coughing (Fig. 9).

SIDE EFFECTS

There were no clinically important side effects during the treatment period in either group.

DISCUSSION

The effects of therapeutic agents for allergic rhinitis on bronchial asthma have been examined widely, with nasal steroid sprays most frequently evaluated clinically. Treatment for allergic rhinitis reduces the risk of asthma and ameliorates airway hyperresponsiveness in non-asthmatic patients,^{15,16} as well as reduces episodes and symptoms of asthma in asthmatic patients.¹⁷⁻¹⁹ LTRAs have also been studied in asthmatic patients,^{20,21} and may reduce symptoms of allergic rhinitis and bronchial asthma. However, studies assessing the effects of LTRAs on airway inflam-

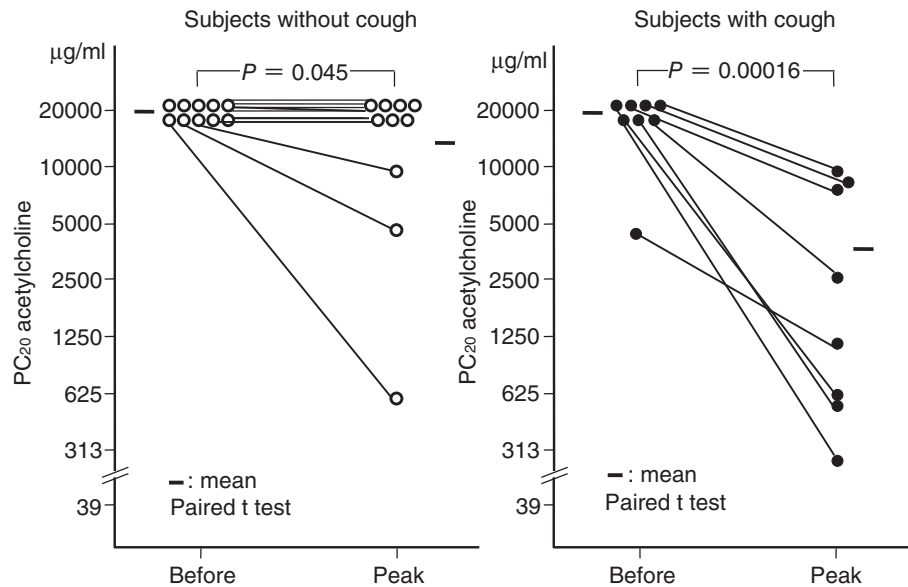


Fig. 8 Seasonal variation of airway responsiveness to acetylcholine (PC₂₀Ach) in subjects receiving fexofenadine and mequitazine. Airway responsiveness to acetylcholine (PC₂₀Ach) increased significantly during the peak pollen season compared with before the pollen season in subjects with and without cough.

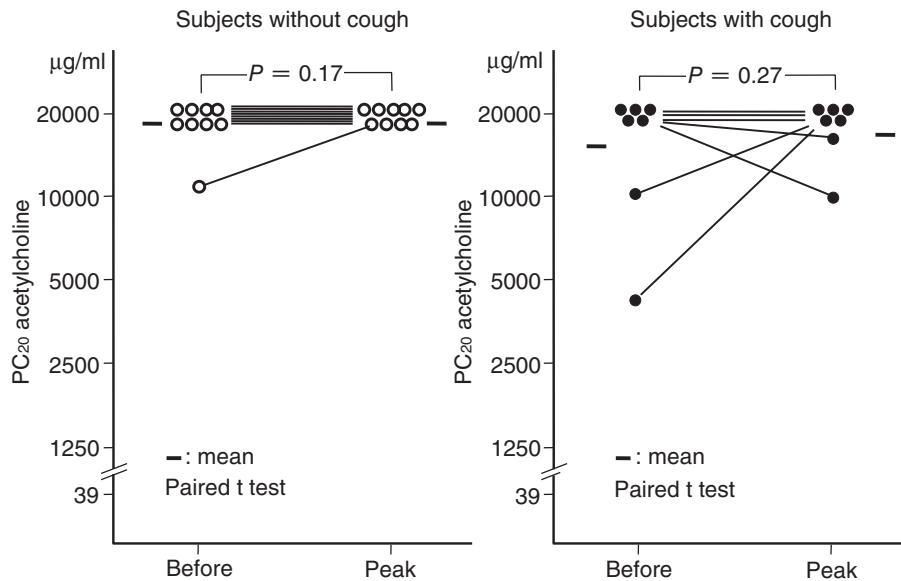


Fig. 9 Seasonal variation of airway responsiveness to acetylcholine (Ach) in subjects receiving pranlukast and mequitazine. Airway responsiveness to acetylcholine (PC₂₀Ach) did not increase significantly during the peak pollen season compared with before the pollen season in subjects with and without cough.

mation and airway responsiveness in non-asthmatic patients have not been performed.

We compared the effects of fexofenadine hydrochloride plus oral mequitazine and pranlukast hydrate plus oral mequitazine on airway responsiveness and other variables in non-asthmatic patients with ce-

dar pollinosis. In the fexofenadine group, airway responsiveness increased during the peak pollen season, compared with that before the pollen season, but in the pranlukast group airway responsiveness did not increase, indicating that pranlukast hydrate inhibits increased airway responsiveness caused by cedar

pollinosis. These findings also suggest that cysteinyl leukotrienes are related to increased airway responsiveness in patients with cedar pollinosis.

Recently, it is well known that there is a relationship between allergic rhinitis and lower airway disorders. It is estimated that allergic rhinitis might impact asthma through several mechanisms, such as the rhinobronchial reflex, an irritant mechanism sustained by postnasal drip, or oral respiration caused by nasal obstruction, but some controversy remains.²² Regarding the relationship between airway hyperresponsiveness and nasal and ocular symptoms, the scores for sneezing, nasal congestion, and symptoms were higher in patients with increased airway responsiveness. There was a strong correlation between airway hyperresponsiveness and symptoms, such as runny nose, sneezing, stuffy nose, and cough (Fig. 7). Stuffy nose showed a correlation with airway responsiveness in multiple linear regression analysis ($p = 0.046$) (Table 4). Stuffy nose scores were lower in the pranlukast group, which included fewer patients with increased airway responsiveness. Controlled, double-blind, multicenter trials in patients with perennial allergic rhinitis have shown that pranlukast hydrate is more effective than second-generation antihistamines for nasal congestion,²³ suggesting that nasal congestion may be related to increased airway responsiveness.

High cedar pollen counts often cause pharyngeal pruritus and coughing, in addition to nasal symptoms.²⁴ Cedar pollen counts were very high in 2005 and about 44% of our patients had coughing during the pollen season. Therefore, we examined if airway responsiveness is related to the frequency and severity of coughing during the cedar pollen season. Scores for both the frequency and severity of coughing were significantly higher in patients with increased airway responsiveness, compared to those with normal airway responsiveness, and also there were strong correlations between airway responsiveness and both the frequency and severity of coughing. These results suggest that airway hyperresponsiveness is related to coughing in patients with cedar pollinosis. In contrast, the frequency and severity of coughing did not differ significantly between the fexofenadine group and the pranlukast group, suggesting that LTRA treatment was ineffective against cough. These findings suggest that cysteinyl leukotrienes contribute minimally to coughing. However, among patients with coughing, the frequency of coughing was significantly lower in the pranlukast group, and Brozmanova *et al.* have recently reported that montelukast inhibits the cough reflex in a guinea pig model of allergic rhinitis.²⁵ Given these findings, further studies are needed to define the relationship between cysteinyl leukotrienes and coughing.

Our results show that cysteinyl leukotrienes influence airway hyperresponsiveness in non-asthmatic

patients with cedar pollinosis. In particular, airway responsiveness markedly increased during the peak pollen season in patients with coughing, suggesting an association between coughing and airway hyperresponsiveness. In contrast, non-asthmatic patients with pollinosis have eosinophilic infiltration of the airway mucosa and elevated interleukin-5 levels, in addition to airway hyperresponsiveness.²⁶ Airway inflammation was not examined in the present study, but pranlukast hydrate inhibited peripheral blood eosinophilia, as well as airway hyperresponsiveness, and is therefore likely to suppress airway inflammation.

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