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Oral Administration of Fexofenadine Hydrochloride can Attenuate Nasal Symptoms and Restore the Impaired Cognitive Function in School-Age Patients With Japanese Cedar Pollinosis

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We conducted a well-controlled observational study attempting to examine whether decreased cognitive functions caused by Japanese cedar pollinosis could be improved by oral administration of fexofenadine hydrochloride particularly in school-age patients. Cognitive functions were evaluated before and after the treatment by employing Trail Making tests（TMT）. Participating patients answered a questionnaire about treatment effects and their satisfaction with fexofenadine hydrochloride. A total of 54 patients aged 7 to 16 were enrolled in this study. A significant improvement was observed with two kinds of TMT（P<0.0001 for both）. The overall ratio of positive answers to the question of overall satisfaction with the drug, concentration in the classroom, symptoms, inconvenience in daily life, and night-time sleep were 88.5%, 71.1%, 88.7%, 60.0%, and 65.3%, respectively. These results taken together suggest that treatment with fexofenadine hydrochloride actually restores nasal symptom-derived decreases in cognitive functions, with no impairment of cognitive functions by the central nervous system（CNS）depressant actions.

Key words : pollinosis, antihistamines, school-age, CNS depression, cognitive function, observational study

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INTRODUCTION

Japanese cedar pollinosis（hereinafter referred to as “pollinosis”）is a type I allergic disease affecting nasal mucosa with three typical symptoms: persistent sneezing, rhinorrhea, and nasal congestion［1］. These nasal symptoms are not life-threatening, but have a great impact on the patient’s quality of life（QOL）and cause significant impairment in cognitive and psychomotor functions［2-10］. The symptoms may also lead to sleep disturbance［11］, which results in daytime sleepiness and further deterioration of cognitive and psychomotor function. For school-age patients, impairment of study efficiency caused by the symptoms could influence their future lives, since the dispersal season of Japanese cedar pollen falls exactly during the period of school entrance examinations in Japan. This is a critical issue for parents as well.

In the treatment of pollinosis, improvement of decreased cognitive and psychomotor functions is an important objective along with the improvement of symptoms. Antihistamines are recommended as a first line medication for the treatment of pollinosis in major guidelines［1, 12］. Antihistamines improve the symptoms primarily by preventing histamines from binding to their H1 receptors（H1 receptor antagonism）. However, once antihistamines cross the blood-brain barrier and block the binding of histamines to their H1 receptors in the brain, central nervous system（CNS）depression, including sleepiness and cognitive impairment inevitably occurs［13, 14］. When the properties of antihistamines are considered, there is a

conflict that pollinosis is treated with antihistamines that have similar impairing effects of the disease itself. This implies that study efficiency of patients receiving antihistamines may be even more disturbed after the treatment even though their symptoms are attenuated.

Fexofenadine hydrochloride is a second-generation antihistamine which shows the lowest H1 receptor occupancy among all the antihistamines available[15, 16]. Fexofenadine hydrochloride not only works as an H1 receptor antagonist, but also as an inverse agonist to prevent activation of H1 receptors even under the condition of no histamine stimulation[17]. In addition to its strong effects on H1 receptors, fexofenadine hydrochloride possesses a variety of anti-inflammatory actions contributing to symptom improvement [18]. Based on these features, Fexofenadine hydrochloride is considered to be the antihistamine which can best attenuate symptoms and restore decreased cognitive functions without impairment of cognitive function caused by drug itself.

To date, the effect of both symptoms and the treatment on cognitive functions has been examined in many studies, however, most of the studies have been conducted in adult patients. Although more accurate evaluation of cognitive functions is possible by using a computer or other dedicated system [19], it is difficult to conduct a study using these systems in a routine clinical setting. We, therefore, conducted a well-controlled observational study in an exploratory manner attempting to examine whether decreased cognitive functions caused by Japanese cedar pollinosis could be restored by a treatment with Fexofenadine hydrochloride in school-age patients with pollinosis.

PATIENTS AND METHODS

Patients

The patients were boys and girls between the ages of 7 and 16 with moderate to most severe pollinosis who were to be treated with fexofenadine hydrochloride, who visited the sites for the first time in the dispersal season of Japanese cedar pollen (January to March). Patients who had used an antihistamine two weeks prior to their first visit in the season and who had other nose conditions including nasal polyp, chronic rhinitis, and chronic sinusitis were not enrolled into this study. Eye drops were allowed in combination with antihistamines. Due to the observational nature of this study in a routine clinical practice setting, treating ENT doctors selected the starting and adjusted dose of fexofenadine hydrochloride, and any concomitant medication for each patient based on approved regimen.

Methods

This observational study was conducted at five hospitals in Shimane prefecture, Japan under a routine clinical setting. The patients who visited the hospitals during the dispersal season of 2008 and 2009 were included in order to collect as much data as possible. Those who met the inclusion criteria and gave informed consent from the patients and their parents were examined for their cognitive function twice, once on their first visit before treatment and again on the second visit after treatment (between 7 and 14 days from the first visit). On their second visit, the effect of the treatment was evaluated by the patients themselves with a questionnaire. In the cognitive function test, the patients as well as their parents were told that the test was not for the evaluation of their intelligence or achievement and their scores were not for comparison with others.

Evaluation of the treatment effect using a questionnaire

The patients subjectively evaluated the treatment effect to answer the questionnaire on their second visit. The question items included overall satisfaction with the drug, concentration in classroom, symptoms, inconvenience in daily life, and nighttime sleep. A 7-point scale from 0 (most positive answer) to 6 (most negative answer), setting 3 for the middle, was used. The questionnaire also included a question related to compliance.

Evaluation of cognitive functions using TMT

The Trail Making Test (TMT) was used for the evaluation of cognitive functions. TMT was originally developed to evaluate higher brain functions by testing the following elements: attention allocation, visual search, rapidity of eye-guided hand movement and information processing time [20, 21]. The test consists of two parts, A and B. Time used for the following tasks by individual patients is evaluated. In part A, the patient draws a line to

connect the numbers 1 to 25 in ascending order. In part B, twelve Japanese Hiragana characters from the top (‘a’ to ‘shi’) as well as the numbers from 1 to 13 are used, and the patient is asked to connect them alternately in ascending order. Prerecorded noises were played during the test.

Statistical analysis

The characteristics of the patients were summarized with descriptive statistics. The distribution of the answers of the question items was provided in percentages. Spearman rank-correlation coefficient was used to measure the association between the answers of each question. We interpreted a coefficient of 0.1 as weak correlation, 0.3 as moderate correlation and 0.5 as strong correlation, according to the correlation criteria used in psychometric analysis described by Cohen [22]. The mean TMT scores of pre- and post- treatment were calculated and compared by using a paired t-test. For this comparison, a two-sided test was employed and the significant level was set at 5%.

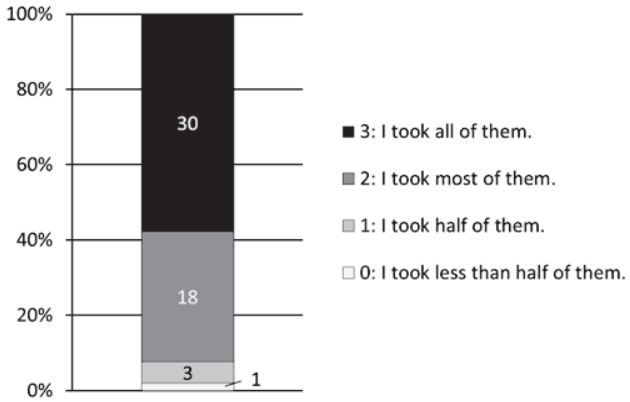
RESULTS

A total of 54 participants were included in this study. Of these, 28 patients were boys (52.8%)

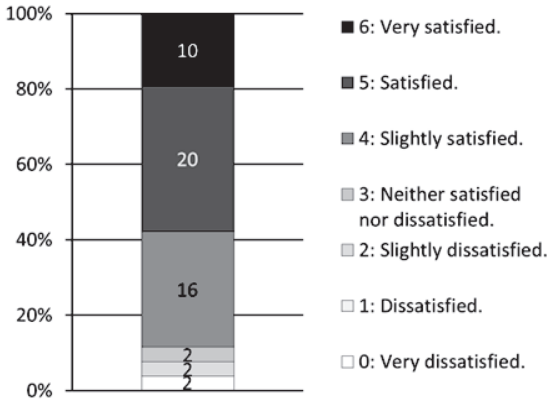
Table 1. Characteristics of the patients (n=54)

Items	Categories	
Gender (n=53)	Male	28 (52.8)
Age (n=53)	Mean ±SD	10.1 (2.5)
	Median [Range]	9 [6, 16]
School year (n=53)	First graders in elementary school	3 (5.7)
	Second graders in elementary school	12 (22.6)
	Third graders in elementary school	11 (20.8)
	Fourth graders in elementary school	9 (17.0)
	Fifth graders in elementary school	2 (3.8)
	Sixth graders in elementary school	5 (9.4)
	First graders in junior high school	5 (9.4)
	Second graders in junior high school	5 (9.4)
	Third graders in junior high school	1 (1.9)
Severity at the initial administration (n=54)	Most severe	0 (0.0)
	Severe	7 (13.0)
	Moderate	47 (87.0)
Severity at the second visit (n=52)	Most severe	0 (0.0)
	Severe	4 (7.7)
	Moderate	30 (57.7)
	Mild	17 (32.7)
	Restored	1 (1.9)
Concomitant drugs (n=30)	pranlukast hydrate	7 (23.3)
	Pimerolast potassium	9 (30.0)
	Fluticasone propionate	10 (33.3)
	Clarithromycin	2 (6.7)
	Levocabastine hydrate	1 (3.3)
	Tranilast	1 (3.3)

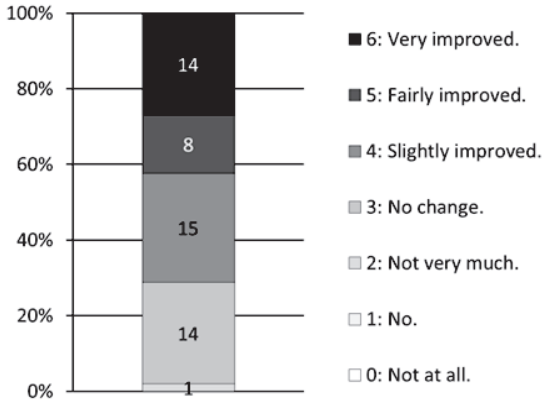
Note: Categories are shown in "n (%)"



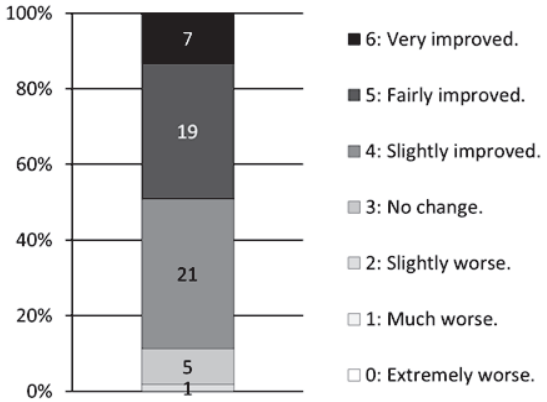
Q1. Did you take all of the medicine given?



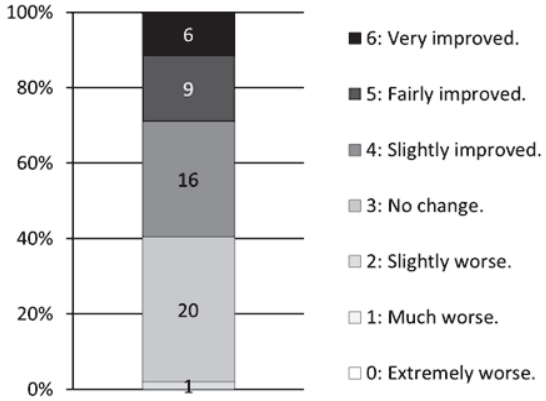
Q2. Are you satisfied with the drug you had taken?



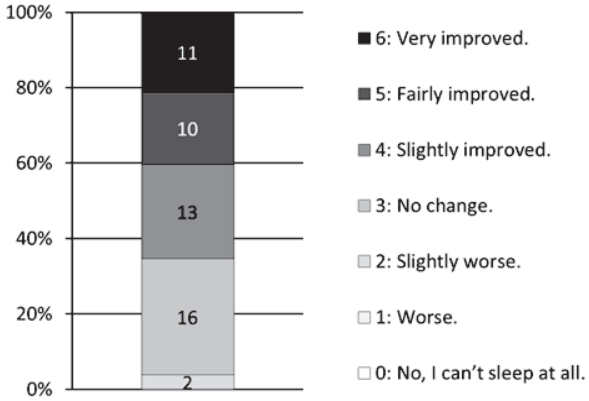
Q3. Did your concentration in class improve than before you take the medicine?



Q4. In general, did your symptoms improve than before you take the medicine?



Q5. Did your troubles in daily life improve than before you take the medicine?



Q6. Did your night-time sleep than before you take the medicine?

Fig. 1. Evaluation of therapeutic effect by the patients

and 42 patients (72.9%) were elementary school students. The mean age of the patients was 10.1 years. For the severity of the disease, 47 patients were diagnosed as moderate (87.0%) and seven patients were diagnosed as severe (13.0%) [Table 1].

Fig. 1 shows the results of the questionnaire. The overall proportion of positive answers ('Slightly satisfied/ Slightly improved', 'Satisfied/Improved' and 'Very satisfied/Very improved') to the question of overall satisfaction with the drug, concentration in classroom, symptoms, inconvenience in daily life, and night-time sleep were 88.5%, 71.1%, 88.7%, 60.0% and 65.3%, respectively. For the question about patient's compliance, 92.3% of them answered he/she took 'most' or 'all' of the medication given. All questions except for night-time sleep showed moderate to strong correlations to each other [Table 2].

The mean score (seconds) of TMT before and after the treatment was 49.8 and 40.9 for part A and 97.6 and 79.4 for part B, all of which were statistically significant (P<0.0001) [Table 3]. No adverse effect was reported.

Table 2. Correlation coefficients of the answers of each question item

	Satisfaction with the drug (Q2)	Concentration in class (Q3)	Symptom improvement (Q4)	Inconveniences in daily life (Q5)	Night-time sleep (Q5)
Satisfaction with the drug (Q2)	1.00	0.40	0.59	0.54	0.27
		0.0029	<.0001	<.0001	0.0546
	52	52	52	52	52
Concentration in class (Q3)	0.40	1.00	0.34	0.72	0.29
	0.0029		0.0013	<.0001	0.036
	52	52	52	52	52
Symptom improvement (Q4)	0.59	0.34	1.00	0.55	0.08
	<.0001	0.013		<0.0001	0.5933
	52	52	52	52	52
Inconveniences in daily life (Q5)	0.54	0.72	0.55	1.00	0.41
	<.0001	<.0001	<.0001		0.0024
	52	52	52	52	52
Night-time sleep (Q6)	0.27	0.29	0.08	0.41	1.00
	0.0546	0.036	0.5933	0.0024	
	52	52	52	52	52

Note: Upper: Spearman rank-correlation coefficient, Middle: P value, Lower: n

Table 3. Transition of TMT (n=53)

Item			Time point	
			Before the treatment	After the treatment
TMT Part A (seconds)	Measurements	Mean (SD)	49.8 (17.5)	40.9 (16.0)
		Median (Min, Max)	48 [21, 110]	40 [18, 93]
		n	53	53
	Change	Mean (SE)	-	-8.9 (1.5)
		Median (Min, Max)	-	-8 [-41, 26]
		n	-	53
		P- value*	-	<0.0001
TMT Part B (seconds)	Measurements	Mean (SD)	97.6 (47.9)	79.4 (30.1)
		Median (Min, Max)	88 [35, 297]	75 [25, 190]
		n	53	53
	Change	Mean (SE)	-	-18.3 (3.9)
		Median (Min, Max)	-	-15 [-178, 21]
		n	-	53
		P-value*	-	<0.0001

* *P*-values were calculated by a paired t-test

DISCUSSION

We conducted a well-controlled observational study to evaluate whether decreased cognitive function in school-age patients with Japanese cedar pollinosis would be improved with fexofenadine hydrochloride by using TMT, a simple test to assess cognitive function.

In the evaluation of the treatment effect, nearly 90% of the patients reported that their symptoms had improved and gave positive answers to the question about their satisfaction with the drug. Also, improvement in classroom concentration, inconvenience in daily life, and night-time sleep were reported among approximately 60% to 70% of the patients. The correlation coefficients between the question items, except that of night-time sleep, were considered to be comparatively high. Although it should be noted that these correlations do not indicate causality, our results suggest that improvement of the symptoms by fexofenadine hydrochloride contributed to improvement of concentration in class and reduction in inconvenience in daily life. Satisfaction with fexofenadine hydrochloride had the highest correlation with symptom improvement, which possibly indicates that symptom improvement is a major factor affecting treatment satisfaction. A survey of ten-thousand adult patients with pollinosis also revealed a high satisfaction with fexofenadine hydrochloride and more than 80% of responses were positive (‘very satisfied’ and ‘somewhat satisfied’)[23]. A higher satisfaction rate was observed in patients with fexofenadine hydrochloride treatment compared to patients treated with other antihistamines [23].

CNS depressant action of antihistamines should be considered as well as its symptom improvement effect when evaluating the factors that influence satisfaction with a given antihistamine. Fexofenadine hydrochloride, the drug used in this study, shows no CNS depressant action, as its histamine H1 receptor occupancy in human brain is quite low. Treatment with an antihistamine having CNS depressant action may lower treatment satisfaction even if patients are satisfied with the symptom improvement effects.

Significant improvement of TMT scores was observed at post-treatment compared to baseline, suggesting that cognitive function was impaired by the symptoms and that the treatment with fexofenadine hydrochloride may restore cognitive functions. TMT contains various elements, including paying attention to the objects on the test paper, drawing lines to connect the objects and using numbers and words (Hiragana characters) alternately, and thus is used widely as the evaluation of higher brain dysfunction in therapeutic areas including cranial nerve and rehabilitation. Our findings demonstrated that scores could react to the effect of the symptoms and treatment on the cognitive functions of patients with pollinosis. It is, however, unclear how the symptoms of the patients could lower the scores, compared to the scores of patients with no symptoms which weren’t measured in this study. In addition, further investigation is necessary to determine how much TMT scores should improve to be a clinically significant improvement for the patient. Fexofenadine hydrochloride, an antihistamine having no CNS depressant action, was used in this study, and thus TMT scores will show a different tendency than if a drug with CNS depressant actions is used. Further investigations are also required to examine how much the depressant effect of antihistamines on CNS may influence TMT score. This study is an observational study designed to be conducted as simply as possible in routine clinical practice by not setting up controls, therefore, these issues need to be investigated further.

CONCLUSION

Antihistamines that do not show depressant action on the central nervous system, and which actually attenuate symptoms as well, are strongly recommended for the treatment of pollinosis if cognitive function improvement is the main purpose of the treatment. This study suggests that symptoms of pollinosis disturb the cognitive functions of the patients, and that cognitive functions are restored by treatment with fexofenadine hydrochloride.

CONFLICTS OF INTERESTS

The authors have no conflicts of interest to declare in relation to this study.

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