

Efficacy of Desloratadine and Levocetirizine in Patients with Cedar Pollen-Induced Allergic Rhinitis: A Randomized, Double-Blind Study

Syuji Yonekura^a Yoshitaka Okamoto^{a,b} Daiju Sakurai^a Tomohisa Iinuma^a
Toshioki Sakurai^{a,c} Riyo Yoneda^a Junya Kurita^a Toyoyuki Hanazawa^a Yohei Kawasaki^d

^aDepartment of Otolaryngology, Head and Neck Surgery, Graduate School of Medicine, Chiba University, Chiba, Japan; ^bChiba Rosai Hospital, Chiba, Japan; ^cChiba Cancer Center, Chiba, Japan; ^dBiostatistics Section, Clinical Research Center, Chiba University Hospital, Chiba, Japan

Keywords

Desloratadine · Levocetirizine · Japanese cedar pollen · Allergic rhinitis · Environmental challenge chamber · Randomized · Placebo controlled · Crossover · Double-blind study

Abstract

Background: No comparative study of antihistamines that differ in structural system has been conducted in allergic rhinitis. **Objective:** This was a randomized, double-blind, crossover comparative study to verify the efficacy of antihistamines that differ in structural system. **Methods:** A total of 50 patients with moderate or more severe Japanese cedar pollen-induced allergic rhinitis were randomized to receive either placebo, desloratadine 5 mg (a tricyclic), or levocetirizine 5 mg (a piperazine). One dose of the study drug was orally administered at 9 pm on the day before a pollen exposure test, which was performed for 3 h (9 a.m. to 12 p.m.) to assess symptoms in an environmental challenge chamber (ECC). Nasal and ocular symptoms were compared at an airborne pollen level of 8,000 grains/m³. The primary endpoint was mean total nasal symptom score (TNSS) from 120 to 180 min in the ECC. Subjects with a difference of ≥ 1 in TNSS between 2 drugs

were extracted to the relevant drug-responsive group. **Results:** The difference in TNSS from placebo was -2.42 ($p < 0.0001$) with levocetirizine and -1.66 ($p < 0.01$) with desloratadine, showing that both drugs were significantly more effective than placebo in controlling symptoms, but with no statistically significant difference between the 2 drugs. There were 12 subjects in the desloratadine-responsive group and 24 subjects in the levocetirizine-responsive group, with no contributor to response was detected. **Conclusion:** Levocetirizine tended to control nasal symptoms more effectively than desloratadine. However, the response to each antihistamine varied among individuals and the predictors to the response are unknown. **Clinical Trial Registration number:** UMIN ID: UMIN000029653.

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Introduction

Allergic rhinitis is an upper respiratory disease with an increasing prevalence in many countries and largely involves the lower respiratory tract as well [1–7]. Allergic rhinitis is not directly fatal, but is shown to greatly affect sleep, learning, and work productivity, and to reduce the

quality of life of patients [8, 9]. Also in Japan, the prevalence of allergic rhinitis is increasing, and Japanese cedar pollen (JCP)-induced allergic rhinitis, among all causes, afflicts more than 26% of the population [7].

Second-generation antihistamine H1 receptor antagonists are widely used in the treatment of allergic rhinitis due to rapid onset and long duration of action as well as high safety, and play a central role in symptomatic treatment [10]. Oral antihistamines are taken by some patients on a regular basis throughout the pollen season, but are actually often taken on an as-needed basis when symptoms worsen.

Due to the availability of a wide variety of antihistamines, the most suitable type is selected for individual patients in view of regimen, efficacy, side effects, costs, and so on. Nonetheless, poor responses to some antihistamines are experienced in clinical settings. Differences in structural system of drugs can partly affect the responses. To date, however, no comparative study of antihistamines that differ in structural system has been conducted, and therefore there is no established evidence of differences in their efficacies.

A crossover study is ideal to compare responses to different antihistamines in the same patients, but is not feasible in the field. More specifically, field testing in pollen-induced allergic rhinitis, which has to be performed during the pollen season, has limitations in the conduct and interpretation of results due to weather, fluctuations in airborne pollen levels, and differences in patient conditions. An environmental challenge chamber (ECC) at Chiba University, which has a capacity of up to 50 persons and exposes subjects to a given pollen level under the same conditions in all seasons, ensures that clinical studies can be conducted in a reproducible manner. This ECC has been used in crossover studies with antihistamines [11, 12]. The present study was designed as a 3-arm, randomized, double-blind, crossover comparative study with desloratadine (a tricyclic), levocetirizine (a piperazine), as well as placebo, to verify the efficacy of different antihistamines among groups consisting of the same subjects.

Methods

Study Subjects

Volunteers with JCP-induced allergic rhinitis aged 20–65 years were included in the study. A diagnosis of JCP-induced allergic rhinitis required nasal symptoms over at least last 2 years and a class 2 or higher serum level of JCP-specific immunoglobulin E (IgE) as determined with ImmunoCAP (SRL, Inc., Tokyo). The IgE level was classified into class 6 (≥ 100 UA/mL), 5 (50.0–99.9 UA/mL), 4 (17.5–49.9 UA/mL), 3 (3.50–17.4 UA/mL), 2 (0.70–

3.49 UA/mL), 1 (0.35–0.69 UA/mL), or 0 (≤ 0.34 UA/mL). In addition, subjects had no nasal symptoms during the pollen-free season when this study was conducted and had moderate or more severe symptoms during screening exposure in the ECC. Moderate severity was defined as mean TNSS (total nasal symptom score) at 3 time points (120, 150, and 180 min) after the start of pollen exposure ≥ 3 when measured as described in “Assessment method” of the *Study Design* section below.

Exclusion criteria were allergy to desloratadine and/or levocetirizine; allergic rhinitis symptoms requiring treatment during the pollen-free season; nasal disease that may complicate study-related assessments; serious concurrent illness under treatment, including respiratory disease, heart disease, liver disease, kidney disease, diabetes mellitus, and autoimmune disease; pregnant or possibly pregnant; lactating; treated for allergy within 2 weeks before the start of the study (e.g., antihistamines, antileukotrienes, nasal spray steroids, oral steroids, Chinese medicine, immunotherapy); and considered by a physician to be inappropriate for the safe conduct of the study.

Sample Size

Based on the results of previous studies at this site, it was assumed that the mean score in the placebo group would be 5 with a standard deviation of approximately 1.5 [11, 12]. A mean score difference of approximately 1 between the desloratadine or levocetirizine group and the placebo group was considered to show a greater efficacy in the drug group than in the placebo group. Given the crossover design of the present study and based on the assumption that the between-group difference would be 1 score with a SD of 1.5, the necessary sample size was calculated to be 50 subjects with a power of 90% at a 2-sided significance level of 5%, even if a conservative correlation coefficient of 0 was used. Since the correlation coefficient was actually expected to be >0 , the target sample size of 50 subjects was determined, with a few dropouts taken into account.

Study Design

Study Schedule and Drug Allocation

This study was a randomized, placebo-controlled, crossover, double-blind study conducted during the JCP-free season from November 2017 to January 2018. In Chiba, cedar pollen dispersion is usually observed from February to April. In 2018, the dispersion started on February 14 and ended on April 21. Subjects were selected on the basis of medical interview, blood collection, and screening pollen exposure test. One dose of the study drug was orally administered at 9 pm on the day before a pollen exposure test, which was performed to assess symptoms. A different study drug was administered after at least 2 weeks of washout for a total of 3 sessions of exposure and assessment. Subjects were randomized through a central registration system at the Data Management Section, Clinical Research Center, Chiba University Hospital with 2 stratification factors: moderate ($3 \leq$ symptom score <6) or more severe ($6 \leq$ symptom score ≤ 12) in the total nasal symptom assessment during screening exposure; and JCP-specific IgE (class 2 or 3, or class 4 or higher).

Study Drugs

Second-generation antihistamine H1 receptor antagonists desloratadine 5 mg tablets (Desalex[®]) and levocetirizine 5 mg tablets (Xyzal[®]) were used, and lactose (Satisfake 02[®]) was used as placebo. These were filled into capsules for drugs (DBcaps[®]; size D)

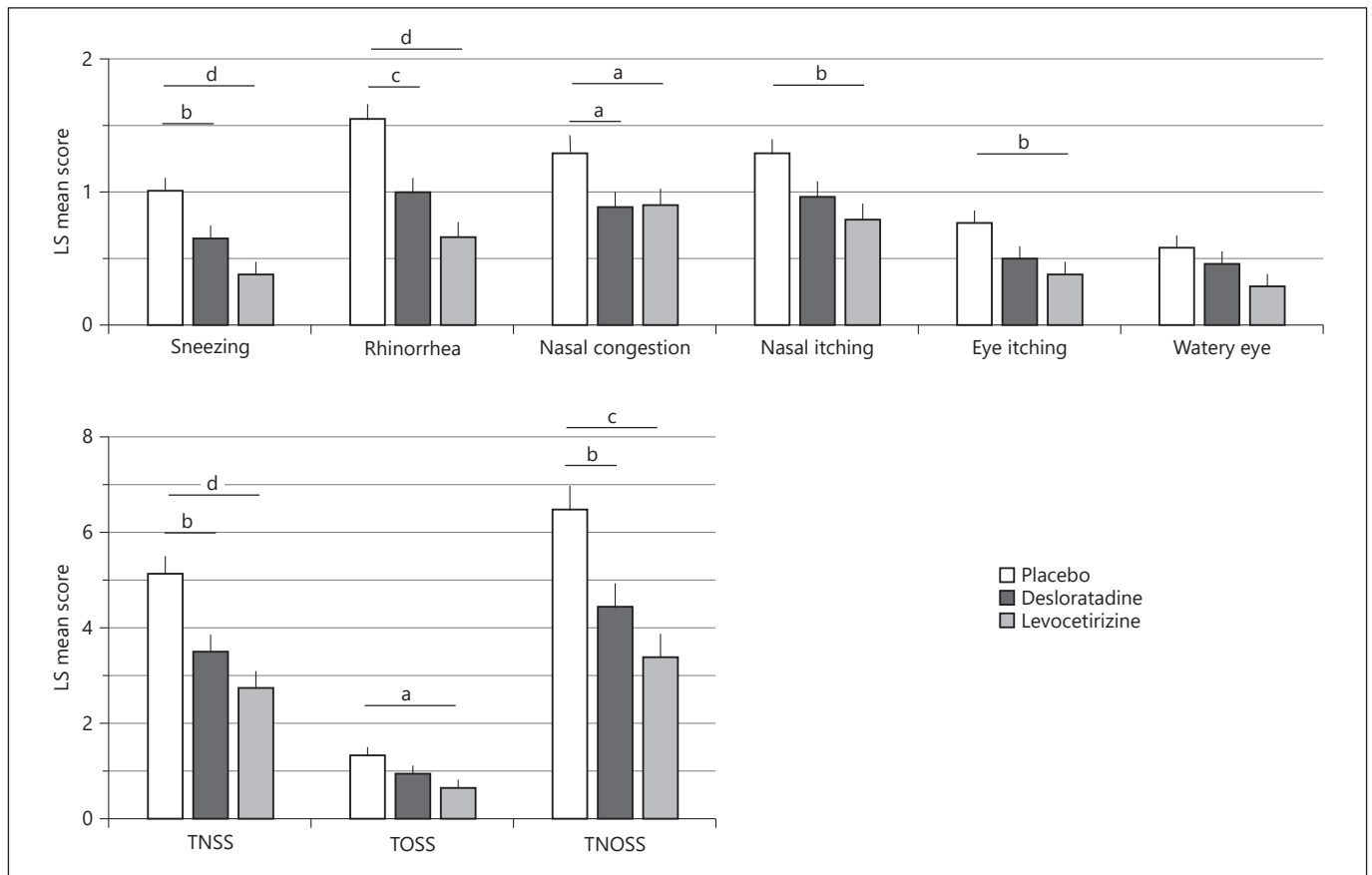


Fig. 1. Comparison of mean symptom scores from 120 to 180 min in ECC. Values represent means $\pm$ SE. a: $p < 0.05$, b: $p < 0.01$, c: $p < 0.001$, d: $p < 0.0001$ vs. placebo group. TNSS, total nasal symptom score; TOSS, total ocular symptom score; TNOSS; total nasal-ocular symptom score; LS mean, least square mean.

so that they could be used in a double-blind manner in terms of color, shape, odor, weight, and so on. The drugs were encapsulated at the Division of Pharmacy, Chiba University Hospital.

Exposure Test in the ECC

The exposure test was performed in the ECC at Chiba University. The standard airborne level of JCP is 8,000 grains/m³, based on the results of previous performance tests [13], and it has been demonstrated that symptoms reach maximum severity after approximately 2–3 h of exposure. The pollen exposure test was performed for 3 h from 9 am to 12 pm to assess symptoms. Fifty-six pollen sensors (SHINYEI Technology Co., Ltd., Japan) were installed in the ECC to monitor airborne pollen levels every 5 min. Rescue medication was prohibited until 9 pm on the day of symptom assessment, but was allowed after 9 pm and on the following day. Fexofenadine 60 mg (Allegra®) was used as rescue medication. In principle, all drugs with an antiallergic effect, including antihistamines, were prohibited during the remainder of the study period.

Assessment Method

Symptoms were recorded in an electronic database via a mobile terminal (Willcom Co., Ltd., Japan) in the ECC. In the ECC, symptoms were assessed every 30 min in terms of sneezing, rhi-

norrrhea, nasal congestion, nasal itching, eye itching, and watery eye on a 4-point scale (0: none, 1: mild, 2: moderate, 3: severe). Symptoms were also recorded in a diary 3, 6, and 9 h after discharge from the ECC (3, 6, and 9 pm, respectively). The total score of 4 nasal symptoms was TNSS (0–12), the total score of 2 ocular symptoms was total ocular symptom score (0–6), and the total of TNSS and total ocular symptom score was total nasal-ocular symptom score (0–18). In addition, the frequency of sneezing and the frequency of nose blowing were recorded. The primary endpoint was mean TNSS at 120, 150, and 180 min in the ECC.

In addition, the difference in TNSS (mean at 120, 150, and 180 min) after oral administration of desloratadine versus levocetirizine was calculated for individual subjects for comparison. Subjects with ≥ 1 lower TNSS after administration of desloratadine were extracted to the desloratadine-responsive group. To the contrary, subjects with ≥ 1 lower TNSS after administration of levocetirizine were extracted to the levocetirizine-responsive group.

Adverse Events

A diary was delivered to all participants to record adverse events and related treatments throughout the study period.

Statistical Analysis

All enrolled and randomized subjects who received at least one dose of the study drug, visited the study site at least once during the intervention period, and had efficacy data were included in the full analysis set (FAS). All subjects in the FAS, excluding those who used prohibited concomitant medication (e.g., drugs with an anti-allergic effect other than the study drugs), were included in the per-protocol set.

For the background characteristics of subjects, the number and proportion of subjects in each category were presented for nominal and ordinal variables. The mean and SD (or the median and range) were presented for continuous variables. For the mean nasal and ocular symptom scores, frequency of sneezing, and frequency of nose blowing, the between-group difference and its 95% CI were calculated using an analysis of variance model with treatment and time as fixed effects and corrected by the Tukey-Kramer procedure in consideration of multiplicity. The response to each drug in individual subjects was compared using 2-sample *t* test, Fisher's exact test, or Wilcoxon rank sum test, as appropriate. The number and proportion of subjects with an adverse event were tabulated for each group to evaluate the safety.

The statistical analyses were performed at a 2-sided significance level of 5%. All study data were managed at the Clinical Research Data Center, Chiba University Hospital, and statistical analyses were performed at the Biostatistics Section, Clinical Research Center. SAS 9.4 (Windows 64-bit) software was used for the analyses.

Results

Background of Participants

Eighty-one patients were screened, and the following patients were excluded: 3 patients with a class 1 or lower level of JCP-specific IgE, 19 patients with a mean TNSS at 120, 150, and 180 min <3, and 1 patient who withdrew for personal reasons. Of the remaining 58 patients, 50 with high TNSS were selected as subjects for analysis. The background characteristics of the 50 randomized participants are presented in Table 1. The study population consisted of 30 females (60.0%) and 20 males (40.0%), with a mean age of 44.9 years. None of the participants were associated with treatment-requiring allergic rhinitis, except for that due to cedar pollinosis. The level of JCP-specific IgE was class 2 or 3 in 31 subjects (62.0%) and class 4 or higher in 19 subjects (38.0%). Of these subjects, 3 used prohibited concomitant medication (chlorpheniramine). These 3 subjects missed an exposure test once in the placebo, desloratadine, and levocetirizine groups, respectively. In addition, 1 and 2 subjects missed an exposure test in the placebo and desloratadine groups, respectively, for personal reasons. As a result, there were 48 subjects in the placebo group, 47 subjects in the desloratadine group, and 49 subjects in the levocetirizine group.

Table 1. Background characteristics of subjects

Background	Total (n = 50)
Gender, n (%)	
Female	30 (60.0)
Male	20 (40.0)
Age, years, mean (SD)	44.9 (10.7)
Age of onset of JCP-induced AR, years, mean (SD)	23.5 (10.1)
Severity of JCP-induced AR, n (%)	
Very severe	15 (30.0)
Severe	22 (44.0)
Moderate	13 (26.0)
Medial history of allergic disease, n (%)	
Bronchial asthma	
Past	4 (8.0)
Current	0 (0)
Atopic dermatitis	
Past	4 (8.0)
Current	1 (2.0)
Food allergy	
Past	1 (2.0)
Current	9 (18.0)
Perennial AR	
Past	3 (6.0)
Current	7 (14.0)
Total IgE, IU/mL, mean (SD)	224.9 (368.9)
Level of JCP-specific IgE, n (%)	
Class 2, 3	31 (62.0)
Class ≥4	19 (38.0)

JCP, Japanese cedar pollen; AR, allergic rhinitis; IgE, immunoglobulin E.

Comparison of Symptom Scores at 120–180 min in the ECC (FAS)

Symptom scores (least squares mean scores) at 120–180 min in the ECC are compared in Figure 1 and Table 2. In the desloratadine group versus placebo group, sneezing score, rhinorrhea score, nasal congestion score, TNSS, and total nasal-ocular symptom score were significantly lower in the desloratadine group. In the levocetirizine group versus placebo group, all parameters except watery eye were significantly lower than in the levocetirizine group. In the desloratadine group versus levocetirizine group, levocetirizine tended to be more effective than desloratadine; however, no statistically significant differences were observed in any parameters.

Change in each Nasal Symptom Score over Time (FAS)

All symptom scores increased after the start of pollen exposure, and the symptoms persisted after discharge from the ECC.

Table 2. Comparison of mean symptom scores from 120 to 180 min in ECC

Symptom	Comparison	LS mean	LS mean difference	Adjusted LS mean 2-sided 95% CI	Adjusted <i>p</i> value
Sneezing	D vs. P	0.65 vs. 1.01	−0.36	−0.67 to −0.04	<0.05
	L vs. P	0.38 vs. 1.01	−0.63	−0.94 to −0.31	<0.0001
	L vs. D	0.38 vs. 0.65	−0.27	−0.59 to 0.04	0.10
Rhinorrhea	D vs. P	0.99 vs. 1.55	−0.56	−0.93 to −0.19	<0.01
	L vs. P	0.66 vs. 1.55	−0.89	−1.26 to −0.52	<0.0001
	L vs. D	0.66 vs. 0.99	−0.34	−0.70 to 0.03	0.084
Nasal congestion	D vs. P	0.89 vs. 1.31	−0.42	−0.81 to −0.03	<0.05
	L vs. P	0.91 vs. 1.31	−0.40	−0.79 to −0.01	<0.05
	L vs. D	0.91 vs. 0.89	0.02	−0.37 to 0.41	0.99
Nasal itching	D vs. P	0.96 vs. 1.29	−0.33	−0.70 to 0.05	0.10
	L vs. P	0.79 vs. 1.29	−0.49	−0.87 to −0.12	<0.01
	L vs. D	0.79 vs. 0.96	−0.17	−0.54 to 0.21	0.54
Eye itching	D vs. P	0.50 vs. 0.77	−0.27	−0.59 to 0.05	0.12
	L vs. P	0.38 vs. 0.77	−0.39	−0.71 to −0.07	<0.05
	L vs. D	0.38 vs. 0.50	−0.12	−0.44 to 0.20	0.65
Watery eye	D vs. P	0.46 vs. 0.58	−0.12	−0.43 to 0.18	0.61
	L vs. P	0.29 vs. 0.58	−0.29	−0.60 to 0.01	0.063
	L vs. D	0.29 vs. 0.46	−0.17	−0.48 to 0.13	0.38
TNSS	D vs. P	3.50 vs. 5.16	−1.66	−2.86 to −0.45	<0.01
	L vs. P	2.73 vs. 5.16	−2.42	−3.62 to −1.22	<0.0001
	L vs. D	2.73 vs. 3.50	−0.77	−1.97 to 0.44	0.29
TOSS	D vs. P	0.95 vs. 1.35	−0.40	−0.96 to 0.16	0.22
	L vs. P	0.66 vs. 1.35	−0.69	−1.25 to −0.13	<0.05
	L vs. D	0.66 vs. 0.95	−0.29	−0.85 to 0.27	0.44
TNOSS	D vs. P	4.46 vs. 6.50	−2.04	−3.67 to −0.41	<0.01
	L vs. P	3.40 vs. 6.50	−3.09	−4.72 to −1.47	<0.0001
	L vs. D	3.40 vs. 4.46	−1.05	−2.68 to 0.57	0.28

ECC, environmental challenge chamber; LS mean, least square mean; D, Desloratadine; L, Levocetirizine; P, Placebo; JC, Japanese cedar; TNSS, total nasal symptom score; TOSS, total ocular symptom score; TNOSS, total nasal-ocular symptom score.

For sneezing (Fig. 2a), the score was significantly lower in the desloratadine group at 90 and 120 min and in the levocetirizine group at all time points from 30 min to 6 pm as compared with the placebo group.

For rhinorrhea (Fig. 2b), the score was significantly lower in the desloratadine group at all time points from 30 to 180 min and in the levocetirizine group at all time points from 30 to 6 pm as compared with the placebo group. In the desloratadine group versus levocetirizine group, the score was significantly lower in the levocetirizine group at 60 and 90 min.

For nasal congestion (Fig. 2c), the score was significantly lower in the desloratadine group at 150 min and in the levocetirizine group at 30 min and all time points

from 150 min to 3 pm as compared with the placebo group.

For nasal itching (Fig. 2d), the score was significantly lower in the levocetirizine group at all time points from 30 to 180 min as compared with the placebo group.

For TNSS (Fig. 2e), the score was significantly lower in the desloratadine group at 30 min and all time points from 90 to 180 min and in the levocetirizine group at all time points from 30 min to 3 pm as compared with the placebo group.

Total Frequency of Sneezing and Nose Blowing (FAS)

The total frequency of sneezing and nose blowing is compared in Figure 3. The frequency was significantly

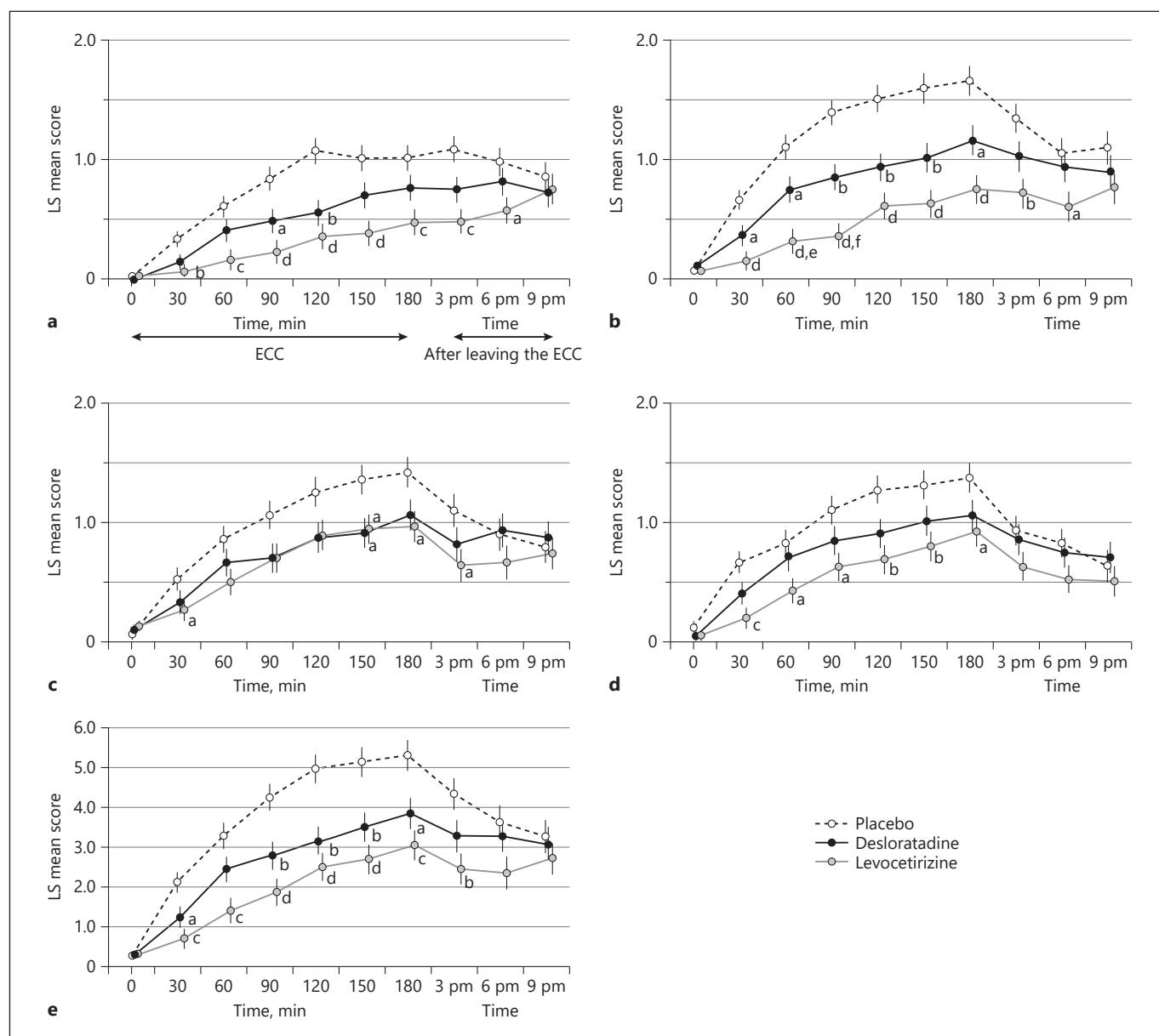


Fig. 2. Change of nasal symptom scores. Sneezing (a), rhinorrhea (b), nasal congestion (c), nasal itching (d), total nasal symptom score (e). Values represent LS means $\pm$ SE. a: $p < 0.05$, b: $p < 0.01$, c: $p < 0.001$, d: $p < 0.0001$ vs. placebo group. e: $p < 0.05$, f: $p < 0.01$, vs. desloratadine. ECC, environmental challenge chamber; LS mean, least square mean.

lower in the desloratadine group in the ECC and in the levocetirizine group in the ECC, after discharge from the ECC, and in total as compared with the placebo group.

Comparison of Response to each Drug in Individual Subjects (FAS)

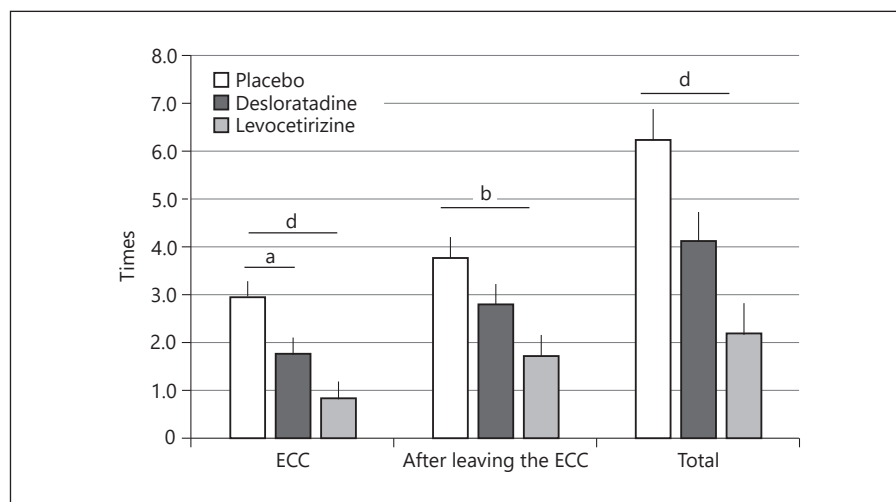
There were 12 subjects in the desloratadine-responsive group and 24 subjects in the levocetirizine-responsive

group. The background factors and symptom scores were compared between these 2 groups, but no factors were found to affect the response to either drug (Table 3).

Adverse Events

In this study, adverse events occurred in 5 subjects: influenza in 2 subjects and cold symptoms in 3 subjects. No adverse events were related to the study drug, and no serious adverse events were reported.

Fig. 3. Comparison of total frequency of sneezing and nose blowing. Values represent mean numbers $\pm$ SE. a: $p < 0.05$, b: $p < 0.01$, d: $p < 0.0001$. ECC, environmental challenge chamber.



Discussion

Desloratadine and levocetirizine are antihistamines most widely used in the treatment of allergic rhinitis. Both drugs were used in the present study, because they are used once daily and virtually nonsedating due to low occupancy of histamine H1 receptors in the brain [14]. Desloratadine, a major active metabolite of loratadine, is a tricyclic antihistamine with a high affinity for histamine H1 receptors [15]. On the other hand, levocetirizine, the R-enantiomer of racemic cetirizine, is a piperazine antihistamine with approximately 2-fold higher antagonistic activity on histamine H1 receptors than cetirizine [16].

In this study, desloratadine and levocetirizine significantly reduced nasal symptoms compared with placebo. As represented by the TNSS, which was the primary endpoint, however, levocetirizine (-2.42 , $p < 0.0001$ vs. placebo) tended to be more effective than desloratadine (-1.66 , $p < 0.01$ vs. placebo) as compared with placebo, but with no statistically significant difference between the 2 drugs. Several studies comparing the efficacy of the 2 antihistamines, desloratadine versus levocetirizine have been reported. In all studies comparing histamine-induced skin redness, wheal, and itch, it was reported that levocetirizine was significantly more effective in controlling the responses than desloratadine [17–22]. Some comparative studies reported the efficacy of desloratadine and levocetirizine on nasal symptoms in patients with allergic rhinitis [19, 23–27]. A previously reported comparative study in an ECC also showed similar results [23], but the difference between the 2 drugs was not as great in the present study as previously reported. The previous study in an ECC [23] was a parallel-group compar-

ative study involving 140 subjects in the desloratadine group, 141 subjects in the levocetirizine group, and 92 subjects in the placebo group, and differed from the current study in many ways, including the study population, study methods, and assessment methods. In 2 crossover studies in 23 patients with allergic rhinitis in a natural environment [19] and in 16 patients on nasal adenosine monophosphate challenge [26], interestingly, it was reported that the efficacy for nasal symptoms was similar between desloratadine and levocetirizine. Most comparative studies of desloratadine versus levocetirizine to evaluate the efficacy on nasal symptoms in allergic rhinitis are small-scale trials involving at most 30 participants [19, 24–27], except the study by Day et al. [23]. Only a few studies reported higher efficacy on nasal symptoms of levocetirizine compared with desloratadine [23, 24]. Study designs varied among these previous studies, and therefore we cannot conclude that sufficient evidence has been established on the compared clinical effects of the 2 drugs. The present study was a crossover clinical trial involving 50 patients (3 groups; a total of 150 person-days) and was the largest-scale crossover comparison study of 2 drugs for pollen-induced allergic rhinitis conducted to date. The use of a pollen exposure chamber was novel. We consider that the results of this study, including even placebo effects, have high precision as well as high reproducibility. Not only overall comparison of 2 drugs but also direct comparison of differences in benefits of each drug among individual subjects provided important new findings in this study.

While antihistamines are generally considered not to be so effective for nasal congestion [28], both desloratadine and levocetirizine were significantly more effective

Table 3. Comparison of responsive groups

Backgrounds	Responsive group		<i>p</i> value
	desloratadine (<i>n</i> = 12)	levocetirizine (<i>n</i> = 24)	
Gender, <i>n</i> (%)			
Female	5 (41.7)	16 (66.7)	0.18
Male	7 (58.3)	8 (33.3)	
Age, years, mean (SD)	43.8 (9.6)	44.7 (11.2)	0.83
Age of onset of JCP-induced AR, years, mean (SD)	27.7 (10.1)	23.3 (9.7)	0.22
Severity of JCP-induced AR, <i>n</i> (%)			
Very severe	5 (41.7)	7 (29.2)	0.43
Severe	5 (41.7)	11 (45.8)	
Moderate	2 (16.7)	6 (25.0)	
Medial history of allergic disease, <i>n</i> (%)			
Bronchial asthma			
None	11 (91.7)	22 (91.7)	1.0
Past	1 (8.3)	2 (8.3)	
Current	0 (0)	0 (0)	
Atopic dermatitis			
None	11 (91.7)	22 (91.7)	1.0
Past	1 (8.3)	2 (8.3)	
Current	0 (0)	0 (0)	
Food allergy			
None	9 (75.0)	21 (87.5)	0.42
Past	0 (0)	1 (4.2)	
Current	3 (25.0)	2 (8.3)	
Perennial AR			
None	8 (66.7)	19 (79.2)	0.28
Past	0 (0)	2 (8.3)	
Current	4 (33.3)	3 (12.5)	
Total IgE, IU/mL, mean (SD)	270.1 (333.9)	206.6 (369.3)	0.62
JCP-specific IgE, UA/mL, mean (SD)	23.8 (18.5)	30.0 (53.9)	0.62
Symptom score in ECC (from 120 to 180 min), mean (SD)			
Sneezing	1.3 (1.1)	1.6 (0.9)	0.51
Rhinorrhea	2.0 (0.8)	2.1 (0.7)	0.75
Nasal congestion	2.0 (0.8)	2.0 (0.9)	0.96
Nasal itching	2.0 (0.9)	2.1 (0.8)	0.64
TNSS	7.3 (3.0)	7.8 (2.4)	0.61

JCP, Japanese cedar pollen; AR, allergic rhinitis; IgE, immunoglobulin E; ECC, environmental challenge chamber; TNSS, total nasal symptom score.

for nasal congestion than placebo, with no significant difference between the 2 drugs. In a study using nasal polyp specimens, it was reported that desloratadine inhibited the release of inflammatory mediators such as ECP, LTC₄, and tryptase from tissues [29]. On the other hand, levocetirizine has been reported to have anti-inflammatory effects such as inhibition of eosinophil migration and expression of intercellular adhesion molecules [30, 31]. Since many of these reports were from *in vitro* experiments at high drug concentrations, future studies are necessary to determine whether these antiallergic and anti-

inflammatory effects can be observed *in vivo*; nonetheless, the effects might underlie the efficacy of the antihistamines for nasal congestion in the present study.

Different responses to the different antihistamines in the same subjects are a very interesting result. In the current study, there were 12 subjects in the desloratadine-responsive group and 24 subjects in the levocetirizine-responsive group. The differences were analyzed based on the background factors of subjects, but unfortunately, no significant contributor to response to either antihistamine was detected. Since many antihistamines with the

same structural system are on the market, the results of the present study should not be interpreted to show that the difference in structural system is directly linked to the difference in response. Also in this study, however, it was clear that some patients may have different responses to different drugs. Responses to drugs are related with individual differences in absorption, distribution, metabolism, and other steps, and pharmacogenetics has shed light on the mechanisms in recent years [32, 33]. Gene polymorphisms related with responses to antihistamines have been reported. In studies in chronic urticaria, it was reported that ORAI1, component 5a receptor 1 (C5AR1), or FCER₁A gene polymorphisms were associated with the efficacy of nonsedating antihistamines, including desloratadine [34–36]. It was also reported that mutations in LyS¹⁹¹ and Thr¹⁹⁴ were associated with binding of levocetirizine to histamine H1 receptors [37, 38]. Individual differences in responses or adverse reactions to antihistamines remain largely to be clarified, but future progress in pharmacogenetics may be helpful.

In the current randomized, crossover, comparative study in an ECC, desloratadine, and levocetirizine significantly controlled nasal symptoms as compared with placebo, and the safety was also demonstrated. Levocetirizine tended to control nasal symptoms more effectively than desloratadine, but the response to each antihistamine varied from individual to individual. A limitation of this study is that we neither estimated cells and mediators in nasal discharges nor examined objective biomarkers such as rhinomanometric values and nasal nitric oxide levels. If any predictor of responses to antihistamines is identified, the most suitable one could be selected for individual patients before the start of treatment; however, this approach is not yet available. Given the established evidence that nasal steroids are more effective than anti-

histamines and antileukotrienes [39, 40], switching to nasal steroids is necessary for patients with a poor response to some antihistamines in clinical settings.

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Statement of Ethics

This study was approved by the Clinical Research Ethical Review Board of Chiba University Hospital (approval no. G28009) and conducted in compliance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects and the Declaration of Helsinki. All participants provided written consent after receiving a verbal and written explanation of the study.

Disclosure Statement

The authors declare no conflicts of interest associated with this manuscript.

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Author Contributions

S.Y. and Y.O.: designed the study and wrote the manuscript. S.Y.: managed the pollen exposure tests and corrected blood samples. T.I., T.S., R.Y., and J.K.: helped the pollen exposure tests. D.S. and T.H.: reviewed the manuscript. Y.K.: checked data and performed a statistical analysis. All authors concurred with the submission.

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