

The effect of cetirizine on sulfidoleukotriene production by blood leukocytes in children with allergic rhinitis

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Twelve children with allergic rhinitis due to monosensitivity to *Dermatophagoides pteronyssinus* (Dp) took part in a placebo-controlled, double-blind, crossover study to evaluate the effect of cetirizine, a second-generation, nonsedating H₁-blocker-type antihistamine, on sulfidoleukotriene releasability by blood leukocytes and to determine its correlation with clinical findings and nasal challenge scores. Sulfidoleukotriene release by blood leukocytes was determined by the cellular allergen stimulation test (CAST), which measures leukotriene (LT)C₄, LTD₄, and LTE₄, all in one assay. Compared to placebo, cetirizine significantly ($P < 0.05$) decreased daily symptom scores of nasal discharge, nasal itching, and sneezing, as well as the number of sneezings after nasal challenge with the antigen, without alleviating nasal obstruction ($P > 0.05$). It also suppressed both early ($P < 0.05$) and late skin reactions to intradermal tests. Although cetirizine did not influence *in vitro* sulfidoleukotriene production by blood leukocytes with buffer or anti-IgE ($P > 0.05$), it substantially reduced the release of these mediators upon challenge with Dp antigen. Furthermore, there was a high correlation between the number of sneezes after challenge and the amount of sulfidoleukotriene released in nine patients ($r = 0.78$; $P < 0.01$). It is concluded that the amount of sulfidoleukotrienes produced by blood leukocytes *in vitro* may reflect the nasal hyperreactivity of the patient, and that cetirizine, which is highly effective in the treatment of allergic rhinitis, owes part of its effect to inhibition of sulfidoleukotriene releasability by blood leukocytes in children.

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Antihistamines have been the mainstay of treatment for allergic rhinitis ever since they were first introduced for clinical use in the 1940s. Cetirizine, a second-generation, nonsedating, H₁-receptor antagonist, is the active metabolite of the first-generation, H₁-receptor antagonist, hydroxyzine (17, 18). In addition to its usual H₁-receptor antagonist effect, cetirizine is claimed to have anti-inflammatory and inhibitory effects on mediator release (5, 12, 15, 20, 22), both of which may contribute to its role in the treatment of allergic disorders. The anti-inflammatory effect is more pronounced on eosinophils (3, 14). Although cetirizine is a promising agent for the treatment of allergic disorders (21), we have only limited knowledge of its efficacy and mechanism of action in children (1, 4, 11, 23).

In a double-blind, placebo-controlled, crossover study in children with perennial allergic rhinitis due

to monosensitivity to the *Dermatophagoides pteronyssinus* (Dp) antigen, we tried to determine the clinical efficacy of cetirizine and its effect on nasal provocation tests and on sulfidoleukotriene (sLT) releasability by blood leukocytes.

Material and methods

The protocol for this study was approved by the ethics committee of Hacettepe University (Ankara, Turkey), and each parent gave written, informed consent before entry to the study.

Patients

Twelve subjects with perennial allergic rhinitis, ranging in age from 5.3 to 14.0 (mean 9.1 ± 0.8) years, were included in the study. All subjects had symp-

toms of rhinitis throughout the whole year and had a 4+ cutaneous reaction to the intradermal injection of 0.02 ml of 50 AU/ml Dp antigen (3) and negative cutaneous reactions to the intradermal injection of other common inhalant and food antigens. However, because of the cross-reactivity, a 2+ to 4+ reaction was obtained with the *Dermatophagoides farinae* antigen, although the magnitude of the reaction was always smaller than that elicited by Dp. Patients were excluded if they had any disorder other than allergic rhinitis or mild asthma, including any infectious episode during the month before the study and during the whole study period. Although 10 of the 12 patients had accompanying mild asthma, each patient had an FEV₁ value above 80% of the predicted value and was not on any regular medication. No subject had received any form of specific immunotherapy. All medications, including antihistamines, topical corticosteroids, and cromolyn sodium, were discontinued beginning 1 month before the study period. Salbutamol was allowed on an on-demand basis, and only one patient needed salbutamol (once) during the whole study period.

Investigations

Nasal provocation tests. All patients were tested between 8 and 9 a.m., to avoid possible circadian variations, by the same investigator at each study period. A volume of 10 µl of Dp antigen was adsorbed on paper disks 4 mm in diameter. These paper disks were placed in the anterior surface of nasal turbinates in both nares. The number of sneezings was recorded for the following 8 h. Paper disks were not removed but were allowed to be expelled by sneezing reflexes and mucociliary action.

Determination of sLT releasability by blood leukocytes. For determination of sLT releasability by blood leukocytes (unpurified buffy coat cells), a newly developed commercially available kit, CAST-ELISA (cellular allergen stimulation test-enzyme-linked immunosorbent assay) (Bühlmann Laboratories AG, Allschwil, Switzerland) was used. The test is described in detail elsewhere (2, 6). In brief, the assay is based on the fact that a single monoclonal antibody detects not only leukotriene (LT)C₄, but also its two metabolites, LTD₄ and LTE₄, with equal sensitivity and specificity. Oxidative metabolism of LTC₄ to LTD₄ and LTE₄ occurs quite rapidly, and the CAST thus measures all of the sLTs that are produced upon cell stimulation by an allergen. sLT production is sensitized and markedly enhanced by addition of interleukin(IL)-3 to the cells. In the CAST assay, three sLT values are determined:

- 1) the background HACM buffer (Hepes buffer with 1 mM Ca²⁺ and 1 mM Mg²⁺) value, which is taken as the negative control
- 2) the positive control value, yielded by stimulation with a monoclonal anti-IgE antibody, Le27, at a concentration of 0.1 µg/ml
- 3) the value yielded by the putative antigen (in this experiment Dp) at a standard concentration of 10 ng/ml.

The absolute sLT level (pg/ml) was found by subtracting the HACM value from the sample value.

All samples in CAST-ELISA are run as duplicates. If the two values fall within 10% confidence intervals of each other, the results are considered acceptable, and the average of two values is taken as the final result.

Study design

Patients were studied in three consecutive phases, a run-in period, and drug and placebo periods, during November and December 1993. During each period, patients were instructed to keep a diary of their nasal symptoms. Symptoms of nasal congestion, nasal discharge, and itching were rated according to the following scale: 0 – none (not present), 1 – mild (occasionally present, not troublesome), 2 – moderate (frequently present, annoying), and 3 – severe (continually present, interfering with activities or sleep). The number of sneezings was rated on a number scale: 0 – none; 1 – 1–5 sneezes per day; 2 – 6–10 sneezes per day; 3 – >10 sneezes per day. Each symptom was rated individually, and then a cumulative score was obtained.

After a 15-day run-in period, patients underwent a thorough physical examination and whole blood counts, differential counts, urinalysis, radiographs of the paranasal sinuses, and pulmonary function tests (Body box 6200 Sensor Medics Company, CA, USA) were obtained. Stools were examined for the presence of parasites. These tests were repeated at the end of each study period. Blood was drawn for determination of total IgE (Abbott Laboratories, IL, USA) and specific IgE (Melja Diagnostics, Kassel, Germany) levels against the Dp antigen. At the end of each study period, an additional 2 ml of blood was drawn to measure sLT releasability by blood leukocytes by CAST-ELISA. On the same day, intradermal skin tests were performed with the Dp antigen (50 AU/ml, Greer Laboratories Inc, NC, USA), histamine dihydrochloride (0.1 mg/ml Allergologisk Laboratories A/S, Denmark), and saline buffer (as the control), and early reactions at 15 min and late reactions at 5 h (if present) were transferred onto millimetric papers using transparent adhesive tape. Nasal provocation tests were performed the next day. At the end of the run-in period, patients were divided randomly into two groups. One group

received placebo and the other cetirizine (Zyrtec[®], UCB Pharma, Belgium) 10 mg at a single dose daily for 7 days. The patients were advised to receive their medications at 8 a.m. every day. After a week of daily treatment, they came for a second visit and underwent the same experimental procedure. Then a washout period of 1 week was allowed, and the crossover medication (drug or placebo) was taken daily for a subsequent week, after which tests were repeated for the third time. Intradermal tests and CAST-ELISA were performed 1 h after the last dose of the drug at each visit.

Compliance

Compliance was reinforced by asking the same parent to give the study medication to the patient every morning. Drug consumption was assessed by counting the number of tablets at the end of each study period.

Adverse effects

Adverse effects were followed from responses to a questionnaire in the diary cards which covered possible central nervous system, gastrointestinal, skin, and anticholinergic effects.

Statistical analysis

The Wilcoxon paired samples *t*-test and covariance analysis were used for the statistical evaluation of the results. Values are expressed as mean $\pm$ standard error of the mean (SEM).

Results

The ages of the patients ranged from 5.3 to 14.0 years with a mean of 9.1 ± 0.8 years. Some characteristics and means of total IgE and RAST tests are shown in Table 1. Counting of the tablets at the end of each study period showed that each patient consumed all the medications that were given, thus showing 100% compliance.

At the beginning of the study, all patients had physical examination findings consistent with allergic rhinitis, including nasal discharge, nasal mucosa paleness, and hypertrophy of the lower turbinates. Thorough physical examination was otherwise normal. Stool examinations in all patients consistently failed to reveal the presence of parasites.

The results of white blood cell counts and differential counts performed manually by a hematologist on a Wright-stained peripheral blood smear did not show any difference between any two study periods ($P > 0.05$) (data not shown). Nor did the parameters

Table 1. Characteristics of patients

Patient no.	Sex	Age (years)	Total IgE (IU/ml)	Dp (RAST U/ml)
1	F	5.6	3003	> 17.5
2	M	7.5	71	5.0
3	M	9.0	134	2.6
4	M	9.0	298	1.1
5	F	6.5	651	> 17.5
6	F	14.0	320	> 17.5
7	M	10.0	1954	> 17.5
8	F	5.3	364	13.2
9	M	11.2	2857	> 17.5
10	F	11.2	519	13.4
11	M	8.0	198	> 17.5
12	M	12.5	209	0.4
Mean		9.1 ± 0.8	881 ± 311	11.7 ± 2.0

in pulmonary function tests show any difference between the study periods ($P > 0.05$) (data not shown).

None of the patients reported adverse effects during the study periods.

Effect of cetirizine on nasal symptoms

Daily scores of nasal congestion were 1.27 ± 0.20 , 0.88 ± 0.25 , and 1.31 ± 0.24 in run-in, placebo, and drug periods, respectively. There was no statistically significant difference between any two ($P > 0.05$). Although nasal congestion did not differ, significant differences were detected in the other three parameters of nasal symptoms. Sneezing score, nasal discharge, nasal itching, cumulative score, and the number of sneezes after nasal challenge were significantly lower after cetirizine than in either the placebo or run-in period ($P < 0.05$) (Table 2).

Effect of cetirizine on skin tests

None of the patients revealed a positive result to the intradermal injection of the control solution. Results of the skin tests are summarized in Table 3. Compared to placebo, cetirizine suppressed both wheal and flare reactions to histamine and Dp significantly

Table 2. Mean of daily symptom scores and number of sneezes after nasal challenge

Symptom score	Means		
	Run-in	Cetirizine*	Placebo
Sneezes	1.13 ± 0.19	0.40 ± 0.17	1.41 ± 0.19
Discharge	0.79 ± 0.24	0.19 ± 0.06	0.99 ± 0.24
Itching	0.63 ± 0.16	0.08 ± 0.03	0.67 ± 0.18
Cumulative score	3.60 ± 0.42	2.17 ± 0.50	4.58 ± 0.52
No. of sneezes after challenge	12.25 ± 2.96	0.92 ± 0.43	10.08 ± 3.28

* Each symptom score, cumulative score, and number of sneezes after challenge were significantly lower in cetirizine group than in run-in and placebo periods ($P < 0.05$).

Table 3. Effects of cetirizine and placebo on agonist-induced wheal-and-flare reactions of patients

	Surface area (mm ²)					
	Run-in		Cetirizine*		Placebo	
	w**	f***	w	f	w	f
Histamine	142±44	1543±351	66±21	452±84	147±50	1040±263
Dp	102±27	1229±271	44±13	221±61	105±30	835±208

* Both wheal and flare reactions in the cetirizine group were significantly reduced compared to placebo and run-in periods ($P < 0.01$). ** Wheal; *** Flare.

($P < 0.01$). Although placebo also seemed to cause a significant reduction in the flare reaction compared to the run-in period ($P < 0.01$), the reduction caused by cetirizine (82%) was significantly greater than that caused by placebo (32%) ($P < 0.01$). In three patients, a late reaction in the form of induration was observed 5 h after the intradermal injection of the antigen. The surface areas of the induration in run-in/cetirizine/placebo periods were as follows: 1054/364/625, 950/336/1165, and 280/180/525 mm².

Effect of cetirizine on sLT releasability by blood leukocytes

In the run-in period, the amount of sLT released upon challenge with anti-IgE was significantly higher than that obtained with HACM buffer ($P < 0.01$). Similarly, Dp-induced sLT release was greater than the amount recovered by anti-IgE stimulation ($P < 0.01$). Results are summarized in Fig. 1. sLT releasability of blood leukocytes upon challenge with HACM buffer did not differ between any two periods ($P > 0.05$). The same was true for the values obtained upon challenge with the anti-IgE antibody Le27 ($P > 0.05$). On the other hand, in stimulation with the Dp antigen, the sLT concentration was significantly lower after cetirizine treatment than in both

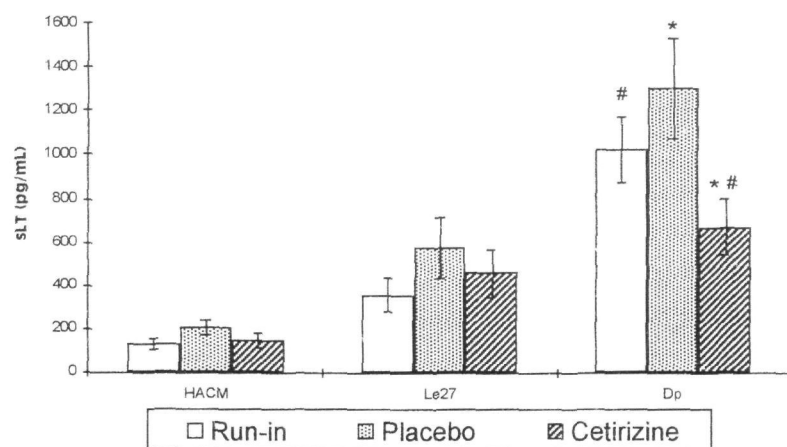


Fig. 1. sLT releasability of blood leukocytes (pg/ml) upon challenge with HACM (buffer), Le27 (anti-IgE), and Dp. * and # denote statistical significance at $P < 0.01$; $n = 12$.

run-in and placebo periods ($P < 0.01$ for both). There was no difference between the placebo and run-in periods ($P > 0.05$).

Correlation analysis

In our study, no component of blood leukocytes, including eosinophil and basophil numbers, showed any correlation with the amount of sLT produced (data not shown). The correlation between IgE values and sLT concentrations at the run-in period was weak. For HACM stimulation, $r = 0.42$; for Le27, $r = 0.26$, and for Dp, $r = 0.28$ ($P > 0.05$ for each). A similar observation was made of the correlation between RAST results and sLT concentrations.

At the run-in period, there was no correlation between the sLT concentration obtained by HACM stimulation and Le27 stimulation ($r = 0.18$). On the other hand, the correlation between Le27- and Dp-induced sLT releasability was quite high ($r = 0.74$, $P < 0.05$).

The number of sneezes after nasal challenge with the Dp antigen showed a very high correlation with Dp-induced sLT releasability in nine patients ($r = 0.78$, $P < 0.01$) (Fig. 2). Symptom scores obtained from the records of the patients failed to show such a correlation with sLT concentrations. More importantly, the correlation between the number of sneezes after challenge and IgE or RAST values was at best weak and statistically insignificant ($r = 0.41$ and 0.31 , respectively) ($P > 0.05$ for both). The size of the wheal-and-flare reactions did not show any correlation with either sLT concentration or the number of sneezes after challenge.

Discussion

Because of its anti-inflammatory properties and suppressive effects on mediator release, cetirizine has

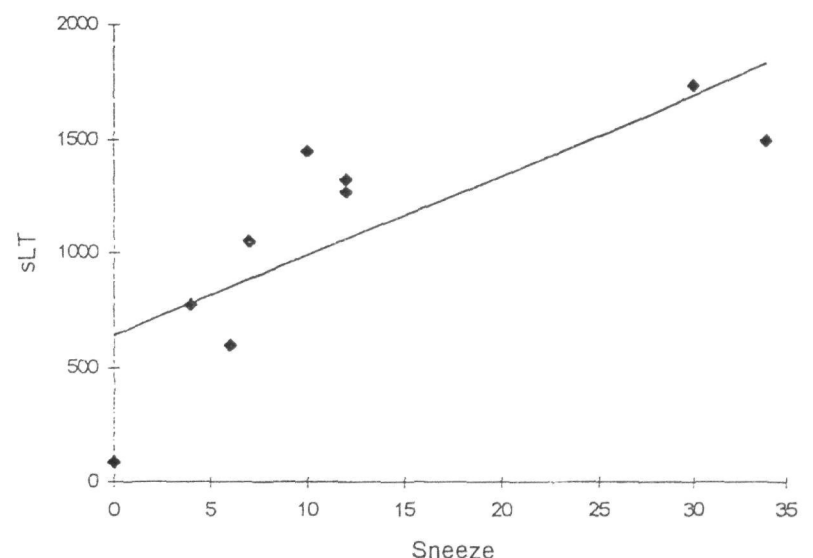


Fig. 2. Correlation of sLT releasability by blood leukocytes with number of sneezes after nasal challenge with Dp antigen in nine patients ($r = 0.78$, $P < 0.01$).

attracted much attention in the treatment of allergic diseases. However, there are only a few studies of children. This study confirms the clinical efficacy of cetirizine and indicates that cetirizine possesses antiallergic properties in addition to its well-known anti-H₁-receptor activity. Although a few studies have shown the inhibitory effect of cetirizine on leukotriene production, they were conducted in adult populations (12, 15).

Cetirizine was highly effective in relieving symptoms of allergic rhinitis, as reflected by a significant decrease in the cumulative symptom scores after treatment. Although the number of sneezes, nasal itching, and nasal discharge all improved, cetirizine failed to relieve symptoms of nasal congestion. In this regard, its behavior was similar to that of other antihistamines (9). After nasal challenge with Dp, the number of sneezes was reduced significantly by cetirizine. In seven patients, it dropped to 0.

Compared with placebo, cetirizine significantly reduced the mean wheal-and-flare response induced by intradermal tests with histamine and Dp after 7 days of treatment (Table 3). The fact that cetirizine significantly reduced the wheal-and-flare reaction induced by histamine injection *in vivo* confirms the anti-H₁ property of this drug. A well-known activity of cetirizine, suppression of the late-phase response, was also apparent in this study, although the small number of patients did not allow statistical analysis. This effect is reported to be independent of cetirizine's anti-H₁ activity and to be due to inhibition of the recruitment of inflammatory cells, especially eosinophils, and to inhibition of mediator release (3, 13).

Our results show that cetirizine effectively blocks sLT release from blood leukocytes upon challenge with the antigen to which the patient is sensitized. However, when blood leukocytes were challenged with HACM buffer, cetirizine failed to show such an inhibitory effect. If it is assumed that the stimulation arising with HACM buffer reflects the ongoing sLT activity *in vivo*, one can conclude that cetirizine does not exert any activity on the actual *in vivo* levels of sLTs unless the cells are exposed to an antigenic stimulus intensively. Although it is well known that the amount of sLT released by basophils upon anti-IgE stimulation is far less than that elicited by the actual antigen (10), one would expect at least some inhibition of sLT release by cetirizine upon anti-IgE stimulation. Surprisingly, although it is an immunologic stimulus, cetirizine had no effect on anti-IgE-stimulated sLT release. This suggests that cetirizine may have effected the mediator release via an IgE-independent mechanism. This observation further suggests that in studies on the effect of drugs on mediator release, results should not be derived from stimulation with anti-IgE alone, but an actual anti-

gen to which the patient is sensitive must also be used.

Since there was no change in the number of leukocytes or in the differential counts during the whole study period, it is clear that this did not contribute to the inhibition of sLT release. It was previously shown that the presence of IL-3 primes only basophils for sLT release and that other leukocytes are not influenced by this mediator (10). However, some studies have also claimed that IL-3 is a positive signal for sLT release for neutrophils and eosinophils (8, 6, 19, 24). In this study, the cellular source of sLTs where the stimulation is inhibited is unclear. This apparent lack of cellular specificity of the CAST-ELISA system, which may be an inconvenience in pharmacologic studies devoted to basophils or other specific cells, may be a bonus when dealing with clinical allergy diagnosis, since it encompasses all leukocytes active in the circulation. Another clinical advantage of the CAST system shown in this study is that it measures all three sLTs in one assay. While LTC₄ is the sLT produced by cells upon challenge, it is rapidly metabolized in biologic fluids to LTD₄ and LTE₄. sLT in biologic fluids are mostly measured by high-pressure liquid chromatography or by radioimmunoassay specific for one or another sLT. These methods, although well appreciated in pharmacologic research, can be cumbersome for routine use in clinical settings. The CAST system, measuring all sLTs in one assay, seems more convenient and practical for clinical diagnosis and research.

Specific IgE and total IgE levels did not correlate with nasal challenge results. Reactions to skin tests also failed to show any correlation with sLT release and nasal challenge results. On the other hand, there was a high correlation between the number of sneezes that occurred after challenge and sLT releasability by blood leukocytes in nine patients. In fact, sLT release was the only parameter in the study that correlated with the number of sneezes observed after nasal challenge. A similar correlation was previously shown between bronchial hyperreactivity and CAST results (7). This reveals another possibility for the CAST-ELISA assay, as it allows nasal and bronchial hyperreactivity of the patients to be assessed.

In conclusion, this study showed that in children cetirizine is effective in the treatment of allergic rhinitis and that in addition to its anti-H₁-receptor activity it acts by decreasing sLT release by blood leukocytes upon challenge with the allergen. We also showed that CAST-ELISA can be useful as a convenient and practical test in clinical allergy diagnosis, especially as it may demonstrate the hyperreactivity of the patient.

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