

Levocetirizine better protects than desloratadine in a nasal provocation with allergen

Cédric Deruaz, MD, Annette Leimgruber, MD, Monika Berney, Estelle Pradervand, and François Spertini, MD *Lausanne, Switzerland*

Background: Direct comparisons of antihistamines are rare but very much needed. Newly available antihistamine preparations, levocetirizine, the R-enantiomer of racemate cetirizine, and desloratadine, an active metabolite of loratadine, have been recently released for allergic rhinitis.

Objective: We sought to compare levocetirizine and desloratadine in a nasal provocation test (NPT) with grass pollen.

Methods: Twenty-four volunteers with grass pollen allergy and a history of rhinitis were enrolled in a double-blind, placebo-controlled, crossover study. Three NPTs were performed in a dose-escalating manner during the out-of-season period 4 hours after a single dose of levocetirizine (5 mg), desloratadine (5 mg), or placebo.

Results: Differences in the mean allergen dose level (primary end point) necessary to reach the NPT threshold indicated improved protection provided by levocetirizine compared with that provided by desloratadine ($P = .02$). Sneezing and rhinorrhea were better inhibited by levocetirizine than desloratadine. Nasal congestion, as assessed by using objective methods, was not limited by either active substances or placebo. In nasal lavage fluid, IL-5, IL-8, eotaxin, and eosinophil cationic protein levels increased at 24 hours, without differences between the groups. In contrast, levocetirizine, but not desloratadine, significantly limited albumin extravasation into nasal lavage fluid in the early-phase response.

Conclusions: This study demonstrates a better overall protection of a single dose of levocetirizine compared with desloratadine in an NPT with grass pollen allergen. In contrast to late-phase inflammatory markers, which were unaffected, extravascular leakage of the early-phase marker albumin was significantly limited by levocetirizine. (*J Allergy Clin Immunol* 2004;113:669-76.)

Key words: Levocetirizine, desloratadine, nasal provocation test, acoustic rhinometry, antihistamine, nasal lavage, early allergic phase, late allergic phase

Antihistamines are first-line treatments for allergic rhinitis. By blocking histamine H₁ receptors, antihistamines relieve most of the manifestations of allergic rhinitis

Abbreviations used

AR: Acoustic rhinometry
ECP: Eosinophilic cationic protein
MCA: Minimal cross-sectional area
NPT: Nasal provocation test
PNIF: Peak nasal inspiratory flow
SQ: Standardized quality unit
VAS: Visual analog scale

(sneezing and rhinorrhea) but generally have less of an effect on nasal congestion. If the use of the first-generation antihistamines was limited by sedation and psychomotor impairment, the second generation expressed those side effects in a far lesser proportion and generally in a dose-dependent manner.¹ Levocetirizine is the R-enantiomer and the active form of cetirizine, itself an active metabolite of hydroxyzine, a first-generation antihistamine.^{2,3} Its small volume of distribution, smaller even than that of cetirizine, confers improved safety because of low hematoencephalic barrier passage and low cerebral receptor binding.⁴ Exclusion of the S-enantiomer leads not only to enhanced peripheral receptor binding compared with that of cetirizine but also to improved overall selectivity specific to the H₁ receptor.⁵ Desloratadine is a metabolite of loratadine, and at the moment, this drug has the strongest in vitro affinity for the histamine receptor,⁶ although its selectivity is relatively poor.⁷ Since the 1980s, the potential anti-inflammatory properties of the second-generation antihistamines have been debated. A growing pool of mainly in vitro studies indicates a downregulating effect of antihistamines on inflammatory mediators, but the clinical relevance of these findings remains to be demonstrated.⁸

In clinical practice antihistamines are largely used on an on-demand basis in the indication of seasonal rhinitis or conjunctivitis.⁹ The goal of this study was thus to compare the protective efficacy of a single dose of levocetirizine or desloratadine in a reproducible and sensitive experimental setting by using a nasal provocation test (NPT) with grass pollen allergen and to examine potential anti-inflammatory activity of the antihistamines on the nasal mucosa.

METHODS

Patients

Twenty-four volunteers with a history of grass pollen-induced rhinitis were enrolled in the study on the basis of the following

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Reprint requests: François Spertini, MD, Division of Allergy and Immunology, Centre Hospitalier Universitaire Vaudois, Rue du Bugnon, 1011 Lausanne, Switzerland. E-mail: Francois.Spertini@chuv.hospvd.ch

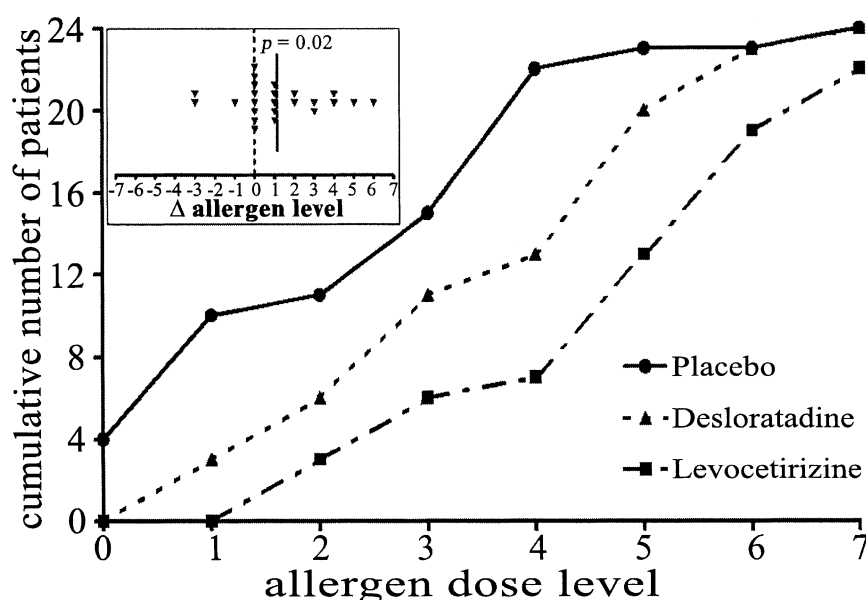
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TABLE I. Differences of allergen dose level to reach threshold between substances*

Thresholds	Placebo, mean (SD)	Levocetirizine, mean (SD)	Desloratadine, mean (SD)	Levocetirizine-placebo, mean Δ (SD), <i>P</i> value (95% CI)	Desloratadine-placebo, mean Δ (SD), <i>P</i> value (95% CI)	Levocetirizine-desloratadine, mean Δ (SD), <i>P</i> value (95% CI)
Combined	2.46 (1.87)	5.08 (1.82)	3.96 (1.73)	2.63 (2.18), <.0001 (1.58-3.67)	1.50 (1.93), <.001 (0.45-2.55)	1.13 (2.21), .020 (0.08-2.17)
Sneezes	3.46 (2.59)	7.29 (1.57)	6.42 (2.00)	3.83 (2.62), <.0001 (2.73-4.93)	2.96 (3.24), <.001 (1.59-4.33)	0.88 (1.73), .021 (0.15-1.60)
Secretions	1.17 (1.37)	3.96 (2.65)	2.58 (2.19)	2.88 (2.88), <.0001 (1.66-4.09)	1.46 (2.04), .002 (0.60-2.32)	1.38 (2.57), .015 (0.30-2.53)
PNIF	4.21 (1.86)	4.17 (1.79)	4.50 (1.47)	−0.04 (1.76), .91 (−0.78-0.70)	0.29 (1.85), .45 (−0.49-1.07)	−0.33 (1.95), .41 (−1.16-0.49)
MCA	3.79 (1.72)	4.50 (1.50)	4.33 (2.08)	0.71 (1.99), .09 (−0.13-1.55)	0.54 (2.25), .25 (−0.41-1.49)	0.17 (2.16), .71 (−0.75-1.08)

*Difference between groups was analyzed by using the paired *t* test.**FIG 1.** Cumulative number of patients reaching the global threshold according to the dose level of grass pollen allergen. *Inset.* Difference (Δ) in allergen dose level necessary to reach the threshold for each of the 24 patients between levocetirizine and desloratadine (in favor of levocetirizine, >0; in favor of desloratadine, <0). Plain vertical line, Mean Δ allergen dose level.

inclusion criteria: (1) age between 18 and 60 years; (2) a positive history of allergic rhinitis during the latest pollen season confirmed by means of either a positive skin prick test response (wheal diameter >3 mm)¹⁰ or specific IgE for grass pollen (>0.70 kU/L) as titrated with a sandwich immunoassay (UniCAP; Pharmacia Diagnostics, Uppsala, Sweden); and (3) a nasal reaction threshold of 10,000 standardized quality units (SQs)/mL grass pollen or less at the screening phase. Volunteers were excluded when any of the following criteria were present: (1) uncompensated asthma (peak expiratory flow rate <80% of normal value); (2) symptoms or signs of allergic, viral, or infectious rhinitis within 2 weeks from the NPT; (3) symptoms or signs of allergic rhinitis during the study; (4) other nasal pathology (major nasal septum deviation or major polyposis); (5) any medication that might affect the test parameters (oral or topical antihistamines, steroids or antidepressants with antiallergic properties); (6) pregnancy or absence of adequate contraception; (7) subjects with hypersensitivity to one of the components of the study;

or (8) a nonspecific nasal reaction (nasal reaction threshold reached with diluent alone at inclusion). The clinical research protocol was approved by the hospital review board, and written informed consent was obtained from each volunteer.

Study protocol

Enrolled volunteers were randomly assigned to receive a single dose of either placebo, 5 mg of desloratadine, or 5 mg of levocetirizine 4 hours before the NPTs in a crossover manner. A washout period of at least 1 week was intercalated between each NPT. Medication blinding was ensured by using opaque gelatin capsules prepared by the hospital pharmacist, who also made the randomization.

NPTs were performed as previously described.¹¹ NPTs started with the determination of nonspecific reactivity. By using a DeVilbiss atomizer, 0.2 mL of PBS was nebulized into each nostril. During the first 10 minutes after the challenge, the number of sneezes and the amount of secretions (by weighing handkerchiefs) were recorded. At

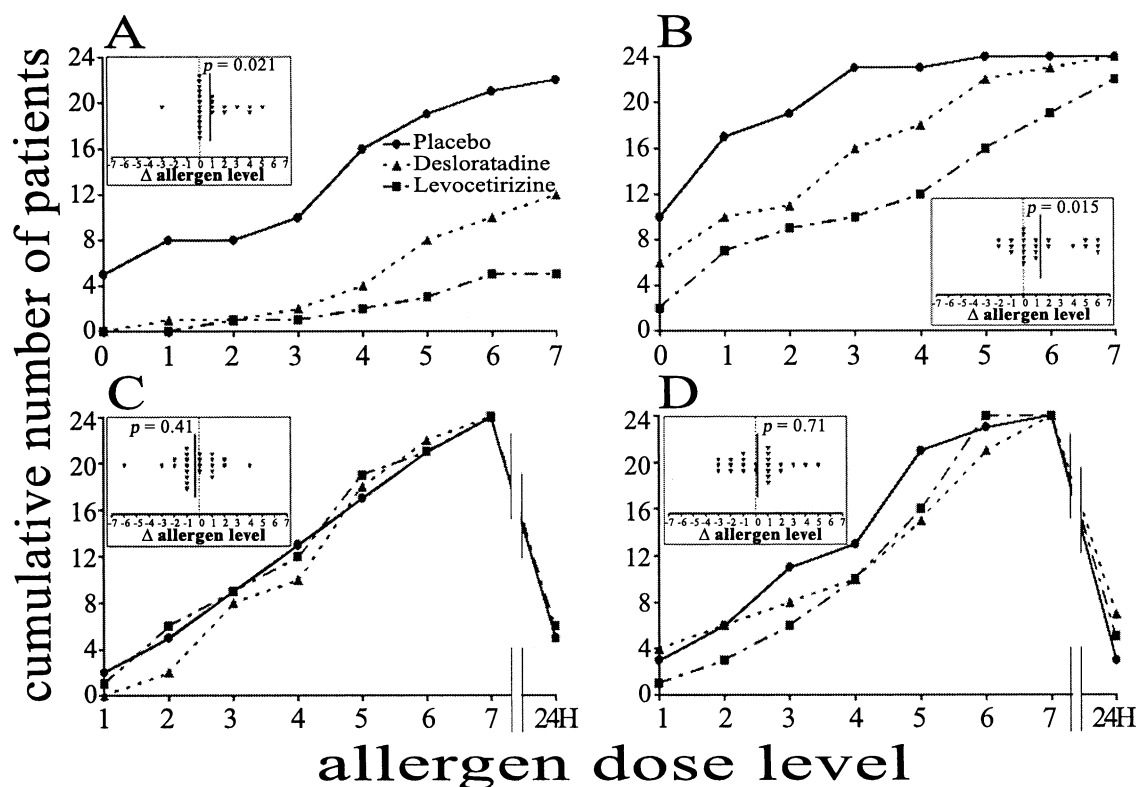


FIG 2. Cumulative number of patients reaching the threshold according to the dose level of grass pollen allergen (X axis) for sneezes (A), secretions (B), PNIF (C), and MCA (D). In Fig 2, C and D, 24H corresponds to the 24-hour time point after the NPT. Insets, results are expressed as described in Fig 1.

the end of the 10-minute observation, nasal itchiness and subjective nasal congestion were evaluated by means of a visual analog scale (VAS; score range, 0 = absent to 10 = severe). Nasal lavage was then performed, followed by the determination of peak nasal inspiratory flow (PNIF) and the minimal cross-sectional area (MCA). The same sequence was repeated at each allergen concentration every 20 minutes. The same batch of standardized allergens (mixture of 6 grass pollens; ALK Wässrig SQ; ALK-Abello, Horsholm, Denmark) was used throughout the study. Serial dilutions of the allergen extract (100, 330, 1000, 3300, 10,000, 33,000, and 100,000 SQs/mL) were prepared immediately before the NPT in PBS. PNIF measurement, MCA measurement, VAS, and nasal lavage were repeated 24 hours later.

The nasal reaction threshold (combined threshold) was reached when at least 2 of the 3 following clinical criteria were fulfilled: (1) 5 or more sneezes; (2) at least 0.5 g of nasal secretion in the first 10 minutes after the challenge; and (3) a decrease in PNIF of 40% or greater or MCA of 30% or greater of baseline values.^{11,12} The primary end point of the study was defined as the difference in allergen dose levels necessary to reach the combined threshold. Each clinical criterion and their respective thresholds were also examined separately.

Nasal congestion

Nasal congestion was evaluated by using 2 objective approaches, acoustic rhinometry (AR), which was volunteer independent, and PNIF, which was volunteer dependent. AR is based on sound reflection analysis and provides an estimate of the cross-sectional area of the nasal cavities as a function of the distance to the nostril. AR was performed with a Rhinoclack RK 100 (Stimotron Medizinische

Geräte, Wendelstein, Germany), as previously described and validated.^{11,13,14} MCA (in square centimeters) was measured at the head of the inferior turbinate of both nostrils and expressed as the mean of MCAs from both nostrils. PNIF (in liters per minute) was measured with a Youlten flow meter (Airmed; Clement Clarke International Ltd, London, England).^{14,15} The best of 3 consecutive measurements of PNIF was registered.

Nasal lavage

Nasal lavage was performed with NaCl 0.9%, according to the method of Naclerio et al.¹⁶ Five milliliters of NaCl 0.9% at room temperature was instilled into one of the nostrils, with the volunteer's neck extended at 30°. The subject was instructed not to breathe or swallow. After about 5 seconds, the subject was asked to flex his or her neck and to expel the sample of mucus and saline for collection. The procedure was then repeated in the other nostril, and the samples were pooled and stuck on ice before freezing at -80°C. Nasal lavage samples were analyzed at baseline, after the 33,000 SQ allergen challenge and after 24 hours.

Nasal cytology and inflammatory markers

Nasal lavage fluids were analyzed for cytology and albumin, tryptase, IL-4, IL-5, IL-8, eotaxin, and eosinophil cationic protein (ECP) levels. Nasal cytology was performed after nasal lavage fluid centrifugation at 2500 rpm at 4°C for 15 minutes, and 50 µL of the cell pellet was transferred to slides by using a cytospin procedure (Thermo Shandon Cytospin 3; DAKO, Glostrup, Denmark) at 500 rpm for 5 minutes. Slides were stained with a rapid staining set for cell differential counts (Diff-Quick; Dade Behring, Düringen,

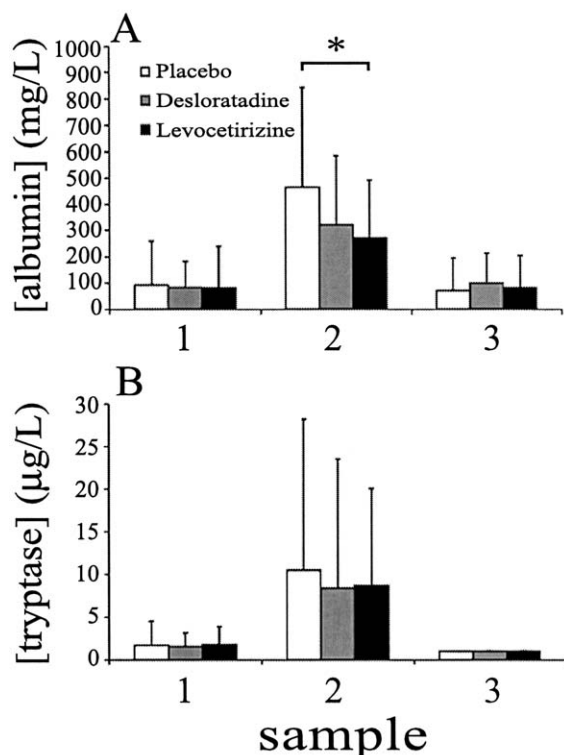


FIG 3. Concentration of albumin (**A**) and tryptase (**B**) in nasal lavage fluid at baseline (sample 1), after the dose of 33,000 SQs of allergen (sample 2), and 24 hours after the NPT (sample 3). Data are expressed as means $\pm$ SDs. *Levocetirizine versus placebo, $P < .05$.

Switzerland). The supernatant was harvested for biochemical measurement. Albumin was measured by means of nephelometry (N Antiserum anti-Albumin, Dade Behring). Tryptase and ECP were measured by using a sandwich immunoassay (UniCAP, Pharmacia Diagnostics). Standard range was 1 to 200 µg/L for tryptase and 2 to 200 µg/L for ECP. IL-4, IL-5, IL-8, and eotaxin were measured by using a solid-phase ELISA (Quantikine; R&D Systems, Minneapolis, Minn). For IL-4, a high-sensitivity quantikine assay was used, with a sensitivity of 0.13 pg/mL and a standard range of 0 to 16 pg/mL. IL-5 was measured with a sensitivity of 3.0 pg/mL and a standard range of 0 to 500 pg/mL, IL-8 with a sensitivity of 10 pg/mL and a standard range of 0 to 2000 pg/mL, and eotaxin with a sensitivity of 5.0 pg/mL and a standard range of 0 to 1000 pg/mL.

Statistical analysis

Statistical analyses were performed by using GraphPad InStat version 3.05 (GraphPad Software, San Diego, Calif). Differences between repeated measures were tested by means of ANOVA, with the Tukey post-test, the paired Student *t* test, and the 1-sample *t* test as parametric tests. Correlations between variables were assessed by using the Pearson correlation coefficient. Two-tailed statistical tests were used in each case.

RESULTS

Volunteers

Forty-three volunteers were screened. Fifteen were excluded because of allergic rhinitis ($n = 13$) to tree pollens and to perennial allergens, as detected by means of

history, skin prick tests, or both, or because of a non-specific nasal reaction at the inclusion NPT ($n = 2$). Twenty-four volunteers were initially enrolled, of whom 4 dropped out and were subsequently replaced. Three of them stopped the study after the first trial period (1 from each treatment phase) because of the discomfort generated by the NPT. One had symptoms and signs of allergic rhinitis during the tree season despite negative skin prick test responses and a negative history of allergy to tree pollens, and this patient was excluded. Twenty-four volunteers (14 women and 10 men) finally completed the whole study and were included in the analysis. The mean age was 24.8 years (range, 18-44 years).

Clinical threshold

The difference in the allergen dose level necessary to reach the combined clinical threshold was defined as the primary end point of the trial. Compared with placebo, both levocetirizine and desloratadine increased the allergen dose level by, respectively, 2.63 ± 2.18 and 1.5 ± 1.93 dose levels (mean $\pm$ SD; levocetirizine vs placebo, $P < .0001$; desloratadine vs placebo, $P < .001$; paired *t* test; Table I). Moreover, levocetirizine was significantly more efficient than desloratadine in increasing the allergen dose level necessary to reach the combined clinical threshold ($\Delta 1.13 \pm 2.21$, $P = .02$). Thirteen (54%) patients were better protected by levocetirizine, eight (33%) were equally protected by both drugs, and 3 (13%) benefited more from desloratadine (Fig 1, *inset*). The relative protection provided by levocetirizine versus desloratadine versus placebo was clearly indicated by a shift to the right in the cumulative patient response curve at threshold (Fig 1).

Individual thresholds for sneezes, nasal secretions, and nasal congestion were further examined (Fig 2; see also Fig E1 in the Online Repository for additional data; www.mosby.com/jaci). Both levocetirizine and desloratadine limited sneezes and secretions, as shown by a shift to the right in the cumulative patient response curve at threshold (Fig 2, A and B). Furthermore, levocetirizine more efficiently limited sneezes and nasal secretions than desloratadine by increasing the allergen dose level necessary to reach the threshold by 0.88 ± 1.73 dose level for sneezes ($P = .021$) and 1.38 ± 2.57 dose level for nasal secretions ($P = .015$, Table I). This corresponded to an improved protection in 10 (42%) patients compared with improvement in only 1 (4%) patient after desloratadine for sneezes. Similarly, 12 (50%) volunteers had less nasal secretions after levocetirizine compared with 5 (21%) after desloratadine (Fig 2, A and B, *insets*). In contrast, neither levocetirizine nor desloratadine were better than placebo in reducing nasal congestion at any allergen level (Table I) and at any measurement time point (Fig 2, C and D). This was demonstrated by objective measurements with PNIF or AR, which did not differ among the 3 treatment phases. Although not statistically different, VAS analysis for congestion suggested an improved protection after levocetirizine compared with that after desloratadine or placebo (data not shown). Similarly, VAS for nasal itchiness also disclosed a trend

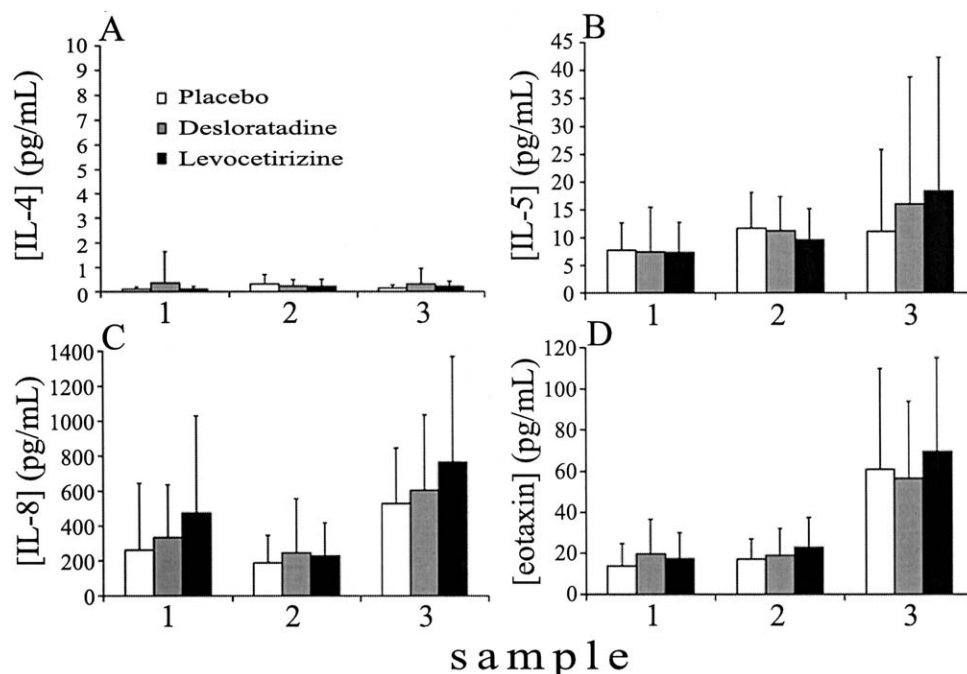


FIG 4. Concentration of the late-phase inflammatory mediators IL-4 (**A**), IL-5 (**B**), IL-8 (**C**), and eotaxin (**D**) in nasal lavage fluid at baseline (sample 1), after the dose of 33,000 SQs of allergen (sample 2), and 24 hours after the NPT (sample 3). Data are expressed as means $\pm$ SDs.

toward more limited symptoms after levocetirizine than after desloratadine.

Early allergic phase markers

As a marker of fluid extravasation, albumin concentration was markedly enhanced in nasal lavage fluid after the allergen dose of 33,000 SQs compared with the pre-NPT concentration (Fig 3, *A*). Compared with placebo, albumin extravasation was significantly limited after levocetirizine ($P < .05$) but not after desloratadine (ANOVA with the Tukey post-test). There was no evidence of albumin extravasation after 24 hours. Another early allergic phase marker, tryptase, was enhanced as expected after challenge but was unaffected by both antihistamines (Fig 3, *B*).

Late allergic phase mediators

With the exception of IL-4, the levels of which were constantly very low in the nasal lavage fluid, the levels of IL-5 and of the 2 chemokines IL-8 and eotaxin steadily increased over time to reach a maximum at 24 hours ($P < .001$ for IL-8, 33,000-SQ sample vs 24-hour sample, and for eotaxin, pre-NPT vs 24-hour sample and 33,000-SQ sample vs 24-hour sample; ANOVA with the Tukey post-test; Fig 4). Levels did not differ after placebo, levocetirizine, or desloratadine. In accordance with these data, nasal lavage fluid eosinophils increased significantly at 24 hours (compared with the pre-NPT sample), together with ECP levels (Fig 5). However, both eosinophil numbers and ECP levels at 24 hours were unaffected by

the single dose of levocetirizine or desloratadine compared with placebo ($P > .05$).

DISCUSSION

This article is the first report comparing the R-enantiomer of cetirizine, levocetirizine, with desloratadine, a metabolite of loratadine, in an NPT with grass pollen allergen. Although levocetirizine appeared superior to desloratadine in 2 recent histamine-induced skin reaction studies, skin reactivity to histamine cannot be used as a surrogate model for allergic rhinitis.¹⁷⁻²² In the present study both desloratadine and levocetirizine were administered 4 hours before starting NPTs to avoid any interference with the metabolism rate. The dose of 5 mg was the daily recommendation for both treatments in seasonal trials.^{23,24} The single-dose therapy was justified by the fact that in the indication of seasonal rhinitis or conjunctivitis, antihistamines are often used on an on-demand basis.⁹ The difference noted between the 2 antihistamines cannot be attributed to an insufficiently high dose of desloratadine because in seasonal trials doses of 5, 7.5, 10, or 20 mg of desloratadine were equally effective.^{23,24} The improved protection provided by levocetirizine was mainly a result of its effect on sneezing and nasal secretions, a well-established benefit of antihistamines. In contrast, there was only a trend toward improvement of nasal congestion after levocetirizine, a result that fits with the rather variable data obtained in other

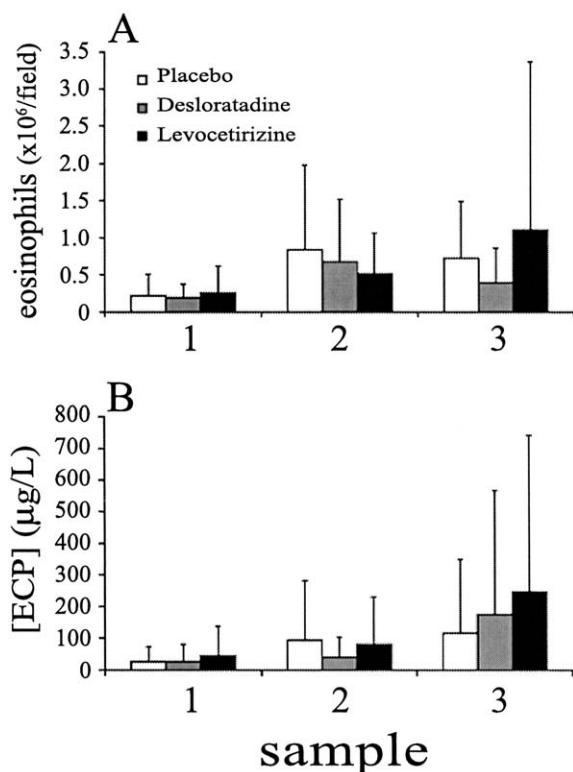


FIG 5. Eosinophil count (A) and ECP concentration (B) in nasal lavage fluid at baseline (sample 1), after the dose of 33,000 SQs of allergen (sample 2), and 24 hours after the NPT (sample 3). Data are expressed as means $\pm$ SDs.

studies on this parameter. Indeed, if a number of studies supported a role for antihistamines in limiting nasal congestion mostly after prophylactic treatment for several days before challenge,²⁵⁻²⁹ others demonstrated this effect even after a single dose.^{11,30,31} Conversely, other pre-challenge, single-dose protocols failed to demonstrate significant differences in the capacity of antihistamines to relieve nasal obstruction.^{23,32,33} Nasal congestion is in large part caused by the direct or indirect actions of early and late allergic phase mediators, such as leukotrienes, prostaglandins, cytokines, or chemokines.³⁴ Their inhibition appears indeed improbable after a single dose of levocetirizine or desloratadine, as shown here for some of them (Fig 4). This might explain the absence of effect on nasal congestion, as measured on the basis of both PNIF and AR. As shown previously by our group and others,^{11,13,14,35} the correlation between PNIF and MCA was excellent (Pearson r coefficient, 0.77 ± 0.12 [mean $\pm$ SD]), and except in 2 volunteers, there were no nonconcordant results between objective (PNIF and MCA) and subjective (VAS) measurements.

In agreement with its inhibition of nasal secretions, levocetirizine, but not desloratadine, significantly impaired albumin extravasation into nasal lavage fluid (Fig 3, A). Albumin in nasal lavage fluid can be considered as an indicator of vascular permeability.¹³ In previous studies a 2-day pretreatment with 20 mg/d cetirizine was sufficient

to significantly limit albumin extravasation into nasal fluid in comparison with placebo.³⁶ A 10 mg/d loratadine pretreatment of 7 days was generally prescribed before albumin measurement in nasal lavage fluid, without direct comparison between the 2 antihistamines.^{26,36-38} However, neither levocetirizine nor desloratadine had any effect on the expected postallergen challenge tryptase release (Fig 3, B).^{13,39,40} Accordingly, most studies could not demonstrate any inhibitory effect of antihistamines on tryptase increase in nasal lavage fluid, even after a 7-day pretreatment.^{26,36} However, a limitation of tryptase secretion was suggested by Jacobi et al⁴¹ after pretreatment for 7 days with topical azelastine (0.14 mg twice daily in each nostril) and cetirizine (10 mg daily). The absence of effect of levocetirizine and desloratadine on tryptase, a major proinflammatory mediator of activated mast cells, has to be put into perspective with the absence of effect in this study of a single dose of antihistamine on late allergic phase mediators (Fig 4).

Extensive *in vitro* studies have suggested a potential anti-inflammatory role of antihistamines, although the relevance of these observations is controversial.⁴² *In vivo*, in nasal challenges with allergen, the IL-4 increase was absent or low and unaffected by a 7-day pretreatment with fexofenadine.^{43,44} An increase in IL-5, IL-8, eotaxin, and ECP levels was generally reported.^{43,45-49} A few studies only indicated an inhibition of IL-8 secretion by astemizole in a nasal challenge with allergen and of ECP and eosinophil influx by cetirizine, loratadine, or azelastine in seasonal trials.⁵⁰⁻⁵³ In this single-dose trial, we could not demonstrate any effect of either levocetirizine or desloratadine at 5 mg on cytokine levels (IL-4 and IL-5), on chemokine levels (IL-8 and eotaxin), or on ECP secretion. This does not exclude a potential inhibitory role of antihistamines when given on a long-term basis, as suggested by seasonal trials,⁵¹⁻⁵³ but our data clearly showed that this was not the case when antihistamines were given on a single-dose basis. Our results are furthermore intrinsically consistent because the increase in the eosinophil antiapoptotic cytokine IL-5 and in the chemokines IL-8 and eotaxin were indeed associated with an enhancement in the number of eosinophils in the nasal lavage fluid after NPTs, as previously observed.^{48,54} The eosinophil increase was most often resistant to antihistamine pretreatment, even of a week's duration.^{37,55}

Seasonal studies and NPTs with allergen are different ways to demonstrate the efficacy of antihistamines. Both approaches have their advantages and disadvantages. In contrast to seasonal observations, NPTs offer excellent reproducibility and experimental control and are sensitive enough to detect small differences between antihistamines, even in relatively restricted numbers of patients.

In conclusion, we clearly demonstrated in this single-dose, placebo-controlled, double-blind, 3-way, crossover allergen provocation trial that levocetirizine offers an overall better effect in an NPT compared with desloratadine. Levocetirizine was significantly better in controlling sneezing and rhinorrhea. Although in this model objective nasal congestion was not influenced by

either of the antihistamines, levocetirizine showed a marked inhibitory effect on albumin extravasation, an early-phase marker of inflammation.

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CORRECTION

With regard to the February 2004 article entitled “Leukotrienes and 8-isoprostane in exhaled breath condensate of children with stable and unstable asthma” (2004;113:257-63): In Table I (page 258), the data pertaining to FEV₁, FEF₂₅₋₇₅, FEV₁/FVC, and 8-isoprostane were presented incorrectly. A correct version of the Table is presented here:

TABLE I. Subject characteristics, lung function data, EBC findings, and FE_{NO} values

	Stable asthma			
	Healthy subjects	Steroid-naïve	ICS-treated	Unstable asthma
N (male subjects)	19 (8)	14 (8)	13 (9)	9 (4)
Age (y)	10.0 ± 0.9*	9.3 ± 0.9*	11.3 ± 0.8*	12.2 ± 1.2*
FEV ₁ (% predicted)	97 ± 2*	93 ± 4*	92 ± 4*	82 ± 3*
FEF ₂₅₋₇₅ (% predicted)	102 ± 8*	88 ± 5*	89 ± 7*	63 ± 6*
FEV ₁ /FVC (%)	88 ± 1*	86 ± 2*	84 ± 3*	78 ± 2*
FE _{NO} (ppb)	6.0 (2.7-9.5)†	40.4 (19.3-50.5)†	14.8 (9.7-20.5)†	50.0 (17.4-59.0)†
Cys-LT(pg/mL)	4.3 (2.0-8.3)†	10.8 (9.3-13.1)†	12.7 (9.9-15.1)†	106.0 (4.2-218.0)†
8-isoprostane (pg/mL)	3.5 (2.6-7.9)†	16.2 (11.7-19.1)†	18.1 (14.8-20.5)†	29.7 (4.8-35.1)†

*Data expressed as means ± SEMs.

†Data expressed as medians and interquartile ranges (IQR).