

Lack of effect of cetirizine on early and late asthmatic response after allergen challenge

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Background: Cetirizine hydrochloride has proved effective in reducing allergic symptoms and can inhibit the infiltration of eosinophils in allergic late-phase responses in the skin. Because eosinophils are likely to play an important role in allergic late-phase reactions, we studied the effect of cetirizine on early and late asthmatic reactions and on levels of eosinophil cationic protein (ECP) in the blood after allergen challenge.

Methods: The effect of 15 mg cetirizine given twice daily was studied in 16 patients allergic to house dust mites in a double-blind, placebo-controlled study. Patients were treated for 3 weeks. Before and after treatment, bronchial challenges with house-dust mites were performed. Blood ECP levels were measured 6 hours after challenge. Methacholine provocation was performed 72 hours before and 24 hours after each challenge.

Results: Early and late asthmatic response—measured as mean maximal fall in forced expiratory volume in 1 second (FEV_1) and the provocative dose of allergen that causes a 15% fall in FEV_1 (PD_{15} allergen)—were not significantly reduced after treatment with cetirizine, compared with placebo. There was also no significant effect on the concentration of methacholine, which causes a 20% fall in FEV_1 (PC_{20} methacholine). The increase in the level of ECP in the blood after allergen challenge was reduced after cetirizine treatment, compared with placebo, but this difference was not statistically significant.

Conclusion: Eighteen days of treatment with cetirizine did not significantly reduce the intensity of the early and late asthmatic responses. (*J ALLERGY CLIN IMMUNOL* 1994;94:231-9.)

Key words: Cetirizine, late asthmatic response, eosinophil cationic protein, bronchial hyperresponsiveness

Cetirizine, the principal metabolite of hydroxyzine, is a member of a new therapeutic class of H_1 antagonists that have little or no adverse effects on the central nervous system. This can be attributed to their selectivity for the H_1 receptor and the limited capacity of these agents to cross the blood-brain barrier.¹⁻⁴

Clinical trials indicate that cetirizine hydrochloride effectively reduces symptoms in patients with allergic rhinitis and chronic urticaria.⁵⁻⁹ In asthmatic patients, cetirizine seems to effectively protect against bronchial histamine challenge and may be effective in patients with severe birch pollen asthma.¹⁰⁻¹² Dijkman et al.¹³ found a significant reduction of asthma symptoms and use of

Abbreviations used

BU:	Biologic unit
EAR:	Early asthmatic response
ECP:	Eosinophil cationic protein
FEV_1 :	Forced expiratory volume in 1 second
LAR:	Late asthmatic response
PC_{20} :	Provocative concentration causing a 20% decrease in FEV_1
PD_{15} :	Provocative dose causing a 15% decrease in FEV_1

rescue medication and an increase in morning peak flows in patients with grass pollen-induced asthma who used cetirizine during the grass pollen season.

An interesting property of cetirizine is its capacity to inhibit the infiltration of eosinophils in allergic skin response. Several studies have demonstrated that cetirizine can inhibit eosinophil migration by 60% to 84% in allergic late-phase responses.¹⁴⁻¹⁷ Eosinophils are likely to play an important role in the late-phase allergic reaction and induction of bronchial hyperreactivity.¹⁸⁻²¹

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Supported by UCB, Pharmaceutical Sector.

Received for publication July 27, 1993; revised Jan. 10, 1994; accepted for publication Feb. 4, 1994.

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0091-6749/94 \$3.00 + 0 1/154935

TABLE I. Clinical data of the patients

Patient	Age	Sex	FEV ₁	FEV ₁ (% pred.)	PC ₂₀ Meth (mg/ml)	Medication
Placebo						
1	24	F	2.96	87.40	0.52	A,B,C,S
2	17	F	3.56	86.10	0.63	B,S
3	26	F	2.32	70.40	0.43	B,C,S,T
4	20	F	3.19	84.20	0.85	C,S
5	19	M	4.30	76.10	2.42	B,S
6	22	F	3.09	98.80	0.93	A,B,C,S
7	24	M	4.05	99.30	0.83	B,C,S
8	20	M	3.99	100.00	1.66	B
Mean	21.5		3.43	87.80	1.03	
Cetirizine						
1	29	F	3.23	98.00	0.47	A,B,C,S
2	21	F	2.57	82.20	7.59	A,C
3	23	F	2.56	65.50	0.29	A,B,C,S
4	19	F	3.27	80.50	0.83	A,S
5	31	M	3.17	78.30	0.41	B,S
6	21	F	3.14	109.30	1.37	B
7	21	M	4.40	108.70	12.08	B,S
8	23	M	3.95	98.50	14.36	C,S
Mean	23.5		3.29	90.10	4.68	

A, Antihistamine; B, beclomethasone or budesonide; C, sodium cromoglycate; S, salbutamol; T, theophylline.

They contain substances such as major basic protein and eosinophil cationic protein (ECP), which may cause respiratory epithelial cell damage, characteristic of asthma.²² Bronchoalveolar lavage fluid after allergen challenge demonstrates accumulation of eosinophils and elevated ECP levels in patients showing late-phase asthmatic reactions.²⁰

The aim of our study was to determine whether 18-day treatment with cetirizine could protect against allergen-induced early- and late-phase bronchial reactions in atopic patients with asthma. We also examined the effect of cetirizine on eosinophil activation after allergen challenge.

METHODS

Patients

Sixteen atopic, nonsmoking patients with mild to moderate asthma (10 women and 6 men, aged 17 to 31 years) participated in the study. The clinical data are presented in Table I. Patients were selected on the basis of positive skin test results or elevated IgE for house dust mite allergen and increased bronchial responsiveness to methacholine inhalation ($PC_{20} \leq 16$ mg/ml). All patients had forced expiratory volume in 1 second (FEV₁) values $\geq 70\%$ of the predicted values and had shown a late-phase bronchial reaction after

challenge with house dust mites. A late-phase reaction was defined as a fall in the FEV₁ value of 15% or more from the baseline value. Patients allergic to pollen were tested outside the pollen season. None of the patients gave a history of respiratory tract infections in the previous 6 weeks or severe asthmatic attacks in the previous 6 months. None had received oral corticosteroids. All of the patients gave informed consent. The study was approved by the medical ethics committee of Asthmacenter Heideheuvel, The Netherlands.

Methacholine provocation

Methacholine chloride was prepared in 0.9% sodium chloride solution to produce a range of doubling concentrations from 0.25 to 32 mg/ml. The solutions were administered through a De Vilbiss 646 nebulizer (De Vilbiss Health Care, Inc., Somerset, Pa.) with a gauged output of 0.13 mg/ml. The nebulizer was mounted to a valve box with an aerosol filter. The nebulization time was 30 seconds, during which the patient was instructed to breathe quietly. The test was started with inhalation of a phosphate buffer aerosol. Before the inhalation, three measurements of vital capacity and FEV₁ were performed with the portable electronic Printer Spirometer II (Micro Medical Ltd., Rochester, Kent, England). Calibration of the spirometer was performed every 2 weeks. No adjustments were necessary. After each concentration, the FEV₁

value was measured. The provocative concentration of methacholine causing a 20% decrease in FEV_1 (PC_{20}) was derived by linear interpolation.

Two PC_{20} methacholine ratios were used to study the treatment effect: the PC_{20} before bronchial challenge after treatment/ PC_{20} before challenge before treatment (ratio 1) and the PC_{20} after bronchial challenge after treatment/ PC_{20} after challenge before treatment (ratio 2).

Inhalation of house dust mites

Allergen solutions were prepared from stock solutions of *Dermatophagoides pteronyssinus*, diluted in phosphate-buffered saline solution with 0.03% human serum albumin and containing 0.5% phenol (Diephuis Laboratories, Groningen, The Netherlands) to produce a range of fivefold increasing concentrations from 80 to 10,000 biological units (BU)/ml. The allergen solutions were administered through a De Vilbiss nebulizer mounted to a valve box with an aerosol filter (output, 0.13 mg/ml). The patients were instructed to breathe quietly during 1 minute for each dose. Increasing doses were given at 15-minute intervals. The challenge procedure was terminated when the FEV_1 value fell 15% or more below the baseline value. After the last inhalation, FEV_1 was recorded at 10-minute intervals for the first hour and hourly thereafter for 12 hours.

The early asthmatic response (EAR) was characterized by the maximum percentage decrease in FEV_1 from initial value during the first hour after allergen challenge; for the late asthmatic response (LAR), the maximum percentage decrease from initial value in the period 3 to 12 hours after challenge was calculated. Because it is possible that the dose of allergen necessary to induce a fall in FEV_1 value of 15% or greater is different in the first and second allergen challenge test, the provocation cumulated dose of allergen necessary to induce a fall in FEV_1 value of 15% from baseline (PD_{15} allergen) was also calculated to characterize EAR and LAR.²³

ECP

Serum samples were stored at -20°C . ECP was assessed by Dr. P. Venge, using a radioimmunoassay method that has been described previously.²⁴

Study design

The study was performed in a randomized, placebo-controlled, double-blind, parallel-group design, with two groups of eight patients, comparing cetirizine, 15 mg taken twice daily during 18 days, with matching placebo. Patients were stratified according to sensitivity to allergen in the initial bronchoprovocation into a group of low-dose responders, reacting to 80 or 400 BU/ml and a group of high-dose responders, reacting to 2000 to 10,000 BU/ml.

The study consisted of three visits: (1) a selection visit, (2) a visit for the house dust mite provocation

before treatment, and (3) a visit for the house dust mite provocation after treatment. Medication was withheld before the study period: inhaled steroids and sodium cromoglycate were stopped 1 week before the study (4 weeks before the allergen challenge after treatment); theophylline drugs, oral β_2 -adrenergic drugs, and antihistamine drugs were stopped 48 hours before the study; and inhaled β_2 -adrenergic drugs were stopped 6 hours before the tests.

At the selection visit patients were assessed clinically. FEV_1 and vital capacity values were measured, and patients underwent methacholine provocation to determine PC_{20} .

Seventy-two hours after the selection visit patients were admitted to the hospital for 3 consecutive days. On the first day, starting at 9:00 AM, control solution was inhaled four times at 15-minute intervals. FEV_1 values were measured immediately and 15 minutes after each inhalation. After the fourth inhalation, FEV_1 was recorded at 10-minute intervals for the first hour and was followed up every hour until 12 hours after the last inhalation. Six hours after the last inhalation, blood sampling was performed for ECP and cetirizine measurements. The second day at 9:00 AM, subjects underwent allergen challenge with house dust mites. Spirometry was performed as on the first day. Blood sampling was performed, 6 hours after the last inhalation, for ECP and cetirizine measurements. On the third day patients underwent a second methacholine provocation.

Patients were then treated with cetirizine or placebo for 18 days. At the end of the treatment period PC_{20} methacholine was determined. Seventy-two hours later, patients were again admitted to the hospital for 3 consecutive days. The same tests as during visit 2 were performed. During this evaluation period the study medication was continued.

Data analysis

Statistical analyses were performed with an SAS statistical software package (SAS Institute, Cary, N.C.). In all statistical tests p values below 0.05 were considered significant.

The two treatment groups were compared with regard to patients' characteristics at selection with the use of Fisher's exact test for the dichotomous variables, the Student t test for the continuous variables, or the Mann-Whitney rank test for the ordinal variables.

The parameters of EAR and LAR were compared by using the analysis of covariance, with the value measured before treatment as covariate. The means after treatment adjusted for initial difference between the treatment groups were calculated. A logarithmic transformation was applied before the statistical analysis of PD_{15} allergen measurements.

The PC_{20} methacholine ratios of the two groups were compared by one-way analysis of variance. The provocation-induced change in ECP blood level in the two treatment groups was compared by using an analysis of covariance. For evaluation of safety, the number of

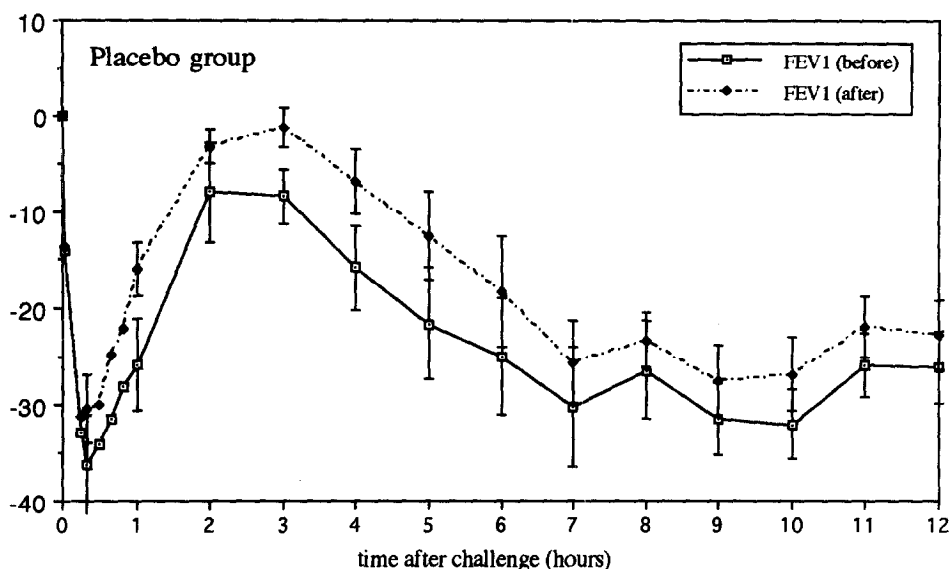
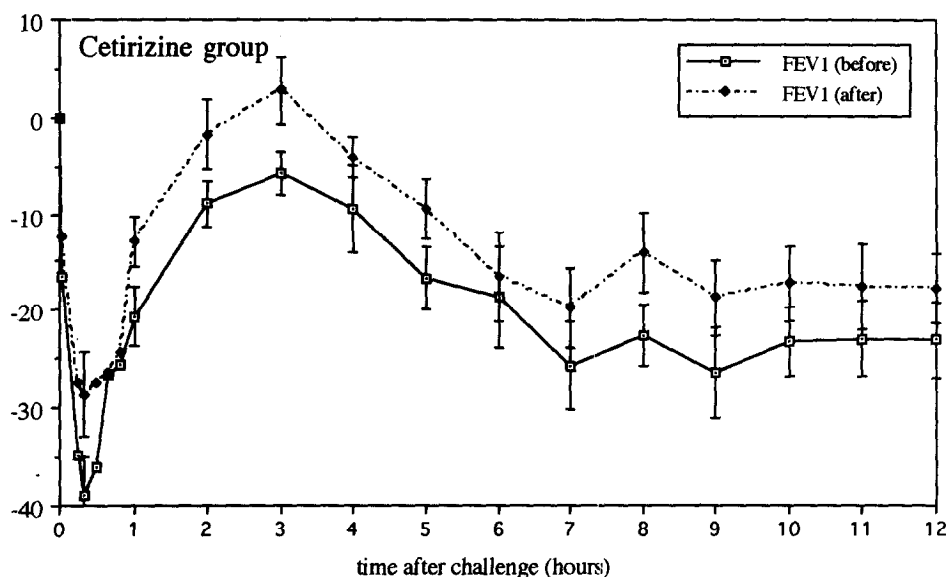
% fall in FEV₁% fall in FEV₁

FIG. 1. The effect of allergen challenge on FEV₁ before and after treatment (mean percent fall in FEV₁ $\pm$ SEM). *Top*, Placebo group; *bottom*, cetirizine group.

patients experiencing adverse reactions was compared between the two treatment groups by using Fisher's exact test.

RESULTS

Demographic characteristics were very similar between the two treatment groups. The (log-transformed) mean values of PC₂₀ methacholine showed no significant difference between the two groups (Table I).

Early and late asthmatic responses

Fig. 1 shows the effect of allergen challenge on FEV₁ value in the placebo and the cetirizine groups before and after treatment. Allergen challenge resulted in a mean maximum fall in FEV₁ value between 0 and 1 hour of $37.9\% \pm 16.7\%$ in the placebo group and $40.2\% \pm 12.2\%$ in the cetirizine group before treatment. After treatment these values were $33.2\% \pm 11.0\%$ in the placebo group and $30.8\% \pm 11.5\%$ in the cetirizine group.

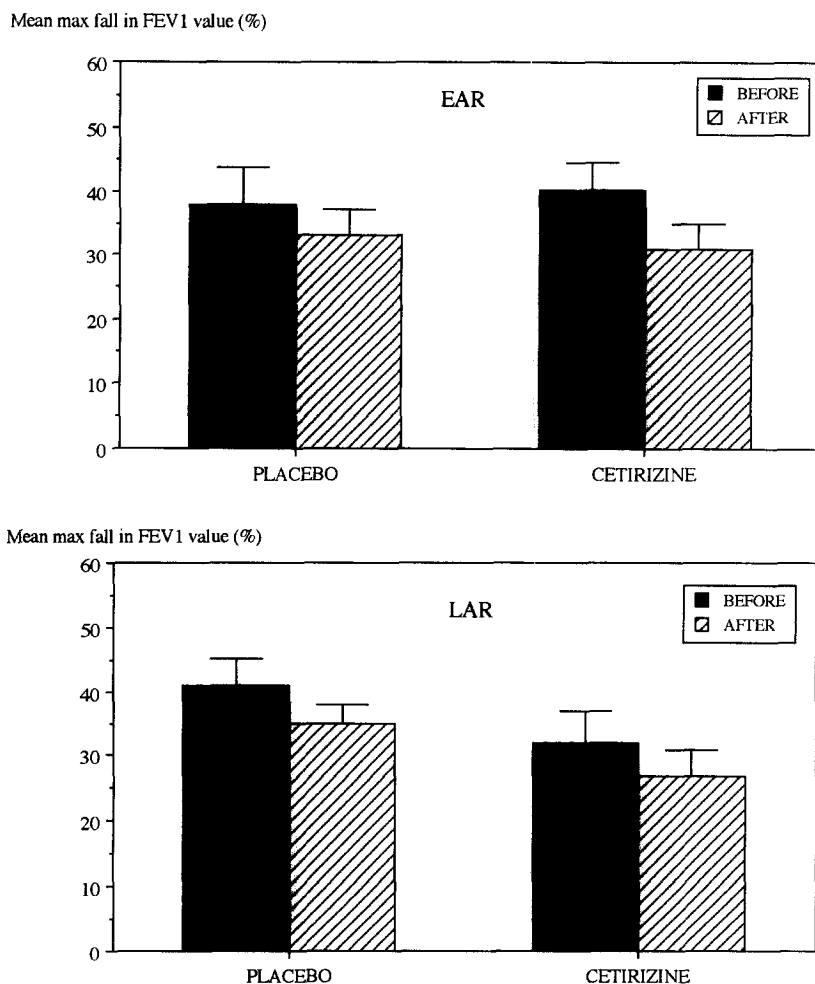


FIG. 2. The mean maximal fall in FEV₁ value 0 to 60 minutes (*EAR*) and 3 to 12 hours (*LAR*) after allergen challenge in both groups ($\pm$ SEM). There was no significant difference between the treatment groups ($p = 0.46$ [*EAR*]; $p = 0.64$ [*LAR*]).

ine group; after adjustment for baseline difference, the mean values were 33.8% in the placebo group and 30.1% in the cetirizine group. This difference was not statistically significant ($p = 0.46$; Fig. 2, *A*). During the late response the mean maximal fall in FEV₁ value, 3 to 12 hours after challenge, was $41.0\% \pm 12.1\%$ in the placebo group and $32.0\% \pm 13.8\%$ in the cetirizine group before treatment. After treatment these values were $34.8\% \pm 9.0\%$ in the placebo group and $26.8\% \pm 11.3\%$ in the cetirizine group; after adjustment for baseline difference, the values were 31.6% in the placebo group and 29.9% in the cetirizine group. This difference was not statistically significant ($p = 0.64$; Fig. 2, *B*).

Because in six patients (three in each group) the allergen concentration required to induce a fall in FEV₁ 15% or more was lower after treat-

ment than before, the PD₁₅ allergen for early and late responses were also calculated. The geometric mean of PD₁₅ allergen 0 to 1 hour before treatment was 611 BU/ml in the placebo group and 800 BU/ml in the cetirizine group. After treatment these values were 386 and 627 BU/ml, respectively. The adjusted geometric means were 427 and 568 BU/ml after treatment with placebo and cetirizine, respectively. This difference was not statistically significant ($p = 0.53$). The geometric mean of PD₁₅ allergen 3 to 12 hours before treatment was 511 BU/ml in the placebo group and 1126 BU/ml in the cetirizine group. After treatment these values were 353 and 772 BU/ml, respectively. The adjusted geometric means were 503 BU/ml in the placebo group and 542 BU/ml in the cetirizine group. This difference was not statistically significant ($p = 0.85$; Fig. 3).

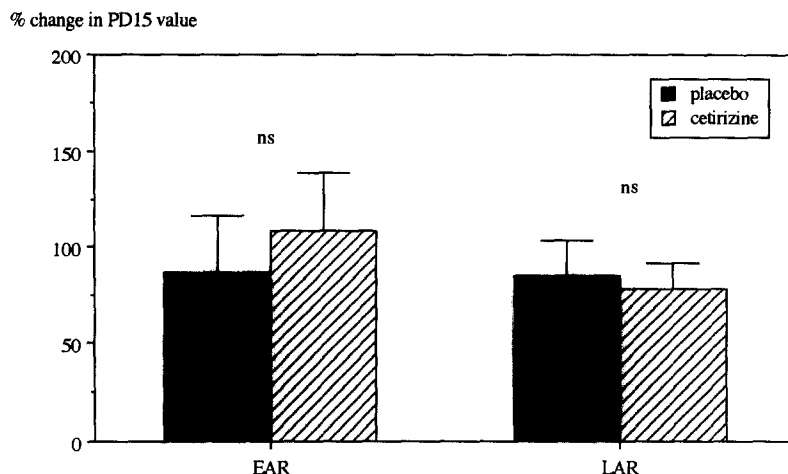


FIG. 3. Percentage change in PD₁₅ value ($\pm$ SEM) of EAR and LAR after treatment in both groups. There was no significant difference between the treatment groups ($p = 0.53$ [EAR]; $p = 0.85$ [LAR]).

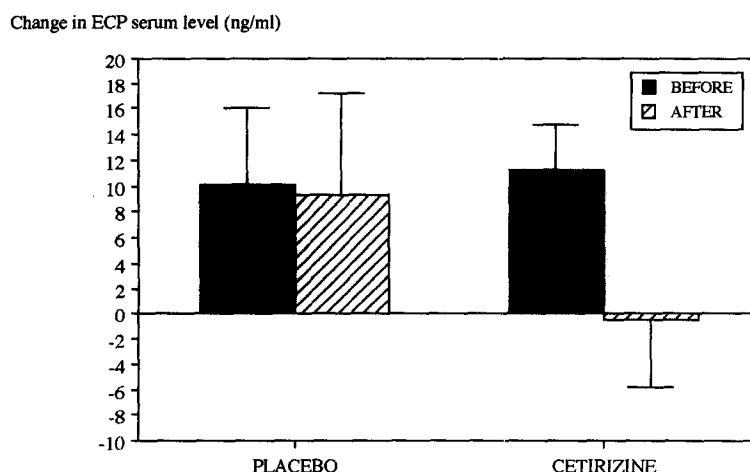


FIG. 4. Allergen challenge-induced change in ECP serum level ($\pm$ SEM) before and after treatment in both groups. There was no significant difference between the treatment groups ($p = 0.34$).

PC₂₀ methacholine

To study the effect of treatment on the hyper-responsiveness, two ratios of PC₂₀ methacholine were calculated in both treatment groups. The mean ratio of PC₂₀ methacholine before allergen challenge (ratio 1) was 1.22 in the cetirizine group and 1.29 in the placebo group. Again, this difference was not statistically significant ($p = 0.89$). The mean ratio of PC₂₀ methacholine after allergen challenge (ratio 2) was 1.13 with cetirizine and 1.71 with placebo, which showed no significant difference ($p = 0.58$).

For the group as a whole ($N = 16$), before treatment allergen challenge did not significantly

change the PC₂₀ methacholine (mean ratio of PC₂₀ after/mean ratio PC₂₀ before = 1.03).

ECP

Allergen challenge resulted in a significant increase in ECP value before treatment ($p = 0.01$). After treatment the adjusted differences were -0.4 ng/ml in the cetirizine group and 9.2 ng/ml in the placebo group (Fig. 4). This difference was not statistically significant ($p = 0.34$).

Blood level of cetirizine

In the cetirizine group seven patients had blood levels ranging from 108 ng/ml to 643 ng/ml. One

patient had no detectable level of cetirizine in the blood (patient 3). In the placebo group no cetirizine was detected in the blood.

Evaluation of safety

There was no significant difference in occurrence of adverse events—symptoms (dyspnea, wheezing, cough) and abnormalities in the blood—between the two treatment groups.

DISCUSSION

Cetirizine has proved effective in inhibiting allergen-induced early responses in the skin, as measured by wheal and flare reactions,^{14, 15, 25} and in the nose, as measured by symptom scores.^{5, 6} Several authors have studied the effect of cetirizine on early mediator release in skin blister models. Charlesworth et al.¹⁶ found a significant reduction in prostaglandin D₂ production until 5 hours after challenge, but no effect on histamine release after the use of 20 mg cetirizine during 3 days. However, Michel et al.¹⁵ found a significant reduction in immediate histamine release after the use of 10 mg cetirizine during 4 days. In a nasal challenge model cetirizine also significantly decreased N- α -tosy-L-arginine methyl ester-esterase activity and leukotriene C₄ production, but had no effect on histamine and prostaglandin D₂ release.²⁶ Thus cetirizine seems to be effective in inhibiting allergen-induced early responses in the nose and skin.

We have demonstrated that 18 days of treatment with Cetirizine did not reduce the intensity of the allergen-induced EAR, measured by maximal fall in FEV₁ value and PD₁₅ allergen during the first 30 minutes after challenge. These findings are in accordance with results of the studies of Rédiér et al.²⁷ and Wasserfallen et al.²⁸ Although there is little doubt about the antihistaminic effects of cetirizine, its antiallergic properties in the airways are not proven. In our study we used a high dose (30 mg cetirizine/day) to study such possible antiallergic effects. In contrast to its action on the nose and skin, cetirizine is not effective in inhibiting early responses in the lower airways. It is possible that the tissue concentration of cetirizine in the lungs is too low to be effective. In patients with exercise-induced asthma, Ghosh et al.²⁹ found that cetirizine was effective in inhibiting the early fall in FEV₁ after exercise after a single inhaled dose, whereas there was no effect after a 1-week course of oral cetirizine. This difference may be due to differences in local tissue concentrations in the airways.

Our data also failed to show a significant effect

of cetirizine on the allergen-induced LAR after allergen challenge, as measured by the maximal fall in FEV₁ and the PD₁₅ allergen during late response. These results are in agreement with the results of a study by Rédiér et al.,²⁷ who also found no significant effect on late response after an 8-day course of cetirizine. However, Wasserfallen et al.²⁸ did find a significant reduction in LAR after cetirizine treatment during 7 days. A possible explanation for these different outcomes may be a difference in severity of asthma in the patients. In our study most patients used inhaled steroids, often in combination with other drugs, for the control of their asthma before the study and had rather low PC₂₀ methacholine values (Table I). In the study of Wasserfallen, however, two patients in each group used no medication for their asthma at the time of the study; the use of medication of the other patients and the degree of hyperresponsiveness was not presented. There is also a difference in patient selection with respect to the type of allergy. Wasserfallen et al.²⁸ studied mostly patients allergic to cats (12 of 16 patients); the degree of exposure to cat allergen at home during the study in the two groups was not presented. In our study, and in the study of Rédiér, most of the patients were allergic to house dust mites (16 of 16 and 8 of 12, respectively).

Late-phase allergic reactions, which are seen in the nose, skin, conjunctiva, and lower airways are associated with the infiltration of various inflammatory cells, such as eosinophils, mononuclear cells, and possibly neutrophils.^{21, 30} Eosinophils are supposed to play an important role in the pathogenesis of the late-phase reaction.³¹⁻³³ Release of basic proteins, such as major basic protein and cationic protein, may cause damage to the bronchial epithelium and is associated with an increase in bronchial hyperresponsiveness.^{34, 35} To study the activation of eosinophils, we measured ECP blood levels during the allergen-induced late-phase response before and after treatment. We found a marked, not not significant, effect of cetirizine on ECP blood levels 6 hours after allergen challenge. Rédiér et al.²⁷ found that cetirizine inhibited the recruitment of eosinophils into the bronchoalveolar lavage fluid 24 hours after allergen challenge. A study by Kyan-Aung et al.³⁶ demonstrated that cetirizine significantly inhibited the adhesion of eosinophils to stimulated endothelial cells. Several authors have demonstrated an inhibiting effect on infiltration of eosinophils during the late-phase response in the skin.¹⁵⁻¹⁶ Despite these findings, there was no

reduction in the clinical manifestation of the LAR in our study and in the study of Rédier et al. This discrepancy in effect of cetirizine on recruitment of eosinophils and on the late-phase reaction measured by lung function is difficult to explain. Perhaps the role of the eosinophil in the late-phase response is more limited than previously thought. Other cells, such as lymphocytes, macrophages, mast cells, or basophils, may be more important in the generation of the late-phase response.²¹ It is also possible that the tissue concentration of cetirizine in the lower airways is too low to be effective.²⁹

We did not find a significant increase in bronchial hyperresponsiveness after the allergen-induced late-phase bronchial response. This is in contrast to several other studies in which allergen-induced asthmatic responses are associated with an increase in bronchial responsiveness to histamine or methacholine.^{37, 38} The methacholine tests before allergen challenge were performed in an outpatient setting during the selection visit, whereas the PC₂₀ measurements after challenge were performed after 2 days of hospitalization. In our hospital the concentration of house dust mite is very low compared with the average. This low exposure may cause a rapid improvement in pulmonary symptoms after only 1 day in the hospital. It is possible that the effect of allergen challenge on the PC₂₀ methacholine is obscured by the effect of hospitalization.

We also failed to find a significant effect of cetirizine on baseline hyperresponsiveness (ratio 1) and on allergen challenge-induced hyperresponsiveness (ratio 2). This is in accordance with the fact that there was no significant effect on the late-phase response. Because both the late-phase response and the nonspecific hyperresponsiveness are manifestations of airway inflammation, it seems that cetirizine has no inhibiting effect on the inflammatory process in the lower airways.

In conclusion, although cetirizine may be effective in the treatment of allergic disorders in the nose and the skin, we failed to find any effect on bronchial early and late response after allergen challenge. This lack of effect may be due to low tissue concentration in the lower airways, although we used a daily dose three times higher than usually recommended. Our data, combined with those of Rédier et al., suggest a discrepancy between the clinical response during the LAR and eosinophil dynamics. This could imply that the role of the eosinophil in the development of the LAR has been overestimated. On the other

hand, a stronger reduction in eosinophil chemotaxis than is achieved with this drug after oral administration may be necessary to suppress the LAR.

We thank Dr. Per Venge for the assessments of ECP.

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