

Effect of cetirizine, a new H₁ antihistamine, on the early and late allergic reactions in a bronchial provocation test with allergen

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Background: Cetirizine is a highly sensitive H₁ antihistamine with particular antiallergic properties, which has been shown to be effective in the treatment of allergic rhinitis, urticaria, and hay-fever-associated asthma.

Methods: To assess the effect of cetirizine on the late allergic reaction to a specific bronchial provocation test (BPT) with allergen, we selected 25 patients with allergic asthma as determined by history, skin tests, and specific IgE levels. They were challenged with increasing doses of a cat or mite extract until a 20% drop in forced expiratory volume in 1 second (FEV₁) was recorded. Sixteen patients (11 men and 5 women with a mean age of 22 years; range, 18 to 48 years) exhibited a dual response (early and late allergic reactions). These 16 patients underwent a second BPT 2 weeks later, and each again showed a dual response. They were then randomized to receive either a placebo (8 patients) or cetirizine, 15 mg twice daily (8 patients) in a double-blind fashion. After 7 days of treatment, they underwent a third BPT with the same allergen dose as given in the second BPT.

Results: The intensity and duration of early allergic reaction were not affected by cetirizine, whereas all parameters of late allergic reaction were statistically significantly improved in the cetirizine group when compared with those of the placebo group (maximum FEV₁ decrease, $p = 0.046$; FEV₁ [area above the curve], $p = 0.027$; maximum airway resistance increase, $p = 0.021$; airway resistance [area under the curve], $p = 0.036$).

Conclusions: Cetirizine produced a significant protective effect against an allergen-induced late allergic reaction in a BPT. Cetirizine might therefore be effective in the treatment of asthma. (*J ALLERGY CLIN IMMUNOL* 1993;91:1189-97.)

Key words: Cetirizine, antihistamine, bronchial provocation test, late allergic reaction, experimental asthma

The role of antihistamines in the treatment of asthma is still controversial. In a bronchial provocation test (BPT) with allergen, the early allergic reaction (EAR) involves the release of several mediators including histamine. It is not surprising therefore that antihistamines can induce some partial protection (up to 50%) against the development of an EAR.¹

Late allergic reaction (LAR) occurs in about

Abbreviations used

AAC:	Area above the curve
AUC:	Area under the curve
BPT:	Bronchial provocation test
EAR:	Early allergic reaction
FEV ₁ :	Forced expiratory volume in 1 second
LAR:	Late allergic reaction
RAW:	Airway resistance
SQ:	Standard quality units

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50% to 60% of BPTs with allergen and seems to be correlated with the severity of asthma, which has been shown to be correlated with bronchial leukocyte infiltration mainly by T lymphocytes and eosinophils.² This LAR is partially inhibited by prior administration of antihistamines (15%) and by nonsteroidal antiinflammatory drugs (26%).³

Cetirizine is a second-generation, nonsedating, highly selective H_1 antihistamine; it is the active carboxylic acid metabolite of the first-generation H_1 -receptor antagonist hydroxyzine. Besides its anti- H_1 -receptor properties, which make it effective in the treatment of both seasonal^{4,5} and chronic^{6,7} allergic rhinitis and chronic urticaria,⁸⁻¹⁰ cetirizine has been shown to have inhibitory properties on eosinophil¹¹⁻¹³ and basophil¹⁴ chemotaxis in a skin model of late-phase reaction. Preliminary studies have shown that cetirizine had a significant protective effect against histamine-induced bronchoconstriction¹⁵ but was not uniformly effective against allergen- or exercise-induced bronchoconstriction^{16,17} in patients with moderate asthma. However, cetirizine in high doses (20 to 30 mg per day) has been shown to be effective in the prophylaxis and treatment of asthma associated with hay fever.¹⁸⁻²¹

The purpose of this study was to assess the effect of cetirizine on the EAR and LAR induced by a BPT with allergen.

METHODS

Between May 1989 and March 1990, 25 patients with clinical history of asthma, positive skin test results, and specific IgE levels for cat and house dust mite underwent a BPT with semilogarithmic increasing doses of a specific inhaled allergen, from 100 to 100,000 standard quality units (SQ), outside the pollen season for those with seasonal asthma. The purpose of this first test (BPT1) was to assess the presence of an LAR defined as a decrease of forced expiratory volume in 1 second (FEV_1) of 15% or greater between 3 and 8 hours after the BPT that had resulted in an EAR characterized by a drop in FEV_1 of 20% or greater immediately after allergen challenge. Nine patients were not included in the study because they did not fulfill this selection criterion.

The remaining 16 patients (11 men and 5 women with a mean age of 28 years; range, 18 to 48 years) underwent a second BPT (BPT2) 2 weeks later with the highest dose of allergen that had induced the dual response at BPT1. If this dose did not induce a 20% drop in FEV_1 , the next incremental dose was administered. All 16 patients experienced a dual response again.

These patients were then randomized into two groups of eight patients each. Two weeks later, they were given either a placebo or cetirizine 15 mg twice daily for 7 days in a double-blind manner. A third BPT (BPT3) was then performed with the same dose of allergen as used in BPT2.

Bronchoprovocation test

All BPTs were performed at the same time of the day with Aquagen SQ (Allergologisk Laboratorium Copenhagen, Copenhagen, Denmark, 100,000 SQ/ml, 12 cat

and 4 house dust mite allergen extracts). The dry lyophilized powder was diluted with an aqueous solution of phenol 5 mg/ml with albumin 0.3 mg/ml. The dilution is stable for 6 months. To avoid any variation in the allergen concentration, a separate vial was assigned to each patient and kept at +4° C between the BPTs, and the dilution was realized immediately before administration.

A Novair nebulizer (Sandoz, Basel, Switzerland) was used (particle size of 0.5 to 7 μ m; airflow of 14 L/min; nebulization of 2 ml in 7 minutes), and the patient inhaled 1 ml of the solution during 5 minutes of tidal breathing. Bronchial volumes were recorded by spirometry (best of three FEV_1 values) and resistances by plethysmography (mean of three airway resistance [RAW] values) with a Body Test chamber (Jaeger, Würzburg, Germany). Measures were recorded before the beginning of the study and 10 minutes after the end of inhalation of the diluent and different allergen doses. As soon as a 20% drop in FEV_1 was documented, the allergen dose progression was stopped. The EAR was assessed every 10 minutes for 1 hour, and the LAR was assessed every hour for 8 hours thereafter. This protocol was approved by the Ethical Commission of our hospital.

Washout period and side effects evaluation

Every treatment other than inhalation of bronchodilators was stopped before the BPTs, and the different washout periods were respected according to the published guidelines.²² Patients refrained from caffeine consumption and cigarette smoking 6 hours before BPT and during the whole test day.

During BPT3, patients were requested to report any side effects experienced during the treatment week. Special attention was focused on sedation. If no spontaneous sedation was reported, specific questions about daytime sleepiness or memory impairment at work or during driving were asked.

Evaluation of EAR and LAR

Four variables were used to evaluate the EAR.

1. Maximal FEV_1 drop (%): Minimal FEV_1 observed between 0 and 60 minutes after provocation expressed as a percentage of the value after diluent
2. AAC FEV_1 (%): Area above the FEV_1 curve between 0 and 60 minutes after provocation, after the FEV_1 values were expressed as a percentage of the value after diluent
3. Maximal RAW increase (%): Maximal increase of resistance (RAW expressed in kPa/L/sec) observed between 0 and 60 minutes after provocation expressed as a percentage of the value after diluent
4. AUC RAW (%): Area under the RAW curve between 0 and 60 minutes after provocation, after the RAW values were expressed as a percentage of the value after diluent

Four variables were used to evaluate the LAR.

1. Maximal FEV₁ drop (%): Minimal FEV₁ observed between 3 and 8 hours after provocation expressed as a percentage of the maximal FEV₁ value observed between the administration of the diluent and 3 hours after bronchoprovocation
2. AAC FEV₁ (%): Area above the FEV₁ curve between 3 and 8 hours after provocation, after the FEV₁ values were expressed as a percentage of the maximal FEV₁ value observed between the administration of the diluent and 3 hours after bronchoprovocation
3. Maximal RAW increase (%): Maximal increase in resistance (RAW expressed in kPa/L/sec) observed between 3 and 8 hours after provocation expressed as a percentage of the minimal RAW value observed between the administration of the diluent and 3 hours after bronchoprovocation
4. AUC RAW (%): Area under the RAW curve between 3 and 8 hours after provocation after the RAW values were expressed as a percentage of the minimal RAW value observed between the administration of the diluent and 3 hours after bronchoprovocation

Statistics

Discrete variables were analyzed with Fishers' exact test. Continuous variables were analyzed both by the *t* test for independent samples and the Mann-Whitney U test. In the case of different conclusions from the two tests, a further analysis was carried out to determine eventual outliers. In the conclusion, the *p* values corresponding to results of the Mann-Whitney U test were reported because in such a small group normal distribution of variables cannot be ascertained. To assess randomization and possible variations around the mean, correlation tests with both Pearson and Spearman correlation coefficients were performed for the whole group and for both cetirizine and placebo groups. The Pearson test results are reported in the text. All statistical tests were carried out in two-tailed fashion at the 5% level of significance.

RESULTS

Patient characteristics

There were no differences in sex, age, weight, and height between the two groups (Table I). All patients were nonsmokers. The duration of the medical history of asthma was highly variable; but its mean value, as well as the mean FEV₁ as determined by spirometry, the number of positive skin test results, and specific IgE dosages (RAST), were similar in the two groups. Only two patients in each group had no treatment for asthma at the time of the study. No other disease or abnormality in routine blood tests could be shown.

TABLE I. Demographic and clinical data

Data (mean + SD)	Placebo	Cetirizine
Number of patients	8	8
Sex (M/F)	6/2	5/3
Age (yr)	28 ± 9	28 ± 8
Weight (kg)	69 ± 9	64 ± 15
Height (cm)	172 ± 9	172 ± 10
Duration of disease (yr)	15 ± 10	14 ± 12
Pulmonary function test at inclusion in study		
FEV ₁ (% of predicted value)	97 ± 17	93 ± 13
Selected allergen		
Cat (no. of patients)	5	7
HDM (no. of patients)	3	1

HDM, House dust mite.

Bronchoprovocation tests

FEV₁ and RAW values during BPT1 were slightly but not significantly worse in the cetirizine group than in the placebo group. This trend was even more marked during BPT2, with patients in the cetirizine group experiencing a greater response than patients in the placebo group (Table II and Fig. 1). The average drop in FEV₁ and increase in RAW were larger both in the EAR and LAR, but this difference did not reach statistical significance. Moreover, correlation analysis of LAR parameters for the whole group between BPT1 and BPT2 showed an excellent correlation coefficient for the FEV₁ values (Pearson *r* = 0.77 to 0.85) and a good correlation coefficient for the RAW values (Pearson *r* = 0.30 to 0.39), indicating a good randomization.

The results of BPT3 show that administration of placebo resulted in a less severe EAR than that observed before treatment (placebo effect). The difference averaged 10% for the maximal drop in FEV₁ (25% vs 34%) and 70% for the maximal increase in RAW (242% vs 311%). The same differences were observed when areas above and under the curve (AAC and AUC, respectively) were considered (Table II).

Conversely, no difference was observed for FEV₁ analysis during LAR, whereas RAW analysis revealed a 70% greater increase in maximal RAW during BPT3 than BPT2 (151% vs 239%). The same trend was observed with the other RAW variables (Table II).

Patients in the cetirizine group, however, showed improved values in both FEV₁ and RAW during EAR: 15% for maximal FEV₁ drop (43% vs 27%), 60% for maximal RAW increase (364%

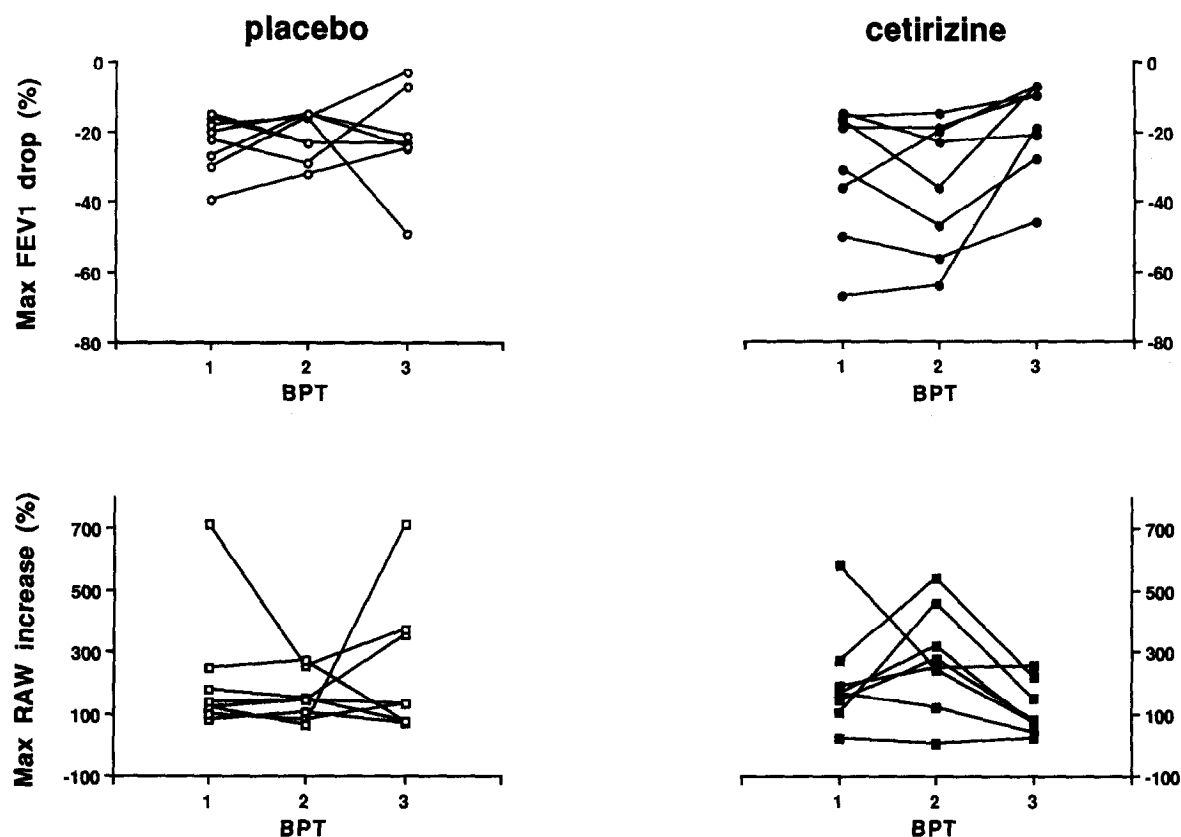


FIG. 1. Individual values of maximal FEV₁ drop (%) and maximal RAW increase (%) during LAR in BPTs 1, 2, and 3. (Left side: placebo group, *n* = 8; right side: cetirizine group, *n* = 8).

TABLE II. Bronchoprovocation tests: reproducibility and evaluation of the treatment phase

	BPT1 (inclusion)		BPT2 (before treatment)		BPT3 (after treatment)	
	Placebo	Cetirizine	Placebo	Cetirizine	Placebo	Cetirizine
EAR						
Max FEV ₁ drop (%)	32 ± 9	38 ± 14	34 ± 10	34 ± 13	25 ± 19	27 ± 15
AAC FEV ₁ (%)	1263 ± 576	1687 ± 881	1507 ± 635	2001 ± 676	1007 ± 761	1210 ± 835
Max RAW increase (%)	229 ± 86	375 ± 166	311 ± 182	364 ± 236	242 ± 143	302 ± 397
AUC RAW (%)	9050 ± 5613	13076 ± 6283	11237 ± 8653	15622 ± 10854	7875 ± 4787	9746 ± 12216
LAR						
Max FEV ₁ drop (%)	24 ± 8	31 ± 19	21 ± 7	35 ± 19	22 ± 14	18 ± 13
AUC FEV ₁ (%)	72 ± 31	113 ± 84	64 ± 26	125 ± 88	72 ± 57	49 ± 44
Max RAW increase (%)	212 ± 209	206 ± 166	151 ± 75	275 ± 170	239 ± 226	113 ± 86
AUC RAW (%)	608 ± 678	644 ± 567	370 ± 169	749 ± 517	635 ± 653	270 ± 300

vs 302%) and LAR, 17% for maximal FEV₁ drop (35% vs 18%), and 160% for maximal RAW increase (275% vs 113%). The same results were observed when AAC and AUC, respectively, were considered (Table II).

On the whole, results for the cetirizine group compared with those for the placebo group show that the protective effect of cetirizine was not different from the placebo effect during EAR (Figs. 2 and 3). A statistically significant protec-

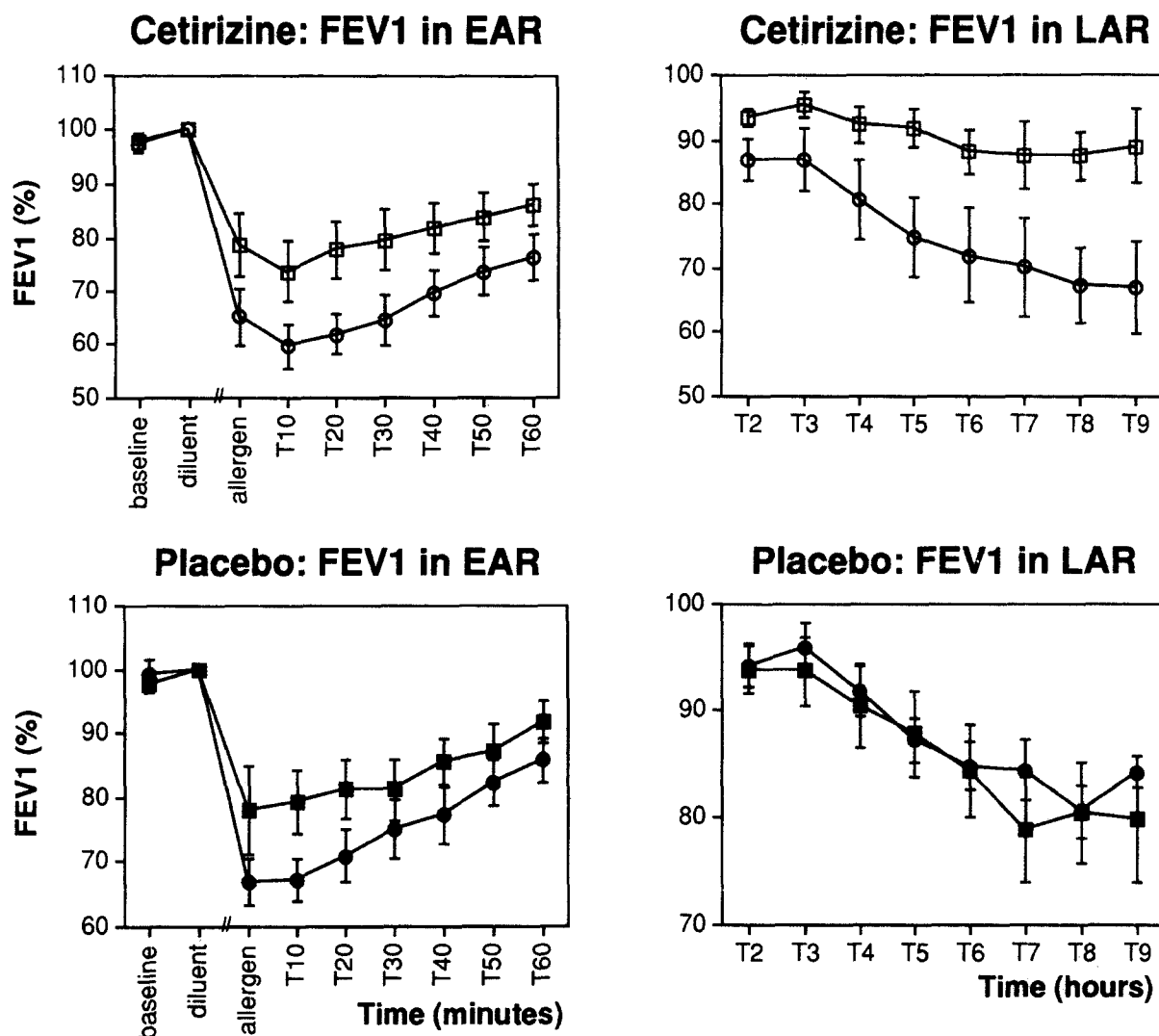


FIG. 2. Results of bronchoprovocation after treatment period on FEV₁ (%) in EAR and LAR (mean $\pm$ SEM, $n = 8$). Circles, Before treatment; squares, after treatment; open line, cetirizine; closed line, placebo.

tive effect was observed during LAR in the cetirizine group, with p values varying between 0.046 for maximal FEV₁ drop (%) and 0.021 for maximal RAW increase (%) (Table III and Figs. 1 to 3).

Correlation analysis for LAR parameters between BPT1 and BPT2 and between BPT2 and BPT3 show an excellent correlation with FEV₁ values in the cetirizine group (Pearson $r = 0.82$ and 0.65 , respectively), despite the improvement in the values observed in BPT3, indicating that these variations are not random. In contrast, the correlation between BPT1 and BPT2 is weaker in the placebo group (Pearson $r = 0.32$) and lost between BPT2 and BPT3 (Pearson $r = -0.19$), suggesting random variations. The same patterns of association apply for RAW parameters (Pear-

son $r = 0.41$ and 0.64 in the cetirizine group vs 0.75 and -0.27 , respectively in the placebo group). These results combined with the fact that the mean BPT3 values for both the FEV₁ and RAW parameters in LAR in the cetirizine group are better than those of BPT1 indicate that the improvement observed during BPT3 is not a mere regression towards the mean after an unusual reaction during BPT2.

Four patients in the cetirizine group did not have an LAR during BPT3, compared with two patients in the placebo group.

Drug tolerance and side effects

None of the subjects complained of any untoward effect; and in particular, none of them reported sedation.

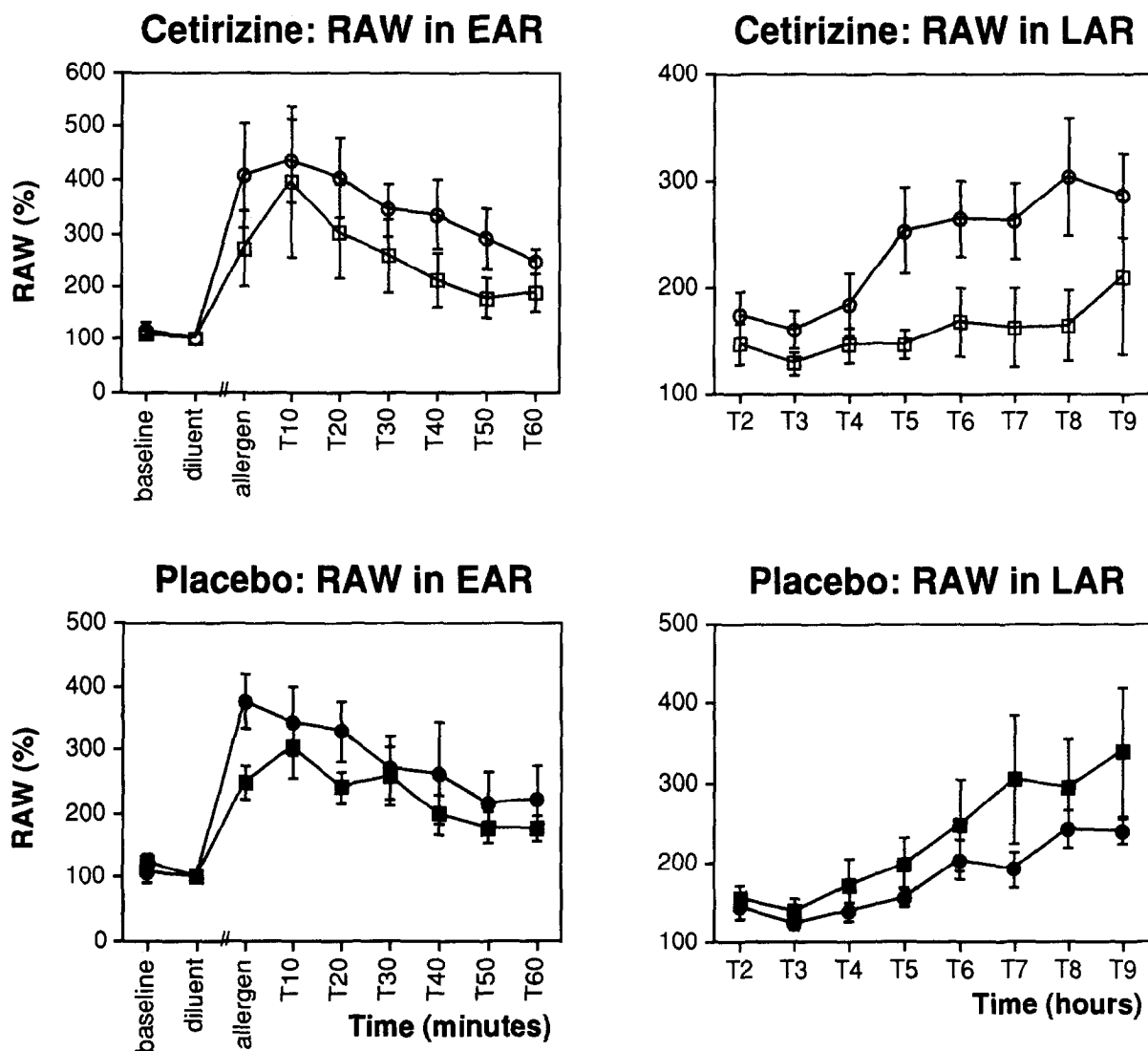


FIG. 3. Results of bronchoprovocation after treatment period on RAW (%) in EAR and LAR (mean $\pm$ SEM, $n = 8$). Circles, Before treatment; squares, after treatment; open line, cetirizine; closed line, placebo.

TABLE III. Comparison of the modifications in BPT results observed after treatment with placebo or cetirizine

BPT3-BPT2 (mean $\pm$ SD)	Placebo	Cetirizine	p Value*
EAR			
Max FEV ₁ drop (%)	-10 $\pm$ 19	-15 $\pm$ 15	0.674
AAC FEV ₁ (%)	-500 $\pm$ 878	-791 $\pm$ 1008	0.529
Max RAW increase (%)	-69 $\pm$ 231	-62 $\pm$ 391	0.600
AUC RAW (%)	-3362 $\pm$ 7866	-9749 $\pm$ 8929	0.203
LAR			
Max FEV ₁ drop (%)	1 $\pm$ 16	-17 $\pm$ 14	0.046
AAC FEV ₁ (%)	8 $\pm$ 65	-76 $\pm$ 68	0.027
Max RAW increase (%)	89 $\pm$ 257	-161 $\pm$ 132	0.021
AUC RAW (%)	265 $\pm$ 719	-479 $\pm$ 464	0.036

*Mann-Whitney U test.

DISCUSSION

This study demonstrates that orally administered cetirizine is able to confer a significant protective effect against the LAR but not the EAR in a BPT with allergen extracts.

The second-generation H_1 antihistamines have been used in BPT with histamine or allergen after they were found to have a slight bronchodilator effect.²³ The protection conferred by administration of H_1 antihistamine is partial (up to 50%), which suggests the release of other mediators. It is generally considered that LAR is associated with an inflammatory response that occurs in the bronchi, which in turn implies subsequent mediator release and induces transient increased bronchial responsiveness.²⁴ This second response is considered to be the experimental equivalent of clinical asthma because the same inflammatory cells can be demonstrated by bronchoalveolar lavage in patients with asthma.²⁵ Studies with terfenadine,²⁶ astemizole,²⁷ and azelastine^{28,29} have shown up to 50% inhibition of allergen-induced EAR. Administration of a nonsteroidal antiinflammatory drug³ showed a trend to diminish the magnitude of the EAR that was not statistically different from that of the placebo. The efficacy of antihistamines on LAR is less impressive than on EAR and averages 10% to 15% for both terfenadine³ and azelastine.²⁷ It is interesting to note that a similar inhibitory effect on LAR was observed after administration of a nonsteroidal antiinflammatory drug³ in patients who were not sensitive to this class of drugs. Moreover, clinical trials of treatment with antihistamines in asthma have shown some efficacy of both terfenadine³⁰ and azelastine.³¹

Cetirizine is a highly selective H_1 antihistamine with some antiallergic properties. It prevents the migration of eosinophils¹¹⁻¹³ and basophils¹⁴ in cutaneous late-phase reactions and might exert the same effect on the bronchial mucosa.³² The drug is effective in inhibiting histamine-induced bronchospasm^{15,33} and pollen-induced bronchospasm in clinical trials on seasonal asthma.¹⁹⁻²²

Our study demonstrated that in a group of 16 nonsmokers who have moderate asthma with reproducible LAR (Table II and Fig. 1), pretreatment with cetirizine 15 mg twice daily during 1 week led to a decrease in the magnitude of the EAR that was not different from the placebo effect observed (Figs. 2 and 3; 15% diminution of the maximal FEV_1 drop vs 10%; 60% diminution in maximal RAW increase vs 70%). This is per-

haps an indication that psychologic factors and the release of mediators other than histamine play a role in EAR and that antihistamines alone cannot block this reaction. The protective effect observed is slightly less significant than the one described with other antihistamines.^{3,28,29} This may be partially explained by the fact that the patients in the cetirizine group had slightly more severe asthma in both EAR and LAR than those in the placebo group (Table II and Fig. 1) and that treatment withdrawal conditions observed before BPTs were less well tolerated in this group than in the other one, as demonstrated by the fact that the EAR observed during BPT2 was more severe than that during BPT1. That difference, however, did not reach statistical significance. This trend could have increased between BPT2 and BPT3, thus artificially lowering the protective effect observed with cetirizine. It is unlikely that these differences might have been accounted for by a sensitization as a result of a previous BPT, because this variation was not observed in the placebo group.

The main finding of the study was the protective effect afforded by cetirizine on the LAR (Figs. 2 and 3). No placebo effect could be detected as far as FEV_1 was concerned, and it was only moderate when RAW values were analyzed. The cetirizine group showed, however, a clear-cut improvement in the magnitude of the LAR that reached statistical significance in all the variables studied ($p = 0.046$ from maximal FEV_1 drop [%], $p = 0.027$ for AAC FEV_1 [%], $p = 0.021$ for maximal RAW increase [%], $p = 0.036$ for AUC RAW [%]) (Table III). This effect was observed despite the fact that LAR during BPT2 was also worse in the cetirizine group than in the placebo group for the same reasons that are mentioned above. Thus the net protection afforded by cetirizine might be more significant than demonstrated here. Correlation analysis confirmed that the improvement observed during BPT3 in the LAR parameters of the cetirizine group is unlikely to illustrate a mere regression towards the mean after an unusually severe reaction during BPT2 but is related to a protective effect of the drug.

Four patients in the cetirizine group but only two in the placebo group did not show an LAR during BPT3. The difference between the two LARs was far more pronounced in the four patients of the cetirizine group than in the two of the placebo group. The small size of both sam-

ples, however, precludes any further conclusion. The drug was very well tolerated, and no patient complained of sedation.

Thus cetirizine treatment in an allergen BPT model offers a statistically significant protective effect against LAR. The kinetics of development of LAR are different from those observed after placebo administration (Fig. 3) and thus cannot be the mere reflection of the bronchodilating properties of this antihistamine. This effect would have led to a more rapid and complete recovery from EAR without affecting the development of subsequent LAR, as was the case in studies with other H₁ antihistamines.^{3,28} Some influence of the antiallergic properties of cetirizine can be postulated. Indeed, the observation that cetirizine is able to inhibit the migration of eosinophils and basophils not only in the skin¹¹⁻¹⁴ but probably also in the bronchial mucosa³² might explain some of the differences observed in the comparison of the protective effect offered by other antihistamines.^{3,28}

Effective protection against asthma can be obtained only with rather high doses of cetirizine.¹⁹ We tested a dose of 15 mg twice daily and noticed that the protection was lost after about 6 hours in the two more severely affected patients, suggesting that higher dosages or multiple administrations during the day might be necessary in the treatment of asthma. This might lead to an increase in side effects, and particularly to sedation, which has not been observed in this study, despite specific inquiry. This drawback could be eliminated by direct administration of cetirizine into the bronchi by aerosol or spray, for example.

In conclusion, cetirizine offers a statistically significant protective effect against allergen-induced LAR during BPT in patients with moderate asthma with reproducible late-phase reactions. Further studies are needed to evaluate the usefulness of this antihistamine in the treatment of clinical asthma.

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