

Comparison of the bronchodilatory effects of cetirizine, albuterol, and both together versus placebo in patients with mild-to-moderate asthma

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Background: Many potential users of the H_1 antihistamine cetirizine are asthmatic and may be using inhaled albuterol. This study was conducted to assess the possible bronchodilatory effect of cetirizine in patients with mild-to-moderate asthma and to determine whether cetirizine interacts with albuterol.

Methods: In a randomized, double-blind, placebo-controlled, crossover study, the effects on pulmonary function of 5, 10, and 20 mg oral doses of cetirizine with and without inhaled albuterol (180 μ g) were determined in 12 patients at 11 time points over 8 hours. The primary measure of efficacy was forced expiratory volume in 1 second (FEV_1).

Results: Cetirizine with or without albuterol significantly increased FEV_1 , peak expiratory flow rate, and forced expiratory flow rate between 25% and 75% of vital capacity relative to baseline and placebo but did not have a significant effect on forced vital capacity. The effect of 20 mg of cetirizine on FEV_1 was generally greater than that of 10 or 5 mg, but the difference was statistically significant only at the 30-minute time point ($p < 0.05$). All three cetirizine doses produced significantly greater increases than placebo in FEV_1 and forced expiratory flow rate between 25% and 75% of vital capacity for 8 hours and in peak expiratory flow rate for 7 hours ($p < 0.02$). Albuterol alone had a significant effect on the four pulmonary function variables from 1 to 5 hours after baseline ($p < 0.05$), which is consistent with albuterol's recommended dosing frequency of every 4 to 6 hours. Albuterol alone increased FEV_1 significantly more than 5 mg of cetirizine alone but not 10 mg or 20 mg of cetirizine alone at 60, 90, and 120 minutes after baseline, but all three doses of cetirizine increased FEV_1 significantly more than albuterol 7 and 8 hours after baseline ($p < 0.05$), indicating that the bronchodilatory action of cetirizine lasts longer than that of albuterol. Cetirizine neither potentiated nor inhibited the bronchodilatory action of albuterol, but the two drugs appeared to have an additive bronchodilatory effect. None of the cetirizine treatments caused a worsening of pulmonary function, and all were well tolerated.

Conclusions: Cetirizine has a significant bronchodilatory effect in patients with mild-to-moderate asthma and can be used to treat concomitant conditions (e.g., allergic rhinitis) without concern that it will interfere with the bronchodilatory effect of albuterol or cause worsening of asthma by itself. (*J ALLERGY CLIN IMMUNOL* 1995;96:174-81.)

Key words: Cetirizine, albuterol, antihistamine, mild-to-moderate asthma, bronchodilation

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Cetirizine, a carboxylated analog of hydroxyzine, is an H_1 antihistamine that is highly selective for H_1 receptors,¹ does not significantly cross the blood-brain barrier,¹ and is minimally metabolized.² In clinical trials cetirizine has been found to be effective in the treatment of seasonal allergic rhinitis,³⁻⁷ perennial allergic rhinitis,⁸⁻¹⁰ and chronic idiopathic urticaria.¹¹⁻¹⁴

Cetirizine also has properties that make it potentially useful in the treatment of asthma. Studies

Abbreviations used

FEF _{25%-75%} :	Forced expiratory flow rate between 25% and 75% of vital capacity
FEV ₁ :	Forced expiratory volume in 1 second
FVC:	Forced vital capacity
PEFR:	Peak expiratory flow rate

have shown that it inhibits the bronchial recruitment of inflammatory cells, primarily eosinophils, after inhaled allergen challenge¹⁵; protects against the bronchoconstriction induced by inhaled histamine¹⁶⁻¹⁸ and bronchial antigens¹⁹⁻²⁴; and reduces use of inhaled β -agonist bronchodilators.¹⁹⁻²² Cetirizine has also been found to be well tolerated by patients with asthma.^{15, 16, 18, 20, 23}

In a study of patients with mild asthma, cetirizine had a modest but statistically significant acute bronchodilatory effect ($p < 0.05$).¹⁶ To date, however, no study has been conducted to determine the duration of the bronchodilatory effect of cetirizine in patients with mild-to-moderate asthma.

In isolated human bronchi, cetirizine has been found to either add to or potentiate the bronchodilatory action of albuterol, depending on the albuterol concentration.²⁵ Many potential users of cetirizine, especially patients with allergic rhinitis, also have asthma and may use an albuterol aerosol. It is therefore important to know whether cetirizine also interacts with albuterol in vivo.

This randomized, double-blind, placebo-controlled study of patients with mild-to-moderate asthma was performed to assess the potential bronchodilatory effect of increasing doses of cetirizine and to determine whether cetirizine potentiates or inhibits the bronchodilatory effect of albuterol.

METHODS

Patients

Six female and seven male patients receiving treatment for mild-to-moderate asthma were enrolled in the study. Patients were considered to have mild-to-moderate asthma if during a prestudy screening examination they had a forced expiratory volume in 1 second (FEV₁) value of between 50% and 80% of predicted value and if this value improved by at least 15% within 15 minutes of receiving 2 puffs of albuterol aerosol (90 μ g per puff) from a metered-dose inhaler.²⁶

No female patient was breast-feeding or pregnant at the time of enrollment, and all female patients were using a reliable method of contraception to ensure that

they did not become pregnant during the study. None of the patients had a medical condition that was likely to interfere with the evaluation of their clinical response to the trial medications or a history of intolerance to antihistamines or bronchodilators. Results of laboratory tests for all of the patients, which were obtained during the screening examination, were normal or, if abnormal, were clinically insignificant.

Patients were required to refrain from using the following drugs or drug classes for appropriate periods before entry into the study and before their visits to the clinic: monoamine oxidase inhibitors, hypoglycemics, antihypertensives, central nervous system depressants, oral corticosteroids, theophylline, inhaled steroids, cromolyn sodium, oral or inhaled bronchodilators, and antihistamines.

The study was approved by the Western Institutional Review Board. All patients enrolled in the study signed a form attesting to their awareness of the objectives and possible risks of the study and consenting to participation.

Study design

Each study participant received the following eight treatments, one during each of eight visits to the clinic:

1. Cetirizine, 5 mg capsule, and albuterol aerosol
2. Cetirizine, 5 mg capsule, and placebo albuterol aerosol
3. Cetirizine, 10 mg capsule, and albuterol aerosol
4. Cetirizine, 10 mg capsule, and placebo albuterol aerosol
5. Cetirizine, 20 mg capsule, and albuterol aerosol
6. Cetirizine, 20 mg capsule, and placebo albuterol aerosol
7. Cetirizine, placebo capsule, and albuterol aerosol
8. Cetirizine, placebo capsule, and placebo aerosol

The administration of the aerosol (2 puffs from a metered-dose inhaler) immediately followed the pulmonary function tests performed 30 minutes after administration of the capsule. The active aerosol contained 90 μ g of albuterol per puff.

Patients received the eight treatments in a random sequence determined by a computer-generated randomization code. The treatments were unknown to both the patient and the investigator. To allow adequate washout of the study drugs, visits were at least 2 days apart, but were no more than 8 days apart.

During each visit, four pulmonary function tests (FEV₁, forced vital capacity [FVC], peak expiratory flow rate [PEFR], and forced expiratory flow rate between 25% and 75% of vital capacity [FEF_{25%-75%}]) were performed at 12 time points according to the standards of the National Asthma Education Program of the National Heart, Lung, and Blood Institute.²⁶ The tests were performed immediately before administration of the capsule (baseline); at 30, 60, 90, 120, 150, and 180

TABLE I. Characteristics of the 12 patients evaluated for efficacy

Characteristic	
Age (yr)	
Mean	27
Range	19-43
Sex (no.)	
Female	5
Male	7
Prestudy FEV ₁ (L)	
Mean	2.86
SD	0.85
Maximum	4.14
Minimum	1.56

minutes after baseline; and at 4, 5, 6, 7, and 8 hours after baseline.

Immediately after the pulmonary function tests performed at 120 minutes after baseline, blood samples were drawn for the measurement of plasma cetirizine concentrations.

The investigator recorded the incidence and severity of all observed or voluntarily reported adverse experiences.

Data analysis

The statistical analysis was performed with Statistical Analysis System Institute statistical software (SAS Institute, Cary, N.C.).

Pulmonary function test values

The measures of bronchodilatory effect were the percent changes in spirometry values from the baseline values at the other 11 time points. Percent change in FEV₁ from baseline was considered the most important indicator of the bronchodilatory effect of a treatment.

To determine whether the baseline pulmonary function test values were comparable from visit to visit, the values were compared by both an analysis of variance model that included patient and visit and a model that included treatment and patient. Percent differences from baseline were analyzed by an analysis of covariance model that included cetirizine dose, inhaler (active or placebo), baseline, patient, and interaction of cetirizine dose and inhaler. Least-squares means, derived from the analysis of covariance, were used to estimate treatment effects adjusted for baseline differences and for placebo effect.

A pairwise *t* test was used to determine whether mean percent changes from baseline in the pulmonary function test values were statistically significant and to determine the statistical significance of the mean percent differences from baseline between treatments. An albuterol effect was considered significantly different from placebo if its *p* value was less than 0.05. A *p* value of 0.05 was also used to identify the significance of effects in the analysis of covariance model. To compare

the effects of the cetirizine doses with placebo, a Bonferroni adjustment in the 0.05 significance level was made. Therefore the effect of a cetirizine dose was considered significantly different from that of placebo only if its *p* value was less than 0.0167.

Plasma concentrations

The plasma concentrations of cetirizine obtained from the blood samples drawn 120 minutes after each of the eight treatments were analyzed by analysis of variance methods to determine the relationship between cetirizine dose and cetirizine plasma concentration, the effect of the presence of albuterol on cetirizine plasma concentration, the relationship between cetirizine concentration and the pulmonary function test results, and the effect of the presence of albuterol on the pulmonary function test results.

RESULTS

One of the 13 patients enrolled, a 48-year-old woman, left the study after 3 days because of illness and was not included in the efficacy analysis. The characteristics of the 12 patients who completed the study are shown in Table I.

Pulmonary function tests

There were no statistically significant differences in the mean baseline values obtained at the eight visits for any of the pulmonary function tests.

The analysis revealed that cetirizine and albuterol did not inhibit or potentiate one another's effects on any of the four pulmonary function variables at any time point. The mean percent increases in FEV₁ indicate, rather, that the two drugs have an additive bronchodilatory effect (Table II).

None of the study treatments caused a worsening of pulmonary function in any of the study patients.

FEV₁. FEV₁ was considered the primary indicator of bronchodilatory effect in this study. The mean percent change from baseline in FEV₁ for each of the eight treatments at each of the 11 time points are shown in Table II. The percent increase in FEV₁ from baseline was greater with the 20 mg dose of cetirizine than with the other two cetirizine doses at all time points except 6 hours, but the difference was statistically significant only at the 30-minute time point (*p* < 0.05). Albuterol alone increased FEV₁ significantly more than 5 mg of cetirizine alone but not 10 or 20 mg of cetirizine alone at 60, 90, and 120 minutes after baseline, but all three doses of cetirizine increased FEV₁ more than albuterol 7 and 8 hours after baseline (*p* < 0.05), indicating that the bronchodilatory action of

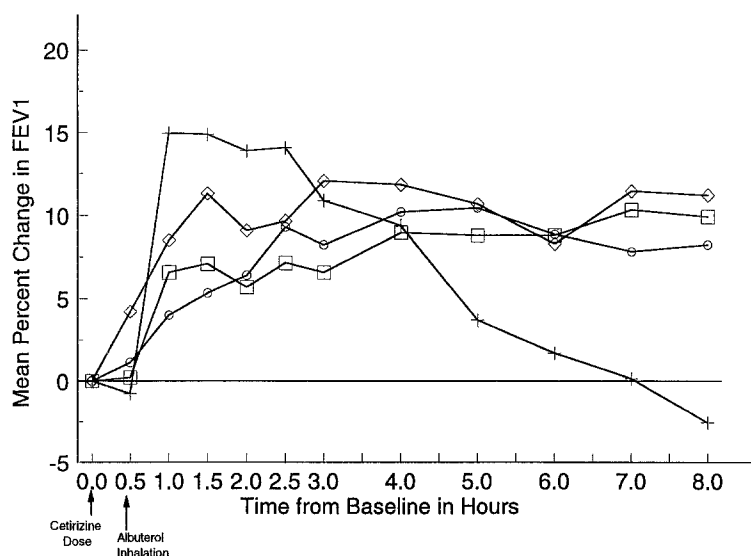


FIG. 1. Mean percent change in FEV₁ adjusted for baseline and placebo effect as a function of time after the administration of oral cetirizine, 20 mg (diamonds), 10 mg (squares), and 5 mg (circles) alone and after administration of inhaled albuterol 180 µg alone (plus symbols) ($n = 12$).

TABLE II. Mean percent change from baseline in FEV₁ in asthmatic patients ($n = 12$) treated with placebo, cetirizine alone, and cetirizine with albuterol (180 µg)

Time	Cetirizine alone				Cetirizine with albuterol			
	Placebo*	5 mg	10 mg	20 mg	Placebo†	5 mg	10 mg	20 mg
30 min	1.66	0.78	2.56	6.68‡	1.56	4.30	2.09	4.36
60 min	2.98	7.58	10.04‡	14.74‡	22.03‡	24.61‡	30.19‡	26.01‡
90 min	4.27	9.28‡	11.91‡	18.12‡	22.94‡	27.58‡	32.08‡	30.10‡
120 min	5.97	12.15‡	11.60‡	18.60‡	23.89‡	29.50‡	32.26‡	27.85‡
150 min	3.88	12.81‡	10.65‡	16.40‡	21.37‡	30.05‡	31.49‡	26.62‡
180 min	4.54	12.29‡	9.79	17.70‡	17.18‡	24.99‡	27.39‡	26.75‡
4 hr	3.50	13.82‡	8.14	17.37‡	13.84‡	23.08‡	29.38‡	22.29‡
5 hr	3.05	12.71‡	7.97	16.93‡	8.26	18.56‡	23.40‡	14.25‡
6 hr	1.18	11.00‡	9.85‡	10.70	6.38	13.26‡	18.05‡	11.80‡
7 hr	1.03	7.66	7.48‡	11.86‡	0.22	8.45	16.51‡	11.04‡
8 hr	-1.24	7.06	6.70‡	10.66‡	-2.42	4.93	11.66	6.80

*Placebo cetirizine capsule and placebo albuterol aerosol.

†Placebo cetirizine capsule and active albuterol aerosol.

‡Statistically significant change from baseline.

cetirizine lasts longer than that of albuterol. Cetirizine in combination with albuterol had the greatest effect on FEV₁.

The mean percent changes in FEV₁ obtained with each of the three cetirizine doses alone and with albuterol alone are shown in Fig. 1.

The 20 mg cetirizine dose increased FEV₁ significantly more than placebo at all time points except 30 minutes ($p < 0.02$). Treatment with 5 and 10 mg of cetirizine yielded significantly greater percent increases than placebo at 150 minutes and at all time points from 4 hours through 8 hours

($p < 0.02$). Albuterol increased FEV₁ significantly more than placebo at all time points from 60 minutes through 4 hours ($p < 0.05$), but not at 5 through 8 hours.

FVC. The mean percent changes in FVC obtained with the three cetirizine doses alone and with albuterol alone are shown in Fig. 2.

None of the cetirizine doses increased FVC significantly more than placebo at any of the 11 time points. Albuterol increased FVC significantly more than placebo at 60, 90, 120, and 150 minutes and at 4 hours ($p < 0.05$).

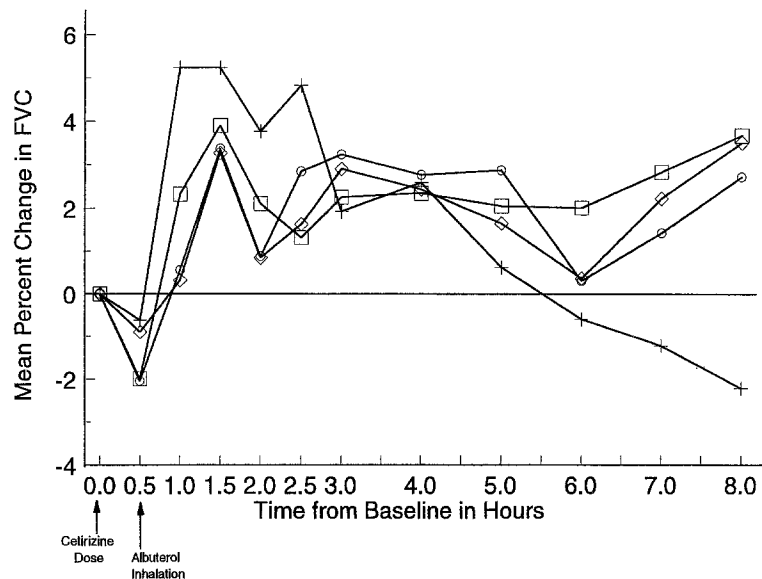


FIG. 2. Mean percent change in FVC adjusted for baseline and placebo effect as a function of time after the administration of oral cetirizine, 20 mg (*diamonds*), 10 mg (*squares*), and 5 mg (*circles*) alone and after administration of inhaled albuterol 180 μ g alone (*plus symbols*) ($n = 12$).

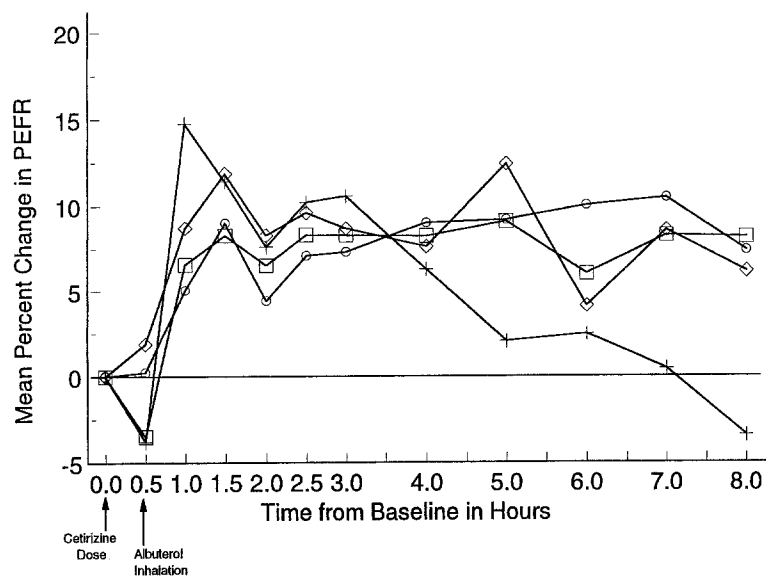


FIG. 3. Mean percent change in PEFR adjusted for baseline and placebo effect as a function of time after the administration of oral cetirizine, 20 mg (*diamonds*), 10 mg (*squares*), and 5 mg (*circles*) alone and after administration of inhaled albuterol 180 μ g alone (*plus symbols*) ($n = 12$).

PEFR. The mean percent changes in PEFR obtained with each of the cetirizine doses alone and with albuterol alone are shown in Fig. 3.

The 20 mg dose of cetirizine increased PEFR significantly more than placebo at 60, 90, and 150 minutes and at 5 and 7 hours ($p < 0.02$). The 10 mg dose of cetirizine increased PEFR significantly

more than placebo only at 7 hours ($p < 0.02$). The 5 mg dose of cetirizine increased PEFR significantly more than placebo at 90 minutes and at 4, 6, and 7 hours ($p < 0.02$). Treatment with albuterol yielded a significantly greater percent increase in PEFR than placebo at all time points from 60 minutes through 4 hours ($p < 0.05$).

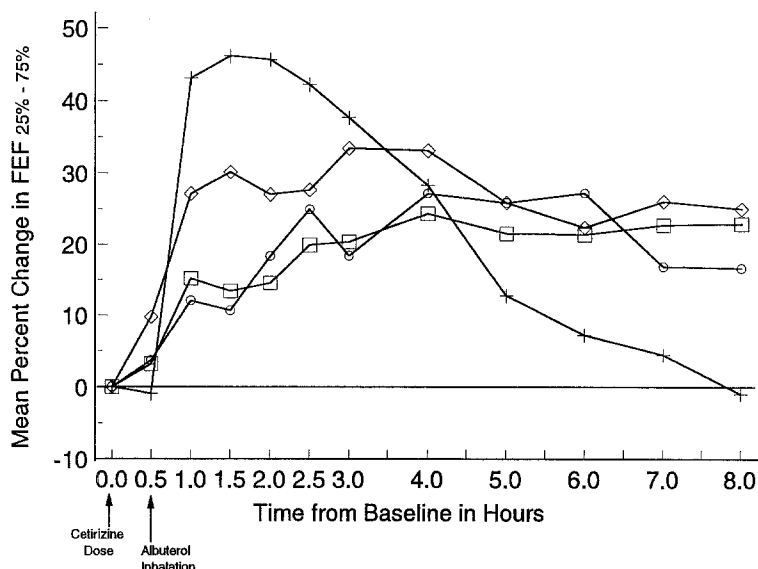


FIG. 4. Mean percent change in $FEF_{25\%-75\%}$ adjusted for baseline and placebo effect as a function of time after the administration of oral cetirizine, 20 mg (diamonds), 10 mg (squares), and 5 mg (circles) alone and after administration of inhaled albuterol 180 μ g alone (plus symbols) ($n = 12$).

$FEF_{25\%-75\%}$. The mean percent changes in $FEF_{25\%-75\%}$ produced by each of the cetirizine doses alone and by albuterol alone are shown in Fig. 4.

Treatment with 20 mg of cetirizine increased $FEF_{25\%-75\%}$ significantly more than placebo at all time points from 30 minutes through 8 hours ($p < 0.02$). The 10 mg dose of cetirizine caused a significantly greater increase in $FEF_{25\%-75\%}$ than placebo at all time points from 4 hours through 8 hours ($p < 0.02$), and the 5 mg cetirizine dose caused a significantly greater increase at 150 minutes and from 4 hours through 7 hours ($p < 0.02$). Albuterol increased $FEF_{25\%-75\%}$ significantly more than placebo at all time points from 60 minutes through 5 hours ($p < 0.05$).

Plasma concentrations

The mean plasma cetirizine concentrations obtained in the absence and presence of albuterol are presented in Table III. As the table shows, the cetirizine plasma concentrations were proportional to the cetirizine dose, and the standard deviations from the mean are proportional to the corresponding mean concentrations. Analysis of variance revealed that the presence of albuterol had no significant effect on cetirizine plasma concentration 120 minutes after the administration any of the three cetirizine doses.

TABLE III. Mean plasma cetirizine concentrations (in nanograms per milliliter) in patients with asthma ($n = 12$) 2 hours after treatment with cetirizine alone and cetirizine and albuterol (180 μ g) together

	Cetirizine		
	5 mg	10 mg	20 mg
Cetirizine alone			
Mean	110.3	242.9	472.7
SD	19.9	74.3	114.6
Cetirizine with albuterol			
Mean	122.9	227.3	466.4
SD	33.0	57.2	104.8

FVC was excluded from the statistical analysis of the relationship between cetirizine plasma concentration and the results of the pulmonary function tests because, as mentioned earlier, none of the three cetirizine doses had a statistically significant effect on FVC. For the other three pulmonary function variables, the analysis revealed that the patients' responses to cetirizine increased as the plasma concentration increased and that the increase was independent of the presence of albuterol.

Adverse experiences

The adverse experiences reported most frequently by patients after taking cetirizine were headache and somnolence. Of the five patients who reported somnolence, one reported four incidents, and four reported one incident each. Reports of somnolence were distributed about evenly for the three doses of cetirizine. No incidents of somnolence were reported after administration of placebo. Nine incidents of headache were reported by patients after taking cetirizine, and five incidents of headache were reported after taking placebo. No other adverse experience was reported by more than one patient after taking cetirizine, with the exception of dry mouth, which was experienced by two patients. All of the adverse experiences reported by the patients were described as mild or moderate.

DISCUSSION

In 1949, Herxheimer²⁷ presented the first experimental evidence that antihistamines (promethazine, pyrilamine, and tripeleminamine) have the ability to dilate the bronchi of patients with asthma. Subsequent clinical studies revealed that chlorpheniramine,²⁸ clemastine,²⁹ and terfenadine^{30,31} also have bronchodilatory activity. Recently, Brik et al.¹⁶ reported that the new H₁ antihistamine cetirizine had a modest but significant bronchodilatory effect in patients with mild asthma (i.e., patients with nearly normal baseline FEV₁ values) who had undergone bronchial challenge with inhaled histamine.

This study was designed to determine whether orally administered cetirizine has an effect on resting bronchial tone in a small number of patients with mild-to-moderate asthma (i.e., patients with baseline FEV₁ values of between 50% and 80% of predicted value). Concomitant albuterol treatment was included in the study to determine whether cetirizine either enhances or inhibits the bronchodilatory action of albuterol. Treatment with placebo and albuterol alone provided "negative" and "positive" controls, respectively, for the evaluation of the bronchodilatory activity of cetirizine.

Cetirizine in doses of 5, 10, and 20 mg with or without albuterol produced statistically significant percent increases over baseline in the FEV₁, PEFR, and FEF_{25%-75%} values of the 12 study patients but did not have a significant effect on FVC values. Twenty milligrams of cetirizine generally had a greater effect on FEV₁ (the primary measure of efficacy in the study) than did 5 and 10

mg, but the difference was statistically significant at only one time point. All three doses of cetirizine produced significantly greater percent increases than placebo in FEV₁, PEFR, and FEF_{25%-75%} for at least 7 hours after administration. Albuterol alone increased FEV₁ significantly more than 5 mg of cetirizine alone but not 10 or 20 mg of cetirizine alone at 60, 90, and 120 minutes after baseline, but all three doses of cetirizine increased FEV₁ significantly more than albuterol 7 and 8 hours after baseline ($p < 0.05$), indicating that cetirizine has a longer duration of bronchodilatory action than albuterol. None of the cetirizine treatments caused a worsening of pulmonary function in any of the study patients.

Albuterol alone had a significant effect on the four pulmonary function variables from 1 to 5 hours after baseline ($p < 0.05$), which is consistent with albuterol's recommended dosing frequency of every 4 to 6 hours.

The results of the analysis revealed that cetirizine neither potentiated nor inhibited the bronchodilatory action of albuterol in the study patients and showed that the presence of albuterol did not significantly affect the cetirizine plasma concentrations obtained 2 hours after the administration of the three cetirizine doses. Cetirizine and albuterol, however, did appear to have an additive bronchodilatory effect (Table II).

A full understanding of the clinical significance of the bronchodilatory effect of cetirizine must await the results of long-term studies performed in larger groups of patients. It is reassuring to know, however, that cetirizine can be used to treat such conditions as allergic rhinitis in patients with asthma without concern that the antihistamine will interfere with the bronchodilatory effect of albuterol. Indeed, cetirizine treatment may provide an extra benefit of additional bronchodilation in patients with allergies of the upper airway and concomitant asthma.

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