

Effect of cetirizine on histamine- and leukotriene D₄-induced bronchoconstriction in patients with atopic asthma

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Cetirizine, a derivative of hydroxyzine, is a new compound with potent antihistaminic property without antiserotonin and anticholinergic activities. The effect of both a single dose (15 mg) and 7 days of treatment (15 mg twice daily) with cetirizine, a potent H₁ antagonist on bronchoconstriction induced by histamine and leukotriene D₄ (LTD₄) has been examined in 10 patients with mild atopic asthma in a placebo-controlled, double-blind, crossover study. Cetirizine, after a single dose and 7 days of treatment with placebo, the geometric mean values of the provocative concentration of histamine causing a 20% fall in FEV₁ (millimolars) were 1.60 (95% confidence interval, 0.82 to 3.11) and 1.67 (0.77 to 3.65), compared with 118.07 (77.22 to 180.54) ($p < 0.0001$) and 53.16 (20.50 to 137.84) after cetirizine administration ($p < 0.0002$). The mean inhibition after a single dose was twofold higher than after 1 week of treatment ($p < 0.05$). After a single dose and 7 days of treatment with placebo, the geometric mean values of the provocative concentration of LTD₄ causing a 20% fall in FEV₁ (micromolars) were 2.26 (1.74 to 2.94) and 2.37 (1.77 to 3.17), compared with 3.90 (2.60 to 5.86) ($p < 0.05$) and 3.21 (2.28 to 4.52) after cetirizine administration. This result suggests that cetirizine is a potent H₁ antagonist in the human airways. Diminished activity after 1 week of treatment suggests subsensitivity of H₁ receptors developing in human airways. The small protective effect after a single dose against LTD₄-induced bronchoconstriction indicates a nonspecific rather than a specific receptor antagonism. (J ALLERGY CLIN IMMUNOL 1991;87:1010-3.)

Patients with asthma demonstrate bronchial hyperresponsiveness to specific and nonspecific stimuli. Although bronchial hyperresponsiveness to inhaled histamine is now well recognized in asthma, the mechanisms involved in its pathogenesis remain unclear. Membrane-derived sulphidopeptide leukotrienes are released in vivo and in vitro after allergen challenge.^{1,2} LTC₄, LTD₄, and LTE₄ are potent bronchoconstrictors in man,^{3,5} and inhaled LTE₄ has also been reported to enhance airway responsiveness to histamine in patients with asthma.⁶

Cetirizine, 2 HCl [2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy] (acetic acid), a derivative of hydroxyzine, is a potent and selective H₁

Abbreviations used

LTC ₄ , LTD ₄ , LTE ₄ :	Leukotrienes C ₄ , D ₄ , and E ₄
PC ₂₀ :	Provocative concentration producing a 20% fall in FEV ₁
PBS:	Phosphate-buffered saline

antagonist with prolonged duration of action. It is devoid of anticholinergic and antiserotonin activities.⁷ In a small study it has been demonstrated to modify the allergen-induced early response in some patients with asthma.⁸ To examine the relationship of histamine and leukotrienes in asthma, we have studied the effect of a single dose (15 mg) and 1 week of treatment (15 mg twice daily) with cetirizine on histamine- and LTD₄-induced bronchoconstriction in patients with mild atopic asthma in a double-blind, placebo-controlled, crossover study.

METHODS

We studied 10 patients (six men), mean age, 34 years (range, 23 to 52 years), with mild extrinsic asthma and

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TABLE I. Baseline FEV₁ in 10 patients

N = 10	Placebo		Cetirizine	
	Day 1	Day 8	Day 1	Day 8
Mean (SEM) FEV ₁ (L)				
Before drug	2.91 (0.20)	2.94 (0.21)	2.96 (0.23)	2.97 (0.21)
After drug	2.97 (0.21)	2.97 (0.22)	2.93 (0.20)	2.94 (0.23)
p Value	NS	NS	NS	NS

NS, Not significant.

positive responses to skin prick tests to at least three common inhaled allergens. None of the patients was taking oral corticosteroids, theophyllines, antihistamine, or anticholinergic agents. Inhaled β_2 -agonists and corticosteroids were stopped at least 12 hours and inhaled cromolyn sodium for 24 hours before the test. The study was approved by the West of Glasgow Hospital Ethics Committee, and informed written consent was obtained from each subject. Patients received either 15 mg of cetirizine twice daily or a matched placebo for 7 days with a washout period of 2 weeks between treatments. Treatments were administered in a double-blind, randomized manner. Inhaled β_2 -agonist and steroids were continued during the study period but stopped 12 hours before each test. Airway responses were assessed by measuring FEV₁ with a dry-wedge spirometer (Vitalograph, Buckingham, England). The best of three attempts was recorded for analysis.

Histamine inhalation challenge was performed before and 2 hours after medication on the first and the eighth day of each treatment period. After baseline FEV₁ had been recorded, patients inhaled 10 breaths of PBS (control) from a Mefar 120 nebulizer (Mefar, Elettromedicali, Brescia, Italy) with a dosimeter set at a constant delivery time (2 seconds) and pressure (25 lb/sq in; 172 kPa). The patient breathed from functional residual capacity to total lung capacity with a breath-hold time of 5 seconds between inhalations. Patients proceeded to histamine challenge if the change in FEV₁ after inhalation of PBS was <5%. Each subject inhaled 10 breaths of histamine diphosphate dissolved in PBS in doubling concentrations (from 0.41 mmol/L to 218.32 mmol/L) until the FEV₁ had fallen by >20% below the lowest FEV₁ value recorded after inhalation of PBS (control). FEV₁ was measured at 30, 90, and 180 seconds after each concentration. The results, expressed as PC₂₀, were obtained from the log dose-response curves. The second histamine challenge was performed 2 hours after drug administration and when FEV₁ readings had returned to within 5% of the baseline value. On the eighth day, before the last dose, histamine challenge was performed 14 hours after the previous evening dose.

The procedure for LTD₄ was similar. The challenge was performed 1 hour after the second histamine inhalation challenge (3 hours after treatment) and when FEV₁ readings had returned to within 5% of posttreatment values. LTD₄ (ICN Biomedicals, High Wycombe, Bucks, England) was stored at -70°C in sealed ampules until use. Normal and reverse-

TABLE II. Mean PC₂₀ histamine and LTD₄ (95% confidence intervals) after a single dose and 7 days of treatment with cetirizine and placebo

	Cetirizine	p	Placebo
Histamine (mmol/L)			
Day 1			
Before drug	1.61 (0.7-3.2)	NS	1.80 (0.8-3.3)
After drug	118.07 (77.2-180.5)	0.0001	1.60 (0.8-3.1)
Day 8			
Before drug	27.96 (8.6-90.2)	0.0009	1.57 (0.8-3.2)
After drug	53.16 (20.5-137.8)	0.0002	1.67 (0.8-3.6)
LTD ₄ (μmol/L)			
Day 1			
After treatment	3.90 (2.60-5.86)	0.05	2.26 (1.74-2.94)
Day 8			
After treatment	3.21 (2.28-4.52)	NS	2.37 (1.77-3.17)

NS, Not significant.

phase high-performance liquid chromatography ascertained the purity of LTD₄ (97%). A stock solution of LTD₄ (20 μg/ml) was prepared on the day of study and then diluted to the appropriate concentrations (from 0.625 μmol/L to 10.08 μmol/L) with PBS (pH 7.4) immediately before solution was placed in the nebulizer. The loss of activity of LTD₄ was not measured; however, the dosimeter method minimizes this loss compared with loss during continuous nebulization.⁹ FEV₁ was measured at 3, 5, 7, 10, and 20 minutes after each inhalation. PC₂₀ LTD₄ was obtained from log dose-response curves. Log PC₂₀ was compared by analysis of variance for crossover design and Student's *t* test.

RESULTS

The subject's mean (SEM) FEV₁ was 91.0% (2.9%) of predicted normal values on entry to the study. There was no significant difference in the mean pretreatment

baseline FEV₁ values on the 4 study days (Table I). Cetirizine and placebo, after a single dose and 7 days of treatment, did not alter the mean baseline FEV₁ significantly. After a single dose and 7 days of treatment with placebo, the geometric mean PC₂₀ (95% confidence interval) for histamine was 1.60 (0.82 to 3.11) and 1.67 (0.77 to 3.65) mmol/L. After a single dose of cetirizine, the geometric mean PC₂₀ was 118.08 (77.22 to 180.54) mmol/L, a 74-fold increase over the placebo value ($p < 0.0001$). After 7 days of treatment with cetirizine, the geometric mean PC₂₀ was 53.16 (20.50 to 137.84) mmol/L, a 32-fold increase over the placebo value ($p < 0.0002$) (Table II). The inhibition after a single dose was more than twofold higher than after 7 days of treatment. The difference was significant ($p < 0.05$). Cetirizine administration also demonstrated significant protection against histamine challenge before administration of the last dose. The geometric mean PC₂₀ for placebo was 1.57 (0.78 to 3.16) mmol/L; geometric mean for cetirizine was 27.96 (8.66 to 90.25) mmol/L ($p < 0.0009$).

All patients had LTD₄ challenge. After a single dose and 7 days of treatment with placebo, the geometric mean PC₂₀ for LTD₄ was 2.26 (1.74 to 2.94) and 2.37 (1.77 to 3.17) μ mol/L. After a single dose of cetirizine, the geometric mean PC₂₀ was 3.90 (2.60 to 5.86) μ mol/L. This small increase compared to placebo was statistically significant ($p < 0.05$). After 7 days of treatment, geometric mean PC₂₀ was 3.21 (2.28 to 4.52) μ mol/L with cetirizine (Table II). The difference was no longer significant. LTD₄ was approximately 1000 times more potent than histamine. No side effects with cetirizine were reported. Overall, there was no change in asthma symptoms during the study periods.

DISCUSSION

In the present study, cetirizine shifted the histamine dose-response curve (PC₂₀) by 74-fold to the right after a single dose and 32-fold after 7 days. Furthermore, the effect was also present up to 14 hours after the penultimate dose since it shifted the dose response curve by 17-fold before administration of the last dose. This contrasts with 8 mg of chlorpheniramine that produces twofold to fourfold shift¹⁰; 10 mg of astemizole, 17-fold shift¹¹; 180 mg of terfenadine, 35-fold shift¹²; and 8.8 mg of azelastine, 45-fold¹³ shift in the histamine dose-response curve.

The mean inhibition of histamine-induced bronchoconstriction was twofold higher with a single dose than after 7 days of treatment, and this difference was significant at 5% level. Taylor et al.¹⁴ have reported a similar development of subsensitivity to chlorpheniramine between 7 and 21 days in skin against

histamine-, morphine-, and allergen-induced wheal-and-flare reactions. These investigators were also able to demonstrate that hydroxyzine, 75 mg, taken daily for 3 weeks, caused partial tolerance not only to its own effect but also to effects of other unrelated antihistamines.¹⁵ Our results indicate that a similar tolerance or subsensitivity can develop in the human airways after continuous treatment with H₁-receptor antagonists. This observation has not been reported previously. This potential loss of activity is difficult to explain. We speculate that this subsensitivity may result from increase in H₁-receptor numbers in the airways. The β -adrenergic-receptor numbers increase in the leukocytes of patients receiving chronic β -blockade with propranolol.¹⁶ The hypothesis of a similar increase in H₁-receptor numbers in patients receiving chronic treatment with antihistamine is also supported by observation of Taylor et al.¹⁴ who demonstrated no significant change in percent suppression of morphine/antigen skin test after doubling the dose of antihistamine. Whether this development of subsensitivity or tolerance to antihistamine is of clinical significance merits additional investigation.

In contrast to the findings with histamine, the bronchoconstrictor response to LTD₄ was minimally inhibited after a single dose of cetirizine with a shift in the dose-response curve by less than twofold. However, after 7 days of continuous treatment, there was no significant difference between cetirizine and placebo. This minimal inhibitory effect of cetirizine is most likely to be nonspecific rather than specific receptor antagonism. In a previous study,¹³ H₁-receptor antagonist, azelastine, did not alter LTC₄-induced bronchoconstriction. Our results further support the observations reported previously that leukotrienes and histamine act independently on the bronchial smooth muscle through specific receptors.^{17,19}

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Effect of H₁-receptor blockade on late cutaneous reactions to antigen: A double-blind, controlled study

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This study is of the effect of the blockade of histamine H₁ receptors by a long-acting antihistamine on the immediate and late clinical response to antigen (Ag) and on the recruitment of eosinophils in the late-phase cutaneous reaction. Ten adult volunteers with late-phase reactions to the intradermal injection of either Dermatophagoides pteronyssinus or Phleum pratense (timothy) pollen performed a double-blind, crossover study. Each volunteer took astemizole, 10 mg, or identical placebo, daily for 2 weeks. Ag in the concentration that induced a late reaction in the screening visit was injected intradermally at the end of each drug period. The early reaction was measured serially for 30 minutes and the late reaction at 4 and 6 hours. Biopsies of the Ag and control sites were also performed at 6 hours. After a 6-week washout period, subjects then took the opposite medication for 2 weeks and returned for skin testing and biopsy. Skin testing demonstrated that astemizole inhibited the immediate response to both histamine and allergen but had no effect on the late response at 4 hours and at 6 hours. Biopsy specimens revealed no significant effect on eosinophil recruitment at 6 hours. We conclude that histamine H₁-receptor blockade has no effect on the late cutaneous reaction to Ag. (J ALLERGY CLIN IMMUNOL 1991;87:1013-9.)

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