

Effect of a non-sedative antihistaminic (loratadine) in moderate asthma

A double-blind controlled clinical crossover-trial

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Seventeen patients with perennial asthma, stable on a moderate dose of inhaled steroid, participated in a crossover study comparing the clinical effect of a non-sedative, potent and highly selective H_1 antagonist (loratadine 10 mg) with placebo. Each treatment period began with 2 weeks run-in followed by 8 weeks on either antihistamine or placebo. During the 8-week periods inhaled steroid was gradually tapered according to a fixed scheme. One patient was withdrawn from active treatment and three from placebo periods because of decreasing lung function ($P > 0.1$). Among the remaining 13 patients there was a threefold (1.8-4.8) decrease in the bronchial sensitivity to histamine during treatment with antihistamine compared to placebo ($P < 0.01$). There was a trend in favour of active treatment with regard to changes in all symptom scores, lung function and use of escape medication, but these differences were not statistically significant. The increase in FEV_1 was $< 5\%$ of predicted normal ($P < 0.05$). We concluded that the bronchial response to histamine can be attenuated by loratadine, an oral H_1 receptor antagonist, but further studies are necessary to assess the clinical usefulness and place of loratadine in the therapy of asthma.

Key words: asthma; non-specific bronchial responsiveness; non-sedative antihistamines; randomized clinical trial.

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With the development of new potent and highly selective H_1 antagonist there has been renewed interest in antihistamines in the treatment of asthma (7). These drugs have relatively little central nervous system or anticholinergic activity and thus cause only infrequent or mild sedation or dryness of the oral mucosa (7). Several studies have already demonstrated a potentially favorable effect of orally administered H_1 antagonists in subjects with asthma by virtue of inhibition of histamine (1, 7, 11), exercise (3, 9) and antigen-induced bronchospasm (2, 7). Moreover, H_1 antihistamines have been demonstrated to cause bronchodilatation in asthmatics (1, 6, 8, 11).

However, from these studies it is difficult to predict the therapeutic usefulness of these drugs in the maintenance therapy of bronchial asthma. The purpose of the present study was to evaluate the clinical effect of one of the newer non-sedative antihistamines in adults with moderate asthma.

MATERIAL AND METHODS

Informed consent was obtained from a total of five men (aged 19 to 56) and 12 women (aged 25 to 63) with endogenous or perennial allergic asthma. All the patients had been followed for some time in our clinic. They had all shown more than 20% variation in peak expiratory

Table 1

The mean difference between the two treatment periods (active - placebo) and 95 % confidence interval for the mean (t distribution)

Patient characteristic	Mean	95 % confidence interval	Statistics
Nocturnal asthma (score)	-0.0	-0.2-0.2	NS
Wheezing (score)	-0.3	-0.6-0.1	NS
Dyspnea (score)	-0.2	-0.6-0.1	NS
Coughing (score)	-0.3	-0.7-0.1	NS
Sputum (score)	-0.2	-0.6-0.1	NS
Morning PEF (% of pred.)	1.2	-4.0-6.4	NS
Evening PEF (% of pred.)	2.1	-2.7-6.9	NS
Salbutamol (puffs/day)	-0.6	-2.2-0.9	NS
FEV ₁ (4 of pred.)	0.8	-3.2-4.7	NS
PC ₂₀ (proportional)	3.0	1.8-4.8	$P < 0.01$

NS: not significant. % of pred.: Per cent of predicted normal.

flow and at least a 15 % improvement in FEV₁ 10 min after inhalation of 0.2 mg salbutamol. Their asthma was well controlled by inhaled beclomethasone dipropionate 200 µg b.i.d. with a baseline FEV₁ above 65 % of predicted normal. They were able to use a pressurized inhaler, keep a daily record card and recorded their peak expiratory flow at home.

No patients had taken oral steroids in the last 2 months or for longer than 3 months during the last year. No patients had other serious diseases or were pregnant.

Peak expiratory flow (PEF) was determined daily in the morning and evening using a Mini-Wright peak flowmeter. Patients were instructed to perform a forced maximal expiratory effort through the instrument after a maximal inspiration. The best of three readings with a variation of < 10 % was considered the true peak flow and entered as the result in the patient diary.

Forced expiratory volume at 1 s (FEV₁) was measured on a drywedge spirometer (Vitalograph Ltd, Buckingham, England) as the largest of two technically correct forced expiratory manoeuvres with a variation of < 5 %.

Bronchial responsiveness was assessed by performing a histamine challenge carried out as a non-cumulative dose response study (5). After an initial saline inhalation, histamine chloride was given in doubling doses from 0.03 mg/ml to 8 mg/ml. Inhalations were performed over 2 min with intervals of 5 min. FEV₁ was meas-

ured at 30 and 90 s after inhalation and the challenge was interrupted when a decrease of at least 20 % of the post saline FEV₁ was observed. A PC₂₀ histamine was calculated by linear interpolation between the two last points on the log dose response curve. Interpolation between FEV₁ saline and FEV₁ threshold dose was never performed.

The same nebulizer was used throughout the study. When driven by compressed air at 1.3 bar and a flow of 13 l/min the output was 150 µl/min (mean of 10 determinations, SD ± 10), and the aerodynamic diameter for the dry particles was for 99 % of the particles within 0.5-1.5 µ.

The study was a double-blind, randomized, placebo-controlled crossover trial. The two treatment periods were separated by a washout period of 3-6 months' duration. The treatment periods were of 10 weeks' duration, and always started with 2 weeks run-in followed by 8 weeks where the patients received either an antihistamine (loratadine 10 mg) or a placebo capsule at bedtime. The order of administering antihistamine and placebo was block-randomized (block-size: 2 patients).

During the run-in period it was ensured that the asthma was stable on inhaled beclomethasone dipropionate 200 µ b.i.d. Data from the run-in periods were used to calculate carry-over and period effects and used as a reference for adjusting recordings from the following 8-week periods. During the 8-week periods the inhaled

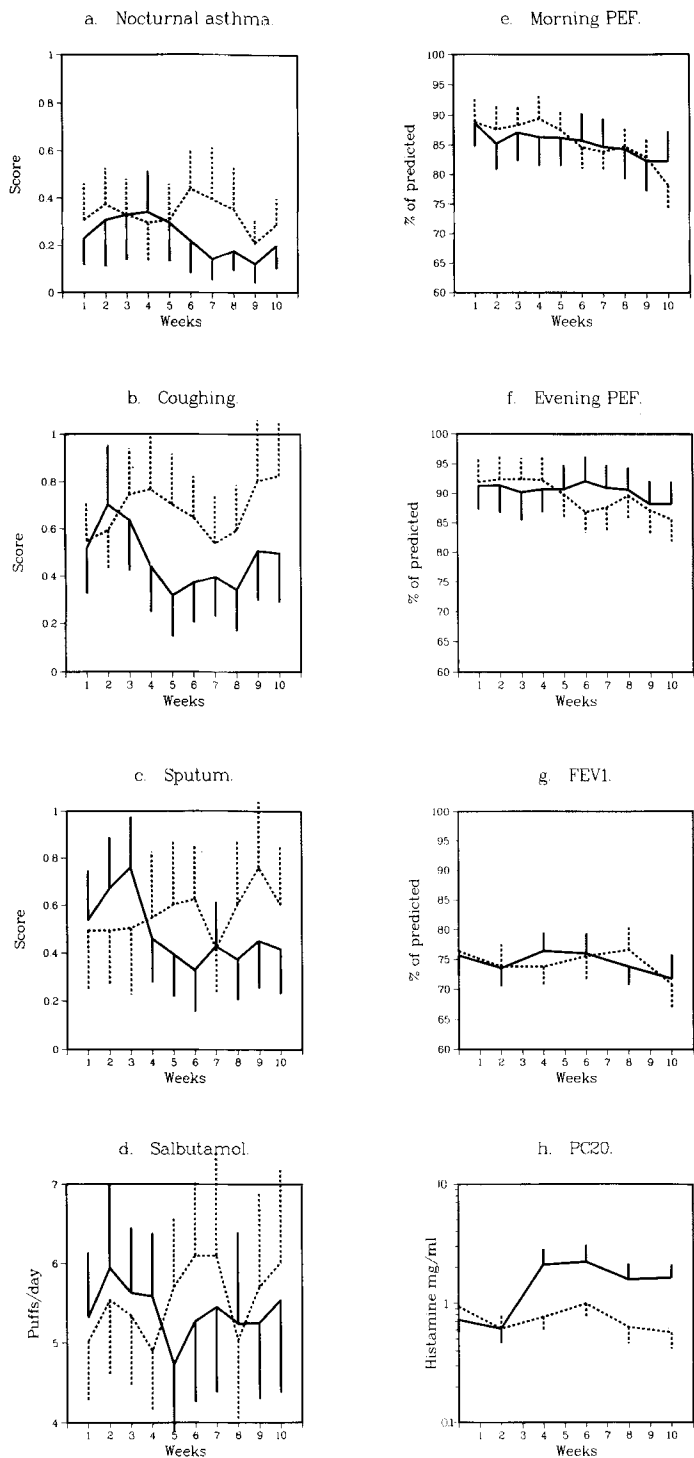


Fig. 1a-h. Symptom scores and test results for the run-in (1st and 2nd weeks) and subsequent 8 weeks' treatment with loratadine (solid line) or placebo (dashed line). The mean and SEM are shown for each week.

steroid was gradually reduced by 50 µg b.i.d. every 2nd week to a total dose of 50 µg b.i.d. for the last 2 weeks.

As escape medication, the patients were supplied with salbutamol inhaler (0.1 mg/puff) which they were instructed to use as required, for immediate relief from exacerbations of their symptoms. All other anti-asthma medication remained constant throughout the study period.

During treatment periods the patients kept a daily record of asthma symptoms (i.e. scores for wheezing, dyspnea, cough, sputum and nocturnal asthma), PEF and use of medication. At the beginning of the study and every 2nd week the patients were seen by one of the investigators, the patient diary was checked, and spirometry and measurement of non-specific bronchial responsiveness were performed.

On all visits to the clinic the patients were questioned about adverse events. The patient was withdrawn from the study if spirometric measurement fell below 50 % of predicted normal.

Statistics

Symptom scores, puffs of salbutamol, PEF, spirometric measures and bronchial responsiveness were summarized for each patient and each treatment period (active and placebo) as the area under the curve (week 3-10). This area was adjusted for the run-in period (week 1-2). The mean difference between the active and placebo periods and the 95 % confidence interval for the mean were then calculated by the *t* distribution (Table 1).

RESULTS

Four patients were not able to complete one of the treatment periods because lung function (FEV₁) decreased below 50 % of predicted normal. One of the patients was on active treatment at the time of withdrawal, while the other three were on placebo ($P > 0.1$).

The results for the remaining 13 patients are summarized in Table 1. It is seen that in overall terms patients had less symptoms (nocturnal

asthma, wheezing, dyspnea, coughing and sputum) on antihistamine than on placebo. However, the differences are not statistically significant. PEF and FEV₁ were slightly better (1-2 % of predicted normal), and the use of escape medication a little less (0.6 puff/day) in the active period, but again this was not significant.

The only statistically significant differences between active and placebo periods was the bronchial sensitivity to histamine, which was three times less during antihistamine treatment ($P < 0.01$).

No carry-over effect, period effect, or adverse reactions were observed.

DISCUSSION

Explanations proposed to account for the poor efficacy of older H₁ antihistamines in asthma included their low potency as competitive antagonists in the presence of high local concentrations of released histamine in the airways, and insufficient drug concentrations at the bronchial H₁ receptors to produce effective antagonism. The use of larger doses of antihistamines to achieve more effective H₁ blockade has been limited by the propensity for these drugs to exert anticholinergic and sedative side effects (7).

Recently, several new potent antihistamines with highly selective pharmacologic actions at H₁ receptors and without sedative or anticholinergic side effects, have been developed. So far only one clinical study of one of these new antihistaminics in the treatment of asthma has been published (12). In this study terfenadine 120 mg twice daily was used, which is twice the usual dose in rhinitis. Fifty-two adults with stable mild allergic perennial asthma were studied in a crossover design and significant changes in symptom scores, salbutamol intake and PEF were found. However, the differences between terfenadine and placebo were small, i.e. in the range of 1-2 % for morning and evening peak flows, and the authors concluded that further clinical studies are warranted to assess the place of terfenadine in the therapy of asthma.

In another recent study (10), 18 grass pollen-sensitive patients with mild seasonal asthma were studied. Baseline spirometric measurements were over 75% of predicted normal and the asthma was well controlled on inhaled beta-adrenoceptor agonists alone. The patients were treated with terfenadine 180 mg three times daily (i.e. 4–5 times the usual dose in rhinitis) and placebo in a crossover design. Terfenadine was found to diminish by approximately one half symptoms of cough and wheeze and bronchodilator inhaler use, and at the same time increased morning and evening PEF by 5–6%.

Our study was designed to titrate the effect of loratadine 10 mg once daily against a decreasing dose of inhaled steroid. We carefully selected patients with moderately severe asthma stable on a medium dose of inhaled steroid. During treatment periods the inhaled steroid was gradually tapered according to a prefixed schedule. The decrease in lung function and increased use of salbutamol in the placebo period (Fig. 1) confirm the steroid dependence of our patients. We planned to estimate the effect of the trial drug as the decrease in inhaled steroid which was feasible without a worsening of the lung function, or an increase in use of salbutamol. However, the results of the study did not allow such an estimate to be made with reasonable precision.

The 95% confidence intervals in Table 1 indicate a power of the study which we consider adequate from a clinical point of view. For instance, an increase of 5% or more in FEV₁ in the average patient treated with loratadine could be disproved as unlikely on the basis of our results ($P < 0.05$). However, it should be noted that the placebo group had a higher use of salbutamol (Fig. 1) and this might have influenced FEV₁ of this group.

The interpretation of our results was hampered by the fact that three patients were withdrawn from the study during a placebo period, because of gradual deterioration of their asthma parallel with the tapering of inhaled beclomethasone dipropionate. Only one patient dropped out of a period with active treatment, and this was caused by an upper respiratory tract infection which always aggravates the asthma of

this particular patient. The three drop outs in the placebo group could be regarded as treatment failures; however, due to the methodology of crossover designs, their results could not be taken into account in the comparison of patient characteristics in the two groups (Table 1 and Fig. 1).

Further, the present study does not give any information on the dose-response curve. The dosage used in this study is the usual dose in rhinitis. It is known from other studies that more than twice the dose of loratadine can be used without sedative or other side effects (4). The extent to which H₁ receptor blockade has been achieved in the present study can be inferred from the decrease in bronchial sensitivity to histamine (Table 1). A threefold decrease is far from the maximal possible blockade (7, 11). This may indicate that with the present dose we were at the low end of the dose-response curve for H₁ blockade in the treatment of asthma, and greater effect on symptoms and lung function may be expected from increasing the dose.

Future studies should deal with these problems, and further clarify the role for non-sedative antihistamines in the treatment of asthma.

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