Effect of cetirizine on exercise induced asthma

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Abstract

The effect of oral and inhaled cetirizine, a potent and specific H_1 receptor antagonist, was studied in patients with exercise induced asthma. Twelve patients (five male; mean age 35.2 years) were given oral placebo or cetirizine 10 mg twice daily for one week, double blind and in randomised order, and exercised on a treadmill for six to eight minutes at a submaximal work load two hours after the final dose. There was no significant change in baseline FEV_1 after treatment and cetirizine failed to inhibit exercise induced bronchoconstriction (maximum falls in FEV_1 28% and 27% of baseline). In a further eight patients (four male; mean age 40.8 years) the effect of 1 ml cetirizine (5 and 10 mg/ml) given through a Wright nebuliser was compared with that of placebo in a double blind trial. The fall in FEV_1 after exercise was reduced after both concentrations of cetirizine by 15.2% of baseline after 5 mg/ml and by 10.2% after 10 mg/ml, compared with 23.7% after placebo. In two patients cetirizine had no effect. In a further study cetirizine (10 mg/ml) given by inhalation displaced the geometric mean PC_{20} histamine 13.1 fold to the right by comparison with placebo. The reason for the difference between the effects of oral and of inhaled cetirizine on exercise asthma is not clear but may be related to differences in local concentration in the airway.

The mechanism of increased airflow obstruction after exercise in patients with asthma remains unclear. Exercise induced asthma has been related to hyperventilation¹ and subsequent airway cooling,² and more recently to the rapid rewarming of airways during the recovery period.³ It is also not clear whether the thermal burden imposed on the airways during exercise has a direct effect on mast cells, leading to release of active mediators such as histamine, or whether it acts through an effect on the vagal irritant receptors. Increased plasma histamine concentrations and a rise in circulating neutrophil chemotactic activity have been found after exercise in asthmatic patients.⁴

We have investigated the role of histamine by the use of a potent and specific H_1 receptor antagonist, cetirizine, given orally and by inhalation in exercise induced asthma.

Methods

We studied 20 patients with mild extrinsic

asthma with documented exercise induced bronchoconstriction (fall in FEV_1 over 20% after treadmill exercise). All patients were non-smokers and all had positive skinprick test responses to at least three common inhaled allergens. None of the patients was taking oral corticosteroids, theophyllines, antihistamines, or anticholinergic drugs. Inhaled beta₂ agonists and corticosteroids were stopped for at least 12 hours and inhaled sodium cromoglycate for 24 hours before each test. The study was approved by the hospital ethics committee and informed consent was obtained from each subject. Treatment was given in double blind, randomised manner. Airway responses were assessed by measuring FEV_1 with a dry wedge spirometer (Vitalograph, Buckingham), the best of three attempts being recorded for analysis.

ORAL CETIRIZINE

We compared the effect of one week's treatment with oral placebo and cetirizine (10 mg twice daily) on exercise induced asthma in 12 patients (five male; mean (SEM) age 35.2 (4.3) years). Patients were asked to take cetirizine or matched placebo for a week and to return on the eighth day after withholding the last dose. On arrival they had baseline FEV_1 measured and the last dose of drug was given. FEV_1 was measured again two hours later and the patient was then exercised on a treadmill for six to eight minutes at a submaximal work load (to achieve 80% of maximum age related heart rate). FEV_1 measurements were repeated two, five, 10, 15, and 30 minutes after exercise. Room temperature on study days varied from 20° to 22°C and relative humidity from 40% to 60%. There was no significant difference in temperature and humidity on study days. The appropriate work load for each patient was determined at a preliminary visit and thereafter kept constant. The procedure was repeated with the alternative treatment after a washout period of at least two weeks.

INHALED CETIRIZINE

The effect of a single dose of 5 and 10 mg of inhaled cetirizine (5 mg/ml and 10 mg/ml) was compared with that of placebo (phosphate buffered saline, pH 7.4) in a further eight patients (four male; mean age 40.8 (3.7) years). After having baseline FEV_1 recorded patients were given 1 ml of cetirizine (5 or 10 mg/ml) or matched placebo (phosphate buffered saline as before) through a Wright nebuliser (nebuliser volume 4 ml, output 0.133 ml/min at a flow rate of 9 litres/min, and pressure 50 lb/in², 344.4 kPa). The treatments were given double blind and in randomised

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Accepted 11 January 1991

Age, sex, work load, and maximum percentage fall in FEV₁ after exercise challenge with placebo and cetirizine given orally and by inhalation

<i>Patient No</i>	<i>Age</i>	<i>Sex</i>	<i>Work load (kpm/min)</i>	<i>Placebo</i>	<i>Cetirizine</i>	
ORAL CETIRIZINE (10 mg twice daily)						
1	26	M	1866	-47	-24	
2	28	F	881	-25	-21	
3	25	M	1279	- 8	-37	
4	50	F	740	-40	- 8	
5	23	F	679	-38	-46	
6	51	F	1009	-28	-42	
7	32	M	1597	-39	-23	
8	51	F	1052	-17	-27	
9	45	F	967	-26	-21	
10	53	M	991	-26	-32	
11	34	F	1040	-10	-25	
12	19	M	1609	-36	-16	
Mean	35.2		1143	-28.2	-27	
SEM	4.3		99	4.2	3.3	
p*					NS	
INHALED CETIRIZINE (5 and 10 mg)						
				<i>5 mg</i>	<i>10 mg</i>	
13	32	M	1689	-21.4	-16.9	- 4.0
14	43	F	826	-24.8	-17.0	-16.9
15	53	F	881	-16.5	-12.3	+ 5.7
16	48	F	1016	-14.8	- 4.9	+ 8.9
17	44	M	1383	-21.7	-16.1	-33.3
18	24	M	1308	-42.4	-13.8	- 8.4
19	51	F	1144	-18.8	-14.7	- 8.5
20	32	M	1438	-29.4	-26.2	-25.8
Mean	40.8		1210	-23.7	-15.2	-10.3
SEM	3.7		105	3.1	2.1	5.1
p*					0.05	0.05

*By comparison with placebo.
kpm—kilopond metre.

order. Thirty minutes after each treatment FEV₁ was recorded. The patients were then exercised at a submaximal work load for six to eight minutes followed by FEV₁ measurement at two, five, 10, 15, and 30 minutes. The tests were separated by at least three days.

All patients underwent histamine inhalation challenge on a further two study days after a single dose of cetirizine (10 mg/ml) or matched placebo given double blind and in random order. After baseline FEV₁ measurement each patient was given 1 ml cetirizine (10 mg/ml) or placebo through a Wright nebuliser. FEV₁ was recorded 30 minutes after treatment and histamine inhalation challenge was carried out according to the method of Cockcroft *et al.*⁵ Patients inhaled histamine diphosphate dissolved in phosphate buffered saline in doubling concentrations (from 0.0625 to 64.0 mg/ml). FEV₁ was

recorded 30, 60, and 90 seconds after each inhalation and the procedure repeated until the FEV₁ had fallen at least 20% below the lowest FEV₁ value recorded after inhalation of buffered saline. The results were expressed as the concentration producing a 20% fall in FEV₁ (PC₂₀), obtained from the dose-response curve.

ANALYSIS

The PC₂₀ values were log transformed before analysis. The maximal changes in FEV₁ after exercise were calculated from post-drug baseline values. The maximal falls in FEV₁ after the exercise challenge in the oral cetirizine study were compared by Student's *t* test. The maximal percentage falls in FEV₁ after exercise and different concentrations of inhaled cetirizine and placebo and the changes in PC₂₀ histamine were compared by analysis of variance.

Results

ORAL CETIRIZINE

The mean (SEM) FEV₁ was 91.0% (2.3%) of predicted at entry to the study. The mean pretreatment baseline FEV₁ was 3.05 (0.24) l on the placebo day and 2.94 (0.23) l on the cetirizine day. Two hours after treatment FEV₁ was similar after placebo and after cetirizine at 3.18 (0.28) and 3.16 (0.33) l (table). Neither placebo nor cetirizine caused a significant change in FEV₁. The mean maximum % fall in FEV₁ after exercise was 28.2 (4.1) and 27.0 (3.3) with placebo and cetirizine respectively. The difference was not significant.

INHALED CETIRIZINE

The mean (SEM) FEV₁ was 83.0% (3.1%) of predicted at entry to the study. Mean FEV₁ values were 2.84 (0.27) l with placebo, 2.94 (0.28) l with cetirizine 5 mg/ml, and 2.82 (0.27) l with cetirizine 10 mg/ml before treatment and 2.94 (0.23), 2.98 (0.27), and 2.94 (0.33) l 30 minutes after inhalation of the drugs. There was no significant difference in baseline FEV₁ on the three study days and neither placebo nor either concentration of cetirizine caused a significant change in the resting FEV₁.

The mean (SEM) maximum % fall in FEV₁ after exercise was 23.7 (3.1), 15.2 (2.1), and 10.2 (5.1) with placebo and 5 and 10 mg/ml cetirizine (figure). The difference between both concentrations of cetirizine and placebo was significant (*p* < 0.05); there was no significant difference between the two doses of cetirizine. Six patients showed protection with cetirizine, the mean (SEM) maximum % fall in FEV₁ after exercise being 23 (4.1), 13 (1.8), and 3.8 (3.9) with placebo and 5 and 10 mg/ml cetirizine.

The geometric mean PC₂₀ (95% confidence interval) for histamine was 0.6 (0.27–1.3) after placebo and 8.16 (3.16–21.08) after 10 mg inhaled cetirizine. Cetirizine caused a 13.1 fold shift to the right in the dose-response curve by comparison with placebo (*p* < 0.001).

Discussion

The increased losses of heat or water or both

Inhibition (*p* < 0.05) of the fall in FEV₁ after exercise by inhaled cetirizine (5 and 10 mg/ml) by comparison with placebo. There was no significant difference between 5 and 10 mg/ml cetirizine.

from the respiratory tract that result from hyperventilation have been suggested as possible triggers of exercise induced asthma.⁶ Breathing cold air during exercise has been shown to potentiate exercise induced asthma.^{2,7} Anderson and colleagues have suggested that airway water loss is a potent stimulus in exercise induced asthma, having shown that inhalation of hyperosmolar aerosol can induce bronchoconstriction in patients with asthma.^{8,9} The most convincing evidence that respiratory heat loss in itself is not an adequate explanation of exercise asthma comes from a series of studies showing that hyperventilation or exercise with hot dry air is as potent a stimulus of bronchoconstriction as is hyperventilation with cold dry air.¹⁰⁻¹² Noviski and colleagues¹³ have shown that part of the bronchoconstriction may be related to the intensity of exercise rather than to change in the temperature or osmolarity of the respiratory tract.

The link between respiratory heat loss and exercise induced bronchoconstriction is not yet clear, and both reflex vagal and humoral mechanisms have been suggested. Mediator release from the lung mast cells may play a part as increased plasma histamine and neutrophil chemotactic activity have been found after exercise.⁴ Attenuation of the bronchoconstrictor response to repeated exercise challenges at short intervals also supports depletion of mediator stores from mast cells.¹⁴

Although histamine has been implicated as a mediator in exercise induced asthma, the use of antihistamines to prevent an exercise induced bronchoconstrictor response has generally been disappointing. This may in part be related to failure to achieve a sufficient concentration of antihistamines at lung H₁ receptor sites, as older antihistamines could not be given in high doses because they caused sedative and anticholinergic side effects. The results with the newer H₁ receptor antagonists in exercise induced asthma have been varied. Inhaled clemastine¹⁵ and oral astemizole have been reported to protect against exercise induced asthma¹⁶ whereas ketotifen, despite its pronounced antihistaminic properties, failed to show any effect.^{17,18} Terfenadine¹⁹ and azelastine²⁰ have been shown to modify exercise induced asthma, though the protective effect of terfenadine was observed only with higher doses.

Cetirizine 2HCl, a derivative of hydroxyzine, is a potent and selective H₁ antagonist and in a recent study²¹ we found a 74 fold shift of the histamine dose-response curve to the right after a single oral dose of 15 mg. It is free of anticholinergic and antiserotonin effect.²² Studies in vitro have shown that it inhibits human basophil anti-IgE induced degranulation and in the rat peritoneal mast cell activation by substance P.²³ In the present study we have been unable to find any protection against exercise induced asthma after one week's treatment with oral cetirizine. In contrast, a single 1 ml dose of inhaled cetirizine at 5 mg/ml and 10 mg/ml caused significant protection against exercise induced asthma in six of the eight patients studied. There was a suggestion of a dose-response effect in these six patients. The difference in the protection between the inhaled

and the oral route is difficult to explain. One possibility is that increased local concentrations by the inhaled route stabilise airway mast cells. Similar differences have been observed with frusemide given by inhalation and orally in patients with exercise induced asthma.²⁴ Further studies of inhaled and oral cetirizine in experimental asthma may help to elucidate these differences.

We thank Mrs J Peter for secretarial assistance; UCB Pharmaceuticals, Belgium, for the supply of cetirizine powder; and Mrs Heather Ambler for technical assistance.

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