

Influence of zafirlukast and loratadine on exercise-induced bronchoconstriction

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Background: Airway obstruction induced by physical exercise is a common feature in asthma, and conventional treatments do not offer optimal protection. There is thus a need for additional therapies for optimal control of exercise-induced bronchoconstriction (EIB).

Objective: The influence of treatment with the antihistamine loratadine and the antileukotriene zafirlukast alone and in combination on EIB was investigated. This combination has previously shown beneficial additive effects in allergen-induced bronchoconstriction.

Methods: In a double-blind cross-over study loratadine (10 mg twice daily) and zafirlukast (80 mg twice daily) were evaluated alone and in combination in 16 nonsmoking patients with mild asthma, previously documented EIB, and airways hyperresponsiveness to histamine.

Results: The mean $\pm$ SE maximum decrease in FEV₁ after a standardized exercise provocation was 21.6% $\pm$ 3% after placebo, 22.8% $\pm$ 3% after loratadine, 13.9% $\pm$ 2% after zafirlukast ($P < .05$ vs placebo), and 10.3% $\pm$ 2% after the combination of loratadine and zafirlukast ($P < .05$ vs placebo). Expressed as the area under the FEV₁ percentage change versus time curve, the mean protection produced by zafirlukast and the combination of zafirlukast and loratadine was 57% and 65%, respectively, whereas loratadine alone had no significant protective effect. There was also no significant difference between the effect of zafirlukast alone or in combination with loratadine.

Conclusion: The study confirmed the beneficial effect of a leukotriene receptor antagonist in EIB but failed to obtain evidence that H₁-receptor antagonism alone or together with the cysteinyl-leukotriene 1 receptor antagonist zafirlukast offers a protective effect. (*J Allergy Clin Immunol* 2002;109:789-93.)

Key words: Histamine, leukotrienes, exercise-induced asthma, leukotriene receptor antagonists

Airway obstruction induced by physical exercise is a common feature in asthma. Symptoms may occur despite

Abbreviations used

AUC: Area under the curve
CysLT₁: Cysteinyl-leukotriene 1
EIB: Exercise-induced bronchoconstriction
H₁: Histamine 1

prophylactic treatment with inhaled corticosteroids and cromones. Furthermore, additional protection with a short- or a long-acting β_2 -agonist may diminish with prolonged use. Clearly, there is a need for additional therapies for optimal control of exercise-induced bronchoconstriction (EIB).

Histamine and prostaglandins have been suggested to be involved in EIB. However, pretreatment with specific H₁-receptor antagonists has given variable results,^{1,2} as have studies in which the effect of different cyclo-oxygenase inhibitors on EIB have been investigated.^{1,3} On the other hand, there are now many studies demonstrating that both leukotriene biosynthesis inhibitors and leukotriene-receptor antagonists inhibit a major part of EIB.⁴⁻¹¹ However, the inhibition is not complete, suggesting that additional mediators are involved.

In an allergen bronchoprovocation study we have previously demonstrated an additive benefit of the H₁-receptor antagonist loratadine and the leukotriene-receptor antagonist zafirlukast in preventing early and late asthmatic responses. In that study loratadine, zafirlukast, and the combination of the 2 drugs afforded protection of the early response to inhaled allergen by 25%, 62%, and 75%, respectively.¹² As a follow-up to this, we used the same specific antagonists (zafirlukast, 80 mg twice daily, and loratadine, 10 mg twice daily) and study design to determine whether this combination therapy has a role in the management of EIB. The effect of this specific treatment strategy in EIB has not been evaluated previously.

METHODS

Subjects

Sixteen nonsmoking subjects with mild asthma completed the study (Table I). The subjects had, within 15 months before the study, demonstrated bronchial hyperreactivity to histamine and at least a 15% decrease in FEV₁ after a submaximal exercise test while breathing dry air. Their asthma was stable and controlled on short-acting β_2 -agonists only in 12 of the subjects, and 4 subjects also used inhaled budesonide at a fixed dose not exceeding 800 μ g daily during the 6 weeks before and during the study. The study was approved by the Local Ethics Committee (Dnr 96-384) and the Swedish Medical Products Agency (Läkemedelsverket, Dnr 151:8/97), and the subjects gave informed consent.

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TABLE I. Patient characteristics

Subject No.	Age (y)	Sex	Height (cm)	Weight (kg)	Methacholine PD ₂₀ (μg)	Work rate (W)	FEV ₁ (% predicted)	FEV ₁ % decrease (randomization)
1	26	M	197	96	115	200	95	19
2	28	F	175	68	120	160	82	22
3	23	M	179	75.5	110	250	102	20
4	30	F	171	64.5	250	165	97	22
5	26	M	180	79.5	190	230	89	28
6	24	F	171	64.5	270	185	91	16
7	31	F	168	64.0	140	150	98	21
8	28	F	173	60.5	140	145	92	22
9	28	F	155	64.5	90	125	93	24
10	27	F	162	57.5	590	180	99	32
11	26	F	168	56.0	160	110	95	20
12	28	F	168	73.5	165	150	102	21
13	28	F	169	65.5	78	130	86	48
14	37	F	160	57.0	110	130	70	39
15	29	M	176	72.0	330	270	73	39
16	29	F	167	60.0	380	125	76	18
Mean	28	12 F/4 M	171	67	173 (geometric)	169	90	25.7
Range	23-37		155-197	57-96	78-590	110-270	70-102	16-48

Study design

First, a repeat submaximal dry-air exercise challenge test resulting in at least a 15% decrease in FEV₁ was required to confirm current responsiveness to exercise. The study was started within 2 weeks (range, 7-13 days) after the screening exercise test and carried out with a double-blind, double-dummy, randomized cross-over design. Subjects underwent 4 identical challenge sessions 3 weeks apart. Treatments with placebo, zafirlukast (80 mg twice daily), loratadine (10 mg twice daily), and the combination of zafirlukast and loratadine in the same doses were started 1 week before each exercise challenge test, which was always performed on the last day of treatment.

Exercise challenge

Exercise challenge tests were always performed at the same time in the morning (± 2 hours) and within 2 ± 1 hours after intake of the last morning dose of study medication. Short-acting β_2 -agonists and nonsteroidal anti-inflammatory drugs were withheld for at least 6 and 24 hours, respectively. Pulmonary function was measured as FEV₁ on a spirometer (Vitalograph MDI Compact, Förbandsmaterial), and the baseline, measured immediately before exercise and defined as the best of 3 efforts, was to be at least 70% of the predicted normal value on all study days. Exercise was performed on a calibrated electrically braked bicycle ergometer (SECA Cardiotest 100, Vogel and Halke) for 5 minutes at a constant submaximal (approximately 80%) work rate. During exercise, the subjects wore nose clips and breathed dry air at room temperature through a mouthpiece from a Douglas-bag reservoir. The individual work rate, on the basis of a prestudy progressive exercise test to exhaustion, was identical at the 4 pretreated challenge sessions. Spirometry was obtained as single FEV₁ measurements immediately and at 1, 3, 5, 8, 10, 15, 20, 30, 40, 50, and 60 minutes after exercise. Heart rate and blood oxygenation were monitored throughout the test. Details of the exercise challenge procedure, its reproducibility, and its sample size requirements have been published, and this study was powered accordingly.¹³

Drugs

Zafirlukast (Accolate), loratadine (Claritin), and their respective placebo formulations were supplied by Zeneca Pharmaceuticals.

Statistics

The area under the curve (AUC; percentage change of FEV₁ vs time) was calculated from the individual data points by using the trapezoidal rule for integration. Repeated-measures ANOVA was used on maximum decreases in FEV₁, AUCs, and baseline FEV₁ values to compare different treatment groups. For specific comparisons between treatments, the Duncan post hoc test was used. Differences were considered to be significant when the *P* value was less than .05.

RESULTS

EIB was markedly reduced after treatment with zafirlukast alone or zafirlukast and loratadine in combination, whereas loratadine offered no protection (Fig 1). The mean $\pm$ SE maximum decrease in FEV₁ was $21.6\% \pm 3\%$ for placebo, $22.8\% \pm 3\%$ for loratadine, $13.9\% \pm 2\%$ for zafirlukast ($P < .05$ vs placebo), and $10.3\% \pm 2\%$ for their combination ($P < .05$ vs placebo). The maximum decrease occurred, on the average, within 15 minutes. There was no effect of any treatment on the time to maximal decrease (Fig 1).

Expressed as the area under the FEV₁ percentage change versus time curve 0 to 60 minutes after challenge, the mean $\pm$ SE values were 606 ± 89 for placebo, 655 ± 126 for loratadine (not significant vs placebo), 258 ± 65 for zafirlukast ($P < .05$), and 206 ± 63 for the combined treatment with loratadine and zafirlukast ($P < .05$). The mean protection produced by zafirlukast and the combination of zafirlukast and loratadine was 57% and 65%, respectively. There was no significant difference between the effect of zafirlukast alone or in combination with loratadine.

Treatment with zafirlukast alone and the combination of zafirlukast and loratadine caused a small improvement of baseline pulmonary function (2.7% and 3.9%, respectively) that was statistically significant compared with results with placebo (Table II) or prescreening baseline values (not shown). However, there was no correlation

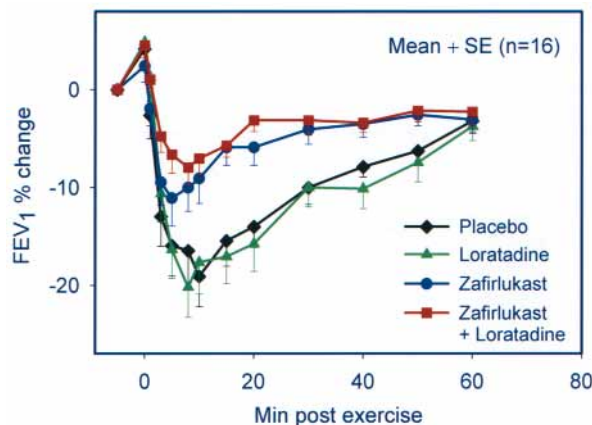


FIG 1. Mean exercise-induced changes in pulmonary function (FEV_1) measured over 1 hour after each of the drug treatments.

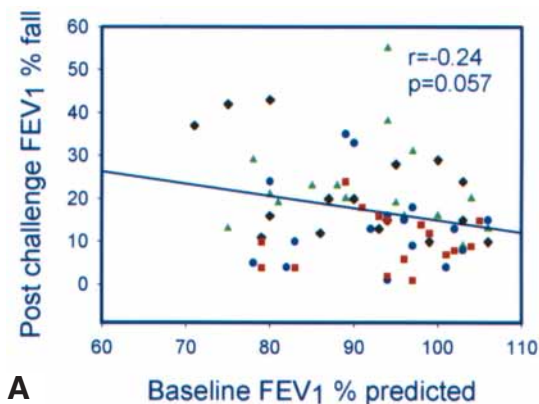
between prechallenge FEV_1 values and the maximum decrease in FEV_1 after exercise (Fig 2, A). Likewise, there was also no correlation between the change of baseline lung function during the active treatments in relation to placebo and the degree of protection against EIB afforded by the respective treatments (Fig 2, B).

The work intensity was identical during the 4 sessions, as evidenced by almost identical maximum heart rates (Table II), and there were no carryover effects of treatments. There were no significant abnormal laboratory values during the treatments and no clustering of the few observed adverse events during any treatment arm. The most common adverse event was abdominal pain, which was experienced by 1 patient while receiving zafirlukast and 2 patients while receiving placebo.

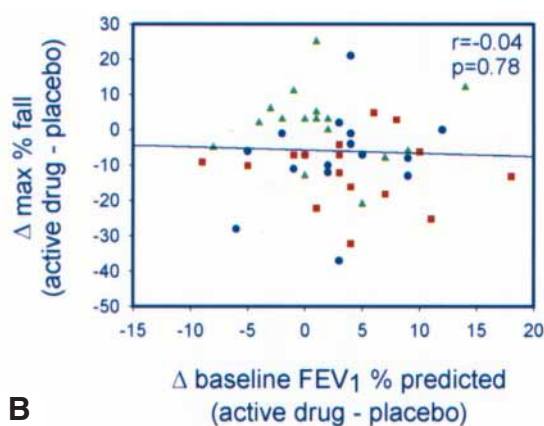
DISCUSSION

EIB is a feature of asthma that causes significant disability, especially in children. This investigation documented that 1 week of pretreatment with the cysteinyl-leukotriene 1 ($CysLT_1$)-receptor antagonist zafirlukast inhibited the bronchoconstrictive response to exercise by 57%. The combination of zafirlukast and the H_1 -receptor antagonist loratadine caused 65% inhibition of the response, but there was no significant difference between the effect of zafirlukast in the presence or absence of the antihistamine. Likewise, loratadine afforded no protection by itself when compared with that afforded by placebo. Thus these findings do not support adding an antihistamine to antileuko-trienes in the management of EIB.

The magnitude of protection afforded by zafirlukast in this study is in keeping with that seen in other studies that have investigated different $CysLT_1$ -receptor antagonists and leukotriene biosynthesis inhibitors in EIB.⁴⁻¹¹ The range of attenuation has varied between 30% and 70%, depending on the dose, time, and route of administration of the antileukotriene drugs investigated and on whether the maximum decrease in FEV_1 or AUC has been used as the endpoint.¹³



A



B

FIG 2. A, Baseline lung function (FEV_1) expressed as the percentage of predicted normal values versus maximum postexercise percentage decrease in FEV_1 at the 4 pretreated exercise challenge tests: black diamonds, placebo; green triangles, loratadine; blue circles, zafirlukast; red squares, zafirlukast and loratadine. **B,** Improvement in baseline lung function (FEV_1) expressed as the difference in FEV_1 values in percentage of predicted normal values between each of the active drug treatments and placebo. Attenuation of the exercise challenge response was expressed as the difference in maximum percentage decrease between the respective active drug treatments and placebo: green triangles, loratadine; blue circles, zafirlukast; red squares, zafirlukast and loratadine.

The lack of protection afforded by loratadine was perhaps surprising given that the H_1 -receptor antagonist terfenadine has been shown to cause a partial reduction in EIB.^{1,14,15} These opposing results imply that the antihistamines loratadine and terfenadine have pharmacologic properties that differ. Terfenadine has been shown to inhibit release of leukotrienes and other mast cell mediators, and it is conceivable that this action is related to its potential to attenuate EIB.¹⁶ Although this may be clinically useful, it makes terfenadine unsuitable in mechanistic studies in which selective antagonism of H_1 -receptors is desired. Of the potent and selective second-generation H_1 -antagonists, cetirizine has also been found to be ineffective in the treatment of EIB.²

Loratadine was selected for this study because it has been documented to be a selective H_1 -antagonist. Thus it does not inhibit release of histamine or leukotrienes from

Asthma, rhinitis,
other respiratory
diseases

TABLE II. Baseline FEV₁, maximum heart rate, and maximum percentage decrease of FEV₁ during exercise on the different challenge days

Subject No.	Placebo			Loratadine			Zafirlukast			Zafirlukast + loratadine		
	FEV ₁ (L)	HR (beats/min)	% Decrease	FEV ₁ (L)	HR (beats/min)	% Decrease	FEV ₁ (L)	HR (beats/min)	% Decrease	FEV ₁ (L)	HR (beats/min)	% Decrease
1	5.17	165	10	5.04	167	16	5.08	159	9	5.47	160	15
2	2.91	184	16	2.93	183	19	2.98	183	4	3.00	186	4
3	4.61	181	15	4.64	182	20	4.64	167	9	4.55	170	8
4	3.50	141	24	3.23	144	19	3.49	146	13	3.34	143	14
5	4.06	160	20	3.97	158	23	4.25	163	16	4.20	164	16
6	3.04	163	12	3.02	167	23	3.17	161	33	3.32	165	15
7	3.30	168	10	3.30	166	13	3.14	166	4	3.03	174	1
8	3.16	172	20	3.17	178	20	3.29	181	13	3.36	183	2
9	2.81	171	29	2.82	163	16	2.66	168	1	2.85	169	6
10	2.93	166	15	3.22	170	7	3.32	169	15	3.26	170	9
11	3.14	156	14	3.20	160	38	3.24	159	15	3.24	161	6
12	3.18	155	28	3.26	153	31	3.26	160	18	3.33	155	12
13	2.71	185	43	3.17	180	55	2.99	183	35	3.08	184	18
14	2.01	159	37	2.21	166	29	2.25	161	24	2.51	161	24
15	3.17	151	42	3.39	155	21	3.27	164	5	3.34	154	10
16	2.55	186	11	2.47	182	13	2.71	188	10	2.57	184	4
Mean	3.27	166	21.6	3.32	167	22.8	3.36*	167	13.9*	3.40*	168	10.3*
Range	2.01-5.17	141-186	10-43	2.21-5.04	144-183	9-55	2.25-5.08	146-188	1-35	2.51-5.47	143-186	1-24

**P* < .05 versus placebo.

the human lung¹⁷ or from human skin after 1 week of treatment at a dosage of 10 mg administered twice daily (ie, the same dosing that was used in this study).¹⁸ The inability of loratadine to inhibit the EIB could theoretically be due to low potency. However, this is not supported by the literature. First, although loratadine had no effect on histamine release or infiltration of inflammatory cells, it abolished the reactivity to histamine in human skin.¹⁸ Because there is a good correlation between the ability of antihistamines to block the effect of histamine in the skin and in the airways,¹⁹ it is more than likely that the loratadine treatment used in this study provided a highly significant H₁-antagonism in the airways as well. Second, 3 days of treatment with loratadine, 20 mg once daily, caused a 13-fold shift in the PC20 value for inhaled histamine.²⁰ However, treatment for 5 days or longer is required before steady-state plasma levels of loratadine are reached.²¹ Therefore the longer treatment used in this study can only have produced a higher blockade of the H₁-receptor. Third, in the allergen challenge setting we found that exactly the same dosing regimen of loratadine attenuated the early and late airway responses by 25% and 40%, respectively.¹²

Mast cells have been implicated in EIB, just as they are important in the pathogenesis of acute bronchospasm after allergen exposure. One theory to explain EIB is that increased minute ventilation causes water loss, leading to an increase in airway osmolarity, which may trigger mast cell mediator release.²² According to that hypothesis, our study results suggest that the amounts of histamine released from the mast cell during this relatively short response are small and insufficient to contribute to the overall bronchoconstriction, whereas mast cell release of cysteinyl leukotrienes, which are much more potent bron-

choconstrictors, explains a major component of the response. However, incomplete blockade of EIB by zafirlukast suggests that other mechanisms or mediators may be involved. One potential mechanism is cholinergic activity, although studies of the effectiveness of ipratropium bromide in attenuating EIB have shown variable results.^{14,23} Another possibility would be that the residual response is due to the bronchoconstrictor properties of PGD₂ because, in a previous study, we found that EIB was associated with significantly increased urinary excretion of the PGD₂ metabolite 9 α 11 β PGF₂, whereas there was no significant increase of urinary excretion of methylhistamine.²⁴ In comparison with histamine, PGD₂ is a considerably more potent bronchoconstrictor.²⁵ In contrast, allergen challenge of atopic asthmatic patients producing both an early and a late phase of bronchoconstriction was found to cause significant urinary excretion of the cysteinyl leukotriene E₄, 9 α 11 β PGF₂, and methylhistamine.²⁶

It may be that a more long-lasting, repetitive, or intense stimulation of the mast cell, such as that produced during a cumulative allergen challenge,²⁷ is required to yield a clinically significant histamine release. It has generally been difficult to measure release of inflammatory mediators in relationship to EIB^{24,28-30} but not after allergen challenge.²⁶ From our own previous studies, it is clear that the release of mediators was much greater and observed for 12 hours after the allergen provocations in comparison with smaller increases that were only detected during the first hour after EIB.^{24,26}

Another possible explanation of the findings is that mast cells release different mediators in response to different challenges. There are *in vitro* data suggesting that mast cells may display differential patterns of mediator release to different types of trigger factors.³¹

In this group of 16 subjects with mild asthma and a mean FEV₁ of approximately 90% of predicted value at screening, there were small but significant improvements of baseline pulmonary function after 1 week of treatment with zafirlukast alone or in the presence of loratadine. The improvement in baseline pulmonary function obtained in this study suggests that cysteinyl-leukotrienes contribute to bronchomotor tone also in subjects with mild asthma. However, the changes in baseline pulmonary function did not affect the magnitude of exercise-induced airway response. First, we demonstrated that the protective effect of zafirlukast on EIB was not related to the prechallenge airway caliber. Second, we found that the prechallenge change in airway caliber had no relation to the protective effect during the challenge. The lack of relation between baseline airway function and the response to EIB has not been examined closely before, but it agrees well with data obtained in other challenges.^{1,32,33}

In conclusion, this study confirmed the beneficial effect of a CysLT₁-receptor antagonist in EIB but failed to obtain evidence that H₁-receptor antagonism alone or together with the CysLT₁-receptor antagonist zafirlukast could enhance the protective effect. Further studies should address combination treatment with antileukotrienes, anticholinergic drugs, and drugs blocking bronchoconstrictor prostaglandins.

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