

Reduced nonspecific bronchial reactivity and decreased airway response to antigen challenge in atopic asthmatic patients treated with the inhaled leukotriene D₄ antagonist, L-648,051

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We studied the effect of the inhaled leukotriene D₄ antagonist, L-648,051, on antigen-induced bronchoconstriction and nonspecific bronchial reactivity. Ten males with mild atopic asthma completed a double-blind, randomized, two-period, placebo-controlled cross-over study. For a 7-day period patients inhaled either placebo or 6 mg of L-648,051 four times daily. Bronchial reactivity to methacholine was measured at base line (day 1) and after 6 days, treatment (day 7). On day 8, after inhaling 6 mg of the antagonist (or placebo), the patients were challenged by inhaled antigen; they received an additional 6 mg of the antagonist (or placebo) 3 h later. Pulmonary function (forced expiratory volume in 1 s, FEV₁) was measured serially through an 8-h post-antigen challenge. Nonspecific airway reactivity was again measured on day 9. Compared to placebo, L-648,051 treatment diminished the methacholine reactivity, on both day 7 (NS) and on day 9 ($P < 0.05$). In addition, the immediate and late bronchial responses to antigen challenge on day 8 were attenuated in the patients when treated with L-648,051. In the immediate phase (0-3 h postchallenge), the airway response was significantly reduced at all recordings between 20 min and 1 h postchallenge. In the late phase (3-8 h postchallenge), the pulmonary response was also reduced. However, the reduction was statistically significant only at the 5-h recording. The results suggest that sulfidopeptide leukotrienes are of importance for nonspecific airway reactivity, and that leukotriene D₄ is a significant mediator in the immediate asthmatic reaction.

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In man, inhaled leukotriene (LT) D₄ has been shown to be a potent bronchoconstrictor (12), suggesting that peptide LTs may be mediators in asthma. Besides their bronchoconstrictor effect, LTs have been shown to have a role in inflammation (23), inducing plasma leakage and edema (11, 24), and they may be of importance for airway nonspecific responsiveness (4, 16, 19). However, an evaluation of their role in allergic asthma and airways reactivity has awaited studies with specific receptor antagonists.

The LT antagonist L-648,051 is a selective and competitive inhibitor of LTD₄ and (to a lesser extent) LTC₄ binding in guinea pig lung homogenates (14). *In vitro*, L-648,051 is more potent than the earlier antagonists FPL-55712 and L-649,923 in pre-

venting LTC₄-induced bronchoconstriction. In guinea pigs, intravenous administration of L-648,051 selectively blocks bronchoconstriction induced by the intravenous LTs C₄, D₄, and E₄ but not bronchoconstriction induced by arachidonic acid, serotonin, or acetylcholine (14).

Using a relatively low dose (800 µg × 2) of inhaled L-648,051 in atopic asthmatic patients, we recently observed a slightly reduced airway response to inhaled antigen (21). In the present study, we used a considerably higher dose (6 mg q.i.d.) of this antagonist to investigate its effect on nonspecific airway reactivity and antigen-induced bronchoconstriction in patients with mild atopic asthma.

Material and methods

Patients

Twelve male nonsmokers with a mean age of 24 years (range 19–31 years) entered the study (Table 1). They all had mild atopic asthma and a history of exacerbations when exposed to their individual antigens. All patients had positive skin prick tests and positive RAST to the antigens chosen for the bronchoprovocations. They were familiar with lung function tests and antigen challenges. Apart from their atopic asthma, they were in good health, according to history and physical examinations, and were taking no regular medications. All had normal electrocardiograms and chest roentgenograms. None had had an upper respiratory tract infection or been vaccinated within the last 6 weeks before the start of the study. The study was conducted outside the relevant antigen season, and symptoms were controlled only by intermittent use of salbutamol or terbutaline sprays. For 2 weeks before the start of the study, patients abstained from any nonregular medicine, but inhaled beta₂-receptor agonists were allowed until 2200 on the day before provocation. Prestudy FEV₁ values (obtained at body temperature, atmospheric pressure, and saturated with water vapor BTPS) ranged from 77 to 108% of the predicted normal values (20).

Safety guidelines for bronchial antigen challenges suggested by the American Thoracic Society (2) were followed. The patients gave informed written consent for their participation; approval was obtained from the Ethics Committee of the Medical Faculty at the University of Lund.

Study design

This was a double-blind, randomized, placebo-controlled study involving two periods separated by 3 weeks. Patients were treated with either L-648,051, 6 mg (4 puffs of 1.5 mg) q.i.d., or matching placebo for 7 days in each period. On day 8, patients inhaled 6 mg of the antagonist 5 min before antigen challenge (before the immediate reaction), and an additional 6 mg 3 h after challenge (before the late reaction).

In each period, a methacholine test was performed before treatment (day 1) and after 6 days of treatment (day 7). On day 8 in both periods, patients were challenged with the same predetermined, fixed concentration of antigen. Following antigen challenge, pulmonary function (FEV₁) was recorded serially for 8 h; patients were kept in the ward overnight. On the next day (day 9), patients underwent a third methacholine challenge prior to leaving the hospital. All methacholine challenges were performed at the same time of day.

Challenge procedures

Aerosolization. For the nebulization a Wright nebulizer (Aerosol Products Ltd, UK) was used. At the methacholine tests, the nebulizer contained a volume of 3 ml, and at the antigen challenges a volume of 2 ml. The same nebulizer was used for all the provocations throughout the study. It was driven by compressed air at 3.5 bar and calibrated to deliver an output of 0.130 ml/min (NaCl 9 g/l; particle mass median diameter = 2.9 µm as measured by the laser diffraction technique [Malvern Master Sizer, UK]); this required an air flow of 7.5 l/min. Wearing a nose clip and breathing tidally, each patient inhaled the aerosols through a mouthpiece for 2 min.

Methacholine challenge. The three methacholine challenges were performed at the same time of day (at 1700). On day 1 and day 7, the patients were not hospitalized; after arrival at the unit they rested for 1 h prior to challenge. On day 9 they were in the hospital.

The methacholine tests were performed according to the method originally described by Juniper et al. (15) and Cockcroft et al. (6). To check the stability and reproducibility of pulmonary function, patients were first trained to perform spirometry correctly. Three technically correct FEV₁ maneuvers were performed and the highest value obtained was used (8-l, water-sealed spirometer, Warren E. Collins, Inc., USA). Volumes are reported at body temperature, atmospheric pressure, and saturated with water vapor (BTPS). An aerosol of phosphate-buffered saline (pH = 4.2) was then inhaled for 2 min with tidal

Table 1. Anthropometric data

Patient No.	Age yr	Height cm	Weight kg	FEV ₁ l	FEV ₁ % of pred.	RAST class	Antigen
1	24	178	81.5	4.77	108	3	Dog
2	22	164	59.0	3.41	84	4	Timothy
3	20	177	63.5	3.88	87	4	Timothy
4	25	181	64.9	4.22	94	3	Cat
5	22	177	71.6	3.84	86	4	Birch
6	31	187	80.5	4.56	101	3	Timothy
7	19	185	96.9	4.48	94	3	Cat
8	20	185	71.0	3.79	78	2	Timothy
9	30	185	85.0	4.26	96	2	Timothy
10	22	180	66.0	3.54	77	0	Dog
11	23	183	69.8	4.60	99	2	Birch
12	29	177	72.2	3.54	84	3	Timothy
Mean	24	180	73.5	4.07	91		
Median	23	181	71.3	4.05	91		
SD	4	6	10.7	0.47	10		

breathing and spirometry was performed twice, at 30 and 90 s, following the inhalation. The lowest of the two FEV₁ values recorded then constituted the (post-saline) base line.

Methacholine inhalations were repeated at 5-min intervals, starting with 0.03 mg/ml and moving upwards by doubling the concentration of methacholine, until a fall of 20% or more in FEV₁ was attained. The methacholine concentration inducing a 20% drop in FEV₁ (PC₂₀) was calculated by logarithmic interpolation between the last two points on the noncumulative dose-response curve.

Prestudy antigen challenges. These were carried out according to the method described by Killian et al. (17). Each patient underwent a skin prick test to a series of 10-fold dilutions of the particular antigen chosen for the challenge. Bronchoprovocation was then performed with increasing concentrations of antigen until a drop in FEV₁ of 20% or more was attained. Antigens used for the provocations consisted of either cat or dog epithelial extracts, or extracts of birch or timothy pollen (Pharmacia AB, Sweden).

A fixed concentration of the selected antigen was then estimated from the titration bronchoprovocation results; this antigen concentration was then tested 3 weeks later by a single bronchoprovocation to ensure that the immediate fall in FEV₁ was about 20–30% of the base-line value. If so, this concentration was used as the fixed concentration for the study challenges. If not, the antigen concentration was adjusted and tested again 3 weeks later.

Study antigen challenges. After treatment for 7 days with L-648,051 or placebo (in the morning on day 8), each patient was challenged with the individually selected, fixed concentration of antigen. Before challenge, a 6-mg dose of L-648,051 (or placebo) was inhaled; this dose of the antagonist (or placebo) was again inhaled 3 h later. There was an interval of 3 weeks between the two antigen challenge days.

Diluent was inhaled first and base-line measurements were carried out 10 min before the antigen challenge. The patient then inhaled an aerosol of the individually predetermined fixed concentration of antigen through 2-min tidal breathing. Pulmonary function (FEV₁) was measured at 10, 20, 30, 40, 50, and 60 min, and at 2, 3, 4, 5, 6, 7, and 8 h after the start of the 2-min antigen inhalation.

FEV₁ was measured in duplicate (two technically correct forced expiratory maneuvers, BTPS), and the highest value was used (8 l, water-sealed spirometer, Warren E. Collins, Inc., USA).

Table 2. Results of methacholine challenges in 12 atopic asthmatics before (day 1) and after (days 7 and 9) treatment with L-648,051 or placebo. PC₂₀ values were obtained by logarithmic interpolation

	PC ₂₀ mg/ml day 1	PC ₂₀ mg/ml day 7	PC ₂₀ mg/ml day 9
L-648,051			
Mean	10.54	22.50	30.71
Median	2.71	4.03	3.15
SEM	5.50	10.76	20.10
Placebo			
Mean	10.86	9.49	14.15
Median	2.65	3.57	2.75
SEM	5.65	3.76	10.37

Statistical analysis

Data were analyzed with the two-factor analysis of variance (ANOVA). The normality assumption was tested by the Shapiro-Wilk statistics. When data were not normally distributed, nonparametric tests were used.

Results

Two of the 12 patients completing the first period were not entered into the second period for reasons not related to the treatment.

Analyses did not reveal any carry-over effects between periods. L-648,051 was well tolerated with no drug-related adverse reactions observed.

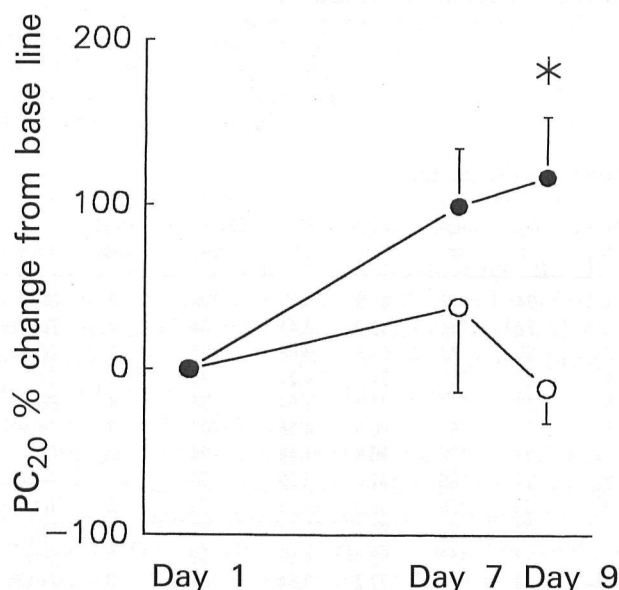


Fig. 1. Time course of reactivity to inhaled methacholine (mean % change from PC₂₀ base line $\pm$ SEM) in 10 atopic asthmatics after treatment with L-648,051 (filled circles) and placebo (open circles). * $P < 0.05$.

Table 3. Mean ($\pm$ SEM) prediluent base line and postdiluent base line of FEV₁ (l) in 10 atopic asthmatics before antigen challenge

	L-648,051	P value	Placebo
Prediluent	4.17 $\pm$ 0.16	0.98	4.17 $\pm$ 0.13
Postdiluent	4.18 $\pm$ 0.15	0.25	4.11 $\pm$ 0.13
Difference	0.11 $\pm$ 0.03		0.06 $\pm$ 0.03
P value	0.07		0.05

Methacholine challenges

The methacholine concentrations required to decrease the FEV₁ by 20% (PC₂₀) are depicted in Table 2. The methacholine reactivity was decreased after treatment with L-648,051 at days 7 and 9 (Fig. 1). Compared to placebo, the decrease was significant ($P = 0.03$) at day 9.

Antigen challenge

Base lines of FEV₁ before and after inhalation of diluent are given in Table 3. Compared to placebo, the airway response to antigen challenge was reduced after treatment with L-648,051 (Fig. 2). In the immediate phase the FEV₁ % changes from base

Table 4. Antigen, challenge concentration, and maximum % fall in FEV₁ from base line in the immediate phase (0-3 h) and the late phase (3-8 h) in relation to treatment

Pat. No.	Antigen	Challenge conc. BU/ml	Max % fall in FEV ₁ immediate phase		Max % fall in FEV ₁ late phase	
			L-648,051	Placebo	L-648,051	Placebo
1	Dog	40000	19	25	4	3
2	Timothy	16667	ND	27	ND	14
3	Timothy ¹	75000	26	28	10	8
4	Cat	80000	59	45	54	55
5	Birch ²	1500	22	25	48	61
6	Timothy ¹	100000	46	ND	53	ND
7	Cat	112500	10	16	18	11
8	Timothy ¹	105000	10	22	2	10
9	Timothy ¹	112500	32	37	4	2
10	Dog	120000	14	30	-1	1
11	Birch ²	45000	59	67	6	8
12	Timothy ¹	15000	23	39	14	19
Mean			29	33	19	18
Median			23	28	10	10
SEM			2	1	2	2

¹ *Phleum pratense*, ² *Betula verrucosa*, ND = not done.

line were significantly reduced at 20, 40, and 50 min ($P < 0.01$) and at 30 and 60 min ($P < 0.05$) post-challenge. Also the late response was reduced after

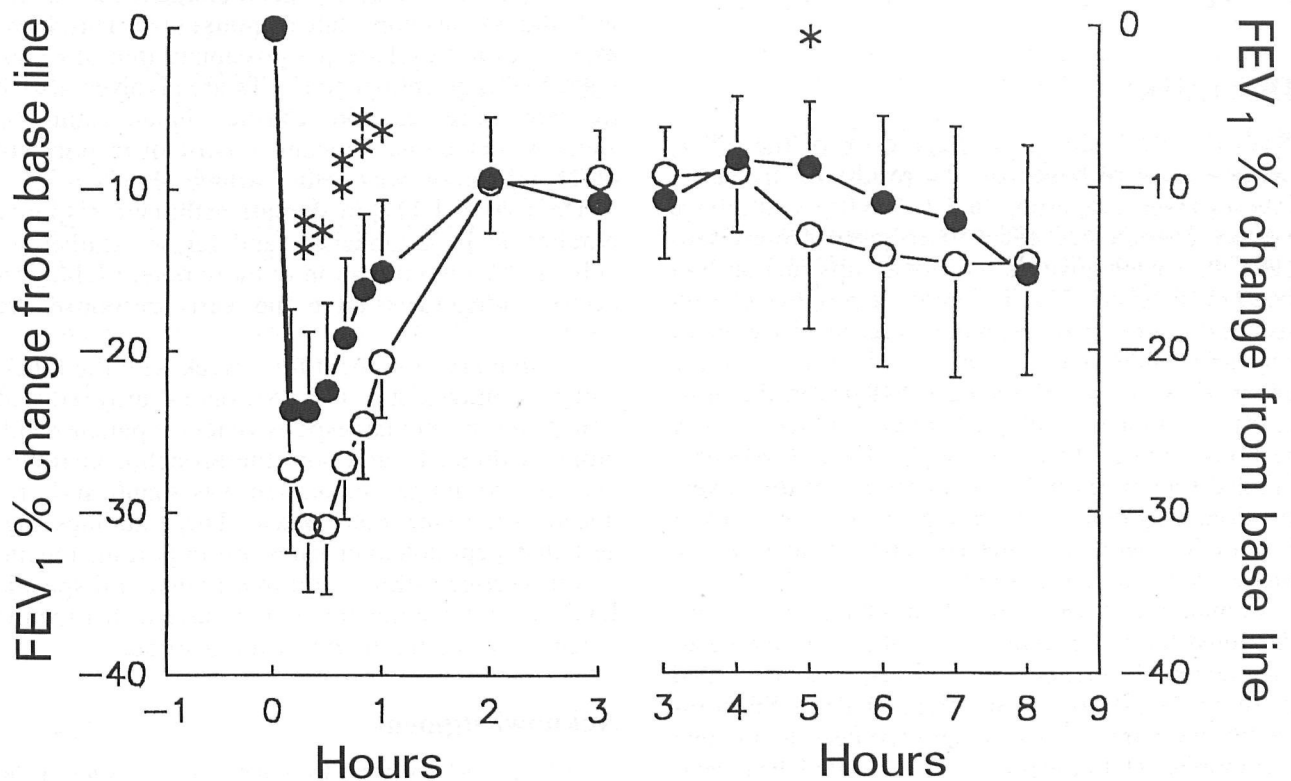


Fig. 2. Time course of airway response to inhaled antigen (mean % change from base line in FEV₁ $\pm$ SEM) in 10 atopic asthmatics after treatment with L-648,051 (filled circles) and placebo (open circles). Left panel: immediate phase; right panel: late phase. * $P < 0.05$, ** $P < 0.01$.

Table 5. Immediate and late airway responses to antigen challenge in 10 atopic asthmatics treated with the leukotriene D₄ antagonist L-648,051 or placebo (mean values of FEV₁ and AUC $\pm$ SEM)

	L-648,051	<i>P</i> value	Placebo
Immediate response			
Max. % change in FEV ₁			
(l) from base line	27.4 $\pm$ 5.7	0.01	33.4 $\pm$ 4.7
AUC FEV ₁ % change from baseline (% 1 $\times$ h)	43.0 $\pm$ 12.2	0.08	51.9 $\pm$ 9.0
Late response			
Max. % change in FEV ₁			
(l) from base line	17.5 $\pm$ 5.9	0.62	18.5 $\pm$ 6.9
AUC FEV ₁ % change from base line (% 1 $\times$ h)	53.5 $\pm$ 23.4	0.60	63.1 $\pm$ 27.6

Immediate response=0–3 h after antigen challenge. Late response=3–8 h after antigen challenge.

treatment with L-648,051, although the reduction reached statistical significance only at the 5-h time point after challenge ($P<0.05$).

After treatment with L-648,051, the immediate maximum % fall in FEV₁ following antigen challenge was significantly reduced (compared to placebo, $P<0.01$), whereas the effect seen in the late phase was not (Table 5). After L-648,051 treatment, the AUC values (% 1 $\times$ h) tended to decrease in the immediate phase (NS; $P=0.08$), whereas no such change was observed in the late phase.

Discussion

Both the study design and the dose of the LTD₄ antagonist were based on the results of an earlier investigation, suggesting that L-648,051 could have a more pronounced effect when given prophylactically than when given after airway obstruction had been established (21). To obtain a prophylactic effect in the present study, patients received 1 week of regular L-648,051 treatment. In addition, since the effect of two doses of 800 μ g L-648,051 in the prior study only modestly affected antigen-induced airway responses (21), a dose of 6 mg (4 puffs) of L-648,051, inhaled four times daily, was chosen for this investigation. This dose was made possible to administer by development of a metered dose inhaler with a higher dose per aerosol burst.

In man, it has been found that inhalation of bronchoconstrictive concentrations of LTD₄ increases the maximal bronchoconstrictor response to inhaled methacholine (9, 16). In addition, inhaled LTE₄ transiently increases airway responsiveness to inhaled histamine (18). In the present study, L-648,051 treatment diminished the response to inhaled methacholine, suggesting that the drug reduced non-specific bronchial reactivity. This finding supports

previous reports suggesting that LTs contribute to the development of increased bronchial reactivity (3, 9, 16).

In the immediate phase, L-648,051 inhibited the maximal % fall in FEV₁. However, the effect in the late phase was less conspicuous. These results do not agree with those of Bel et al. (8) showing that inhaled L-648,051 in a dose of 12 mg 20 min before antigen challenge, and 12 mg 4 h later, had no effect on bronchial responses. Part of the discrepancy between the present results and those of Bel et al. (8) may be attributed to the 1-week regular treatment with the antagonist preceding antigen challenge in the present study, and to the fact that we did not include patients with perennial allergy.

In previous studies, LTD₄-antagonists have been less effective in the late than in the immediate phase (10, 21), suggesting that sulfidopeptide LTs mainly are generated early after antigen challenge. This view is further supported by the finding that the urinary excretion rate of LTE₄ after antigen challenge is maximally increased during the immediate bronchoconstrictor response to antigen (22).

In a study by Higgins & O'Byrne (13) a small group of atopic asthmatic subjects, developing a late response after antigen inhalation, were given LTD₄ by inhalation. The doses given were sufficient to cause bronchoconstriction of similar magnitude to the early response after inhaled antigen. These subjects did not develop a late response (13). This, however, does not exclude the possibility that after antigen challenge endogenous LTs are involved also in the late-phase reaction. Further, in an asthmatic sheep model, a dual bronchoconstrictor response to LTD₄ inhalation was demonstrated (1, 25).

The role of LTD₄ in the late asthmatic response remains to be established, and further studies involving the administration of more potent LTD₄ receptor antagonists after the early response are needed.

In summary, treatment for 1 week with the LTD₄ receptor antagonist, L-648,051, significantly reduced nonspecific bronchial responsiveness in patients with atopic asthma. In addition, the bronchoconstrictor response to antigen inhalation was significantly reduced in the immediate phase. These findings suggest that peptidoleukotrienes are important mediators in allergic asthma, and that potent and specific LTD₄ receptor antagonists may have a therapeutic potential in the treatment of the disorder.

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