

Prolonged protection against exercise-induced bronchoconstriction by the leukotriene D₄-receptor antagonist cinalukast

Ellinor Ädelroth, MD, PhD,^a Mark D. Inman, MD, PhD,^a Edie Summers,^a Dan Pace, PhD,^b Marlene Modi, PhD,^b and Paul M. O'Byrne, MB^a Hamilton, Ontario, Canada, and Nutley, N.J.

Objectives: The degree and duration of protection against exercise-induced bronchoconstriction afforded by three doses of a specific leukotriene D₄ receptor antagonist, cinalukast, were assessed after an initial dosing and after 1 week of therapy.

Methods: A placebo-controlled crossover study was performed in eight male patients who had mild, stable asthma and exercise-induced bronchoconstriction. Treatment consisted of four 7-day periods of placebo and three dose levels of the drug (10, 50, and 200 mg administered orally). Exercise challenge was performed at 2 hours and 8 hours after treatment on the first and seventh treatment days. The response was measured as the area under the FEV₁-time effect curve (AUEC).

Results: On the first day of treatment, the mean ($\pm$ SEM) AUEC at 2 hours was 24.2 ± 3.3 L $\cdot$ min after placebo and was 5.5 ± 2.2 L $\cdot$ min, 6.3 ± 2.7 L $\cdot$ min, 3.3 ± 3.8 L $\cdot$ min after 10 mg, 50 mg, and 200 mg, respectively ($p < 0.05$ for all values compared with placebo). The AUEC at 8 hours on the first day was 25.1 ± 4.4 L $\cdot$ min after placebo and was 6.8 ± 4.1 L $\cdot$ min, 11.2 ± 2.5 L $\cdot$ min, and 5.0 ± 2.8 L $\cdot$ min after 10 mg, 50 mg, and 200 mg, respectively ($p < 0.05$ for all values compared with placebo). The protection afforded by 10 mg of cinalukast was lost after 7 days of treatment but persisted with 50 mg and 200 mg doses.

Conclusion: Orally administered cinalukast provides at least 8 hours of protection against exercise-induced bronchoconstriction. This protection is lost with regular treatment for 1 week for the lowest dose studied. (*J Allergy Clin Immunol* 1997;99:210-5.)

Key words: Asthma, exercise bronchoconstriction, cysteinyl leukotriene

Exercise is a common stimulus for bronchoconstriction in patients with asthma.^{1,2} The exact mechanism causing exercise-induced bronchoconstriction (EIB) has not yet been fully elucidated, although release of bronchoconstrictor mediators caused by changes in airway temperature and/or osmolality likely plays a major role.^{3,4} The cysteinyl leukotrienes (LTs) C₄, D₄, and E₄ are potent bronchoconstrictor mediators^{5,6} involved in causing EIB. Increased urinary excretion of LTE₄ by patients with asthma after exercise has been shown in one⁷ but not in another study.⁸ However, the most compelling evidence is that several different LT receptor antagonists have been shown to attenuate EIB.⁹⁻¹² Considerable variation exists in the degree of protection afforded against EIB by the different antagonists. However, the different antagonists have varied in potency,

Abbreviations used

AUEC:	Area under the FEV ₁ -time effect curve
EIB:	Exercise-induced bronchoconstriction
LT:	Leukotriene

selectivity, and mode of administration. To date, neither the duration of protection nor the effects of regular treatment on the degree of protection have been reported.

The objective of this study was to assess the degree and duration of protection afforded by a new orally delivered, potent and specific LTD₄ receptor antagonist, cinalukast,¹³ against EIB. Also, the effects of single dosing and dosing for 7 days were studied. The protection was measured at both 2 hours and 8 hours after the first and last dose during each of four multiple-dose 7-day treatment periods with 10, 50, and 200 mg or placebo taken orally three times per day. An additional objective was to measure plasma concentration profiles at each dose level to determine whether variations in protection against EIB were associated with differences in drug pharmacokinetics after regular dosing.

From ^athe Asthma Research Group, McMaster University, Hamilton; and ^bthe Department of Clinical Pharmacology, Hoffmann-LaRoche Inc., Nutley. At the time of the study, Dr. Ädelroth was at McMaster University; she is now at University of Lund, Sweden.

Received for publication Apr. 2, 1996; revised June 19, 1996; accepted for publication July 8, 1996.

Reprint requests: Paul M. O'Byrne, MB, Department of Medicine, Division of Respiratory, McMaster University, 1200 Main St., West, Hamilton, Ontario, Canada L8N 3Z5.

Copyright © 1997 by Mosby-Year Book, Inc.

0091-6749/97 \$5.00 + 0 1/1/76578

METHODS

Subjects

Eight male subjects with mild stable asthma and documented EIB (Table I) gave written informed consent before taking part in the study, which was approved by the Research Ethics Committee of McMaster University. All subjects had asthma that was controlled by inhaled β_2 -agonists taken only as needed, were taking no other medications, and had a baseline FEV₁ greater than 70% of predicted normal value on all study days.¹⁴ Before the study, all subjects had to be free of respiratory tract infections for at least 4 weeks. We have previously shown, in a reproducibility study, that eight subjects are sufficient to demonstrate a 50% attenuation of EIB attributable to treatment effects.¹⁵

Study design

Subjects attended the laboratory on 10 occasions. Subjects were not permitted to use inhaled β_2 -agonists for at least 8 hours before each visit. At the first visit, screening history, physical examination, spirometry, and resting electrocardiogram were performed. Providing that results of these tests were normal, a stage 1 incremental exercise test was performed on a cycle ergometer^{16,17} to assess work capacity. FEV₁ was measured before and after exercise by using a water-filled spirometer (Collins) to document the presence of EIB. On the second visit, subjects performed a 5-minute exercise challenge with a constant work rate on the cycle ergometer while breathing dry room air (<10% relative humidity). The work rate was chosen to produce a drop in FEV₁ of at least 15% and to increase the heart rate to approximately 80% of maximum. On this day, venous blood and urine samples were obtained to ensure normal chemistry values. In some subjects, in whom the fall in FEV₁ was less than 15% or was considered to be too great, this screening visit was repeated at a correspondingly higher or lower work rate. The work rate used in the final screening challenge was used in all subsequent exercise challenges during treatment.

After successful screening, all subjects returned for 8 treatment visits, corresponding to days 1 and 7 of each of four treatment periods. All treatment periods were separated by at least 10 days. On the first and seventh days of each treatment period, subjects arrived at the laboratory at 7:30 AM and had baseline spirometry and vital signs (heart rate, respiratory rate, blood pressure) measured. The first dose of drug was then orally administered. Exercise challenges were performed 2 hours and 8 hours after drug administration. FEV₁ was measured before and immediately after completion of the challenge and again at 1, 3, 5, 8, 10, 15, 20, 30, 40, 50, and 60 minutes after exercise. Vital signs were monitored at the same times as FEV₁.

Treatment

Treatment was given according to a double-blind, placebo-controlled, randomized, crossover trial design.¹⁸ Treatment consisted of four 7-day periods corresponding to placebo and three dose levels of the drug. Tablets (10, 50, or 200 mg) were orally administered three times per day, except on the seventh day, on which only the morning dose was given. The first doses on day 1 and day 7 were administered in the laboratory; the remaining medication was provided for the subjects in blister packs for each treatment day.

Pharmacokinetics

Blood samples (7 ml) were collected by venipuncture into heparinized tubes before drug administration and at 1, 2, 3, 4,

TABLE I. Subject characteristics

Subject No.	Age (yr)	Height (cm)	Weight (kg)	FEV ₁ (% pred)	FVC (% pred)
1	24	180	80	77	105
2	40	176	76	91	87
3	22	183	77	88	83
4	36	175	80	94	96
5	21	173	76	81	108
6	19	185	75	87	95
7	22	183	84	88	92
8	22	180	79	85	91

FVC, Forced vital capacity.

6, and 8 hours after dosing on days 1 and 7 to determine plasma concentrations of cinalukast. The blood samples were centrifuged immediately, and the plasma was stored at -70°C until analysis. One milliliter of 0.1 mol/L sodium phosphate solution, pH 4.3, was added to the plasma samples, and the samples were thoroughly mixed. After liquid-liquid extraction with ether-chloroform (4:1 vol/vol), the sample was analyzed by reverse-phase high-performance liquid chromatography with fluorescence detection (excitation, 358 nm; emission, 405 nm). The mobile phase consisted of acetonitrile: 0.05 mol/L NaH_2PO_4 buffer (pH 4.3, 65:35, vol/vol). The lower limit of assay sensitivity was 2 ng/ml with 0.5 ml. The calibration curve was linear with 0.5 ml samples from 2 to 1000 ng/ml. The interassay coefficient of variation for the quality control samples (2 to 1000 ng/ml) was less than 10%.

Analysis

The degree of EIB was assessed as both the maximum percent fall in postexercise FEV₁ below the pre-exercise baseline levels and the area below the FEV₁-time effect curve during the hour after exercise (the pre-exercise FEV₁ was used as a baseline for area measurements). Treatment, duration of protection, and effect of multiple daily dosing for 1 week were assessed by using a three-way repeated-measures analysis of variance.¹⁹ The levels in this analysis were dose (placebo: 10 mg, 50 mg, 200 mg), time (2 hours, 8 hours), and study day (day 1, day 7). Post hoc comparisons were made by using Newman-Keuls tests after significant main effects or interactions were observed. Statistical significance was set at $\alpha < 0.05$.

RESULTS

Baseline airway function was not affected by cinalukast treatment in these patients with mild asthma. Measurements of FEV₁ obtained 2 and 8 hours after administration of all doses of cinalukast were not different from those obtained under placebo conditions ($p > 0.05$) (Table II). This was true on days 1 and 7 of all treatment periods.

All doses of cinalukast provided protection against EIB after a single administration. All FEV₁ (maximum percent fall) and area under the FEV₁-time effect curve (AUEC) (liters $\cdot$ minutes) values are presented in Table III. On the first treatment day, the mean maximum fall in FEV₁ ($\pm$ SEM) was $25.8\% \pm 3.0\%$ at 2 hours after placebo administration, compared with $14.6\% \pm 2.9\%$ after 10 mg, $16.6\% \pm 2.6\%$ after 50 mg, and $14.6\% \pm 4.3\%$ after 200 mg of cinalukast. All doses provided a

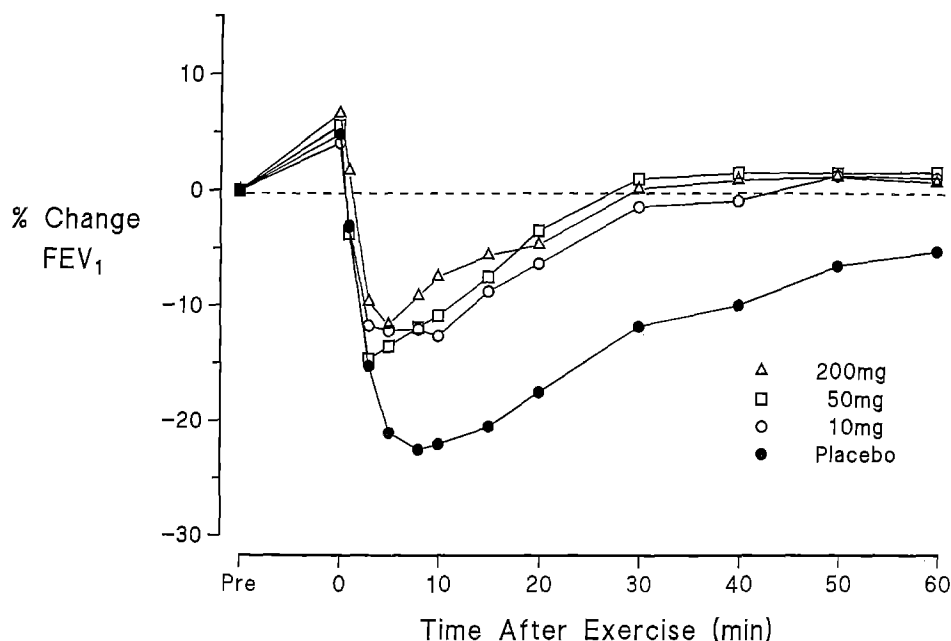


FIG. 1. Time course of FEV₁ changes during the hour after the initial exercise challenge on the first day of treatment, 2 hours after dosing. Equal protection is afforded by all three doses of cinalukast compared with placebo, against EIB.

TABLE II. FEV₁ values measured 2 and 8 hours after placebo and three dose levels of cinalukast on treatment days 1 and 7

Day	Placebo		Cinalukast (10 mg)		Cinalukast (50 mg)		Cinalukast (200 mg)	
	2 hr	8 hr	2 hr	8 hr	2 hr	8 hr	2 hr	8 hr
1	3.6 ± 0.1	3.5 ± 0.2	3.7 ± 0.2	3.5 ± 0.2	3.5 ± 0.1	3.5 ± 0.1	3.6 ± 0.2	3.5 ± 0.2
7	3.5 ± 0.2	3.5 ± 0.2	3.7 ± 0.2	3.6 ± 0.1	3.6 ± 0.1	3.4 ± 0.2	3.6 ± 0.1	3.4 ± 0.2

TABLE III. Magnitudes of EIB as determined by maximum percent fall in FEV₁ and area under the curve

Dose	Fall in FEV ₁ (%)				AUEC (L·min)			
	Day 1		Day 7		Day 1		Day 7	
	2 hr	8 hr	2 hr	8 hr	2 hr	8 hr	2 hr	8 hr
Placebo	25.8	26.6	21.2	23.5	24.2	25.1	17.3	16.0
Cinalukast								
10 mg	14.6	16.6	20.6	24.3	5.5	6.8	14.3	20.5
50 mg	16.6	21.8	14.7	13.9	6.3	11.2	6.7	3.2
200 mg	14.6	14.4	14.1	11.4	3.3	5.0	3.8	2.1

significant protection compared with placebo ($p < 0.05$), but the fall in FEV₁ with each of the three doses was not different from that with any other dose ($p > 0.05$) (Fig. 1). Subject 1 was given 200 μ g of inhaled salbutamol 20 minutes after exercise challenge on the first day of placebo treatment. This was done to relieve breathing discomfort associated with a 48% fall in FEV₁. Because of this, all of subject 1's data were excluded from AUEC analysis. For the remaining seven subjects, the mean AUEC was 24.2 ± 3.3 L·min 2 hours after placebo

administration, compared with 5.5 ± 2.2 L·min after 10 mg, 6.3 ± 2.7 L·min after 50 mg, and 3.3 ± 3.8 L·min after 200 mg of cinalukast. All doses provided a significant protection compared with placebo ($p < 0.05$) (Fig. 2).

The protection afforded by cinalukast lasted for at least 8 hours on the first treatment day (Fig. 2). The AUEC was 25.1 ± 4.4 at 8 hours after placebo, compared with 6.8 ± 4.1 after 10 mg, 11.2 ± 2.5 after 50 mg, and 5.0 ± 2.8 after 200 mg ($p < 0.05$ compared with

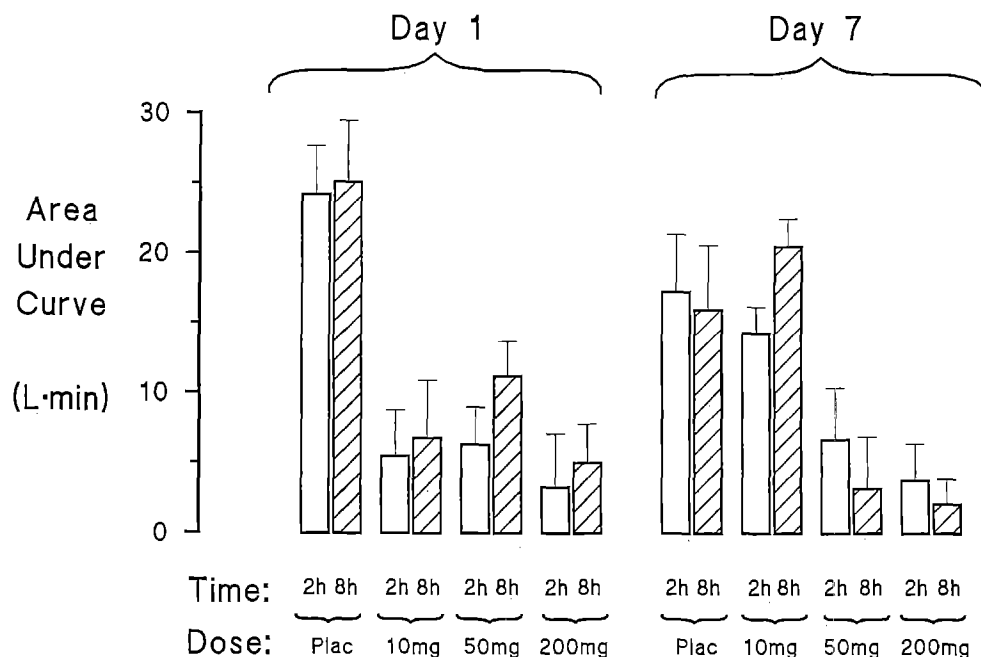


FIG. 2. Degree of EIB as measured by AUEC. On the first day of treatment, the protective effect at each dose was maintained for at least 8 hours. After 1 week of treatment, the protective effect was lost for the lowest (10 mg) dose but preserved for the two higher doses. Values are expressed as means $\pm$ SEM.

placebo). All AUEC and percent fall in FEV₁ values were not significantly different from the respective 2-hour measurements ($p > 0.05$).

The protection afforded by the lowest dose of cinalukast was lost after 7 days of treatment. The AUEC values at 2 hours after administration of placebo and 10 mg of cinalukast were not significantly different, being 17.3 ± 4.1 and 14.3 ± 1.9 , respectively ($p > 0.05$) (Fig. 2). However, the protective effect persisted after 7 days of treatment with the 50 mg doses and the 200 mg doses of cinalukast, the AUEC being 6.7 ± 3.7 and 3.8 ± 2.6 , respectively ($p < 0.05$ compared with placebo) (Fig. 2). After the 8-hour exercise challenge, the AUEC values for the placebo and 10 mg dose were again not statistically different, being 16.0 ± 4.6 and 20.5 ± 2.0 , respectively ($p > 0.05$). Once again for the higher doses, the protection lasted for at least 8 hours. For the 50 and 200 mg doses, the mean AUEC values were 3.2 ± 3.7 and 2.1 ± 1.8 ($p < 0.05$ compared with placebo) (Fig. 2). The power of these comparisons was calculated by using standard tables¹⁹ and was found to be 0.92. The statistical findings were the same when the results were analyzed as maximum fall in FEV₁.

There was a significant reduction in both AUEC and maximum percent fall in FEV₁ after 1 week of placebo treatment (see Table III and Fig. 2) ($p < 0.05$). The maximum percent fall in FEV₁ on the first day of placebo treatment (mean $\pm$ SEM, 25.9 ± 3.0) was not significantly different from the value measured during screening (mean $\pm$ SEM, 23.5 ± 1.6), suggesting that the change in the exercise response after 1 week of placebo

administration was a true effect, as commonly occurs with regular placebo treatment.

Compliance was assessed by having subjects return blister packs at the end of each treatment period. Compliance was $94.1\% \pm 1.45\%$, $95.4\% \pm 1.45\%$, $95.4\% \pm 1.45\%$, and $92.8\% \pm 2.45\%$ for placebo, 10 mg, 50 mg, and 200 mg treatment periods, respectively. No subject took less than 15 of the 19 tablets during any treatment period. All subjects took the first tablet on days 1 and 7 of all treatment periods.

Cinalukast plasma concentration peaked at 2 hours after dosing, except for the 200 mg dose on day 1 (Fig. 3). Eight hours after dosing, cinalukast concentrations had decreased to less than 20% of maximum. Cinalukast did not accumulate substantially on multiple dosing except for the highest dose (Fig. 3). The increasing plasma concentration associated with increasing dose (Fig. 3) was not associated with a greater degree of protection against EIB.

Two subjects experienced adverse events, which were judged to be possibly related to cinalukast administration. One subject experienced a 20% decrease in FEV₁, beginning 90 minutes after the first 50 mg cinalukast dosing and lasting for approximately 2 hours. This same subject, however, did not experience similar events after subsequent 50 mg doses or after any 200 mg dose. A second subject experienced mild nausea, beginning 1 hour after the first 200 mg dosing and lasting for approximately 9.5 hours. This subject did not experience similar episodes after subsequent 200 mg doses or after any other dose. No significant effects or trends were

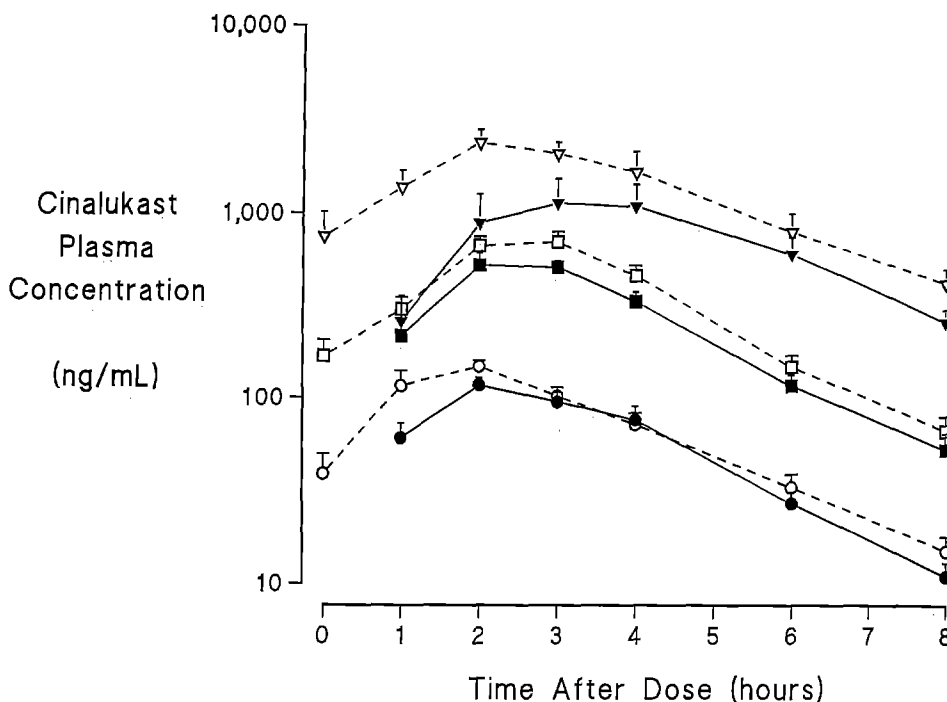


FIG. 3. Plasma cinalukast concentration profile after 10 mg (circles), 50 mg (squares), and 200 mg (diamonds) doses. Solid symbols and lines represent measurements made on the first treatment day, on which the first sample was taken 1 hour after dosing. Open symbols and dashed lines represent measurements made on the seventh treatment day, on which the first sample was taken immediately before dosing. Values are expressed as means $\pm$ SEM.

found for any blood chemistry variables measured before and after each dosing period.

DISCUSSION

This study has demonstrated that pretreatment with the specific LT receptor antagonist, cinalukast, affords significant protection against EIB in patients with asthma. This is in accordance with a number of studies investigating the effects of other LT antagonists on EIB.⁹⁻¹² In addition, this study has examined the duration of the protection and the effects of multiple dosing on the magnitude of protection of three doses of cinalukast. The duration of protection afforded by the initial single administration of all three doses of drug lasted for at least 8 hours, and the degree of protection did not differ between the 2-hour and 8-hour challenges. The results were analyzed as both maximum percent fall in FEV₁ and AUEC. The AUEC analysis provides additional information about both the magnitude and the extent of the protection afforded by the antagonist against EIB. After regular treatment for 1 week with the 10 mg dose of cinalukast, the protective effect against EIB was not different from that observed with placebo, whereas the protective effect of 50 mg and 200 mg doses, compared with placebo, was maintained for both the 2-hour and 8-hour challenges after treatment on day 7.

The significant reduction in EIB after 1 week of placebo treatment clearly illustrates the importance of including placebo control conditions in studies of this

nature. This response to placebo does not influence the interpretation of results presented here, because all analyses of treatment effects were made relative to placebo effects.

The importance of the cysteinyl LTs in causing EIB has been suggested by a number of previous studies, which have shown that a variety of LT receptor antagonists with different chemical structures attenuate EIB.^{9,12} The magnitude of protection in this study is similar to that described for other antagonists, such as MK 571⁹ and ICI 204,219.^{10,12} All of these studies have demonstrated a residual bronchoconstrictor response, resistant to LT antagonism. This residual bronchoconstriction is of short duration (see Fig. 1) and probably represents another bronchoconstrictor mediator, such as histamine, released along with the cysteinyl LTs. However, the effects of H₁-receptor antagonists together with LT antagonists on this response have not yet been studied.

The currently recommended management of EIB consists of pretreatment with either an inhaled β_2 -agonist or cromoglycate 5 to 20 minutes before exercise.²⁰ The duration of protection afforded by these drugs is less than 4 hours.²¹ More prolonged protection against EIB may be useful in children with asthma, in whom pretreatment before each of their repeated bouts of exercise is often impractical. Prolonged protection against EIB has been demonstrated after treatment with the long-acting inhaled β_2 -agonist, salmeterol, with pro-

tection that lasts more than 12 hours.^{21, 22} However, regular treatment for 4 weeks with salmeterol results in loss of this protective effect against EIB.¹⁴ Interestingly, as with inhaled salmeterol, we have found that regular treatment with the lowest dose of cinalukast for 1 week results in loss of the protection against EIB. The reasons for the loss of the protection are unknown. This effect has not been previously reported for LT receptor antagonists, possibly because the effects of single compared with multiple dosing have not been studied. This new observation is strengthened by the power of our analysis (0.92) and the fact that the loss of protection was evident at both the 2-hour and 8-hour challenges after 1 week of 10 mg dosing. One possible explanation for this finding is enhanced metabolism and clearance of the drug after regular treatment. This seems unlikely, because the plasma levels after the 10 mg dose are the same on days 1 and 7. However, the possibility exists that the clearance of active metabolites (not measured in this study) may be altered after multiple dosing. Another perhaps more plausible explanation is that upregulation of the LT receptor occurs after regular treatment with a receptor antagonist, resulting in loss of efficacy of low doses of the antagonist, an effect overcome by higher doses. Further studies need to be performed to determine whether the loss of protection afforded for the 10 mg dose after 1 week would occur with longer periods of treatment at higher doses. Also, whether loss of protection occurs with low doses taken less frequently would be important to know; this is because it is possible that low doses taken once daily would provide protection against EIB throughout the day without loss of protection with prolonged use.

In conclusion, this study has demonstrated that treatment with the LT receptor antagonist cinalukast protects against EIB for at least 8 hours. However, the protection is not maintained during treatment with low doses of the antagonist for 1 week. Finally, this study has demonstrated that administration of cinalukast for 1 week in the dose range reported was safe, with few adverse events being associated with the study drug.

REFERENCES

- Anderson SD. Exercise-induced asthma: the state of the art. *Chest* 1985;(suppl 87):191-5.
- McFadden ER Jr. Exercise-induced asthma: assessment of current etiological concept. *Chest* 1987;(suppl 91):151-7.
- Gilbert IA, Fouke JM, McFadden ER Jr. Heat and water flux in the intrathoracic airways and exercise-induced asthma. *J Appl Physiol* 1987;63:1681-91.
- Finnerty JP, Holgate ST. Evidence for the roles of histamine and prostaglandins as mediators in exercise in exercise-induced asthma: the inhibitory effect of terfenadine and flurbiprofen alone and in combination. *Eur Respir J* 1990;3:540-7.
- Weiss JW, Drazen JM, McFadden ER Jr. Airway constriction in normal humans produced by inhalation of leukotriene D₄: potency, time course, and effect of aspirin therapy. *JAMA* 1983;249:284-7.
- Adelroth E, Morris MM, Hargreave FE, O'Byrne PM. Airway responsiveness to leukotriene C₄ and D₄ and to methacholine in patients with asthma and normal subjects. *N Engl J Med* 1986;315:480-4.
- Kikawa Y, Miyanoma T, Saito M, Nakai A, Shigematsu Y, Hosoi SE. Urinary leukotriene E₄ after exercise challenge in children with asthma. *J Allergy Clin Immunol* 1992;89:1111-9.
- Taylor IK, Wellings R, Taylor GW, Fuller RW. Urinary leukotriene E₄ excretion in exercise-induced bronchoconstriction. *J Appl Physiol* 1992;73:743-8.
- Manning PJ, Watson RM, Malgorske DJ, Williams VC, Schwartz JL, O'Byrne PM. Inhibition of exercise-induced bronchoconstriction by MK-571, a potent leukotriene D₄-receptor antagonist. *N Engl J Med* 1990;323:1736-9.
- Finnerty JP, Wood-Baker R, Thomson H, Holgate ST. Role of leukotrienes in exercise-induced asthma. Inhibitory effect of ICI 204219, a potent leukotriene D₄ receptor antagonist. *Am Rev Respir Dis* 1992;145:746-9.
- Robuschi M, Riva E, Fucella LM, Vida E, Barnabe R, Rossi ME. Prevention of exercise-induced bronchoconstriction by a new leukotriene antagonist (SK&F 104353). A double-blind study versus disodium cromoglycate and placebo. *Am Rev Respir Dis* 1992;145:1285-8.
- Makker HK, Lau LC, Thomson HW, Birks SM, Holgate ST. The protective effect of inhaled leukotriene D₄ receptor antagonist ICI 204,219 against exercise-induced asthma. *Am Rev Respir Dis* 1993;147:1413-8.
- O'Donnell M, Crowley HJ, Yaremko B, O'Neil N, Welton AF. Pharmacologic actions of Ro 24-5913, a novel antagonist of leukotriene D₄. *J Pharmacol Exp Ther* 1991;259:751-8.
- Morris JF, Koski A, Johnson LC. Spirometer standards for healthy non-smoking adults. *Am Rev Respir Dis* 1971;103:57-67.
- Inman MD, Watson RM, Woolley KL, Manning PJ, O'Byrne PM. Reproducibility of bronchoconstriction following dry air exercise challenge [abstract]. *Am Rev Respir Dis* 1994;149:A1048.
- Anderson S. A simple guide to clinical exercise testing. *Aust NZ J Med* 1984;14:803-6.
- Jones N. Clinical exercise testing. 3rd ed. Philadelphia: WB Saunders, 1988:135-44.
- Jones B, Kenward M. Design and analysis of cross-over trials. London: Chapman and Hall Ltd, 1989:197-9.
- Keppel G. Design and analysis: a researcher's handbook. 2nd ed. Englewood Cliffs (NJ): Prentice Hall, 1982.
- National Heart and Lung Association, US Department of Health. Guidelines for the diagnosis and management of asthma. 1991;No. 91.
- Malo JL, Ghezzo H, Trudeau C, L'Acheveque J, Cartier A. Salmeterol, a new inhaled beta 2-adrenergic agonist, has longer blocking effect than albuterol on hyperventilation-induced bronchoconstriction. *J Allergy Clin Immunol* 1992;89:567-74.
- Anderson SD, Rodwell L, DuToit J, Young IH. Duration of protection by inhaled salmeterol in exercise-induced asthma. *Chest* 1991;100:1254-60.