

Comparative effects of long-acting β_2 -agonists, leukotriene receptor antagonists, and a 5-lipoxygenase inhibitor on exercise-induced asthma

Albert Coreno, MS, Mary Skowronski, MEd, Chakradhar Kotaru, MD, and E. R. McFadden, Jr, MD *Cleveland, Ohio*

Background: Exercise-induced asthma (EIA) is a common problem that can be controlled with long-acting β -agonists and leukotriene-modifying compounds. There is, however, limited information on the comparative effectiveness of the two classes of drugs, as well as the relative potencies of the antileukotriene agents.

Objective: The purpose of the present study was to provide data on the above issues.

Methods: We performed a random-order, blinded, double-dummy, placebo-controlled trial in 10 patients with EIA. Each subject received standard single doses of salmeterol, montelukast, zafirlukast, zileuton, and placebo on separate days. The participants performed 4 minutes of cycle ergometry while breathing frigid air 1, 4, 8, and 12 hours after administration of the test agents. The primary endpoint was the extent of the decrement in the FEV₁ 10 minutes after exertion.

Results: With placebo, symptomatic airway narrowing developed at all times (mean $\pm$ SE decrease in FEV₁ ranged between 21% $\pm$ 5% and 26% $\pm$ 5%). Salmeterol acted quickly and significantly blunted the obstructive response for 12 hours (Δ FEV₁ first hour: 8% $\pm$ 3%; Δ FEV₁ twelfth hour: 8% $\pm$ 3%; $P < .0001$ vs placebo and $P = .72$ vs time). The leukotriene-modifying agents produced effects within 1 hour of ingestion. Like salmeterol, montelukast and zafirlukast also offered long-lasting protection, and there were no significant differences between them (montelukast Δ FEV₁ twelfth hour: 9% $\pm$ 4%; zafirlukast Δ FEV₁ twelfth hour: 11% $\pm$ 2%; $P = .75$) or the β_2 -agonist (montelukast vs salmeterol: $P = .72$; zafirlukast vs salmeterol: $P = .48$). Zileuton provided equivalent prophylaxis for the first 4 hours (Δ FEV₁ fourth hour: 11% $\pm$ 2%); however, by 8 hours, it was less efficacious than all of the other active compounds, and by 12 hours it did not differ from placebo (Δ FEV₁ twelfth hour: 19% $\pm$ 4%; $P = .33$).

Conclusions: Single doses of the currently available

leukotriene receptor antagonists provide prompt effective and persistent defense against EIA that equals that seen with a long-acting β_2 -agonist. The synthesis inhibitor zileuton affords a comparable magnitude of prophylaxis but has a considerably shorter duration of action. (*J Allergy Clin Immunol* 2000;106:500-6.)

Key words: Exercise-induced asthma, β_2 -agonist, leukotriene receptor antagonist, 5-lipoxygenase inhibitor

Exercise-induced asthma (EIA) is a common problem that can materially interfere in the daily activities of affected patients.¹ In this condition regularly scheduled medications are not required for control, and patients can be effectively protected by pretreating them before they undertake activities that produce problems.^{1,2} Traditionally, the use of a sympathomimetic agent 10 to 15 minutes before strenuous exertion has been the method of choice.^{1,2} This approach provides good prophylaxis, but the benefits only last a few hours, and repetitive dosing is required to shield against the consequences of unscheduled physical activities.² With the development of sustained acting β_2 -agonists, such as salmeterol and formoterol, the duration of protection has lengthened considerably,^{3,4} and effective prophylaxis for 12 or more hours has become a practical reality after a single dose.

Recently, a new class of agents, the leukotriene modifiers, has increased the therapeutic options. The currently available receptor antagonists, montelukast and zafirlukast, and the 5-lipoxygenase inhibitor, zileuton, are all known to attenuate EIA,⁵⁻⁷ but there is virtually no information to guide the practitioner on the choice of compound to use. The time to onset, the duration of action, and the relative potencies of these drugs are unknown, and it is unclear whether single or repetitive dosing is required to produce an effect. Equally importantly, there is limited information as to whether the protection they offer is similar to that provided by more traditional forms of treatment like salmeterol.^{3,8} The present study was undertaken to provide data on these issues.

METHODS

Ten nonsmoking asthmatic patients (6 women and 4 men with a mean age of 29 $\pm$ 3 [mean $\pm$ SEM] years) served as our subjects (Table I). EIA was considered to be present if there were symptoms of airway obstruction after exertion that were associated with a decrease in the FEV₁ of 15% or more from the baseline value. None of the participants had upper respiratory tract infections or had taken any oral glucocorticoids in the 6 weeks before the study, and

From the Division of Pulmonary and Critical Care Medicine and the Airway Disease Center of University Hospitals of Cleveland, and the Department of Medicine of Case Western Reserve University School of Medicine, Cleveland.

Supported in part by grants HL-33791 and HL-07288 from the National Heart Lung and Blood Institute and a General Clinical Research Center Grant (MO 1 RR 00080) from the National Center for Research Resources of the National Institutes of Health.

Received for publication Mar 9, 2000; revised June 13, 2000; accepted for publication June 16, 2000.

Reprint requests: E. R. McFadden, Jr, MD, Division of Pulmonary and Critical Care Medicine, University Hospitals of Cleveland, 11100 Euclid Ave, Cleveland, OH 44106-5067.

Copyright © 2000 by Mosby, Inc.

0091-6749/2000 \$12.00 + 0 1/109425

doi:10.1067/mai.2000.109425

Abbreviation used

EIA: Exercise-induced asthma

no one had previously used antileukotriene medications. All β -adrenergic agonists were withdrawn for 24 hours before any challenge, and specific H_1 antihistamines were held for 72 hours. Inhaled steroids were permitted and kept at a constant dose. The institutional review board for human investigation approved the protocol, and all participants gave informed consent.

The investigation was a random-order, blinded, double-dummy trial in which the subjects took either two puffs (42 μ g) of salmeterol (Serevent, Glaxo Wellcome), 10 mg of montelukast orally (Singular, Merck Co), 20 mg of zafirlukast orally (Accolate, Zeneca), 600 mg of zileuton orally (Zyflo, Abbott), or placebo on separate occasions. A technician set out the test drugs in the morning for each subject according to a random code, and they were given in a blinded fashion to the participants. On the placebo day, the subjects received both an inert pill and an inhaler. In the active arms the test medication was given along with the appropriate placebo (pill and placebo inhaler or inhaler and oral placebo). All test agents were administered in the laboratory in the early morning after the subjects completed baseline measures of spirometry. The forced expirations were performed in triplicate, and the curves with the largest FEV₁ were chosen for analyses.

The exercise provocation consisted of 4 minutes of exhausting work on a cycle ergometer while breathing frigid air.⁹ During cycling, the subjects exhaled into a dry gas meter so that minute ventilation could be continuously recorded. The temperature of the inspired air was also measured. Recovery occurred under ambient room conditions.¹⁰ The degree of obstruction that developed 10 minutes after the completion of the workload was taken as the response. The largest FEV₁ at this time point was analyzed. The first challenge took place 1 hour after receiving each investigational drug and was repeated 4, 8, and 12 hours later. Only one study was conducted per week to ensure washout of the longer acting medications.

The data were analyzed with a multifactorial repeated-measures ANOVA, one-factor ANOVA, and paired *t* tests.¹¹ A Bonferroni adjustment for multiple testing was applied. All statistical tests were two sided, and a *P* value of less than .05 was considered significant. The study was powered to detect a 50% change in the FEV₁ with greater than 99% certitude.

RESULTS

The mean FEV₁ on entrance into the trial was 93% $\pm$ 4% of the predicted value, and the workload averaged 790 $\pm$ 73 kilopond meters per minute (Table I). At enrollment, 6 subjects were using albuterol, 3 were taking salmeterol, and 1 was taking an over-the-counter sympathomimetic. Six were using inhaled glucocorticoids, and two were taking selective antihistamines. The mean values for the minute ventilations ranged between 43 $\pm$ 3 and 50 $\pm$ 4 L/min (drug-by-time interaction, *P* = .98), and the temperature of the inspired air varied from $-5^\circ\text{C} \pm 2^\circ\text{C}$ to $-16^\circ\text{C} \pm 4^\circ\text{C}$ (drug-by-time interaction, *P* = .05; Table II). The significant difference in temperatures resulted from switching refrigeration systems during the experiment because of a leak. By chance, it primarily affected the montelukast trial (temperature range, -5°C to -11°C ; *P* = .05). The other trials were unaffected

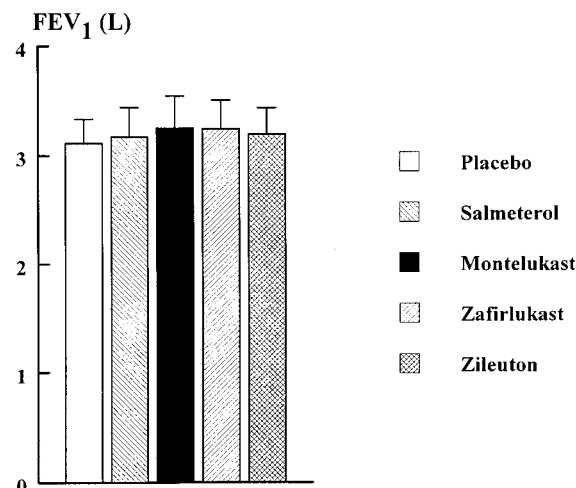


FIG 1. Baseline lung function before receiving placebo, salmeterol, montelukast, zafirlukast, and zileuton. The heights of the bars are mean values, and the brackets indicate 1 SEM.

TABLE I. Characteristics of subjects with EIA

Characteristic	Value
Sex (M/F)	4/6
Age (y)	29 $\pm$ 3
Workload (kilopond meter/min)	790 $\pm$ 3
FEV ₁ (L)	3.32 $\pm$ 0.28
FEV ₁ (% predicted)	93 $\pm$ 4

Data are mean values $\pm$ 1 SE.

(drug-by-time interaction: placebo, *P* = .40; salmeterol, *P* = .85; zafirlukast, *P* = .71; zileuton, *P* = .50). There were no significant differences between drugs (*P* > .30 for all comparisons).

The baseline FEV₁ before receiving any of the test agents fluctuated between 3.11 $\pm$ 0.24 and 3.25 $\pm$ 0.30 L, and there were no significant differences from trial to trial (*P* = .99; Fig 1). Placebo, zafirlukast, and zileuton had no effect on prechallenge lung function (Fig 2). Salmeterol increased the FEV₁ by 13% $\pm$ 3% in the first hour (*P* < .001), and the effect persisted throughout the period of observation. Montelukast also produced bronchodilation, but the magnitude was less than that found with salmeterol, slower to develop, and not as long lasting. With montelukast, the FEV₁ rose by 4% $\pm$ 2% (*P* = .01) by the first hour and peaked at 7% $\pm$ 2% at 4 hours (*P* = .001). Bronchodilation dissipated by 12 hours (*P* = .21).

The percentage fall in FEV₁ from the prechallenge value for all agents is displayed in Fig 3. After placebo, the FEV₁ decreased by 21% $\pm$ 5% to 26% $\pm$ 5% over the day (*P* < .001). There were no significant differences among the responses at any time point (*P* = .87). Salmeterol reduced the level of bronchoconstriction by approximately 70%, and the effect persisted for the 12 hours of observation (Δ FEV₁ after exercise: first hour, 8% $\pm$ 3%, and twelfth hour, 8% $\pm$ 3%; *P* < .0001 vs placebo; *P* = .72 vs time). Montelukast and zafirlukast also provided prolonged prophylaxis. On average, the severity of obstruc-

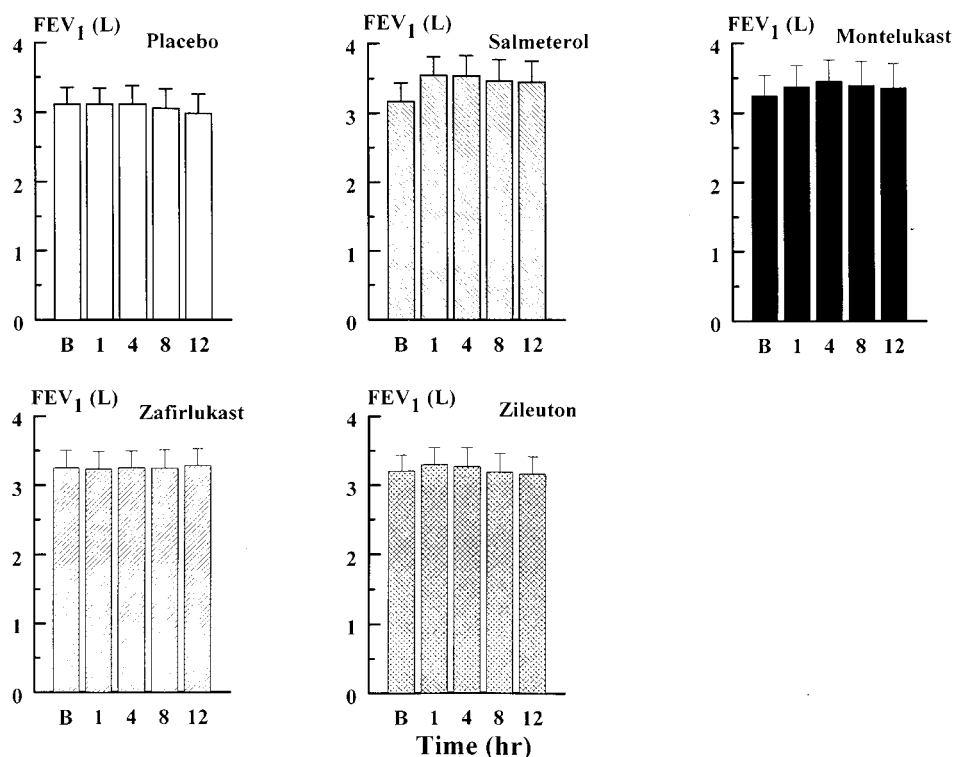


FIG 2. The effects of receiving placebo, salmeterol, montelukast, zafirlukast, and zileuton on prechallenge lung function. The heights of the bars indicate mean values, and the brackets indicate 1 SEM. Lanes B, Baseline before receiving medication; numbered lanes, hours after treatment that the exercise challenges were performed.

TABLE II. Minute ventilation and temperature of inspired air during each challenge

Hours after drug	Placebo	Salmeterol	Montelukast	Zafirlukast	Zileuton
Minute ventilation (L/min)					
1	47 ± 4	46 ± 3	46 ± 4	43 ± 3	43 ± 3
4	48 ± 3	47 ± 3	46 ± 3	43 ± 3	43 ± 3
8	49 ± 3	48 ± 4	47 ± 4	45 ± 3	44 ± 2
12	50 ± 4	50 ± 4	47 ± 3	45 ± 3	46 ± 2
Temperature of inspire (°C)					
1	-5 ± 2	-6 ± 3	-7 ± 2	-8 ± 3	-12 ± 3
4	-8 ± 2	-10 ± 3	-11 ± 1	-9 ± 3	-16 ± 4
8	-9 ± 2	-7 ± 4	-5 ± 1	-10 ± 3	-11 ± 3
12	-8 ± 2	-7 ± 4	-5 ± 1	-12 ± 3	-11 ± 3

Data are mean values ± 1 SE.

tion was 70% less with montelukast (Δ FEV₁ after exercise: first hour, 8% ± 3%, and twelfth hour, 9% ± 4%; $P = .80$ vs time) and 57% with zafirlukast (Δ FEV₁ after exercise: first hour, 14% ± 4%, and twelfth hour, 11% ± 2%; $P = .32$ vs time; $P < .001$ vs placebo for all comparisons for both drugs). Zileuton reduced the exercise response by 52% initially (Δ FEV₁ after exercise: first hour, 9% ± 2%), but the benefits progressively waned ($P = .06$ vs time). The 8-hour observation, although still better than placebo ($P = .02$), was significantly smaller than those in the first and fourth hours ($P = .003$ for both comparisons). By the twelfth hour, zileuton had lost all effectiveness (Δ FEV₁ after exercise: twelfth hour, 19% ± 4%; $P = .33$ vs placebo).

The absolute changes in FEV₁ with each drug are displayed in Fig 4 compared with placebo and Fig 5 compared with salmeterol. These representations are presented to provide a better perspective of the patterns of responses found. As can be seen in Fig 4, all of the data points for salmeterol and montelukast lie above 1 SE of the placebo observations (Fig 4, shaded area), and these drugs were indistinguishable from each other (Fig 5). The protection with zafirlukast was slower to develop, and the first-hour observation overlapped with those with placebo (Fig 4). Thereafter, the magnitude of the attenuation improved but still only reached the lower limit of the salmeterol range (Fig 5). By all analyses, zileuton was less effective. The benefits offered at 1 and 4 hours

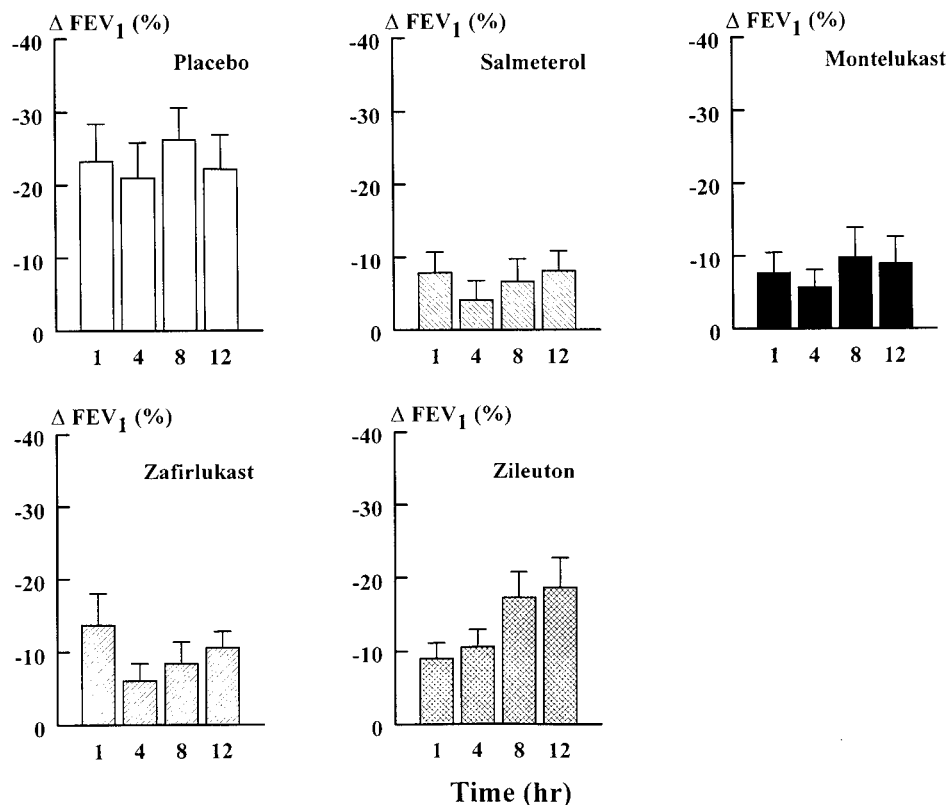


FIG 3. The relative effects of placebo, salmeterol, montelukast, zafirlukast, and zileuton on the response to exercise over time. The heights of the bars represent mean values, and the brackets represent 1 SEM. Numbered lanes indicate the provocations performed 1, 4, 8, and 12 hours after the test agents were administered.

were only slightly better than placebo (Fig 4) and thereafter dissipated. Even at its maximum, zileuton was still not as potent as salmeterol (Fig 5).

DISCUSSION

Although there is no doubt that antileukotriene compounds attenuate EIA,⁵⁻⁷ to our knowledge, there have not been any investigations that have examined either the pharmacodynamics of the effect or the duration of benefits provided by single doses. The literature on this subject contains the tacit assumption that leukotriene-modifying agents have to accumulate in the blood stream before attenuating EIA; hence study participants have been treated for 1 or more days before challenge.^{5,6,12-15} It also seems that long delays between administration and the onset of protection were anticipated, and exercise provocations have been deferred anywhere from 2 to 24 hours after the last dose.^{5-7,12-15} Finally, with a single exception,¹³ serial challenges have not been performed.^{5-7,12-15} In the initial report on zileuton, it was administered 4 times daily for 2 days and then again 2 hours before challenge.⁵ With montelukast, the typical experimental paradigm has been to give the agent for several days to weeks and then not perform a provocation for 20 to 24 hour after the final treatment.^{6,12-15} Zafirlukast has been the only compound dispensed as a single dose, but exercise testing

was not undertaken for 4 hours.⁷ Although such experimental designs clearly show that the antileukotriene drugs work, they do not allow one to decide which agent achieves the best results, appreciate the time to onset, or appreciate the duration of action.

Our data confirm that all of the leukotriene-modifying drugs presently on the US market share the ability to inhibit EIA. Each compound has a reasonably rapid onset of action, and clinically important prophylaxis can be detected within 1 hour of ingestion. The leukotriene D₄ receptor antagonists montelukast and zafirlukast are quite long lasting and are equivalent to each other in both magnitude and duration of effect. In contrast, the 5-lipoxygenase inhibitor is somewhat less potent and considerably shorter acting. In contrast to prevalent assumptions, a single dose is all that is required to produce a beneficial result, and there is no need to establish a stable blood level; hence long-term or repetitive use is not a prerequisite. This observation should greatly simplify treatment regimens. We appreciate that the antileukotriene agents are not currently prescribed intermittently, but such an approach may prove quite beneficial as either first-line or adjunct therapy in elite or recreational athletes in whom EIA is the primary manifestation of their illness.

Intuitively, one would expect that there would be a close relationship between the doses of the drugs required to modulate the underlying asthmatic diathesis

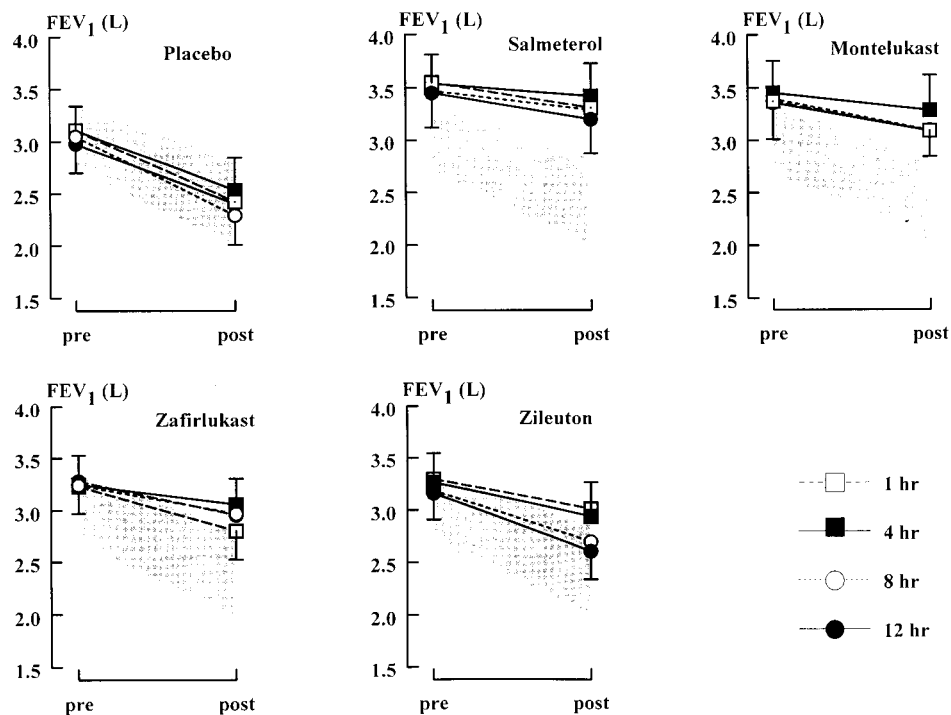


FIG 4. The absolute effects of placebo, salmeterol, montelukast, zafirlukast, and zileuton on the response to exercise over time. The shaded area in each panel represents the mean $\pm$ one SE of the placebo effect. The data points are mean values, and the brackets are 1 SEM. Pre and post indicate data before and 10 minutes after the challenges performed at 1, 4, 8, and 12 hours.

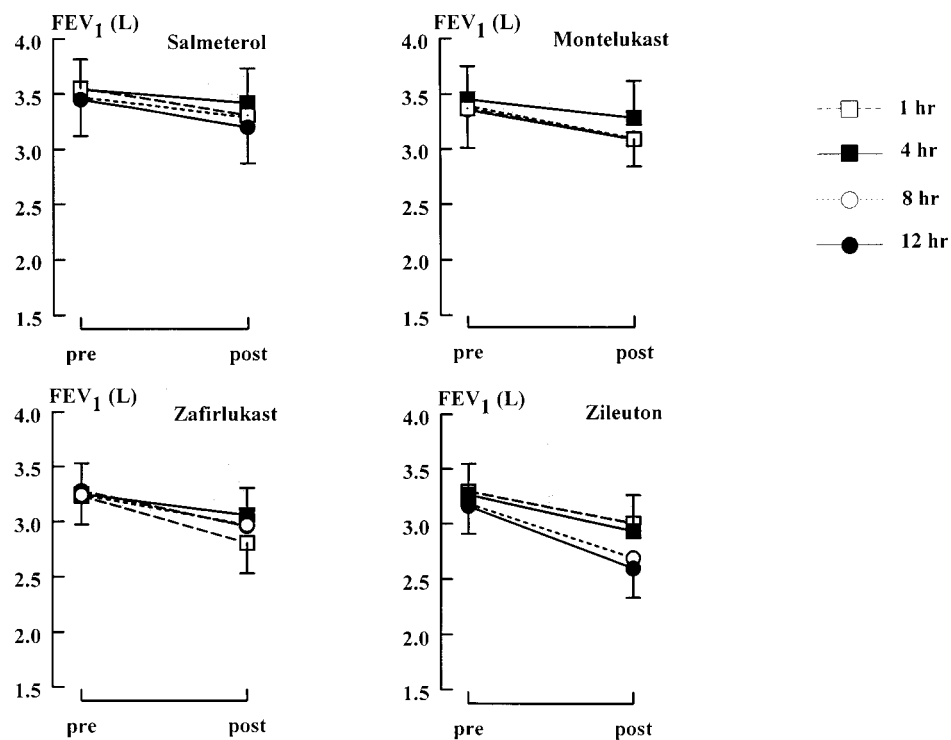


FIG 5. The absolute effects of salmeterol, montelukast, zafirlukast, and zileuton on the response to exercise over time. The shaded area in each panel indicates the mean $\pm$ 1 SE of the salmeterol response. The format is otherwise identical to that in Fig 4.

and those needed to protect against postexercise obstruction, but that does not seem to be the case, at least for the receptor antagonists. For the former use, zileuton is given 4 times daily to help control asthma, zafirlukast twice daily, and montelukast once daily. It is of interest that only the 5-lipoxygenase inhibitor has the shortest half-life. Whether this is the result of inherent difference in selectivity between the two classes of drugs or simply because of differences in pharmacokinetics is unknown. Given that there are data that show that there is no relationship between the plasma concentrations of the leukotriene receptor antagonists and the degree of attenuation of EIA,¹⁵ the latter former interpretation may be the one that is operational. Further experimentation will be required for clarification.

It has been suggested that montelukast is superior to salmeterol in blunting EIA.⁸ Unfortunately, the study design used does not allow one to share in the authors' certitude. The comparisons were made at a time when montelukast was known to be effective (ie, 20-24 after the previous evening dose) and when salmeterol was known to be waning (ie, 8-12 hours after the morning dose). Thus it is unclear whether one compound was unfairly put at a disadvantage relative to the other. The head-to-head assessments made in the present study eliminate these concerns and demonstrate that the drugs have equivalent potencies when used acutely. As shown in Fig 5, there is little to choose between them. In a chronic situation, however, montelukast, unlike salmeterol, does not appear to lose its protective effect over time,^{16,17} and therefore it may be more advantageous. It is unclear whether zafirlukast is similar to montelukast in this regard, but it is possible that all of the leukotriene receptor agonists share a common therapeutic profile. Each of the drugs of this class examined thus far (ie, montelukast, zafirlukast, and cinalukast) provides protection against EIA 3 to 6 times longer than does a 5-lipoxygenase inhibitor.^{6,15,18,19}

As in other investigations,¹⁷ our study was designed to provide data of practical clinical relevance to physicians concerned with the treatment of EIA. To this end, we studied patients with symptomatic asthma who are representative of individuals who would be seen in a typical practice setting. Their response to the exercise challenge is characteristic of such people, and the magnitude of protection afforded by each of the test agents is consistent with that previously reported.^{5-8,13-15} We also designed the study to avoid any extraneous influences that could influence the results, such as the *refractory period*. This phenomenon is seen when exercise challenges are repetitively performed within 1 and 2 hours of each other^{20,21} and results in a reduction in the magnitude of the obstructive response. The variance of the temperatures in the montelukast trial, although statistically different, was really quite small (6°C) and would have produced a negligible physiologic effect.²² On the basis of the induced differences in respiratory heat exchange,²³ the size of the obstructive responses would have changed less than 5%. Thus it is unlikely that any of these factors biased our results.

We appreciate that our investigation is small, but on the basis of the data in the literature, we anticipated large distinctions between experimental drugs and placebo, and it was powered to detect the differences sought. Although it is possible that a larger sample size might have further differentiated between montelukast and zafirlukast, it is probable that any such findings would be subtle and would not affect the pharmacologic events that comprise the main thrust of the study.

In summary, it appears that the antileukotriene compounds with the best activity against EIA are the receptor antagonists. Like the sustained acting β_2 -agonists, these drugs can be given in single doses and offer protection when needed throughout the waking day.

REFERENCES

- McFadden ER Jr, Gilbert IA. Exercise-induced asthma. *N Engl J Med* 1994;330:1362-7.
- Rossing TH, Weiss JW, Breslin FJ, Ingram RH Jr, McFadden ER Jr. Effects of inhaled sympathomimetics on obstructive response to respiratory heat loss. *J Appl Physiol* 1982;52:1119-23.
- Kemp JP, Dockhorn RJ, Busse WW, Bleecker ER, Van As A. Prolonged effect of inhaled salmeterol against exercise-induced bronchospasm. *Am J Respir Crit Care Med* 1994;150:1612-5.
- Patessio A, Podda A, Carone M, Trombetta N, Donner CF. Protective effect and duration of action of formoterol aerosol on exercise-induced asthma. *Eur Respir J* 1991;4:296-300.
- Meltzer SS, Hasday JD, Cohn J, Bleecker ER. Inhibition of exercise-induced bronchospasm by zileuton: a 5-lipoxygenase inhibitor. *Am J Respir Crit Care Med* 1996;153:931-5.
- Leff JA, Busse WW, Pearlman D, Bronsky EA, Kemp J, Hendeles L, et al. Montelukast, a leukotriene-receptor antagonist, for the treatment of mild asthma and exercise-induced bronchoconstriction. *N Engl J Med* 1998;339:147-52.
- Pearlman DS, Ostrom NK, Bronsky EA, Bonuccelli CM, Hanby LA. The leukotriene D₄-receptor antagonist zafirlukast attenuates exercise-induced bronchoconstriction in children. *J Pediatr* 1999;134:273-9.
- Villaran C, O'Neill SJ, Helbling A, vanNoord JA, Lee TH, Chuchalin AG, et al. Montelukast versus salmeterol in patients with asthma and exercise-induced bronchoconstriction. *J Allergy Clin Immunol* 1999;104:547-53.
- Gilbert IA, Fouke JM, McFadden ER Jr. Intra-airway thermodynamics during exercise and hyperventilation in asthmatics. *J Appl Physiol* 1988;64:2167-74.
- McFadden ER Jr, Lenner KA, Strohl KP. Postexercise airway rewarming and thermally induced asthma: new insights into pathophysiology and possible pathogenesis. *J Clin Invest* 1986;78:18-25.
- Zar JH. Biostatistical analysis. 2nd ed. Englewood Cliffs (NJ): Prentice-Hall; 1984.
- Kemp JP, Dockhorn RJ, Shapiro GG, Nguyen HH, Reiss TF, Seidenberg BC, et al. Montelukast once daily inhibits exercise-induced bronchoconstriction in 6- to 14-year-old children with asthma. *J Pediatr* 1998;133:424-8.
- Bronsky EA, Kemp JP, Zhang J, Guerreiro D, Reiss TF. Dose-related protection of exercise bronchoconstriction by montelukast, a cysteinyl leukotriene-receptor antagonist, at the end of a once-daily dosing interval. *Clin Pharmacol Ther* 1997;62:556-61.
- Finnerty JP, Wood-Baker R, Thomson H, Holgate ST. Role of leukotrienes in exercise-induced asthma. *Am Rev Respir Dis* 1992;145:746-9.
- Reiss TF, Hill JB, Harman E, Zhang J, Tanaka WK, Bronsky E, et al. Increased urinary excretion of LTE₄ after exercise and attenuation of exercise-induced bronchospasm by montelukast, a cysteinyl leukotriene receptor antagonist. *Thorax* 1997;52:1030-5.
- Edelman JM, Turpin J, Bronsky EA, Grossman J, Kemp JA, Ghannam AF, et al. Oral montelukast compared with inhaled salmeterol to prevent exercise-induced bronchoconstriction. *Ann Intern Med* 2000;132:97-104.
- Nelson JA, Strauss L, Skowronski M, Ciufo R, Novak R, McFadden ER Jr. Effect of long-term salmeterol treatment on exercise-induced asthma. *N Engl J Med* 1998;339:141-6.

18. Calhoun WJ. Summary of clinical trials with zafirlukast. *Am J Respir Crit Care Med* 1998;157:s238-46.
19. Adelroth E, Inman MD, Summers E, Pace D, Modi M, O'Byrne PM. Prolonged protection against exercise-induced bronchoconstriction by the leukotriene D₄-receptor antagonist cinalukast. *J Allergy Clin Immunol* 1997;99:210-5.
20. Silverman M, Anderson S. Standardization of exercise tests in asthmatic children. *Arch Dis Child* 1972;47:882-9.
21. Edmunds AT, Tolley M, Godfrey S. The refractory period after exercise induced asthma: its duration and relation to the severity of exercise. *Am Rev Respir Dis* 1978;117:247-54.
22. Stearns DR, McFadden ER, Breslin F, Ingram RH. Reanalysis of the refractory period in exertional asthma. *J Appl Physiol Respir Environ Exercise Physiol* 1981;50:503-8.
23. Deal EC Jr, McFadden ER Jr, Ingram RH Jr, Strauss RH, Jaeger JJ. The role of respiratory heat exchange in the production of exercise-induced asthma. *J Appl Physiol* 1979;46:467-75.

Receive tables of contents by e-mail

To receive the tables of contents by e-mail, sign up through our Web site at

<http://www.mosby.com/jaci>

Choose *E-mail notification*. Simply type your e-mail address in the box and click the *Subscribe* button.

Alternatively, you may send an e-mail message to

majordomo@mosby.com

Leave the subject line blank and type the following as the body of your message:

subscribe jaci_toc

You will receive an e-mail message confirming that you have been added to the mailing list.

Note that TOC e-mails will be sent out when a new issue is posted to the Web site.