

Montelukast versus salmeterol in patients with asthma and exercise-induced bronchoconstriction

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Background: Montelukast, a leukotriene receptor antagonist, and salmeterol, a long-acting β_2 -receptor agonist, each have demonstrated benefits in the treatment of exercise-induced bronchoconstriction (EIB) in short-term studies. Direct comparisons between these agents in long-term studies are limited. **Objective:** We sought to compare montelukast and salmeterol in the long-term treatment of EIB.

Methods: One hundred ninety-seven patients with mild asthma and a postexercise fall in FEV₁ of at least 18% were randomized (double-blind) to receive montelukast 10 mg once daily or salmeterol 50 μ g twice daily for 8 weeks. Exercise challenge was repeated at day 3, week 4, and week 8 after randomization near the end of the dosing interval for both drugs. The primary efficacy endpoint was the maximal percent fall in postexercise FEV₁ at week 8.

Results: Montelukast was effective in treating EIB without inducing tolerance and provided superior ($P \leq .001$) protection than salmeterol at weeks 4 and 8, with comparable protection at day 3. The frequency of respiratory clinical adverse events ($P = .046$) and discontinuations because of clinical adverse events ($P = .052$) were less with montelukast.

Conclusion: The effect of montelukast was greater than that of salmeterol in the chronic treatment of EIB over a period of 8 weeks in patients with mild asthma as demonstrated by effect size, maintenance of effect, and fewer respiratory clinical adverse events during the study period. Montelukast may be a better alternative to salmeterol as a controller agent for the

chronic treatment of EIB. (*J Allergy Clin Immunol* 1999;104:547-53.)

Key words: Tolerance, tachyphylaxis, leukotrienes, montelukast, salmeterol, exercise-induced asthma

Exercise is one of the most common triggers of acute asthmatic symptoms. Exercise-induced bronchoconstriction (EIB) affects approximately 70% to 80% of patients with clinically diagnosed asthma¹ and may signal an overall lack of asthma control. Therefore long-term controller agents may have a role in treating patients with frequent symptoms of EIB.² EIB may be demonstrated in nearly all asthmatic patients when presented with the appropriate stimuli, such as vigorous exercise in a cold, dry environment.³ Even asthmatic patients with mild disease may have significant EIB,⁴ limiting participation in sports and recreation and thereby impairing quality of life. One goal of asthma therapy is to control the disease process and maximize exercise capacity.

In addition to controller agents, such as inhaled corticosteroids, current treatment strategies for EIB include the use of short- and long-acting β -agonists, such as salbutamol and salmeterol, respectively, delivered through an inhaler. Although effective, the β -agonists are limited by the development of tolerance.⁵⁻⁸

Cysteinyl leukotrienes mediate abnormalities of airway function, such as increased mucus production, decreased mucociliary clearance, increased vascular permeability, smooth muscle contraction, and recruitment of inflammatory cells by activation of leukotriene receptors. Montelukast, a potent and selective leukotriene receptor antagonist (LTRA), and other LTRAs have been shown to attenuate EIB.⁹⁻¹⁴ As a controller agent, montelukast also improves asthma symptoms and outcomes¹⁵⁻¹⁸ and is an alternative to long-acting β -agonists based on its once-daily oral dosage form, persistence of effect,^{14,17,19,20} and effects on asthmatic inflammation.^{17,21,22}

We therefore conducted a multicenter, randomized, double-blind, double-dummy, parallel-group study in patients with mild asthma and EIB to compare montelukast with salmeterol when used in the long term.

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Abbreviations used

AUC_{0-60min}: Area under the curve from 0 to 60 minutes
 EIB: Exercise-induced bronchoconstriction
 LTRA: Leukotriene receptor antagonist

METHODS

Three hundred thirty-three patients with a clinical history of mild asthma for at least 1 year (males and females, aged 14 to 45 years) were screened at 25 centers in 12 countries. Patients had an improvement in FEV₁ of at least 12% after administration of a β -agonist (68% of patients) or airway hyperresponsiveness (defined by a PC₂₀ in FEV₁ in response to ≤ 4 mg/mL of methacholine or histamine) within the previous 6 months. They were in good health except for asthma and were nonsmokers for at least 1 year, with a smoking history of 20 pack-years or less.

Patients were excluded if they had emergency treatment for asthma within 1 month of the first visit, hospitalization for asthma within 3 months, an unresolved upper respiratory tract infection within 3 weeks, or sinus infection within 1 week. Excluded asthma medications included corticosteroids within 1 month (except for up to 25% of patients already taking inhaled corticosteroids 200 to 500 μ g daily who were allowed to continue this dose unchanged throughout the study); cromolyn, nedocromil, leukotriene synthesis inhibitors, or LTRAs within 2 weeks; and theophylline or aminophylline, oral or long-acting inhaled β -agonists, and inhaled anticholinergic agents within 1 week of the first visit. The protocol was approved by the ethical review committees of all participating centers, and written informed consent was obtained from all participants.

There were 5 study visits. One prestudy visit was performed to assess EIB followed by a 2-week, single-blind, placebo run-in period (tablet and inhaler) after which a second exercise challenge was performed. If both challenges were positive ($\geq 18\%$ fall in FEV₁), patients were randomized according to a computer-generated allocation schedule to treatment with montelukast sodium 10 mg once daily at bedtime or salmeterol 50 μ g twice daily administered by means of a metered-dose inhaler for 8 weeks. A standardized exercise challenge was performed in the evening 20 to 24 hours after the previous evening dose of montelukast and 8 to 12 hours after the morning dose of salmeterol (trough of dosing interval of each agent) at approximately 3 days, 4 weeks, and 8 weeks after randomization.

Short-acting antihistamines were permitted but withheld for at least 48 hours before study visits; inhaled salbutamol was allowed "as needed" and was withheld for at least 6 hours before study visits. Patients were discontinued from the study if they interrupted their study drug for more than 6 consecutive days, if they experienced adverse events (at the discretion of the investigator), if they became pregnant, or if their asthma symptoms worsened and required treatment with oral or inhaled corticosteroids.

Exercise challenges were performed at all 5 visits. Pre-exercise spirometry was performed 20 and 5 minutes before exercise. The average of the best of 3 attempts at each time point was considered the pre-exercise FEV₁ and was required to be at least 65% of the predicted value for the exercise challenge to be performed. After a 1- to 2-minute warm-up, the patient exercised for 6 minutes on a treadmill while inhaling compressed dry air at room temperature delivered through a one-way valve and a face mask at a workload that increased the heart rate to 80% to 90% of the individual's age-predicted maximum (220 – age). Spirometry was performed immediately after exercise (0 minutes) and at 5, 10, 15, 30, 45, and 60 minutes. A standard spirometer (Puritan-Bennett PB 100) was used at all sites, and spirometric maneuvers achieved American Thoracic

Society acceptability and reproducibility criteria.²³ The best FEV₁ value from each set of measurements was used for analysis. At any time during the exercise challenge rescue with β -agonist could be administered at the discretion of the investigator. Of the 333 screened patients, 136 were ultimately not randomized: 94 for failing to demonstrate the required fall in FEV₁ after exercise, 13 for not demonstrating the required FEV₁ reversibility/hyperresponsiveness criteria, 10 for having an FEV₁ of less than 65% at baseline, and 19 for miscellaneous reasons (ie, abnormal laboratory values, inability to run on a treadmill, disallowed concomitant medications, current smoking, withdrawal of consent, and lower back pain).

The exercise challenge endpoints included the maximal percentage fall in FEV₁ after exercise (primary endpoint); the area under the curve (AUC), which summarizes both the extent and duration of bronchoconstriction after exercise (AUC_{0-60min} of percentage fall in FEV₁ versus time); and the time to recovery of FEV₁ to within 5% of the pre-exercise value (Fig 1). Only the area below the pre-exercise baseline FEV₁ was counted in calculating the AUC; a reduction in AUC represented improvement.¹⁴ If β -agonist was administered during an exercise challenge, subsequent FEV₁ values were excluded from the analysis, and the last FEV₁ measurement before rescue was carried forward for the remaining time points. The time to recovery was defined as the time required to return to within 5% of the pre-exercise FEV₁ value from the time of the maximal fall in FEV₁ and was estimated by linear interpolation. If a patient was rescued after exercise or FEV₁ did not recover within 75 minutes, the time to recovery was defined as 85 minutes minus the time of the maximal fall. If a patient's FEV₁ did not fall by greater than 5%, the time to recovery was assigned a value of zero.

The efficacy analyses were based on the intention-to-treat approach (all patients treated); that is, inclusion of all patients with a baseline and at least one postbaseline measurement for all exercise endpoints. The comparison of change from prandomization baseline to week 8 was the primary analysis for all endpoints and was done with an ANOVA model with factors for treatment, concomitant inhaled steroid use, and center. A 2-sided *t* test was used to analyze the within-group change from baseline. A 95% confidence interval was constructed for the mean difference in the maximum percent fall in FEV₁ between the montelukast and salmeterol groups.

The persistence of effect of montelukast and salmeterol over time (day 3 through week 8) was assessed by investigating the rate of change over the treatment period for the endpoints by using a mixed-effects ANOVA model with a compound symmetry overall covariance matrix. Tolerance was defined as a significant (positive) difference from zero in the slope of the time-response profile of the treatment effect from day 3, week 4, and week 8 for each of the efficacy endpoints. Fisher's exact test was used to compare between-group differences in the frequency of β -agonist rescue and the incidence of adverse experiences.

This study was designed to have a 95% power to detect a 7% difference in the mean change for the maximal percentage fall in FEV₁ between treatments at the 2-sided .05 significance level based on a standard deviation of 12.5% from an earlier montelukast study.¹⁴

RESULTS

One hundred ninety-seven patients were randomized to study medication: 102 to montelukast and 95 to salmeterol (Table I). There were no important differences between the 2 groups in baseline demographic characteristics. Although the protocol allowed up to 25% of patients to continue receiving inhaled corticosteroid therapy throughout the study, only 20 patients (10%) were so

TABLE I. Baseline demographics of randomized patients

Characteristic	Montelukast (n = 102)	Salmeterol (n = 95)
Age, y (range)	27 (15-45)	27 (14-45)
<18 y	8 (8%)	8 (8%)
≥18 to 45 y	94 (92%)	87 (92%)
Sex		
M	53 (52%)	45 (47%)
F	49 (48%)	50 (53%)
Race		
White	77 (75%)	71 (75%)
Asian	2 (2%)	1 (1%)
Mixed race	23 (23%)	23 (24%)
Duration of asthma, y (SD)	15.4 (8.8)	13.0 (9.2)
Pre-exercise FEV ₁ % predicted (SD)	86.6 (13.7)	87.2 (14.0)
Maximal % fall in FEV ₁ after exercise (SD)	33.3 (12.1)	30.2 (10.5)
Smoking History		
Smoked	17 (17%)	10 (11%)
Never smoked	85 (83%)	85 (89%)

treated (14 receiving montelukast and 6 receiving salmeterol). One hundred eighty-eight (95%) completed the study, with 100 (98%) receiving montelukast and 88 (93%) receiving salmeterol. The majority of patients (66%) had day 3 measurements 3 days after randomization; a small number had measurements on days 2 (12%) and 4 (21%), and one patient had measurements on day 5. Baseline pulmonary function in these patients was (near) normal, and approximately 62% had symptoms on 3 or fewer days per week (20% had symptoms on only one day per week), meeting the definition of mild persistent asthma in the Global Initiative of Asthma treatment guidelines.²⁴

The maximal percentage fall in FEV₁ after exercise decreased (improved) significantly from prerandomization baseline to week 8 in both treatment groups ($P \leq .001$; Table II and Figs 2 and 3). The improvement was significantly ($P = .001$) larger in the montelukast treatment group (mean decrease, 17.2 percentage points [52% inhibition]) than in the salmeterol treatment group (mean decrease, 10.7 percentage points [35% inhibition]). Throughout the study, the improvement in maximal percentage fall in FEV₁ was greater with montelukast treatment than with salmeterol treatment (Fig 3). The mean decrease in the maximal percentage fall in FEV₁ with salmeterol was most pronounced at day 3 compared with weeks 4 and 8. In the montelukast group the decrease remained stable from day 3 through week 8. Throughout the study, there was no significant difference between treatment groups in pre-exercise FEV₁, although there was a small but statistically significant change from prerandomization baseline (baseline values: montelukast, 3.30 L; salmeterol, 3.34 L) in both treatment groups (day 3 FEV₁, 3.41 L and 3.49 L; week 4 FEV₁, 3.35 L and 3.46 L; week 8 FEV₁, 3.38 L and 3.43 L for montelukast and salmeterol, respectively). As a corroborative analysis, an analysis of change from baseline in minimum FEV₁ after exercise (ie, FEV₁ at maximal percentage

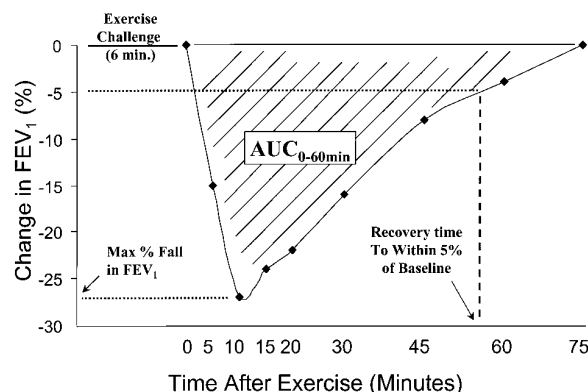


FIG 1. Schematic representation of endpoints used to assess the degree of EIB. Endpoints included the maximal percentage fall in FEV₁ after exercise; the AUC, which summarizes both the extent and duration of bronchoconstriction after exercise (AUC_{0-60min} of percent fall in FEV₁ versus time); and the time to recovery of FEV₁ to within 5% of the pre-exercise value.

fall) was also performed, yielding similar results (data not shown). The treatment effect with both therapies was consistent across subgroups of sex and age. In addition, treatment group differences were maintained in patients using concomitant inhaled steroids (maximum FEV₁ percent fall of 21.7% at week 8 from a baseline of 35.7% fall with montelukast; maximum FEV₁ percent fall of 32.6 at week 8 from a baseline of 38.4% fall with salmeterol). The mean time since the last dose of montelukast and salmeterol until the exercise challenge was 21 hours and 9 hours, respectively. There was some heterogeneity of response. For example, 64% of patients receiving montelukast versus 59% receiving salmeterol had FEV₁ decreases of less than 20% after exercise at week 8 (62% vs 46% at week 4). Similarly, at week 8, 24% of patients receiving montelukast had a maximum percentage fall in FEV₁ of 5% or less compared with 14% of patients receiving salmeterol.

The AUC_{0-60min} decreased significantly from prerandomization baseline to week 8 in both treatment groups ($P \leq .001$). The decrease was significantly ($P = .002$) larger in the montelukast treatment group (mean decrease, 596% × min [57% inhibition]) than in the salmeterol treatment group (mean decrease, 286% × min [30% inhibition]). The difference was also significant at 4 weeks. Throughout the study, the mean decrease in AUC_{0-60min} was significantly or borderline significantly larger in the montelukast group than in the salmeterol group (Fig 3).

The time to recovery decreased significantly from prerandomization baseline to week 8 in both treatment groups ($P \leq .001$). The decrease was significantly ($P = .005$) larger in the montelukast treatment group (mean decrease, 23.9 minutes [50% inhibition]) than in the salmeterol treatment group (mean decrease, 11.3 minutes [25% inhibition]). The difference was also significant at 4 weeks. Throughout the study, the decrease in time to recovery was greater with montelukast treatment than with salmeterol treatment (Fig 3).

TABLE II. Efficacy (Intention-to-treat) analysis of change from baseline

					Change from baseline		Between-group comparison		
	Treatment	n	Baseline mean	Day or week mean	Mean (SD)	95% CI	Least-square mean	95% CI	P values
Day 3									
Maximal % fall in FEV ₁	Montelukast	98	33.3	17.7	−15.6 (13.5)	−18.3, −12.9	−3.1	−6.9, 0.8	.123
	Salmeterol	88	30.5	18.0	−12.5 (12.9)	−15.2, −9.7			
AUC _{0-60min} (% × min)	Montelukast	98	1051	441	−610 (686)	−747, −472	−168	−343, 6	.059
	Salmeterol	88	951	531	−420 (576)	−542, −297			
Recovery time to within 5% of prechallenge baseline (min)	Montelukast	98	47.5	22.4	−25.1 (32.1)	−31.5, −18.6	−3.3	−11.6, 5.0	.439
	Salmeterol	88	45.6	24.5	−21.2 (27.5)	−27.0, −15.3			
Week 4									
Maximal % fall in FEV ₁ (%)	Montelukast	97	33.1	17.3	−15.8 (13.8)	−18.6, −13.0	−8.8	−13.1, −4.5	<.001
	Salmeterol	83	30.9	23.5	−7.3 (14.7)	−10.5, −4.1			
AUC _{0-60min} (% × min)	Montelukast	97	1043	475	−569 (763)	−722, −415	−428	−655, −201	<.001
	Salmeterol	83	964	820	−144 (782)	−315, 27			
Recovery time to within 5% of prechallenge baseline (min)	Montelukast	97	47.7	24.3	−23.5 (32.4)	−30.0, −16.9	−14.8	−23.8, −5.7	.002
	Salmeterol	83	44.7	36.2	−8.5 (28.3)	−14.7, −2.3			
Week 8									
Maximal % fall in FEV ₁ (%)	Montelukast	97	33.1	15.9	−17.2 (14.3)	−20.1, −14.3	−7.2	−11.4, −3.0	.001
	Salmeterol	86	30.9	20.2	−10.7 (14.3)	−13.7, −7.6			
AUC _{0-60min} (% × min)	Montelukast	97	1043	448	−596 (689)	−734, −457	−313	−509, −117	.002
	Salmeterol	86	960	675	−286 (610)	−416, −155			
Recovery time to within 5% of prechallenge baseline (min)	Montelukast	97	47.7	23.8	−23.9 (31.6)	−30.3, −17.5	−13.0	−22.2, −3.9	.005
	Salmeterol	86	44.9	33.7	−11.3 (29.5)	−17.6, −4.9			

Over the 8-week treatment period, the slope of the time-response profile (based on the change from prerandomization baseline at day 3, week 4, and week 8) of the treatment effect of the montelukast group for all 3 endpoints was not different from zero, indicating that the treatment effect of montelukast persisted over time. In contrast, for 2 of the 3 endpoints (AUC_{0-60min} and time to recovery) in the salmeterol group, the slope was positive and was significantly different from zero ($P \leq .050$ and $P \leq .010$, respectively), which is consistent with a loss of treatment effect over time. A between-group comparison showed no significant difference between the slopes for maximal percentage fall in FEV₁ and AUC_{0-60min}, but there was a significant ($P = .045$) difference between the slopes for time to recovery. There was no significant difference between the montelukast and salmeterol groups in the proportion of patients requiring β -agonist rescue medication after exercise challenge at any visit during the double-blind treatment period (18% vs 25% for montelukast and salmeterol at week 8, respectively). In a post hoc analysis a significant reduction in absolute blood eosinophils was seen in the montelukast group (18%, $P \leq .01$) and in eosinophils as a percentage of total white blood cell count (0.94% points, $P \leq .001$). The salmeterol group showed no change in absolute eosinophil numbers (5.7% reduction, $P > .05$) but a significant reduction in the percentage of total white blood cell count (0.50% points, $P \leq .05$).

Montelukast and salmeterol were generally well tolerated, with similar adverse experience profiles in most body systems. The exception was the respiratory system; patients in the salmeterol treatment group had a significantly ($P = .046$) higher incidence of respiratory clinical adverse events (54%) than patients in the montelukast group (39%). The 4 most frequent clinical adverse events in the montelukast and salmeterol groups, respectively, were bronchoconstriction (24% and 32%), headache (10% and 8%), pharyngitis (6% and 7%), and upper respiratory tract infection (3% and 8%). All other adverse experiences occurred with a frequency of 5% or less, and most of these occurred with a frequency of 1% or less. Altogether, 7 patients in the salmeterol group discontinued the study compared with 2 in the montelukast group. Of these, 4 patients in the salmeterol group discontinued because of clinical adverse experiences (worsening asthma/asthma attacks), and none discontinued for this reason in the montelukast group ($P = .052$). In addition, one patient in the salmeterol group discontinued because of insufficient therapeutic response. There were no other significant differences in the frequency of clinical or laboratory adverse experiences in the 2 groups.

DISCUSSION

We found that montelukast had a greater effect than salmeterol in the chronic treatment of EIB over 8 weeks.

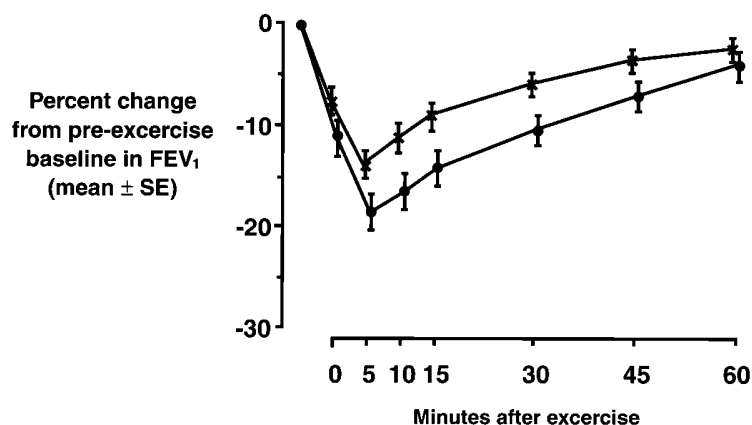


FIG 2. Treatment with montelukast (x , $n = 97$) caused a significant ($P \leq .005$) improvement compared with salmeterol (filled circles, $n = 86$) in all endpoints of EIB, including maximum percentage fall in FEV₁ after exercise, AUC_{0-60 min}, and time to recovery to within 5% of pre-exercise FEV₁. Values are from an 8-week analysis (means $\pm$ SEM).

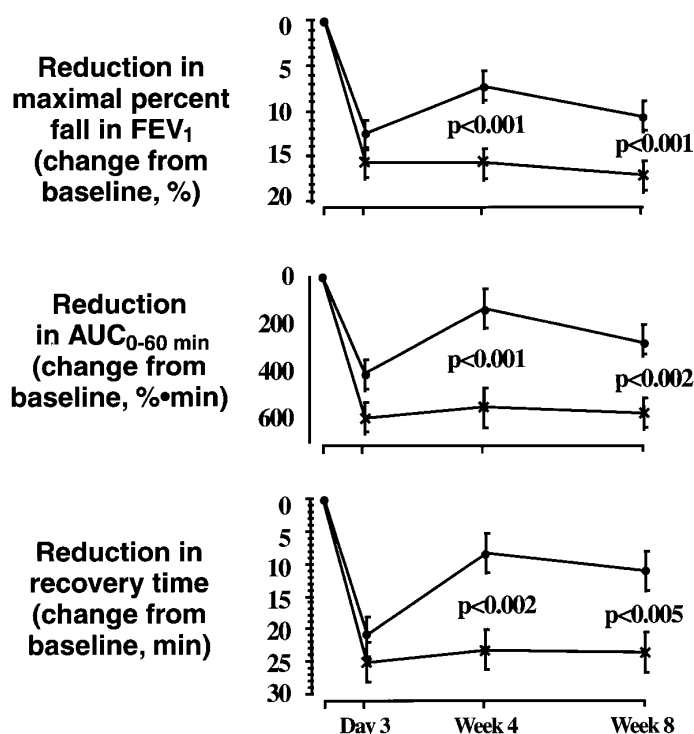


FIG 3. Treatment with montelukast (x , $n = 97$ or 98) caused a significant reduction compared with salmeterol (filled circles, $n = 83$ to 88) in change from baseline in maximum percentage fall in FEV₁ after exercise (*top panel*), AUC_{0-60 min} (*middle panel*), and time to recovery to within 5% of pre-exercise FEV₁ (*bottom panel*) at weeks 4 and 8 of treatment. Values are means $\pm$ SEM.

Protection by montelukast was evident by day 3 and persisted throughout the 8-week treatment period without development of tolerance. All 3 exercise endpoints supported this conclusion. Similarly, other montelukast studies in chronic asthma also support the lack of tolerance to treatment.¹⁷⁻²⁰ The effects with montelukast were comparable to those seen in previous exercise studies in which clinically important protection against EIB was

observed without development of tolerance.^{9,11,13,14} The important role of leukotrienes in the pathogenesis of EIB is further supported by these data and those observed with other leukotriene modifiers.^{10,12,25-27}

In contrast, the protective effects of salmeterol, although evident at day 3, appeared to wane over time such that by weeks 4 and 8, montelukast provided significantly ($P \leq .005$) better results than salmeterol. The

difference in improvement with montelukast versus salmeterol was not confounded by pre-exercise bronchodilation because pre-exercise FEV₁ values were similar in both treatment groups. Also, exercise challenge was performed well within the dosing interval of both agents. Protection at day 1 has previously been shown to be similar at 6 and 12 hours after exercise with salmeterol.⁵ It is possible that the day 3 salmeterol protection was not maximal because tolerance to salmeterol may occur even within 24 hours.⁷ Improvement with both drugs was heterogeneous, with some patients having greater protection against EIB and some less. Because the baseline degree of EIB was quite substantial (approximately 32% fall in FEV₁), complete protection may not be a reasonable expectation in these particular patients. Indeed, a study with milder falls in FEV₁ after exercise demonstrated almost complete protection with another LTRA (MK-571).¹⁰

The reduced effect over time with salmeterol is consistent with previous studies indicating tolerance to bronchoprotective properties of long-acting β -agonists. Ramage et al⁵ observed significant protection against EIB 6 and 12 hours after the first dose of salmeterol, but after 4 weeks of treatment there was no significant protection against EIB. In another study tolerance developed even with only once-daily salmeterol dosing given concomitantly with inhaled corticosteroids for 4 weeks.²⁸ These results are also consistent with another similarly designed study in which montelukast demonstrated persistent and greater improvement in EIB than salmeterol.²⁹ That study was performed in a similar population of patients with EIB, except none was taking concomitant inhaled steroids, as was allowed in this trial. One week of treatment with regular short-acting β -agonist (albuterol) has also been shown to worsen baseline airway caliber and postexercise FEV₁ and reduce protection against EIB from albuterol.⁸ Tolerance to bronchoprotection with salmeterol has also been demonstrated with methacholine,^{7,30} allergen challenge,³¹ and with formoterol.³² The mechanisms of tolerance to β -agonist therapy and its clinical relevance in asthma are currently a matter of debate.³³ Some authorities believe that tolerance to clinically relevant environmental stimuli does not occur. Further study in this area is required.

The patients treated in this study with concomitant inhaled steroids showed the same effect as those not treated with these agents. It is relevant that tolerance to bronchoprotection is not prevented by concomitant inhaled steroid therapy.^{6,28,34}

Results from studies such as this and others have led to the recommendation that salmeterol not be used as monotherapy for chronic asthma but instead should be used together with inhaled corticosteroids.²⁴ Because montelukast is also often used in addition to inhaled corticosteroids, it will be of interest to see how these 2 options compare in the treatment of chronic asthma.

Montelukast and salmeterol were generally well tolerated, with few clinical and laboratory adverse events, which were usually mild and transient. There were, how-

ever, significantly more ($P = .046$) respiratory clinical adverse experiences with salmeterol than with montelukast. Similarly, there were more discontinuations because of clinical adverse events (worsening asthma or asthma attacks) with salmeterol (4) than with montelukast (0, $P = .052$). This is consistent with the favorable tolerability profile of montelukast in large trials of up to 3 months^{16,17} and in limited numbers of patients for longer periods.^{19,20}

These data imply that salmeterol may have limitations in the chronic treatment of EIB, even in patients receiving concomitant inhaled steroids. Montelukast, as an oral agent that does not induce tolerance, may offer advantages in these patients.

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