

Effect of different antiasthmatic treatments on exercise-induced bronchoconstriction in children with asthma

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Background: Exercise-induced bronchoconstriction occurs in a large proportion of children with asthma, limiting everyday activities important for their physical and social development. **Objective:** The purpose of this randomized, double-blind, placebo-controlled study was to compare the ability of different patterns of antiasthmatic treatment, recommended in childhood asthma, to protect patients from exercise-induced bronchoconstriction.

Methods: Children 6 to 18 years of age with atopic asthma were randomized to a 4-week, placebo-controlled, double-blind trial. Patients were randomly allocated to receive daily 200 µg budesonide (twice daily, 100 µg per dose) + 9 µg formoterol (twice daily, 4.5 µg per dose; n = 20); 200 µg budesonide + 5 or 10 mg montelukast (once daily at bedtime; n = 20); 5 or 10 mg montelukast (n = 20); 200 µg budesonide (n = 20); or placebo (n = 20). A standardized treadmill exercise challenge was performed before and after treatment.

Results: Exercise-induced bronchoconstriction, reflected by area under the curve for the FEV₁ values from exercise over the 20-minute period and by maximum percent fall in FEV₁ after exercise, was significantly diminished after 4 weeks in all active treatment groups, and compared with placebo. Exercise-induced bronchoconstriction protection improved more significantly in the budesonide + montelukast and montelukast groups compared with other therapeutic options.

Conclusion: These data indicate differences in effects on exercise-induced bronchoconstriction between therapeutic options recommended in childhood asthma. Control of childhood asthma with exercise-induced bronchoconstriction can be obtained by using regular controller treatment.

Clinical implications: These data indicate differences in effects on exercise-induced bronchoconstriction between therapeutic

options recommended in childhood asthma. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: Asthma, children, exercise, antiasthmatic treatment

Asthma is one of the most common chronic disease worldwide, imposing a substantial social burden on both children and adults.¹ Normal lung function is one of the goals of asthma management.¹ Exercise-induced bronchoconstriction (EIB) occurs in a large proportion of children with asthma,^{2,3} limiting everyday activities important for their physical and social development.

Regular antiasthma treatment with inhaled glucocorticosteroids (ICSs) and leukotriene modifiers alleviates exercise-induced bronchoconstriction in children.⁴⁻⁶ In contrast with bronchodilators, which children often forget to take as needed, these medications do not have to be taken immediately before the exercise, and they modify airway hyperresponsiveness. It is known that inhalation of a single dose of long-acting β₂-agonists (LABAs) effectively blocks EIB for several hours, but influence of regular daily therapy on EIB is still under the investigation.

The purpose of this randomized, double-blind, placebo-controlled study was to compare the ability of different patterns of antiasthmatic treatment, recommended in childhood asthma, to protect patients from exercise-induced bronchoconstriction.

METHODS

Patients

One hundred fifty patients were screened with an exercise test. Fifty patients (33.3%) did not meet criteria of a fall of 20% or more in FEV₁ postexercise. Participants in the 8-week study were 100 children with a history of typical symptoms of asthma, who were sensitive only to house dust mites as shown by positive skin prick tests (SPTs) to *Dermatophagoides pteronyssinus* and/or *Dermatophagoides farinae*. Diagnosis of asthma was established by symptoms of asthma and improvement in the prebronchodilator FEV₁ ≥ 12% after administration of salbutamol (200 µg).¹ During the previous 6 months, before the study, all patients had been treated with inhaled steroids (budesonide; average dose, 400 µg/d) and montelukast sodium (5 mg or 10 mg, according to age) or long-acting bronchodilator. Antihistamines, nasal steroids, and nasal nedocromil were also used. Asthma was stable in all patients, there had been no exacerbations of disease or need for other

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Abbreviations used

- AUC: Area under the curve
 AUC_{0-20min}: Area under the curve for the FEV₁ values from exercise over the 20-minute period
 EIB: Exercise-induced bronchoconstriction
 ICS: Inhaled glucocorticosteroid
 LABA: Long-acting inhaled β_2 -agonist
 SPT: Skin prick test

treatment for 6 months, and no hospitalizations due to asthma had occurred in the previous 6 months before the study.

For the purposes of the study, SPTs (Allergopharma, Darmstadt, Germany) to standard allergen extracts were performed; a mean wheal diameter ≥ 3 mm at 15 minutes was defined as a positive response. SPTs were positive against both *D farinae* and *D pteronyssinus* extracts in all subjects. None of enrolled subjects was allergic to other perennial and seasonal allergens. Subjects were recruited from our Allergy Clinic Center.

Inclusion criteria

Male and female outpatients age 6 to 18 with a clinical diagnosis of bronchial asthma with a duration of at least 6 months before the first visit were enrolled. To be included in the study, patients had to have a resting FEV₁ of 70% or more and a documented decrease in FEV₁ of 20% or more after a standard exercise challenge test.

Exclusion criteria

Study exclusions included active upper respiratory tract infection within 3 weeks before the study and acute sinus disease requiring antibiotic treatment within 1 month before the study, previous intubation, or asthma hospitalization during the 3 months before the prestudy visit. Additional criteria were other clinically significant pulmonary, hematologic, hepatic, gastrointestinal, renal, endocrine, neurologic, cardiovascular, and/or psychiatric diseases or malignancy that either put the patient at risk when participating in the study or could influence the results of the study or the patient's ability to participate in the study as judged by the investigator. Medications that resulted in patient exclusion included β -blockers (eye drops included) or oral corticosteroids within 1 month before the first visit. Patients receiving immunotherapy were also excluded.

Study design

The study was conducted from April 2005 to October of 2006, when the exposure to dust mites was at the constant level.⁷ This was a randomized, double-blind, placebo-controlled trial comparing the effects of budesonide with formoterol, budesonide with montelukast, montelukast, budesonide, or matching placebo on EIB. Children 6 to 14 years received 5 mg montelukast (Singulair; MSD, Whitehouse Station, NJ), and children >14 years old received a 10-mg oral tablet once daily at bedtime. Budesonide (Pulmicort turbuhaler; AstraZeneca, London, United Kingdom) was administered 200 μ g per day (twice daily, 100 μ g per dose). Formoterol (Oxis turbuhaler; AstraZeneca) was administered 9 μ g per day (twice daily, 4.5 μ g per dose). Montelukast, placebo, and turbuhalers containing drug or no drug were blinded by the hospital pharmacy. They converted these units to placebo by breaking them open. The part of the turbuhaler containing a reservoir of powder with active ingredient was replaced with inert placebo powder (from training turbuhalers). Montelukast and matching placebo (lactose) were prepared in wafers. The active drugs were submitted by researchers.

There were 1 prestudy and 2 study visits. At the prestudy visit, LABAs, steroids, and montelukast sodium were stopped, and patients were put on inhaled β_2 -agonist (Ventolin; GlaxoSmithKline, Philadelphia, Pa) as needed for symptomatic relief purposes. They were informed of the aim of the study and were told how to use the inhalers. At the first visit, 4 weeks after the prestudy visit, a standardized treadmill exercise challenge was performed. At the same visit, patients were randomized according to a computer-generated allocation schedule for antiasthma treatment with the following:

- Budesonide, formoterol, montelukast placebo (20 patients): budesonide with formoterol group (B+F)
- Budesonide, montelukast, formoterol placebo (20 patients): budesonide with montelukast group (B+M)
- Montelukast, formoterol placebo, budesonide placebo (20 patients): montelukast group (M)
- Budesonide, montelukast placebo, formoterol placebo (20 patients): budesonide group (B)
- Montelukast placebo, formoterol placebo, budesonide placebo (20 patients): placebo group (P)

At the second visit (after 4 weeks of treatment), a standardized treadmill exercise challenge was performed. This always took place at the same time of day (11 AM) and on the same day of the week. Before exercise challenge, short-acting inhaled β_2 -agonists were withheld for 6 hours. In addition, at visits 1 and 2, routine physical examinations were performed, and vital signs and results of electrocardiograms were obtained.

FEV₁

Pulmonary function was tested with a LUNGTEST 1000 unit (MES, Cracov, Poland). Flow and volume were measured with a pressure screen-type pneumotachograph, calibrated daily. All measurements were performed by trained investigators. Measurements were taken in a familiar and quiet room. Standing height and weight were assessed: subjects were measured without shoes, wearing light summer clothing. During measurements, children were instructed to sit upright, and a nose clip and a noncompressible mouthpiece were used. When needed, an adult accompanied the subject during testing. Predicted values for all lung function variables were based on a previous study of healthy controls, provided by the lung function test equipment manufacturer.^{8,9} The tests were performed according to American Thoracic Society standards.¹⁰ The highest of 3 successful measurements was taken.

EIB

Exercise-induced bronchoconstriction was tested at the second and third visit by the use of a motor-driven treadmill (Kettler, Enneparsit, Germany). The children were instructed to run for 8 minutes with a submaximal exercise load.¹¹⁻¹³ The exercise test consisted of a 2-minute warm-up and 6 minutes of steady-state running on a treadmill inclined to produce a heart rate of at least 95% of the maximum predicted for age (calculated as $220 - \text{age} [\text{years}]$). The slope of the treadmill was 5.5% (3°). Small adjustments in workload (treadmill speed) were made, if necessary, to achieve targeted heart rates. Nasal clips were used during the test, and heart rate was continuously monitored (electronic heart rate scanner; Kettler). The submaximal run on the treadmill was performed at the same speed (exercise load) on both test occasions (at randomization and after 4 weeks of treatment) for each child. The ambient temperature in the air-conditioned laboratory was kept stable at 22°C, and the humidity was stable between 40% and 50% on each day of the study. Differences of 1°C in temperature and 5 mg H₂OxL⁻¹ of air humidity on the test days on each patient were considered acceptable.¹⁴ FEV₁ was measured before running, immediately after, and 3, 6, 10, 15, and 20 minutes after running. Maximum percentage fall in FEV₁ after exercise test was calculated by using the following formula:

TABLE I. Characteristics of patients who completed the study and who did not complete the study (dropouts): demographic and baseline* values for efficacy end points

Characteristics	Budesonide with formoterol group (N = 18)	Budesonide with montelukast group (N = 17)	Montelukast group (N = 17)	Budesonide group (N = 20)	Placebo group (N = 19)	Dropouts (N = 9)	P value (ANOVA)
Age (y), median (range)	11.3 (6-18)	12.2 (7-18)	11.8 (7-17)	11.9 (6-16)	12.1 (7-15)	12.0 (7-15)	.88
Pre-exercise FEV ₁ (% of predicted), means $\pm$ SDs	91.1 $\pm$ 11.2	90.2 $\pm$ 10.2	93.5 $\pm$ 11.4	92.2 $\pm$ 13.5	92.4 $\pm$ 12.7	94.7 $\pm$ 15.8	.78
AUC _{0-20min} (% of predicted $\times$ min), geometric means $\pm$ SEMs (range)	469.8 $\pm$ 15.3 (374.4-611.0)	477.7 $\pm$ 14.8 (378.5-570.5)	481.4 $\pm$ 16.3 (374.5-590.0)	481.0 $\pm$ 12.2 (400.5-656.0)	460.2 $\pm$ 10.1 (402.5-564.0)	478.1 $\pm$ 19.1 (388.5-580.5)	.50
Maximum % fall in FEV ₁ , means $\pm$ SEMs (range)	25.2 $\pm$ 0.77 (21-35)	25.5 $\pm$ 0.74 (20-32)	24.8 $\pm$ 0.72 (21-32)	25.0 $\pm$ 0.66 (21-29)	24.3 $\pm$ 0.45 (21-27)	24.8 $\pm$ 0.95 (20-32)	.43

*First visit after washout period.

$[(\text{pre-exercise FEV}_1 - \text{lowest postexercise FEV}_1) / \text{pre-exercise FEV}_1] \times 100$. The FEV₁ values were plotted against time for each treatment. The area under the curve (AUC) for the FEV₁ values from exercise over the 20-minute period were calculated by using a trapezoidal rule.

Statistical methods

The results were analyzed according to well known statistical methods by using StatSoft Statistica for Windows, release 6.0 (StatSoft, Inc, Tulsa, Okla). Data were presented as SEMs or SDs (for demographic data). Before analysis, AUC was logarithmically transformed to approximate the normal distribution; therefore, this parameter was expressed as geometric means. To determine differences within groups and to compare changes with treatment between groups, all parameters were analyzed by using ANOVA. In the ANOVA model, a multiple comparison adjustment (Tukey test) for all between-group comparisons was applied. *P* values $< .05$ were considered significant. In this analysis, the dependent factor, change in maximum decrease in FEV₁ or AUC, was compared between all study groups (including placebo group).

The study was designed to have 95% power (for 16 completing patients per treatment arm) to detect a difference between active and placebo group of 40% in the fall of FEV₁ after exercise, on the assumption that variability was similar to that observed in previous study.¹⁵⁻¹⁷ An allowance was made for 20% dropout rate.

Ethics

This study was approved by the Medical Ethics Committee of the Medical University. All parents or guardians gave their written consent for participation in this study. The families were fully informed that treatment withdrawal during washout period might result in a significant exacerbation of asthma and they were given a specific plan to manage any exacerbation that might occur.

RESULTS

Ninety-one patients completed the study, 18 from the budesonide with formoterol group, 17 from the budesonide with montelukast group, 17 from the montelukast group, 20 from the budesonide group, and 19 from the placebo group. Nine patients were withdrawn from the study during the active treatment period because asthma exacerbation (caused by respiratory tract infection) required an increase in the dose of inhaled steroids or the use

of systemic steroids, an emergency department visit, and/or hospitalization. Characteristics of the patients who completed and who did not complete the study are presented in Table I.

Exercise-induced bronchoconstriction (reflected by AUC of time response curve and by maximum percentage fall in FEV₁ after exercise) significantly diminished after 4 weeks of treatment with budesonide with formoterol, budesonide with montelukast, montelukast, and budesonide within groups and compared with placebo (Table II; Figs 1 and 2).

Changes between before and after 4-week treatment in AUC and maximum percentage fall in FEV₁ in all groups are presented in Table III. ANOVA showed significant differences between active treatment groups in changes of measured parameters. The effects of treatment with budesonide with montelukast and with montelukast alone on AUC and maximum percentage fall in FEV₁ were greater than effect of treatment with budesonide or budesonide with formoterol. There were no significant differences between the budesonide with montelukast and montelukast groups in changes of AUC and maximum percentage fall in FEV₁ after treatment (Figs 1 and 2). We also observed a greater effect of combined treatment with budesonide and formoterol than with budesonide alone on AUC; however, differences were not significant (Table III; Fig 1, C).

DISCUSSION

To the best of our knowledge, this is the second study comparing the ability of different patterns of antiasthmatic treatment, recommended in childhood asthma, to protect patients from EIB. In previous studies, the effects of only a single drug treatment on EIB were assessed.¹⁸⁻²¹ Our study showed that 4-week treatment of budesonide, montelukast, budesonide with montelukast, and budesonide with formoterol was effective on EIB, as evidenced by an increase in AUC for the FEV₁ values from exercise over the 20-minute period (AUC_{0-20min}) and by reduction in maximum percentage fall in FEV₁. The protection effect of monotherapy with montelukast and combined therapy of montelukast with budesonide on EIB was greater than that of other 2 active treatment groups.

TABLE II. AUC_{0-20min} (% of predicted × min) and maximum percentage fall in FEV₁ before and after treatment in all groups

	Before treatment		After treatment		<i>P</i> value
	Mean*	SEM	Mean*	SEM	
AUC _{0-20min} (% of predicted × mins)					
Budesonide with formoterol group	469.8	15.3	506.5	17.9	.003
Budesonide with montelukast group	477.7	14.8	563.9	14.5	<.001
Montelukast group	481.4	16.3	560.5	13.8	<.001
Budesonide group	481.0	12.2	499.4	14.8	.031
Placebo group	460.2	10.1	429.4	9.4	.029
Maximum % fall in FEV ₁					
Budesonide with formoterol group	25.2	0.77	18.9	0.65	<.001
Budesonide with montelukast group	25.5	0.74	12.1	1.13	<.001
Montelukast group	24.8	0.72	11.5	0.97	<.001
Budesonide group	25.0	0.66	16.9	1.00	<.001
Placebo group	24.3	0.45	26.6	0.61	.36

*Geometric mean for AUC_{0-20min}.

Petersen et al¹⁸ revealed that a 4-week treatment with low-dose beclomethasone exerted a significant reduction in airway hyperreactivity to exercise in 25 children with mild intermittent or mild persistent asthma. Their study showed a reduction in maximum fall in FEV₁ after exercise from 28% to 21%, similar after treatment with 2 doses of beclomethasone—50 μ g and 100 μ g.¹⁸ Similarly, in our study, 4-week treatment with low-dose budesonide decreased the grade of exercise-induced bronchial hyperreactivity, with maximum percentage fall in FEV₁ after exercise reduced from 25% to 17%. The magnitude of the protective effects in all other studies¹⁹⁻²² seemed greater than the effects achieved in our study and in the study by Petersen et al.¹⁸ Opposite to all remaining studies (twice daily dosing ICS), the study by Petersen et al¹⁸ dosed beclomethasone dipropionate once daily, which can be less effective. However, in the current study, ICSs were administered twice daily with protective effects similar to the results of the study by Petersen et al.¹⁸ Twelve-week treatment with budesonide 100 or 200 μ g/d reduced the postexercise fall in lung function from 25% to 5% to 7%,²¹ and 3-week treatment with fluticasone propionate 100 μ g from 33% to 9%.¹⁹

Results of many studies with a single dose of LABA revealed their protection effectiveness against EIB in children with asthma.²³⁻²⁷ However, a study by Zarkovic et al²⁸ revealed the loss of protection against bronchoconstricting factors after the first week of treatment with salmeterol, and complete lack of protection after 6 months. In the current study, formoterol was combined with budesonide, and the observed bronchoprotective effect was similar to the effect in the group treated with budesonide alone. This suggests little effect of regular treatment with LABA on EIB in children with asthma. In addition, tolerance to the protective effects of LABA, even in combined therapy with ICSs, was previously observed.²⁹⁻³¹

Previous studies revealed that montelukast reduced the immediate and late phase of bronchoconstriction after exercise.³²⁻³⁴ In the current study, we observed that montelukast, both in combined therapy with budesonide and in

monotherapy, provided the best protection against EIB compared with other therapies. The protection effect obtained by montelukast in our study was around 50%, which is comparable to the previous literature.³⁵ There were no differences in the degree of EIB protection between the 2 groups receiving montelukast. This suggests a lack of additional effect of budesonide on EIB protection in combined therapy with montelukast. However, an explanation for this finding might be inadequate sample size leading to a lack of power to detect differences. Vidal et al,³⁵ in the crossover study, observed better protection against EIB with budesonide therapy compared with montelukast therapy, showing striking individual variations in responses to both therapies. For comparison of the protective efficacies of both montelukast and budesonide against EIB, their patients received 10 mg montelukast daily for 3 days and 400 μ g budesonide twice daily for 15 days.³⁵ In our study, patients received 4 times lower daily doses of budesonide for 4 weeks and regular therapy with montelukast. Hofstra et al¹⁹ showed that in childhood asthma, the protection against EIB afforded by corticosteroids was not time-dependent and dose-dependent. However, it can not be excluded that the improvement of EIB protection in the budesonide groups would be much better with prolonged follow-up and with higher doses of corticosteroids. Subbarao et al³⁶ compared the effect of 4 doses of inhaled ciclesonide on EIB in subjects with asthma (age range, 14-27 years) and concluded that the dose-response characteristics over time differed between lower (≤ 80 μ g) and higher (≥ 160 μ g) doses of ciclesonide. Another article suggests that there may be differences in time and dose responses between patients with elevated sputum eosinophils and other patients.³⁷ The current study included only patients with allergy. That may have influenced the time response. It is important that our study addresses the population of children with EIB (children with asthma who also experience bronchoconstriction with exercise) but does not address children with exercise-induced asthma (bronchoconstriction that occurs only with exercise).

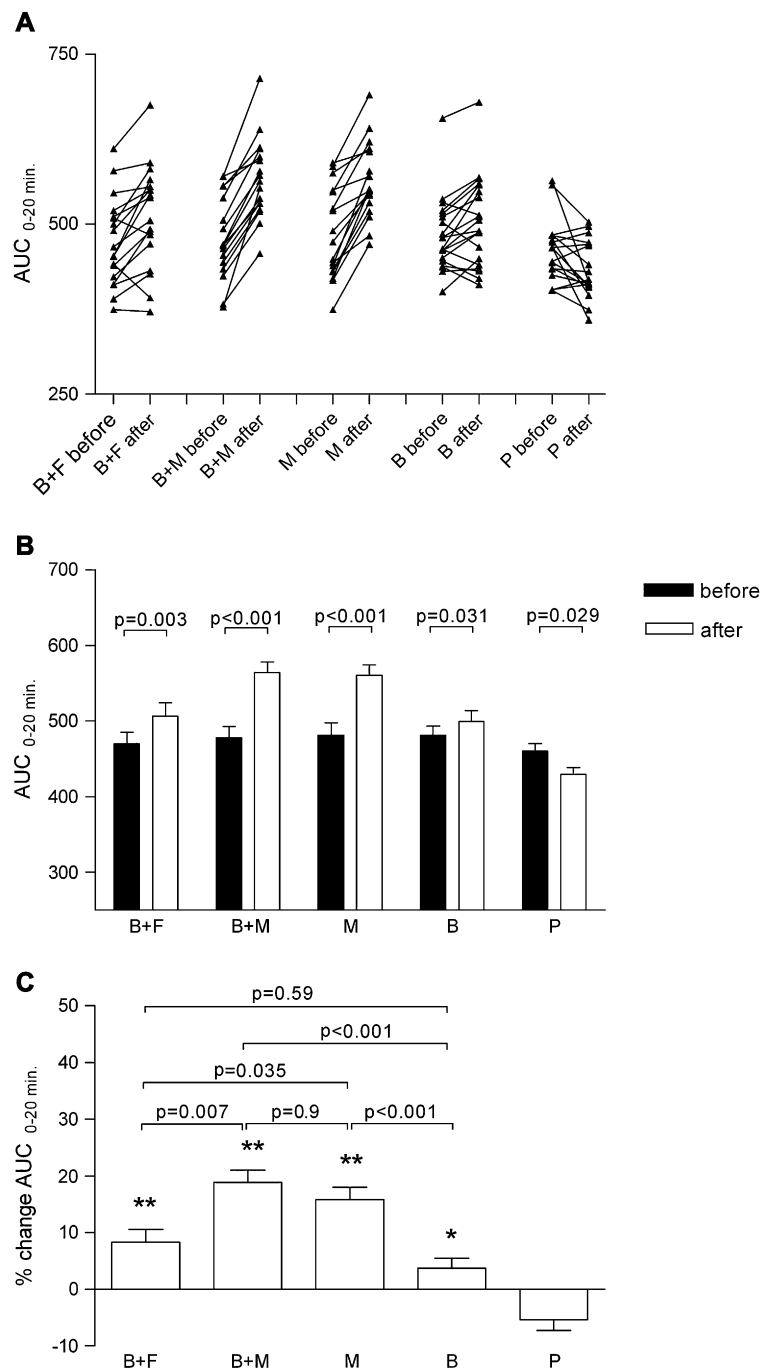


FIG 1. AUC_{0-20min} (% of predicted $\times$ minute). Data are presented as each individual before and after treatment (**A**) and as a geometric means with SEMs (**B**). **C**, Percent of change in AUC_{0-20min} is given and presented as means with SEMs. *Comparison with placebo group at the level $P < .01$. **Comparison with placebo group at the level $P < .001$.

What is the clinical significance of our findings? First, these data indicate differences in effects on EIB between therapeutic options recommended in childhood asthma. Second, the protection effect obtained by montelukast was around 50% with a mean posttreatment fall around 12%.

Third, low-dose steroid therapy also improved EIB protection; however, it can be argued that adding montelukast should be recommended to achieve better control of EIB in children with asthma. Our results are enhancing and demand verification in the future.

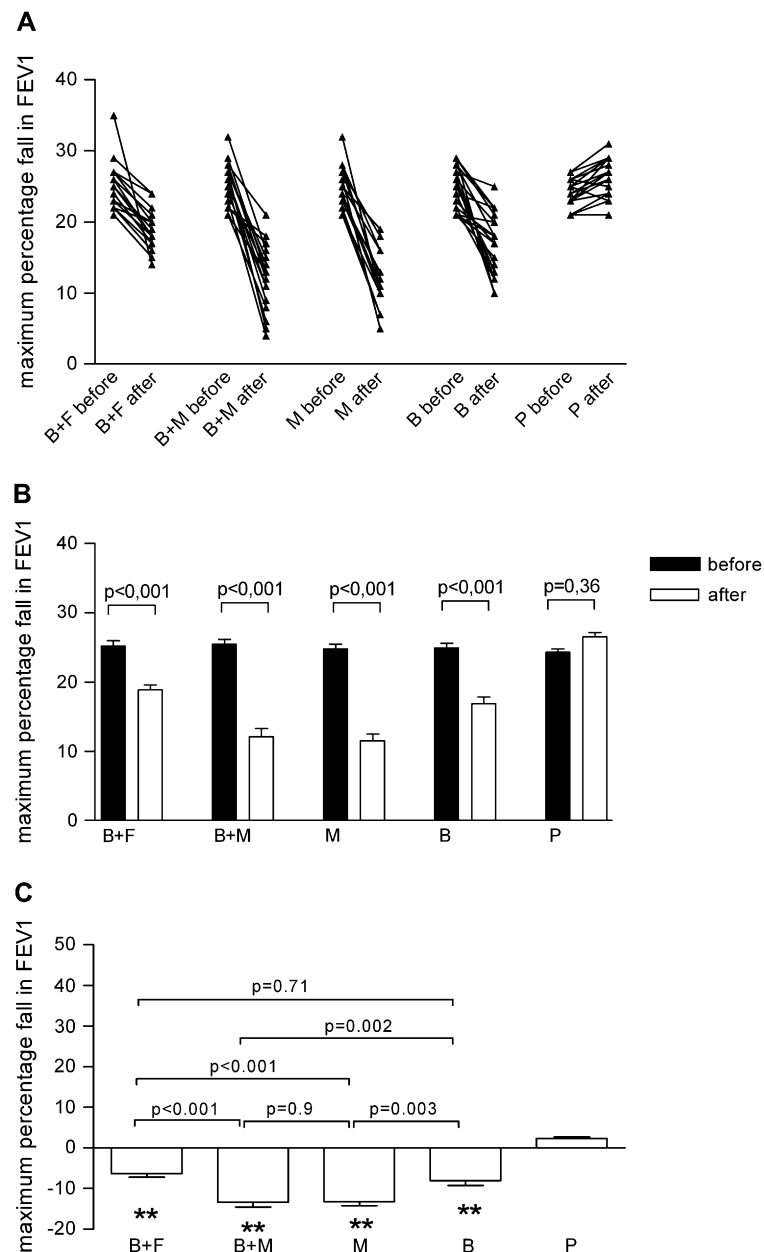


FIG 2. Maximum percentage fall in FEV₁. Data are presented as each individual before and after treatment (**A**), and as means with SEMs (**B**). **C**, Change in maximum percentage fall in FEV₁ is given and presented as means with SEMs. Comparison with placebo group at the level $P < .001$.

TABLE III. Changes between before and after 4-week treatment in AUC_{0-20min} and maximum percentage fall in FEV₁ in all groups (% change from baseline)

	AUC _{0-20min}		Maximum % fall in FEV ₁	
	Mean	SEM	Mean	SEM
Budesonide with formoterol group	8.18	2.13	-24.4	2.59
Budesonide with montelukast group	18.35	2.17	-52.1	4.60
Montelukast group	16.75	2.22	-53.5	3.62
Budesonide group	4.07	1.62	-31.5	4.11
Placebo group	-6.25	2.07	9.4	1.77

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