

A 1-year study of salmeterol powder on pulmonary function and hyperresponsiveness to methacholine

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Background: Long-acting β_2 -sympathomimetic agonists such as salmeterol have been proved safe and effective for the treatment of asthma. However, controversy still exists as to the appropriateness of scheduled long-term therapy with these agents.

Objective: This study assessed the degree of bronchodilation provided by treatment with salmeterol for a period of 52 weeks and evaluated bronchial hyperresponsiveness to methacholine during and after the treatment period.

Methods: Three hundred fifty-two patients with mild to moderate asthma were assessed by 12-hour serial spirometry and serial methacholine challenge tests.

Results: The mean area under the FEV₁ curve above baseline over 12 hours after drug at day 1 was significantly greater with salmeterol powder compared with placebo (5.06 liter hours vs 0.77 L/h) and did not change significantly over 1 year. The mean increase in the log₂ of the provocative cumulative methacholine dose producing a 20% decrease in FEV₁ (PD₂₀FEV₁) during treatment was significantly higher in the salmeterol-treated patients than in the placebo group (1.02 doubling doses vs 0.43 doubling doses at week 4, 1.06 doubling doses vs 0.41 doubling doses at week 24). At week 52 the increase from baseline in log₂PD₂₀FEV₁ was not significantly different between salmeterol and placebo (1.08 vs 0.69 doubling doses). Seven days after treatment the log₂PD₂₀FEV₁ was -0.60 doubling doses lower than baseline for salmeterol compared with 0.10 doubling doses for placebo ($P = .031$). Long-term salmeterol use was not associated with a deleterious effect on asthma control during and after treatment.

Conclusion: This study demonstrates that the bronchodilator properties of salmeterol are sustained over 52 weeks and that bronchial hyperresponsiveness to methacholine is decreased to a modest degree during treatment. Clinically significant increases in hyperresponsiveness did not develop after discontinuation of salmeterol treatment. (J Allergy Clin Immunol 1999;104:1189-97.)

Key words: Salmeterol xinafoate powder, pulmonary function, bronchial hyperresponsiveness, methacholine, placebo, asthma therapy

Inhaled β_2 -sympathomimetic agonists have been a mainstay of the symptomatic control of asthma for more than 2 decades. Most of these agents have a short half-life, often necessitating administration of the drug at 6-hour intervals. Recently, however, the introduction of a longer acting β_2 -sympathomimetic agonist, salmeterol, has facilitated twice-a-day dosage.¹ Trials of this agent show that, compared with albuterol administered 4 times daily and placebo with albuterol rescue therapy as needed, twice-daily administration of salmeterol resulted in improved control of symptoms and improved pulmonary function over a 12-week period.^{2,3} In another study over a 52-week period, salmeterol given twice per day resulted in improved symptom control and pulmonary function compared with albuterol 4 times daily.⁴ Salmeterol and albuterol were equally well tolerated in these studies, and there appeared to be no attenuation of the bronchodilatory effect of salmeterol over the course of these studies. Nevertheless, despite several studies demonstrating the safety and efficacy of salmeterol for periods of up to a year,²⁻⁵ controversy persists as to the appropriateness of using scheduled bronchodilator therapy with either short-acting or long-acting β_2 -agonist agents as opposed to the use of short-acting β_2 -agonists on an as-needed basis.⁶⁻⁸ For example, it has been reported that regular therapy with fenoterol, a short-acting β_2 -agonist, provides inferior control of asthma symptoms compared with using fenoterol as needed.⁹ On the other hand, the authors of a more recent study concluded that, in patients with mild asthma, neither deleterious nor beneficial effects were derived from the use of regularly scheduled therapy with albuterol beyond those derived from using albuterol as needed.¹⁰ Further concerns about the desirability of long-term regular administration of β_2 -agonists arose with the publication of a number of influential studies: a report of increased mortality in patients who used more than one metered-dose inhaler (MDI) canister of short-acting β_2 -agonist per month¹¹ reports that the regular use of short-acting β -agonists as monotherapy was associated with decreases in lung function¹² and

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Supported by a grant from Glaxo Wellcome Inc., Research Triangle Park, NC. Received for publication Feb 4, 1999; revised Aug 19, 1999; accepted for publication Aug 19, 1999.

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0091-6749/99 \$8.00 + 0 1/1/102352

Abbreviations used

AUC _{BL} :	Mean area under the FEV ₁ curve above baseline
CBU:	Cumulative breath units
CFC:	Chlorofluorocarbon
MDI:	Metered dose inhaler
PD ₂₀ FEV ₁ :	Provocative cumulative methacholine dose producing a 20% decrease in FEV ₁
PEF:	Peak expiratory flow

with increases in hyperresponsiveness both during¹³ and after discontinuation of such treatment,¹⁴ and several studies that suggested the development of tolerance to the bronchoprotective effects of β_2 -agonists against exercise,¹⁵ methacholine,¹⁶⁻¹⁸ and other challenges.¹⁹

The purpose of the current study was to compare the efficacy of salmeterol administered twice daily over a 52-week period to that of placebo. Albuterol rescue therapy was provided in both arms of the study. Asthma control was assessed by spirometry, patient self-rating of peak expiratory flow (PEF) and symptom scores, and by assessment of the use of albuterol as rescue therapy. In addition, serial methacholine challenges were performed over the same time period to assess whether nonspecific hyperresponsiveness changed during salmeterol therapy. The patient population selected for this study included patients with mild to moderate asthma so that patients who would be receiving placebo (with albuterol as needed) for a year would not be compromised and to permit bronchoprovocation testing without undue risk.

METHODS

Patients

A total of 352 patients aged 12 years or older with a history of asthma of at least 6 months' duration were entered into the study to receive 50 μ g of salmeterol xinafoate (Serevent Inhalation Powder, Glaxo Wellcome, Research Triangle Park, NC) twice daily or placebo twice daily with use of the Diskhaler. (Glaxo Wellcome, Research Triangle Park, NC). Inclusion criteria included (1) a baseline FEV₁ of 70% to 90% of the predicted value, (2) reversibility over baseline of $\geq 15\%$ or an increase to 100% of predicted FEV₁ within 30 minutes after inhalation of 2 to 4 puffs (180-360 μ g) of albuterol through a pressurized MDI (Ventolin Inhalation Aerosol, Glaxo Wellcome), and (3) 2 positive methacholine challenges. A positive methacholine challenge was defined as a provocative cumulative dose of methacholine that produced a 20% decrease in FEV₁ (PD₂₀FEV₁) of ≤ 7.5 mg/mL of methacholine or 55.5 cumulative breath units (CBU, number of breaths multiplied by the methacholine concentration) and 2 PD₂₀FEV₁ values within a 3-fold change of each other. Exclusion criteria included infection of the upper or lower respiratory tract, sinus, or middle ear within 6 weeks of study entry, tobacco use within the past year, ≥ 10 pack-years history of tobacco use, or continuing passive (>4 h/d) exposure to tobacco smoke. Inhaled corticosteroids were allowed as concomitant therapy for the treatment of asthma if treatment had been initiated 3 months before screening and a stable regimen was maintained throughout the study (including the posttreatment period).

Study design

This multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical trial was conducted at 18 centers in the United

States. Each center obtained approval from an Investigational Review Board, and informed written consent was obtained from all patients before entry into the trial.

The study had 3 phases: screening, treatment, and posttreatment. The single-blind screening phase lasted 18 to 30 days: the initial screening visit and 2 to 3 subsequent visits to establish consistent responsiveness to methacholine challenge. During the double-blind, 52-week treatment phase patients were assessed on treatment day 1 and at 4-week intervals through treatment week 52. Patients were also assessed at 1, 2, 7, and 14 days after treatment.

Treatment

All patients were dispensed single-blind placebo powder at the screening visit and continued this treatment until they were randomized at treatment day 1. At treatment day 1 patients were randomly assigned to salmeterol powder or placebo powder in a 1:1 ratio. At treatment week 52 patients were dispensed single-blind placebo powder and continued this treatment for 2 weeks until the final posttreatment visit. Ventolin MDI was used for the duration of the study (screening through posttreatment) as back-up medication for relief of asthma-related symptoms. Compliance to treatment regimens was determined by comparing used or returned blisters of product plus lost blisters as a percentage of the total number of blisters scheduled during the treatment period.

Patient self-rating of PEF, albuterol use, nighttime awakenings, and asthma symptoms

For each day of the study, from the screening visit through the posttreatment period, each patient was instructed to record on a diary card a self-rating for each of the following: morning and evening PEF, frequency of albuterol use (rescue medication), nighttime awakenings, and asthma symptoms (chest tightness, shortness of breath, wheezing, and coughing). All patients recorded PEF in the morning and evening of each day at or near the end of the dosing interval. Asthma symptoms were rated on a scale of 0 (no symptoms), 1 (symptoms for 1 short period during the day), 2 (symptoms for 2 or more short periods), 3 (symptoms for most of the day that did not interfere with daily activities), 4 (symptoms for most of the day that did interfere with daily activities), and 5 (symptoms so severe that the patient could not go to work or school or perform normal daily activities).

Pulmonary function

Spirometry was performed at each clinic visit with use of calibrated spirometry equipment that met or exceeded the minimal performance recommendations of the American Thoracic Society.²⁰ During the treatment phase, 12-hour serial spirometry was performed on treatment day 1 and at week 8, week 20, and week 48. Assessments were performed at 30 minutes predose, immediately predose, at 0.25 and 0.5 hours postdose, and at subsequent hourly time points up to 12 hours postdose.

Bronchial hyperresponsiveness

The methacholine challenge was performed according to the procedure described by Rosenthal²¹ with use of a methacholine dose range of 0.025 to 75 mg/mL and a breath-actuated nebulization dosimeter (Rosenthal-French, Laboratory for Applied Immunology, Fairfax, Va) with an attached DeVilbiss 646 jet nebulizer (DeVilbiss, Somerset, Pa). To reduce potential variation in the output of the nebulizer, the straw and baffle (which are typically removable parts) were fixed in place. The same nebulizer was used for the same patient during all methacholine challenges. The dosimeter automat-

ically administered preservative-free buffered saline solution or methacholine at the onset of inhalation at a flow of 0.5 L/s. The procedure was modified by the inclusion of 4 additional gradations of methacholine concentration, as shown in Table I.

Methacholine challenges were performed before administration of the morning dose of study medication. Each patient was instructed to take 5 tidal breaths from the nebulizer. After 1 minute FEV₁ was measured. Three baseline FEV₁ measurements were taken after the saline solution and each concentration of methacholine; the highest FEV₁ value was used to calculate the patient's PD₂₀FEV₁. Successively higher doses of methacholine were administered until either the FEV₁ had fallen by ≥20% from the value measured after the saline solution challenge was inhaled or until the highest dose had been given.

During the screening phase patients received up to 3 methacholine challenges on 3 different days. Patients who had a PD₂₀FEV₁ ≤7.5 mg/mL methacholine (55.5 CBU) with less than 3-fold variation in PD₂₀FEV₁ on 2 (of a total of 3 potential tests) successive tests during the screening phase were randomized. However, during the treatment and posttreatment periods a provocative concentration of up to 75 mg/mL could be used, and patients who did not respond to 75 mg/mL (555.5 CBU) were allowed to continue in the study and were assigned a PD₂₀FEV₁ of 555.5 CBU (the highest dose of methacholine delivered during each challenge) for statistical analysis. Serial methacholine challenge tests were performed at treatment weeks 4, 12, 24, and 52 and also at days 1, 2, and 7 after treatment.

Data analysis

This study was designed to have >80% statistical power of detecting a difference in FEV₁ of 0.18 L between the 2 treatment groups with use of a 2-sample *t* test with a significance level of .05 and a difference of greater than 1 doubling dose of methacholine, a difference that clinical investigators have deemed to be clinically significant and greater than normal variation expected for a group of asthmatic patients followed over a period of time.^{22,23} The 12-hour serial FEV₁ measurements were analyzed with use of ANOVA on the area under the curve above baseline. For any patient unable to complete the 12-hour evaluation, the last FEV₁ value obtained before intervention with back-up albuterol was carried forward for the remainder of the serial tests. The definition of baseline for all four 12-hour serial pulmonary function test days was the average of the 2 predose evaluations on treatment day 1 (30 minutes and immediately before dosing). The intent-to-treat population (ie, all patients treated) was used to analyze pulmonary function and diary card data.

Analysis of PD₂₀FEV₁ values (after a logarithm transformation) was based on the analysis of covariance with the baseline PD₂₀FEV₁ as the covariate. The baseline PD₂₀FEV₁ was defined as the average of all valid pretreatment values collected during the screening visits. The efficacy population, which included only those patients who reasonably adhered to protocol specifications regarding inclusion criteria, reactivity, or reproducibility of methacholine challenge or compliance with protocol visit windows, was used in the analysis of the methacholine challenge. The population was defined before unblinding of the treatment groups.

The doubling doses were calculated for each patient at each visit. PD₂₀FEV₁ values were transformed by log₂ before analyses were completed. The rationale for using logarithm transformation was to normalize the data.²⁴ The base 2 was chosen because each incremental unit in the log₂ scale represents a doubling from the previous amount; consequently, 1 unit in this case represents a doubling of the dose of methacholine. The unit of the difference in log₂ is reported as the doubling dose.

TABLE I. Methacholine challenge administration

Dose	Concentration (mg/mL)*	No. of breaths	CBU†
1	0.025	5	0.125
2	0.075	5	0.5
3	0.25	5	1.75
4	0.75	5	5.5
5	2.5	5	18
6	7.5	5	55.5
7	25	5	180.5
8	75	5	555.5

*In nebulizer.

†Concentration of methacholine × number of breaths.

RESULTS

Demographics

Of the patients who entered the 52-week double-blind phase of the study, 176 were randomized to receive placebo powder and 176 to receive 50 µg of salmeterol powder. Two hundred sixty-five (75%) patients completed 52 weeks of treatment, 134 (76%) in the placebo treatment group and 131 (74%) in the salmeterol treatment group. Ninety percent (90%) of the patients in the placebo group complied with the dosing regimen, as did 91% of the patients in the salmeterol treatment group.

Both treatment groups were comparable with regard to baseline demographic parameters and disease severity as determined by spirometry test results, measurements of bronchial hyperreactivity (methacholine challenge), and daily use of rescue albuterol (Table II).

Pulmonary function

Assessments of the area under the serial FEV₁ curve above baseline (AUC_{BL}, the area below baseline subtracted from area under the FEV₁ curve) over the full 12 hours were completed at treatment day 1, week 8, week 20, and week 48 (Fig 1). On the 4 assessment days, AUC_{BL} values were significantly higher after salmeterol administration than those observed after placebo (*P* < .001). On day 1 the mean AUC_{BL} (±SE) for all patients treated with salmeterol was 5.06 ± 0.29 liter hours compared with 0.77 ± 0.27 liter hours for all patients treated with placebo. After 48 weeks of treatment, the mean AUC_{BL} for salmeterol-treated patients had increased to 5.79 ± 0.49 liter hours, whereas the mean AUC_{BL} for placebo-treated patients decreased to 0.19 ± 0.44 liter hours, demonstrating that the bronchodilatory effect of salmeterol was sustained for the entire treatment period.

The mean predose FEV₁ at the methacholine challenge treatment visits was assessed for all patients treated with placebo and salmeterol (Fig 2). On day 1 the mean predose FEV₁ (±SE) was comparable (*P* = .861) for patients treated with placebo (2.88 ± 0.06 L) and salmeterol (2.86 ± 0.06 L). After 4 weeks of salmeterol treatment (day 28), the mean predose FEV₁ values had significantly increased compared with baseline (3.08 ± 0.06 L) and compared with placebo (2.89 ± 0.05 L) (*P* < .001). The increase in mean predose FEV₁ for salme-

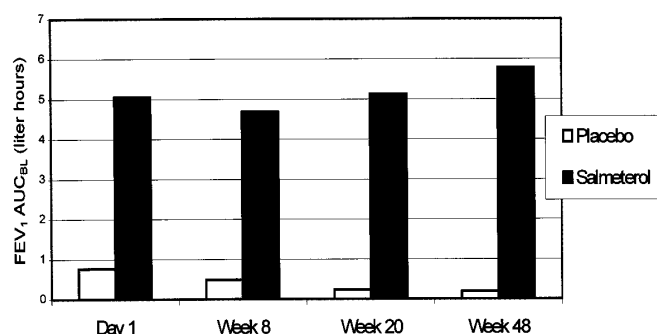


FIG 1. Means of FEV₁ curve (AUC_{BL}) over 12 hours for treatment day 1, week 8, week 20, and week 48 for patients treated with salmeterol and placebo. AUC_{BL} is expressed as liter hours.

TABLE II. Baseline patient demographics

	Placebo (n = 176)	Salmeterol 50 µg bid (n = 176)
Sex		
Male/female ratio	89:87	90:86
Age range (y)	12-67	12-65
Median age (y)	28	29
Age groups (No. [%])		
12-17 y	32 (18)	32 (18)
18-34 y	78 (44)	89 (51)
35-49 y	53 (30)	47 (27)
50-64 y	12 (7)	7 (4)
65 y	1 (<1)	1 (<1)
Duration of asthma (No. [%])		
6 mo-<2 y	11 (6)	9 (5)
2-<10 y	47 (27)	65 (37)
≥10 y	118 (67)	102 (58)
No. of hospitalizations for asthma in previous 12 mo (No. [%])		
0	175 (>99)	171 (97)
1	1 (<1)	3 (2)
≥2	0 (0)	0 (0)
Frequency of nocturnal symptoms that interfere with sleep (No. [%])		
None	74 (42)	76 (43)
<1 d/wk	22 (13)	33 (19)
≥1 and ≤3 d/wk	60 (34)	46 (26)
≥4 d/wk	20 (11)	21 (12)
Daytime symptoms that interfere with regular daily activities (No. [%])		
None	54 (31)	51 (29)
<1 d/wk	18 (10)	22 (13)
≥1 and ≤3 d/wk	70 (40)	54 (31)
≥4 d/wk	34 (19)	49 (28)
Smoking history (No. [%])		
Never smoked	141 (80)	132 (75)
Previous smoker	35 (20)	44 (25)
Current smoker	0 (0)	0 (0)
FEV ₁ (L)		
Predose mean (SD)	2.9 (0.6)	2.9 (0.6)
Mean % predicted (SD)	78.8 (6.3)	78.5 (6.6)
Baseline methacholine challenge log ₂ (PD ₂₀ FEV ₁) (mean [SD])	2.66 (0.15)	2.63 (0.15)
Patients receiving inhaled corticosteroids at baseline (No. [%])	71 (40)	92 (52.0)
No. of puffs of back-up Ventolin (mean [SD])	2.7 (0.2)	2.7 (0.2)

bid, Twice daily.

terol-treated patients was sustained throughout the entire treatment period, with mean predose values at week 52 (day 365) (3.15 ± 0.07 L) not significantly different from the day 28 predose value. Fourteen days after treatment

(day 379), the mean predose FEV₁ value for patients in the salmeterol treatment group (2.92 ± 0.07 L) was not significantly different from baseline or from placebo (2.87 ± 0.06 L) ($P = .110$).

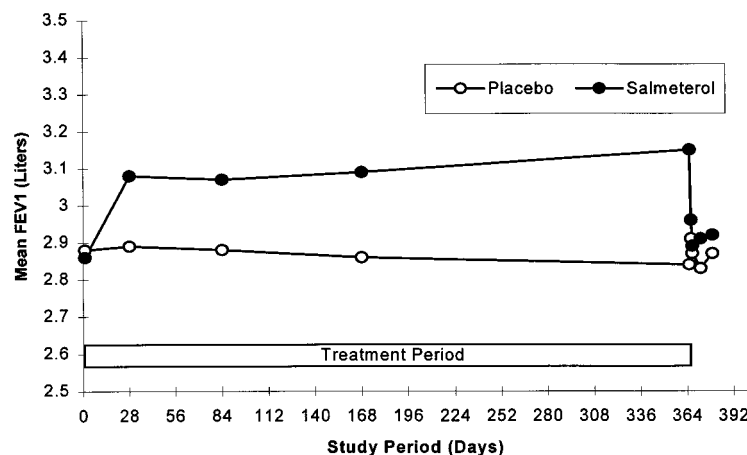


FIG 2. Mean predose FEV₁ over entire study period for all patients treated with salmeterol and placebo. FEV₁ is expressed in liters.

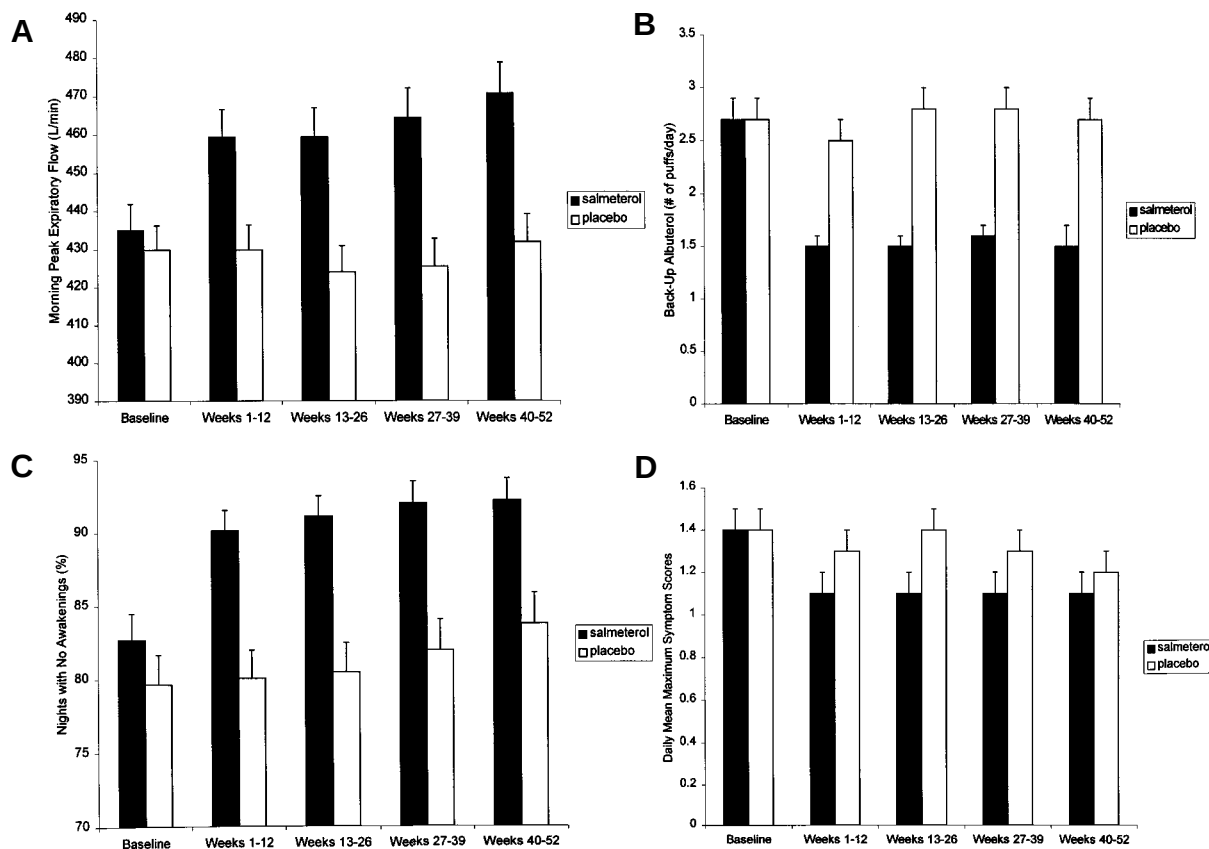


FIG 3. Patient self-rating of morning PEF (A), albuterol use (B), nighttime awakenings (C), and asthma symptom scores (D) at baseline and during treatment period. All differences between salmeterol and placebo during treatment period were statistically significant.

Patient self-rating of PEF, albuterol use, nighttime awakenings, and asthma symptoms

Treatment groups were comparable at baseline for mean morning PEF and evening PEF. Salmeterol-treated patients had significantly greater mean improvements in

morning PEF (435.0 L/min at baseline to 470.6 L/min, Fig 3, A) and evening PEF (460.2 L/min at baseline to 485.3 L/min) over the treatment period than placebo-treated patients did. Patients assigned to the placebo treatment group had no significant change in morning or evening PEF.

Over the course of treatment, use of rescue albuterol in

TABLE III. Posttreatment patient self-rating of PEF, albuterol use, nighttime awakenings, and asthma symptoms

	Placebo			Salmeterol 50 μg bid			Statistical significance*
	No.	Mean	SE	No.	Mean	SE	
Morning PEF (L/min)							
Baseline	150	427	7	144	438	8	$P = .314$
Posttreatment period	150	431	7	144	458	8	$P = .003$
Evening PEF (L/min)							
Baseline	137	452	7	134	465	8	$P = .113$
Posttreatment period	137	463	7	134	478	9	$P = .495$
No. of puffs of back-up albuterol MDI daily							
Baseline	138	2.6	0.2	134	2.8	0.2	$P = .844$
Posttreatment period	138	2.7	0.2	134	2.4	0.2	$P = .061$
Percentage of nights with no awakenings							
Baseline	152	81.2	2.1	145	83.7	1.9	$P = .563$
Posttreatment period	152	85.8	2.2	145	84.6	2.3	$P = .077$
Daily mean maximum symptom scores							
Baseline	138	1.3	0.1	134	1.4	0.1	$P = .413$
Posttreatment period	138	1.3	0.1	134	1.5	0.1	$P = .244$

bid, Twice daily.

the placebo group did not change significantly from baseline (2.5 to 2.8 puffs/d), whereas the salmeterol group showed a mean decrease from 2.7 to 1.5 puffs per day ($P < .001$, Fig 3, B).

At baseline the percentage of nights with no awakenings was similar for patients in the salmeterol group compared with patients in the placebo group (82.7% vs 79.7%, respectively; $P = .618$) (Fig 3, C). Over the study period salmeterol-treated patients had a significantly ($P < .020$) higher percentage of nights with no awakenings (90.2% to 92.3%) than did patients in the placebo group (80.2% to 83.9%). Also, over the treatment period salmeterol-treated patients showed significantly larger decreases in mean maximum symptom scores (shortness of breath, chest tightness, and wheezing) than did patients in the placebo treatment group ($P = .12$, Fig 3, D).

Values for morning and evening PEF, rescue albuterol use, nighttime awakenings, and asthma symptom scores were monitored for all patients who completed the posttreatment visits (Table III). One to 14 days after discontinuation of treatment, none of the evaluations, with the exception of morning PEF, were significantly different for patients in the salmeterol or placebo groups. Morning PEF values remained 20 L/min higher than pretreatment baseline values for patients treated with salmeterol and were higher than values for patients in the placebo group ($P = .003$) despite a reduction in rescue albuterol use (from 2.8 to 2.4 puffs). The total number of puffs of rescue albuterol used by patients in the placebo treatment group increased from 2.6 at baseline to 2.7 puffs during the posttreatment period. For patients in both treatment groups the percentage of nights with no awakenings was

TABLE IV. Methacholine challenge

	Placebo						
	N	n	PD ₂₀ (CBU) mean*	Log ₂ PD ₂₀		Doubling dose†	
				Mean	SE	Mean	SE
Treatment visit							
Baseline	176	164	6.29	2.7	0.15		
Week 4	169	160	8.4	3.1	0.18	0.4	0.16
Week 12	165	145	8.66	3.1	0.19	0.3	0.17
Week 24	154	142	8.43	3.1	0.21	0.4	0.18
Week 52	134	123	11.1	3.5	0.24	0.7	0.20
Posttreatment visit							
Day 1	131	124	9.69	3.3	0.23	0.4	0.22
Day 2	126	118	9.53	3.3	0.25	0.3	0.22
Day 7	132	117	7.38	2.9	0.25	0.1	0.23

N, Total number of patients at each visit; n, total evaluable data points.

*Values presented are geometric means of PD₂₀ measurements.

†Values presented are least square mean estimation from analysis of covariance model.

‡Treatment comparisons of doubling dose are based on analysis of covariance with baseline as covariate.

slightly higher during the posttreatment period than at baseline. Mean maximum symptom scores did not significantly change from baseline to posttreatment.

Methacholine challenge

Compared with placebo, salmeterol was more effective in protecting against methacholine-induced bronchial hyperresponsiveness; this difference was statistically significant at treatment weeks 4 and 24 (Table IV). During treatment $\log_2 PD_{20} FEV_1$ values were 0.65 to 1.08 doubling doses higher than baseline for patients treated with salmeterol and 0.3 to 0.69 doubling doses higher than baseline for patients in the placebo group. At week 52 the increase from baseline in $\log_2 PD_{20} FEV_1$, although greater on salmeterol, was not significantly different between salmeterol and placebo (1.08 ± 0.21 doubling doses vs 0.69 ± 0.20 doubling doses, respectively, $P = .149$).

At posttreatment day 7 the $\log_2 PD_{20} FEV_1$ ($\pm SE$) declined to -0.60 (± 0.25) doubling doses relative to baseline for salmeterol-treated patients. For patients in the placebo group, posttreatment day 7 values declined to 0.10 (± 0.23) doubling doses ($P = .031$). The difference from baseline for salmeterol-treated patients and for patients in the placebo group was less than one doubling dose, the minimum level judged to be clinically significant in our study design.

DISCUSSION

The results of the current study demonstrate that in adolescent and adult patients with chronic mild to moderate asthma the use of salmeterol powder twice daily for 52 weeks, with albuterol rescue as needed, provided improved asthma control compared with placebo with rescue albuterol. The improvement in asthma control is based on serial 12-hour spirometry and results and analysis of data on patients' diaries including self-rating of

morning and evening PEF, frequency of albuterol use, nighttime awakenings, and asthma symptoms. The superior control of asthma was apparent at all treatment visits throughout the 52-week study period. The study also shows that salmeterol provides a modest reduction in hyperresponsiveness to methacholine that is sustained throughout the treatment period. After salmeterol was discontinued, clinically significant increases in airway hyperresponsiveness did not develop.

In previous long-term studies salmeterol was delivered by a pressurized MDI. However, to comply with provisions of the Montreal protocol,²⁵ alternative chlorofluorocarbon (CFC) propellant-free delivery systems have been developed. One alternative to CFC-propelled MDIs, as we have demonstrated in our study, is the use of micronized powder formulations delivered by a breath-actuated inhaler.^{26,27}

The findings of the current study concerning the preservation of the bronchodilator properties of salmeterol are consistent with the findings reported by Pearlman et al² and D'Alonzo et al³, who also found superior control of asthma with salmeterol compared with the combination of scheduled placebo and rescue albuterol. However, the latter studies were of only 3 months' duration, whereas the study by Sears et al,⁹ who found worse control with regular fenoterol administration, was of 6 months' duration. The longer duration of the current study therefore provides further reassurance that the apparent deterioration in asthma control associated with regular fenoterol administration does not develop with salmeterol. The explanation for differences in the findings of the current study with those of Sears et al⁹ is likely to be multifactorial. Fenoterol is a short-acting bronchodilator, whereas salmeterol is a long-acting agent, and the effects of scheduled administration of long- and short-acting β_2 -agonists may be different. In addition, fenoterol may not be representative of all short-acting bronchodilators. Although fenoterol was the only β_2 -ago-

Salmeterol							
N	n	PD ₂₀ (CBU) mean*	Log ₂ PD ₂₀		Doubling doses†		Statistical significance‡
			Mean	SE	Mean	SE	
176	159	6.01	2.6	0.15			
168	152	12.46	3.6	0.22	1.02	0.16	$P = .007$
162	146	10.71	3.4	0.22	0.65	0.17	$P = .122$
151	135	12.24	3.6	0.24	1.06	0.19	$P = .011$
132	124	12.29	3.6	0.22	1.08	0.21	$P = .149$
131	117	7.52	2.9	0.26	0.15	0.23	$P = .443$
130	113	6.32	2.7	0.26	-0.09	0.23	$P = .221$
127	105	4.8	2.3	0.26	-0.6	0.25	$P = .031$

nist in the regular arm of the study by Sears et al,⁹ a variety of short-acting β_2 -agonists were used in the intermittent arm of the study. In contrast, a more recent study of patients with mild asthma reported that scheduled albuterol treatment had no deleterious or beneficial effects compared with intermittent as-needed use.¹⁰ The suggestion that the effects of scheduled treatment with long-acting and short-acting β_2 -agonists may be significantly different is further supported by the study by Pearlman et al,² which, in addition to demonstrating superior asthma control with salmeterol compared with scheduled albuterol, failed to show any difference in asthma control with scheduled albuterol compared with the combination of scheduled placebo with albuterol rescue over a 3-month period. Therefore, although the results of the current study showing that regular use of salmeterol improves asthma control over a prolonged period are reassuring, the appropriateness of the scheduled use of short-acting β_2 -agonists remains controversial.^{6,8}

In the current study there was no evidence that the bronchodilator properties of salmeterol became attenuated over the 1-year time period. The finding of no significant diminution in bronchodilation with salmeterol in this study is consistent with the findings of 1-year studies by Britton et al in adults,⁴ Simons et al in children,²⁸ and other 3-month studies in adults.^{2,3} Studies whose findings have suggested that tolerance may develop to the bronchodilator effects of β_2 -agonists have usually been undertaken in patients in whom β_2 -agonist therapy had been initiated after a period of abstinence from such agents.^{29,30} Some of these patients may manifest a degree of bronchodilator tolerance after β_2 -agonist therapy has been initiated or reinstated. However, the degree of tolerance that develops does not appear to be of clinically significant magnitude and may only affect duration without affecting peak effect.²⁹ There is no evidence that tolerance is progressive in patients with stable asthma after the first few weeks of therapy. The patients in the current study required daily administration of albuterol rescue therapy during the pretreatment washout period, and this may explain why no evidence of tolerance was seen, even at the beginning of the study.

In the current study $\log_2 PD_{20} FEV_1$ increased after 4 weeks of treatment with salmeterol and was sustained throughout the study. The increase in $\log_2 PD_{20} FEV_1$ was greater than one doubling dose compared with baseline but less than one doubling dose compared with placebo. However, although the decrease in hyperresponsiveness was relatively modest, it was maintained for 1 year while the subjects were taking the drug. The most likely explanation for the increase in $\log_2 PD_{20} FEV_1$ during the treatment period is a combination of functional antagonism on airway smooth muscle³⁰ and a change in airway caliber.³¹ Subtle changes in prechallenge airway diameter can result in marked effects on response to methacholine³¹ because resistance to laminar airflow is inversely proportional to the fourth power of the radius (Poisson's law). Although the methacholine challenges

took place before the scheduled morning dose of salmeterol, residual functional antagonism and subtle bronchodilator effects of the preceding dose were likely to have persisted. Conversely, after the salmeterol was discontinued at the end of the study and was subsequently cleared from the lung, the $\log_2 PD_{20} FEV_1$ decreased as expected. Although statistical significance was achieved, the difference between the treatment groups was less than one doubling dose and thus was unlikely to be clinically relevant.^{22,23} Furthermore, the increase in hyperactivity was not associated with worsening of asthma control as measured by FEV_1 , morning and evening PEF, rescue albuterol use, nighttime awakenings, and asthma symptoms. These results are similar to the results of a recent 1-year study of salmeterol conducted in a pediatric population with asthma that also showed no significant change in hyperresponsiveness and no evidence of rebound hyperresponsiveness after discontinuation of salmeterol treatment.²⁸ Although salmeterol has been shown to have *in vitro* anti-inflammatory properties, the lack of convincing evidence of sustained significant anti-inflammatory activity in clinical studies suggests that the decrease in airway hyperresponsiveness is more likely to be the result of a bronchodilator effect than of a reduction in bronchial inflammation.³⁰

In the current study, as in several other studies comparing salmeterol to albuterol or placebo,²⁻⁴ patients who were taking inhaled corticosteroids before study entry were allowed to continue on their maintenance anti-inflammatory therapy. Conversely, anti-inflammatory therapy was not initiated in the remaining study population. However, although the results of the current study provide reassurance concerning the long-term efficacy and safety of salmeterol, they should not be used to advocate monotherapy with salmeterol because the majority of patients who currently receive salmeterol in clinical practice have more severe asthma than the patients in the current study. Concurrent administration of anti-inflammatory therapy with long-acting β_2 -agonists continues to be the recommended therapeutic option.³² The recommendation for concurrent administration of salmeterol and inhaled corticosteroids is supported both by studies demonstrating that the addition of salmeterol to an inhaled corticosteroid regimen improves asthma control to a greater degree than doubling the dose of the corticosteroid^{33,34} and conversely by studies showing that, compared with treatment with an inhaled corticosteroid alone, salmeterol monotherapy results in inferior control of symptoms and pulmonary function in children with asthma.^{28,35}

In conclusion, scheduled administration of salmeterol over 1 year, combined with albuterol rescue therapy as needed, provides superior control over placebo and rescue albuterol. The study also shows that the degree of bronchial hyperresponsiveness to methacholine remains decreased throughout the treatment period and that, after discontinuation of salmeterol, clinically significant increases in airway hyperresponsiveness did not develop.

We would like to acknowledge the following investigators who contributed greatly to this study: Paul Chervinsky, MD, New Eng-

land Research Center, Inc, Dartmouth, Mass; Stanley Galant, MD, Pediatric and Adult Allergy and Clinical Immunology, Orange, Calif; Pinkus Goldberg, MD, Memorial Clinic, Indianapolis, Ind; Jay Grossman, MD, Allergy Care Consultants, Ltd., Tucson, Ariz; Joe Ramsdell, MD, Clinical Trials Center, San Diego, Calif; Richard Rosenthal, MD, Laboratory for Applied Immunology, Fairfax, Va; Paul Scanlon, MD, Thoracic Diseases, Rochester, Minn; Gail Shapiro, MD, A.S.T.M.A., Inc., Seattle, Wash; Tommy Sim, MD, University of Texas, Galveston, Tex; David Tinkelman, MD, Atlanta Allergy and Immunology Research Foundation, Atlanta, Ga; Philip Korenblat, MD, St Louis, Mo; Zev Munk, MD, Memorial City, Houston, Tex; Harold Nelson, MD, National Jewish Center, Denver, Colo; Mark Vandewalker, MD, Clinical Research of the Ozarks, Rolla, Mo; and James Wolfe, MD, Allergy and Asthma Associates, San Jose, Calif. We also thank Larry E. East for his expert assistance in the preparation and review of this manuscript.

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