

Salmeterol, a new inhaled β_2 -adrenergic agonist, has a longer blocking effect than albuterol on hyperventilation-induced bronchoconstriction

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The duration of the blocking effect of salmeterol (50 μ g), albuterol (200 μ g), and a placebo were compared in a double-blind study in 12 adult subjects with asthma who underwent hyperventilation tests with cold dry air (-20° C) on 4 study days. On the first day, the hyperventilation test was performed at various time intervals (baseline, 1, 4, 6, 8, 12, and 24 hours) with spontaneous functional recovery between each test to determine the within-day within-subject variability of the response. The response was assessed by interpolating the dose of cold dry air causing a 20% fall in FEV₁. On the 3 remaining days, separated by an interval of at least 5 days, the active or placebo medication was administered after spontaneous recovery from the first hyperventilation test. Spirometry was assessed 15 minutes and 1 hour later. The hyperventilation test was then performed and repeated 4 hours after administration of the drug. The test was repeated 6, 8, 12, and 24 hours later to detect any significant blocking effect. The improvement in FEV₁ 15 minutes and 1 hour after the drug was administered was 19.8% and 20.4%, as compared to baseline for albuterol, and 16.3% and 16.8% for salmeterol (not significant). The mean duration of the blocking effect was 0.25 hour for the placebo, 3.5 hours for albuterol, and 15.9 hours for salmeterol ($F = 24.5$; $p < 0.001$; Newman-Keul's test was significant for every contrast). Eight of the 12 subjects still demonstrated some blocking effect 8 hours after taking salmeterol; this was true for only one subject receiving albuterol. We conclude that salmeterol has a significantly longer effect than albuterol on bronchoconstriction induced by hyperventilation. (J ALLERGY CLIN IMMUNOL 1992;89:567-74.)

Key words: Bronchial provocation tests, asthma, bronchi

Several studies have investigated the duration of effectiveness of various inhaled β_2 -adrenergic agents in subjects with asthma.¹¹ Effectiveness is usually assessed by measuring the degree of bronchodilatation induced by the preparation during a fixed period of time. Asthma, however, is defined not only by variability in bronchomotor tone but also in terms of bron-

Abbreviations used

MVV: Maximal voluntary ventilation
PD₂₀: Provocative dose of cold dry air causing a 20% fall in FEV₁
VE: Minute ventilation

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chial hyperresponsiveness,² which can be assessed by several means, including pharmacologic agents, exercise, and hyperventilation of unconditioned air. The latter has been suggested as a stimulus to reproduce exercise-induced asthma. It has been used by us and by other investigators³⁻⁶ and has the advantage over pharmacologic agents of being closer to what would be encountered in real life. Unlike exercise in which the response is of the all-or-nothing type, hyperventilation can be performed in dose-response fashion.

Salmeterol is a new sympathomimetic agent with

TABLE I. Baseline anthropometric, clinical, and functional results

No.	Sex	Age (yr)	Height (cm)	Duration of asthma (yr)	Atopy*	Medication	FEV ₁ (% pred)	FEV ₁ /FVC (% pred)	PD ₂₀ † (L/min)
1	F	43	165	9	—	β ₂ , Be 1000	46	63	32
2	F	50	175	17	—	β ₂ , Be 1000	80	98	42
3	F	55	165	4	—	β ₂ , Be 800	75	74	36
4	F	54	158	5	+	β ₂ , Be 1000	103	115	59
5	F	54	160	53	+	β ₂ , Be 1000	58	68	40
6	F	58	170	3	+	β ₂ , T, Be 1000	56	90	25
7	F	28	162	28	+	β ₂ , T, Be 1000	65	85	36
8	F	57	170	3	+	β ₂ , Be 1000	68	78	40
9	M	20	170	8	+	β ₂ , Be 1000	57	85	36
10	F	44	155	34	+	β ₂ , Be 1000	89	105	36
11	M	18	160	2	+	β ₂ , Be 100	115	138	40
12	M	53	173	8	+	β ₂ , T, Be 2000	70	95	43
MEAN:		45	165	15			74	91	38
SD:		15	6	16			20	21	1.2

β₂, Inhaled β₂-adrenergic agent; T, sustained-release theophylline preparation; Be, inhaled beclomethasone with daily dose.

*At least one immediate skin reaction by the prick method to 15 common inhaled allergens.

†Arithmetic means and standard deviation, except for PD₂₀, for which logarithmic transformation was used.

highly selective and long-lasting action on the β₂-receptors of the bronchial smooth muscle. Compared to current β₂-agonists, the preparation has a longer bronchodilator effect in subjects with asthma,⁷ blocks nocturnal flare-ups,⁸ and provides a better control of asthma, as was demonstrated in a recent 2-week duration study.⁹ Salmeterol may also have nonbronchodilator properties, as demonstrated by the protection against allergen-induced asthma and its blocking effect on the related changes in bronchial responsiveness.¹⁰

The purpose of this study was to compare the efficacy and duration of the blocking effect of salmeterol (50 μg) as compared to albuterol (200 μg) and a placebo on bronchoconstriction induced by hyperventilation of dry, cold air in subjects with asthma.

METHODS

Subjects

Twelve adult subjects (nine women and three men) who satisfied the criteria for a diagnosis of asthma of by the American Thoracic Society² and were in a clinically stable state (no nocturnal awakenings because of asthma or no modification in their need for inhaled bronchodilators in the previous month) were included in the study (Table I). Atopic subjects were not exposed to clinically relevant allergens (pollens and animal danders) except for house dust during the course of the study. A written consent form was signed by each eligible subject, and the project was approved by the ethics committee of the hospital.

Study design

This design was a double-blind, three-treatment, cross-over study. On the first day (day 1), after a 15-minute rest in the laboratory, spirometry was assessed.¹¹ The within-day within-subject variability of the response to the cold-air challenge, as assessed by PD₂₀, was determined by repeating the test several times, once to establish the baseline (time 0), and then 1, 4, 6, 8, and 12 hours later. The test was also repeated at 24 hours to ensure that the subject was in a functional stable state. Spontaneous functional recovery (FEV₁, value within 10% of the first test) was required before each subsequent test.

On the next 3 study days, after a 15-minute rest, spirometry was assessed. Baseline FEV₁ had to be within 10% of the first value obtained on day 1 to proceed; the first cold-air challenge was then performed. This first cold-air challenge had to be reproducible from one visit to the next, that is, <2 SD of the 95% confidence interval for the reproducibility of the test as assessed in our laboratory.¹² This finding corresponds to 0.28 on a log_e scale. On the 3 treatment days (days 2, 3, and 4), which were separated by at least 5 days and performed within a maximum interval of 4 weeks, the study drug was administered after spontaneous recovery from the first cold-air challenge (FEV₁ within 10% of baseline). This was done with a standard metered-dose inhaler under the direct supervision of a technician who made sure the subject inhaled slowly to inspiratory capacity and held his/her breath for 10 seconds at the end. Subjects randomly received either salmeterol, 50 μg (two puffs of 25 μg), albuterol, 200 μg (two puffs of 100 μg), or a placebo (two puffs). Pulse rate, sitting systolic and diastolic

pressure, as well as tremor, with a recommended tremor scale,¹³ were assessed before and 15 minutes after the drug was inhaled and with each subsequent cold-air challenge.

The cold-air challenge was repeated 1 hour after administration of the treatment drug. If there was no evidence of blockade of the bronchial response to cold air (see below), the study day was terminated. If significant blockade was demonstrated, the cold-air challenge was repeated 4, 6, 8, 12, and 24 hours after administration of the drug, that is, until no significant blockade could be demonstrated on two consecutive tests.

Subjects were asked to stop using their inhaled β_2 -adrenergic agents 12 hours before each visit. Sustained-release theophylline preparations were withheld for at least 48 hours before any study day. Subjects using daily inhaled corticosteroids were challenged in a constant relationship to their last dose. The dose of inhaled corticosteroid was not changed for the duration of the study.

Cold-air inhalation test

The test was performed with an air-jet breathing device (FTS Systems, Inc., Stone Ridge, N.Y.) described elsewhere.¹² The temperature of the inspired dry air was kept at -20°C and checked with a probe at a distance of 1 cm from the mouth. A dose-response curve was generated by administering doubling doses of cold air to the subject, increasing VE from 7.5 to 15, 30, and 60 L/min and MVV for 3-minute periods. After each 3-minute interval, the response was assessed by measuring FEV₁ at 30, 90, and 180 seconds, and every 2 minutes thereafter, if FEV₁ continued to decrease, until the lowest value was recorded. Once FEV₁ started to increase, the subject was asked to continue inhaling cold air at an increased VE. The test was stopped when FEV₁ had decreased by 20% or more over the lowest pretreatment value or when MVV was achieved. Subjects listened to a tape recording of increasing breathing frequency (15 and 30 breaths per minute). Tidal volume was established by continuous examination of tidal volume recording and by instructing the subject to breathe less, more, or the same. MVV was obtained either by asking subjects to breathe as fast and as deeply as possible or by adjusting the breathing frequency to 37 breaths per minute on the tape recording. Spirometry was recorded on a Collins 9L water spirometer (W. E. Collins, Inc., Braintree, Mass.).

Analysis of results

Dose-response curves for cold air were drawn on a non-cumulative, semilogarithmic scale by relating VE on the abscissa and the percentage change in FEV₁ on the ordinate. PD₂₀ was interpolated on the dose-response curve. PD₂₀ was extrapolated in the case of changes between 16% and <20% in FEV₁ since this part of the dose-response curve is linear.¹⁴ Reference values for FEV₁ and FEV₁/FVC were obtained from Knudson et al.¹⁵ Logarithmic transformation of PD₂₀ was used in the analysis of results.

The within-day variability of PD₂₀ for each subject was determined by the study of the distribution of PD₂₀ results

on day 1 at times 0, 1, 4, 6, 8, and 12 hours, the mean of these results being baseline PD₂₀. To define the changes in PD₂₀ between time intervals on each treatment day, we determined the standardized change in PD₂₀ as (PD₂₀ [1, 4, 8, 12, or 24 hours] - PD₂₀ baseline/within-day variability of PD₂₀ on day 1). Any change in PD₂₀ on a treatment day was therefore corrected for within-day variability, as observed on the control day (standardized change). This standardized change was considered significant if it exceeded 2 SD (i.e., >2 SD from the control-day mean). A value between 2 and 10 was considered a partial blockade; a complete blockade resulted in a <15% change in FEV₁, even after MVV, corresponding to a standardized change >10. The interval for the return of the change in standardized PD₂₀ to a value equal to 2 was interpolated from individual dose-response curves and compared by analysis of variance with contrasts (Newman-Keul's). Categorical analysis of the results (no blockade, partial blockade, or complete blockade) was performed with logistic regression for ordered categorical variables.^{16,17} The between-day changes in FEV₁ and the changes in FEV₁ 1 hour after inhaling the bronchodilator on the 3 treatment days were analyzed through repeated-measures analysis of variance with contrasts (Newman-Keul's).

RESULTS

Nine women and three men, aged 18 to 57 years, took part in the study (Table I). The duration of asthma varied from 2 to 53 years. Nine subjects were atopic. All subjects were taking a daily dose of inhaled beclomethasone between 100 and 2000 μg . Eight subjects had FEV₁ <80% predicted, including seven who also had a significantly reduced FEV₁/FVC. Baseline FEV₁ and FEV₁/FVC were not significantly different from one visit to the next on treatment days ($F = 0.06$ and 1.06, respectively; $p > 0.05$). No tachyphylaxis was observed comparing the six PD₂₀ results of day 1 ($F = 1.67$; $p > 0.05$). The reproducibility of the test was satisfactory; 1 SD of the mean baseline PD₂₀ of the no-treatment day was 0.15, 0.17, 0.17, 0.08, 0.25, 0.19, 0.06, 0.16, 0.28, 0.15, 0.21, and 0.19, respectively, in the 12 subjects. Only two subjects had standard deviation values from the mean PD₂₀ >0.215 on the log_e scale, which corresponds to 1 SD of the within-day variability of the test in subjects with asthma in our laboratory.¹²

The mean changes in FEV₁ 15 minutes after the drug was administered and after the first cold-air challenge, as compared with the baseline value of spirometry for each treatment day, was $19.8\% \pm 13.2\%$ (SD) for albuterol, $16.3\% \pm 12.5\%$ (SD) for salmeterol, and $5.4\% \pm 13.1\%$ (SD) for the placebo treatment ($F = 5.19$; $p = 0.01$), the contrast being significant ($p < 0.05$) for the comparisons between albuterol and the placebo treatment as well as between salmeterol and the placebo treatment but not between

TABLE II. PD₂₀ values (liters per minute) according to treatment days at various time intervals in subjects Nos. 1 to 6

No.	Day	Baseline	1 hour	4 hours	6 hours	8 hours	12 hours	24 hours
1	No treatment	32	32	25	38	26	33	36
	Placebo	41	38	(-)	(-)	(-)	(-)	(-)
	Albuterol	39	53	37	(-)	(-)	(-)	(-)
	Salmeterol	38	59	42	(-)	(-)	(-)	(-)
2	No treatment	42	46	32	37	39	53	36
	Placebo	54	60	(-)	(-)	(-)	(-)	(-)
	Albuterol	54	90	50	(-)	(-)	(-)	(-)
	Salmeterol	54	NR	NR	NR	NR	62	(-)
3	No treatment	36	30	45	42	46	48	38
	Placebo	35	44	(-)	(-)	(-)	(-)	(-)
	Albuterol	38	NR	58	50	37	(-)	(-)
	Salmeterol	39	NR	NR	NR	58	50	NR
4	No treatment	59	56	50	60	59	58	64
	Placebo	54	58	(-)	(-)	(-)	(-)	(-)
	Albuterol	71	NR	51	(-)	(-)	(-)	(-)
	Salmeterol	61	NR	NR	NR	NR	NR	67
5	No treatment	40	37	23	22	33	25	35
	Placebo	31	35	(-)	(-)	(-)	(-)	(-)
	Albuterol	33	NR	36	(-)	(-)	(-)	(-)
	Salmeterol	38	NR	NR	NR	NR	NR	NR
6	No treatment	25	26	16	26	22	23	29
	Placebo	30	36	(-)	(-)	(-)	(-)	(-)
	Albuterol	30	NR	30	(-)	(-)	(-)	(-)
	Salmeterol	24	NR	NR	45	NR	34	42

NR, Not reached, that is, changes in FEV₁ <15% at the last level of ventilation; (-), not done.

albuterol and salmeterol treatment. After 1 hour, the values for improvement in FEV₁ were 20.4% ± 13.4% (SD) for albuterol, 16.8% ± 12.8% (SD) for salmeterol, and 3.3% ± 8.1% (SD) for the placebo ($F = 9.98$; $p < 0.001$), the contrasts being significant between the placebo and albuterol or salmeterol treatment but not between albuterol and salmeterol treatment. After 4 hours, the changes in FEV₁ from baseline values were still superior for the days after salmeterol was administered (18.1% ± 11.1%) as compared with the days after albuterol was administered (7.1% ± 6.1%) ($p < 0.001$; $N = 11$).

The individual values of PD₂₀ are presented in Tables II and III. The mean durations of the blocking effect defined as a return to the upper limit of 2 SD from the mean PD₂₀ values on the control day (day 1) were 0.25 (±0.83) hours for placebo treatment, 3.5 (±2.7) hours for albuterol treatment, and 15.9 (±9.6) hours for salmeterol treatment ($F = 24.5$; $p < 0.001$, all contrasts being significant by the Newman-Keul's method; $p < 0.05$). The categoric analysis of the blocking effect is presented in Table IV. The analysis could be performed for 1 and 4 hours after the medication was taken. At 1 hour, the fit of

the model was satisfactory with a deviance of 2.8 and two degrees of freedom ($p > 0.2$) for the first run and a deviance of 0.5 with one degree of freedom for the second model ($p > 0.2$). The log odds for the blocking effect of albuterol compared to that of placebo was 3.57 (1.2 SD); salmeterol log odds compared to that of placebo, 5.02 (1.3 SD); of salmeterol log odds compared to that of albuterol, 1.5 (0.9 SD). These results demonstrate that the difference between the two active treatments was marginally significant 1 hour after taking the medication ($p = 0.09$), eliciting a slight superiority for salmeterol. As presented in Table IV, 10 subjects had a complete blocking effect after taking salmeterol, but only six after taking albuterol. For these data corresponding to 4 hours after medication, we analyzed the difference between the two active treatments because there was only one patient left in the placebo-treated group. The fit of the model was satisfactory with a deviance of 0.19 and one degree of freedom ($p > 0.2$). The log odds for the blocking effect of salmeterol compared to that of albuterol was 3.67 (1.1 SD). Four hours after the drug was taken, the difference between the two active treatments was highly significant ($p < 0.001$), favoring

TABLE III. PD₂₀ values (liter per minute) according to treatment days at various time intervals in subjects Nos. 7 to 12

No.	Day	Baseline	1 hour	4 hours	6 hours	8 hours	12 hours	24 hours
7	No treatment	36	34	30	33	33	34	36
	Placebo	25	28	(-)	(-)	(-)	(-)	(-)
	Albuterol	28	42	35	28	(-)	(-)	(-)
	Salmeterol	27	42	44	42	47	39	36
8	No treatment	40	36	38	50	42	32	31
	Placebo	43	NR	48	(-)	(-)	(-)	(-)
	Albuterol	50	49	(-)	(-)	(-)	(-)	(-)
	Salmeterol	52	NR	NR	NR	48	(-)	(-)
9	No treatment	36	45	34	35	21	22	31
	Placebo	22	19	(-)	(-)	(-)	(-)	(-)
	Albuterol	37	85	33	(-)	(-)	(-)	(-)
	Salmeterol	36	58	64	(-)	(-)	(-)	(-)
10	No treatment	36	38	30	31	30	24	33
	Placebo	44	36	(-)	(-)	(-)	(-)	(-)
	Albuterol	43	NR	43	(-)	(-)	(-)	(-)
	Salmeterol	44	NR	NR	NR	NR	NR	NR
11	No treatment	40	29	30	46	52	47	40
	Placebo	41	41	(-)	(-)	(-)	(-)	(-)
	Albuterol	57	NR	NR	NR	NR	56	(-)
	Salmeterol	56	NR	NR	92	NR	79	69
12	No treatment	43	43	28	27	35	38	37
	Placebo	45	45	(-)	(-)	(-)	(-)	(-)
	Albuterol	49	67	54	(-)	(-)	(-)	(-)
	Salmeterol	45	NR	NR	NR	48	(-)	(-)

NR, Not reached, that is, changes in FEV₁ <15% at the last level of ventilation; (-), not done.

salmeterol. Indeed, 11 subjects demonstrated complete or partial blocking after taking salmeterol, whereas only three subjects demonstrated blocking after taking albuterol. Eight subjects still demonstrated a blocking effect 8 hours after inhaling salmeterol; six subjects, after 12 hours, and two subjects after 24 hours.

The correspondence between the bronchodilator effect and the blockade of hyperventilation-induced bronchoconstriction 1 hour after administering albuterol and salmeterol is presented in Table V. It is interesting to note that five subjects who demonstrated a minor bronchodilator effect after inhaling salmeterol ($\leq 10\%$ improvement in FEV₁) had a complete blocking effect on hyperventilation-induced bronchoconstriction.

No tremor and no significant changes in pulse rate and systolic and diastolic blood pressure were noticed after either albuterol or salmeterol treatment.

DISCUSSION

Salmeterol is a highly potent, selective, long-acting β_2 -agonist agent that was recently developed and assessed in clinical studies. Ullman and Svedmyr⁹ per-

formed a double-blind, crossover study comparing the efficacy of inhaled albuterol administered four times a day and salmeterol taken twice a day among 12 subjects with asthma followed for 2 weeks with each medication; the washout period between each treatment was 1 week. Several indices favored salmeterol: fewer asthma symptoms, better night's sleep, improved baseline FEV₁ values after the study period, and improved morning and evening peak expiratory flow rates. Furthermore, there was no evidence of tachyphylaxis. The long duration of action of this preparation was further demonstrated in 20 subjects with nocturnal asthma who demonstrated improvement while they were taking salmeterol as compared to taking a placebo.⁸ The longer duration of action is believed to be caused by the presence of a long lipophilic side chain that interacts with a binding domain in the vicinity of the β_2 -receptor.^{10, 18} Recent results demonstrated that salmeterol protects against allergen-induced immediate and late asthmatic reactions in eight subjects challenged with *Dermatophagoides pteronyssinus*.¹⁰ The preparation also blocked the changes in nonspecific bronchial responsiveness related to the late-phase component of the reaction.¹⁰

TABLE IV. Efficacy of bronchodilators in blocking hyperventilation-induced asthma

Interval since inhaling medication	Effect*			Total No. assessed
	Complete	Partial	Absent	
1 hour				
Placebo	1	0	11	12
Albuterol	6	4	2	12
Salmeterol	10	1	1	12
4 hours				
Placebo	0	0	1	1
Albuterol	1	2	8	11
Salmeterol	10	1	1	12
6 hours				
Placebo	0	0	0	0
Albuterol	1	0	2	3
Salmeterol	8	2	0	10
8 hours				
Placebo	0	0	0	0
Albuterol	1	0	1	2
Salmeterol	7	1	2	10
12 hours				
Placebo	0	0	0	0
Albuterol	0	0	1	1
Salmeterol	4	2	2	8
24 hours				
Placebo	0	0	0	0
Albuterol	0	0	0	0
Salmeterol	1	1	4	6

See text for the results of the statistical analysis.

TABLE V. Correspondence between bronchodilator and blocking effects of albuterol and salmeterol 1 hour after administering medication

Bronchodilator effect*	Blocking effect					
	Albuterol			Salmeterol		
	Complete	Partial	Absent	Complete	Partial	Absent
≥20%	2	2	1	3	1	1
11%-19%	3	1	0	1	0	0
≤10%	1	1	1	5	1	0

*Percent improvement in FEV₁ from prebronchodilator value.

The acute bronchodilator effect of salmeterol as compared to that of albuterol was explored in a study of eight subjects with asthma by Ullman and Svedmyr.⁷ The magnitude of the peak effect of albuterol and salmeterol was not significantly different. Similar results were obtained in our study. Although FEV₁ values returned to baseline within 6 hours after albuterol was taken, more than half of the bronchodilator effect was still present 12 hours after inhaling salmeterol, as demonstrated by Ullman and Svedmyr.⁷ Even if the design of our study did not allow us to

conclude firmly on the duration of the bronchodilator effect, it is interesting to note that baseline airway caliber was significantly higher after salmeterol treatment than after albuterol treatment 4 hours after taking the medication.

The relevance of studying the blocking effect of inhaled β_2 -adrenergic agents, other than obtaining information on their bronchodilator effect, is twofold. First, bronchial hyperresponsiveness is a key feature of asthma.² Second, the blocking effect is not necessarily related to the bronchodilator effect, as was

demonstrated in this study. Similar bronchodilator effects were demonstrated after taking albuterol and salmeterol, but a tendency for a complete blocking effect on hyperventilation-induced bronchoconstriction was more often observed after salmeterol treatment. We demonstrated that the mean duration of the blocking effect of salmeterol was 16 hours compared with only 3.5 hours for that of albuterol. Ten subjects still demonstrated a blocking effect 4 hours after inhaling salmeterol, eight after 6 hours, seven after 8 hours, four after 12 hours, and one subject after 24 hours. Pauwels et al.¹⁹ also demonstrated that salmeterol protected against methacholine-induced bronchoconstriction up to 12 hours after it was inhaled, as published in an abstract form.

The relevance of studying the blocking effect of inhaled β_2 -adrenergic agents is also tied to the fact that their bronchodilator and blocking effects are not equivalent. We demonstrated this phenomenon in a previous work,²⁰ and it was confirmed by this study. Five subjects (Nos. 2, 3, 4, 6, and 8 in Table I) who had demonstrated a minimal bronchodilator effect after inhaling salmeterol ($\leq 10\%$ improvement in FEV₁) had a complete blocking effect on hyperventilation-induced bronchoconstriction assessed 1 hour later. In these subjects, there was possibly still room for bronchodilatation since four of the five subjects had baseline FEV₁ $\leq 80\%$ predicted (Table I). However, this could have only been verified by generating dose-response curve and administering increasing doses of salmeterol instead of a fixed dose, as in this study. In that sense, a clear distinction between the protective and bronchodilating effect of salmeterol could have only been satisfactorily obtained by comparing the bronchodilator and the blocking effects in a dose-response protocol, that is, by increasing the dose of salmeterol on each visit until a plateau of bronchodilator or blocking response is reached without causing too significant side effects. Performing such studies is obviously difficult in humans. From a theoretical point of view, the explanation for different bronchodilator and blocking effects could be explained by the fact that, although the mechanisms of exercise- and hyperventilation-induced bronchoconstriction are still being debated, the application of both stimuli results in the release of mediators with effects that might specifically be inhibited by inhaling β_2 -adrenergic agents.²¹

We used a standardized change in PD₂₀, which takes into account the within-day variability of the test as measured on six different occasions on a control day, to assess the blocking effect. We believe, however, that the significance of the blocking effect that we observed is not only statistical but also physiologic. Indeed, changes in PD₂₀ were considered to be sig-

nificant beyond a mean value of 0.36 on a log_e scale. This corresponded to the mean upper limit of 2 SD from the within-day variability of the test for each subject. Since the mean PD₂₀ was 38 L/min, any blocking effect was considered to be significant if the value reached 54 L/min, a mean increase of 42% reflecting a real physiologic change.

The other interesting point is that administering neither salmeterol nor albuterol induced significant side effects in terms of tremor or changes in heart rate and blood pressure. Ullman and Svedmyr⁷ also found no differences in side effects between salmeterol and albuterol treatment.

Preliminary results have recently demonstrated that the administration of short-acting, inhaled β_2 -agonists may result in less satisfactory control of asthma if they are taken on a four-times-a-day basis, compared with an "as needed" regimen.²² However, such results need to be confirmed. The advent of long-acting β_2 -agonist preparations, such as salmeterol that need to be taken only every 12 hours, coupled with their possible non-bronchodilator effect,¹⁰ might circumvent the possible caveats of short-acting β_2 -agonists. It is also likely that compliance will improve. It appears likely that the long-acting β_2 -agonists will be beneficial to many subjects with asthma, although their precise place in the treatment of asthma still remains to be clarified, as recently discussed.²³

We demonstrated that the blocking effect of salmeterol was still present 12 hours after the drug was administered in four subjects. This might suggest that salmeterol administration could be considered on a "once-a-day" regimen in some subjects. It would be interesting to study these subjects at other time intervals between 12 and 24 hours after the medication was administered to document the duration of the effect in a more precise way. Moreover, the dose of salmeterol, which was administered, was 50 μ g. It would appear relevant to know whether doubling this dose might increase the duration of the blocking effect. If this is the case, the chronopharmacology of salmeterol should be investigated to determine the best timing (morning or evening) for administering the medication.

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