

Improved bronchodilation with levalbuterol compared with racemic albuterol in patients with asthma

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Background: Racemic albuterol is an equal mixture of (R)-albuterol (levalbuterol), which is responsible for the bronchodilator effect, and (S)-albuterol, which provides no benefit and may be detrimental.

Objective: We sought to compare 2 doses of a single enantiomer, levalbuterol (0.63 mg and 1.25 mg), and equivalent amounts of levalbuterol administered as racemic albuterol with placebo in patients with moderate-to-severe asthma.

Methods: This was a randomized, double-blind, parallel-group trial. Three hundred sixty-two patients 12 years of age or older were treated with study drug administered by means of nebulization 3 times daily for 28 days. The primary endpoint was peak change in FEV₁ after 4 weeks.

Results: The change in peak FEV₁ response to the first dose in the combined levalbuterol group was significantly greater compared with the combined racemic albuterol group (0.92 and 0.82 L, respectively; $P = .03$), with similar but nonsignificant results after 4 weeks (0.84 and 0.74 L, respectively). Improvement in FEV₁ was similar for levalbuterol 0.63 mg and racemic albuterol 2.5 mg and greatest for levalbuterol 1.25 mg. Racemic albuterol 1.25 mg demonstrated the weakest bronchodilator effect, particularly after chronic dosing. The greatest increase in FEV₁ was seen after levalbuterol 1.25 mg, especially in subjects with severe asthma. All active treatments were well tolerated, and β -adrenergic side effects after administration of levalbuterol 0.63 mg were reduced relative to levalbuterol 1.25 mg or racemic albuterol 2.5 mg. At week 4, the predose FEV₁ value was greatest in patients who received levalbuterol or placebo when compared with those who received racemic albuterol. The difference was more evident and was statistically significant in patients who were not receiving inhaled corticosteroids.

Conclusion: Levalbuterol appears to provide a better therapeutic index than the standard dose of racemic albuterol.

These results support the concept that (S)-albuterol may have detrimental effects on pulmonary function. (*J Allergy Clin Immunol* 1998;102:943-52.)

Key words: Asthma, levalbuterol, racemic albuterol, bronchodilators, lung function, S-albuterol

Bronchodilators (specifically the short-acting β_2 -adrenergic agonists) are required for the relief and prevention of bronchospasm in all severities of asthma.^{1,2} The most commonly prescribed β_2 -agonist, racemic albuterol (eg, Ventolin or Proventil), is a 50/50 mixture of 2 mirror-image enantiomers termed (R)- and (S)-albuterol.^{3,4} (R)-albuterol (levalbuterol) is responsible for the rapid bronchodilator effects of the racemate, whereas (S)-albuterol has essentially no bronchodilator properties and was considered to be biologically inert.⁵

However, the role of (S)-albuterol has been reexamined recently, fueled in part by controversies about the possible deleterious effects of β_2 -agonists, as well as the Food and Drug Administration's mandate to quantify the risks of stereoisomeric drugs.⁶ The new evidence suggests that (S)-albuterol is not inert, but rather may exaggerate airway reactivity and cause loss of asthma control. Specifically, (S)-albuterol increases intracellular calcium,^{7,8} enhances experimental airway hyperresponsiveness to spasmogens,⁹⁻¹² and may have proinflammatory effects as gauged by eosinophil superoxide production in response to IL-5.¹³ (S)-albuterol is metabolized 10-fold more slowly than levalbuterol.¹⁴⁻¹⁶ With repeated frequent dosing, this slower metabolism increases the proportion of (S)-albuterol to levalbuterol in vivo and exposes the patient to relatively more of the potentially adverse effects of (S)-albuterol than the beneficial effects of levalbuterol.

This study evaluated the benefits and risks associated with the use of optically pure (R)-albuterol (levalbuterol) in the treatment of asthma in comparison with racemic albuterol and placebo.

METHODS

Subjects

Four hundred twenty-four patients at 33 outpatient asthma clinics in the United States (see Appendix) were enrolled in the study. Eligible patients were nonsmoking males or females 12 years of age or older who had at least a 6-month history of chronic and stable

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Supported by a grant from Sepracor Inc, Marlborough, Mass.

Received for publication June 3, 1998; revised Aug 24, 1998; accepted for publication Aug 27, 1998.

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0091-6749/98 \$5.00 + 0 1/1/94588

Abbreviations used

AUC:	Area under the curve
ECG:	Electrocardiogram
MDI:	Metered-dose inhaler

asthma (as defined by the American Thoracic Society) requiring pharmacotherapy. Patients were eligible if they had moderate-to-severe lung compromise, defined as an FEV₁ between 45% and 70% of predicted normal value for age, gender, height, and race after abstaining from short-acting β_2 -agonists for at least 8 hours. At the first visit, all patients demonstrated at least a 15% improvement in FEV₁ in response to a single 2.5-mg dose of racemic albuterol administered by means of nebulization. Patients were allowed to take other medications for asthma or allergic rhinitis, including inhaled and intranasal corticosteroids, sodium cromoglycate (Intal), and nedocromil sodium (Tilade) if taken at stable doses throughout the study and if withheld for a sufficient period of time before study visits. Bronchodilators, such as theophylline and ipratropium, were not permitted. Patients who required oral steroids for the treatment of asthma exacerbations were allowed to take 1 course of therapy with prednisone or its equivalent at 60 mg/day for 5 days. If more than 60 mg/day or a course longer than 5 days was required, the patient was discontinued from the study. Patients who were discontinued from the study were included in the statistical analyses as part of the intent-to-treat population. All patients were provided with a racemic albuterol metered-dose inhaler (MDI) to be used on an as-needed basis for relief of asthma symptoms.

Design and procedures

This multicenter, randomized, double-blind, placebo-controlled, parallel-arm clinical trial was conducted according to the principles of Good Clinical Practices and the Declaration of Helsinki (1989). Ethics committees approved the protocol and the informed consent form before initiation, and consent was obtained from all patients before enrollment. Patients meeting all eligibility criteria were entered into a 1-week, single-blind, placebo period to establish a baseline for asthma and to provide an appropriate washout for other medications. Afterwards, patients were randomly assigned to receive 1 of the following nebulization treatments 3 times daily for 4 weeks: 0.63 mg levalbuterol (rounded value; actual amount administered was 0.625 mg), 1.25 mg levalbuterol, 1.25 mg racemic albuterol, 2.5 mg racemic albuterol, or placebo. Doses were selected to facilitate milligram-to-milligram comparisons of levalbuterol in its pure form as opposed to levalbuterol in a racemic mixture (the 2.5 mg racemic albuterol dose contained 1.25 mg levalbuterol and the 1.25 mg dose of racemic albuterol contained 0.625 mg levalbuterol).

Serial pulmonary function testing was performed after the first dose (week 0), and at weeks 2 and 4. Nonserial pulmonary function testing was done at week 5 (1 week after double-blind therapy ceased and all patients were receiving single-blind placebo). On each serial pulmonary function testing day, FEV₁ was measured before the first dose, immediately after the dose, at 15 minutes after the dose, at 30-minute intervals for the first 2 hours, and then hourly for 6 hours. Serial pulmonary function testing was rescheduled for another day if the patient had used inhaled or nebulized albuterol or oral corticosteroids within 8 hours of the start of the testing period.

Safety endpoints included adverse events, clinical laboratory tests, vital signs, 12-lead electrocardiogram (ECG) data, and physical examination. Physical examinations, 12-lead ECGs, and routine clinical chemistry, hematology, and urinalysis were conducted at screening and after 4 weeks of treatment. During the serial pul-

monary function testing, vital signs were monitored, and a 12-lead ECG was obtained before dosing and at 15, 30, 60, 120, and 180 minutes after the dose was given. Additionally, a blood specimen was obtained for electrolyte and glucose determinations before and at 60 minutes after dosing.

All patients used a standard nebulizer (PARI LC PLUS with a DURA-NEB 2000 compressor; Pari Respiratory Equipment, Inc, Richmond, Va) and received detailed instruction on how to self-administer the study drug. The identity of the study drug was concealed from all investigators and patients. The blinded study drug was a clear and colorless solution provided in identical 3-mL single-use unit dose vials. A randomization schedule provided to the investigators dictated study treatment allocation.

The sponsor of the study, Sepracor Inc (Marlborough, Mass), provided study medications and coordinated all aspects of the study. The data analysis was performed by Pharmaceutical Product Development (PPD Pharmaco, Inc, Wilmington, NC).

Statistics

Treatment arms were compared for differences in mean peak change in FEV₁, FEV₁ area under the curve (AUC), and other pulmonary function parameters on the basis of an ANOVA model with the SAS MIXED procedure. Effects in the model included investigator and treatment. If the overall treatment F test was significant, then pairwise comparisons of all active treatment arms versus placebo, as well as the combined levalbuterol groups versus the combined racemic albuterol groups, were performed.

On the basis of prior studies, it was assumed that the standard deviation of the change from baseline in FEV₁ would be 0.55 L. Therefore a sample size of 60 patients per treatment arm would provide at least 80% power to detect a difference in peak change in FEV₁ of 0.29 L between any active treatment arm relative to placebo. This calculation was based on an ANOVA with a significance level (α) equal to .05.

Secondary efficacy endpoints included AUC and use of rescue racemic albuterol MDI. Safety endpoints included spontaneously reported drug-related adverse events, standard clinical laboratory tests, and electrocardiography. Inferential statistics were also performed on the number of patients reporting adverse events. In particular, chi-square tests were used to assess differences by body systems across all treatment groups. If the overall test was significant, all pairwise comparisons were performed with Fisher's exact test. All safety and efficacy analyses were performed on the intent-to-treat population, which consisted of all patients randomized to treatment ($n = 362$). All significance testing was conducted with a significance level (α) equal to .05.

RESULTS

Demographics and disposition

A total of 424 patients enrolled in the study. Sixty-two patients were withdrawn before randomization, 35 (56.5%) of whom did not meet enrollment criteria. Twelve patients (19.4%) voluntarily withdrew, 9 patients (14.5%) were withdrawn because of adverse events (including asthma exacerbation), and 6 patients (9.6%) were lost to follow-up or withdrew for other causes. Of the 362 patients who were randomized into the double-blind treatment period, 328 (90.6%) completed the study and 34 were withdrawn early. The most common reason for early withdrawal (22 of 34 patients) was an adverse event (see Safety in the Results section). The majority of

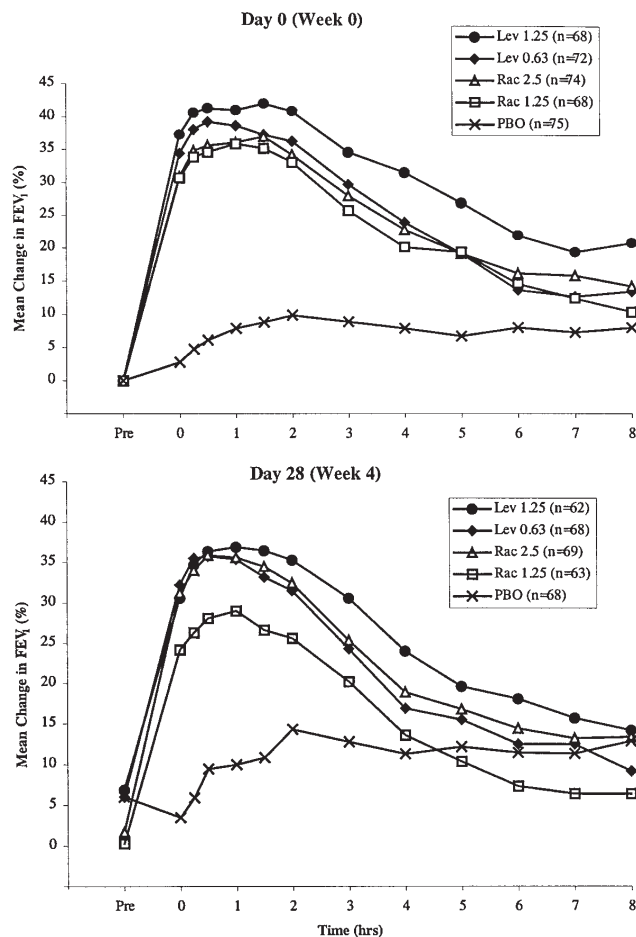


FIG 1. Mean percent change from baseline in FEV₁ after the first dose (week 0, *top panel*) and after 4 weeks (week 4, *bottom panel*) of study treatment. Week 0 mean peak change (L): $P < .001$ placebo (PBO) versus active treatments; $P = .03$ levalbuterol (Lev) versus racemic albuterol (Rac). Week 4 mean peak change: $P \leq .001$ placebo versus active treatments; $P = .13$ levalbuterol versus racemic albuterol.

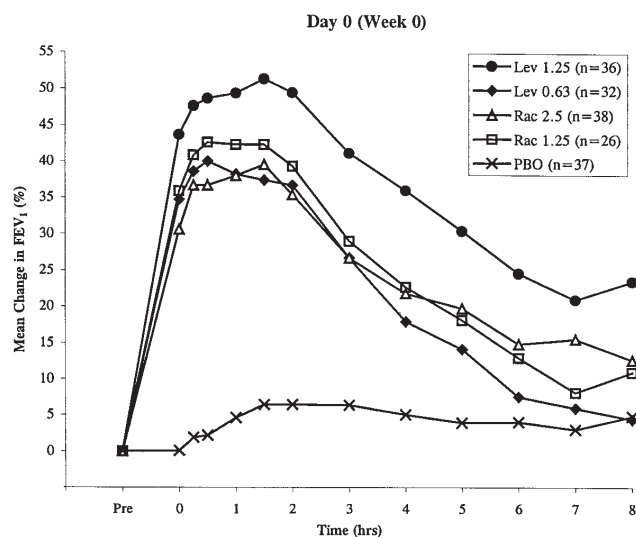


FIG 2. Mean percent change in FEV₁ after the first dose in a subgroup of patients with pretreatment FEV₁ of 60% or less of predicted normal value. Mean peak change P value = .0476 levalbuterol (Lev) versus racemic albuterol (Rac).

TABLE I. Baseline demographic characteristics

	Levalbuterol 0.63 mg (n = 72)	Levalbuterol 1.25 mg (n = 73)	Racemic albuterol 1.25 mg (n = 68)	Racemic albuterol 2.5 mg (n = 74)	Placebo (n = 75)	Total (n = 362)
Mean age (SD)	36.2 (14)	35.0 (13)	37.9 (15)	38.3 (16)	35.2 (15)	36.5 (15)
Sex (%)						
M	36	48	41	38	39	40
F	64	52	59	62	61	60
Race (%)						
White	86	82	88	88	79	85
Black	11	8	9	8	8	9
Other	3	10	3	4	13	6
FEV ₁ % of predicted mean (SD)	60.0 (8)	60.0 (7)	60.1 (7)	59.5 (7)	59.7 (8)	59.8 (7)
FEV ₁ % reversibility mean (SD)	40.9 (20)	41.6 (22)	39.9 (21)	39.7 (20)	37.1 (17)	39.8 (20)
Concomitant medications						
Inhaled corticosteroids (%)	46	49	43	59	37	47
Cromolyn/nedocromil (%)	1.4	4.1	8.8	4.1	2.7	4
Baseline FEV ₁ < 60% (%)	44	49	43	57	52	49

TABLE II. Use of racemic albuterol MDI rescue medication during weeks 0 to 4

	Levalbuterol 0.63 mg (n = 72)	Levalbuterol 1.25 mg (n = 73)	Racemic albuterol 1.25 mg (n = 68)	Racemic albuterol 2.5 mg (n = 74)	Placebo (n = 75)
Percent using any rescue medication	95.8	95.9	97.1	97.3	97.3
Mean puffs per day	3.5 (3.2)	2.7 (2.5)	3.6 (3.0)	3.8 (2.9)	4.9 (4.1)
<i>P</i> value (vs placebo)	.006	<.0001	.012	.042	—
Change in mean puffs per day compared with baseline	−0.25	−0.74	+0.01	−0.50	+0.33
<i>P</i> value	.372	<.001	.99	.056	.019

the patients who were withdrawn did so during the first 2 weeks after randomization.

Baseline demographic characteristics of patients in the 5 treatment arms were comparable (Table I). The mean age was 36.5 years (range, 12 to 80 years), and 60% of the patients were female. Eighty-five percent of the patients were white. The treatment arms had comparable pulmonary function at baseline; the mean percent predicted FEV₁ value was 59.8% (range, 44% to 77%), and the mean percent reversibility in response to nebulized racemic albuterol was 39.8% (range, 15% to 115%). Thirty-seven to sixty percent of patients used inhaled corticosteroids, and a small percentage in each arm used cromolyn sodium or nedocromil. About 50% of patients overall (range, 43% to 57%) had severe asthma as characterized by a baseline FEV₁ less than 60% of predicted value.

Efficacy data

The mean percent change in FEV₁ relative to study baseline for the 8-hour period after the first dose of study medication (week 0) and after 4 weeks of treatment (week 4) is shown in Fig 1. On a percent basis, clinically significant (>15%) improvement was observed for all active treatment arms immediately after nebulization,

and this improvement was maintained for at least 5 hours for all active treatments after the first dose and after 4 weeks of dosing. At both times, mean peak change in FEV₁ was significantly higher than placebo in all active treatment arms ($P < .001$).

The combined levalbuterol treatment group had a significantly greater improvement in mean peak FEV₁ than the combined racemic albuterol group after the first dose ($P = .03$) but not at week 4 ($P = .13$). The results at week 2 revealed a trend similar to that seen at week 4, and all active treatment arms were significantly better than placebo ($P < .001$; data not shown). After both the first dose and after 4 weeks of treatment, the greatest peak improvement and longest duration of improvement were observed for patients treated with levalbuterol 1.25 mg. Overall, the weakest bronchodilator effect and shortest duration were seen when patients received racemic albuterol 1.25 mg. Levalbuterol 0.63 mg and racemic albuterol 2.5 mg had similar peak improvements and duration of action at weeks 0, 2, and 4.

A similar pattern was seen in the FEV₁ AUC analysis. Levalbuterol treatment was significantly better than racemic albuterol treatment after the first dose ($P = .02$; not shown). At week 4, the combined levalbuterol group had higher mean AUC values than the combined racemic

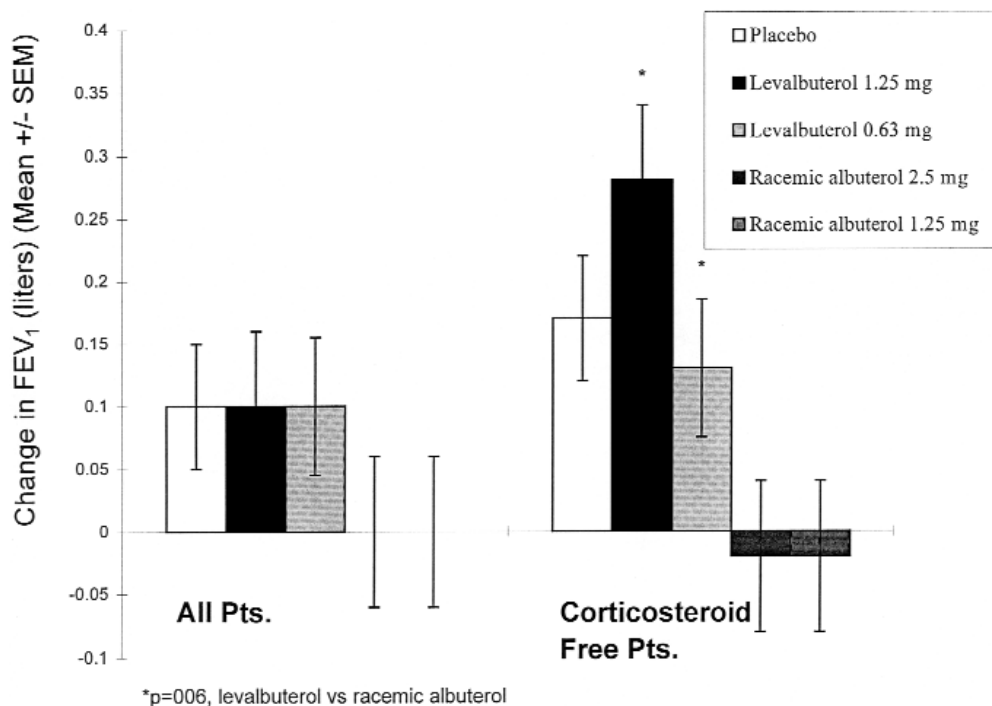


FIG 3. Mean change from study baseline in predose FEV₁ (L) after 4 weeks of treatment for all patients (*All Pts.*) and subgroup of patients who were not taking concurrent inhaled corticosteroid therapy. All patients: $P = .41$ across all treatments; inhaled corticosteroid-free patients: $P = .006$ levalbuterol versus racemic albuterol.

albuterol group, but these were not statistically significant ($P = .14$). Racemic albuterol 1.25 mg was not significantly different from placebo at week 4, whereas all of the other treatments were significantly better than placebo at both week 0 and week 4 ($P \leq .01$). Significant bronchodilator subsensitivity was observed for each of the active treatment arms when comparing their week 4 AUC results with their week 0 AUC results ($P < .04$).

The improvement in pulmonary function after the first dose was evaluated in patients with more severe pulmonary compromise at baseline, defined as an FEV₁ less than 60% of predicted normal value (Fig 2). A significant improvement in efficacy was observed in the combined levalbuterol group when compared with the combined racemic albuterol group (mean peak change; $P = .0476$). The responses to 0.63 mg levalbuterol and 2.5 mg racemic albuterol were similar, with racemic albuterol having a slightly longer duration of action. In this subset of subjects with severe asthma, the improvement and duration of improvement observed with 1.25 mg levalbuterol were consistent with the results seen in the entire patient population (Fig 1) but with an even greater improvement in peak FEV₁ compared with 2.5 mg racemic albuterol.

Overall, the rank order of efficacy regarding change in FEV₁ for all analyses was as follows: 1.25 mg leval-

buterol > 0.63 mg levalbuterol = 2.5 mg racemic albuterol > 1.25 mg racemic albuterol.

Over 95% of patients in each treatment arm used rescue medication (racemic albuterol MDI) at one time or another while receiving double-blind treatment (Table II). Patients in all of the active treatment arms used significantly less rescue medication when compared with the placebo group. Compared with baseline use during the single-blind week before randomization, patients who received placebo increased rescue medication use significantly during the double-blind phase of the study ($P = .019$). Only the 1.25 mg levalbuterol arm had a significant decrease in rescue medication use during double-blind treatment ($P < .001$). The decrease in rescue medication use with racemic albuterol 2.5 mg was of marginal significance ($P = .056$).

To determine the effect of chronic dosing on lung function, the mean predose change from baseline in FEV₁ at week 4 for all patients and for the subset of patients who received no concomitant inhaled corticosteroids was examined (Fig 3). When the total study population was analyzed, there was a 0.1 L (~6%) improvement in predose FEV₁ in the placebo and levalbuterol arms, which was not observed in the racemic albuterol arms. The improvement in predose FEV₁ was even more profound and significant in the subset of patients who did

TABLE III. Potentially drug-related adverse events*

	Levalbuterol 0.63 mg (n = 72)	Levalbuterol 1.25 mg (n = 73)	Racemic albuterol 1.25 mg (n = 68)	Racemic albuterol 2.5 mg (n = 74)	Placebo (n = 75)
Subjects with any adverse events, n (%)	12 (16.7)	23 (31.5)	14 (20.6)	20 (27.0)	14 (18.7)
Asthma	5 (6.9)	4 (5.5)	5 (7.4)	6 (8.1)	7 (9.3)
Asthma increase	1 (1.4)	3 (4.1)	2 (2.9)	2 (2.7)	2 (2.7)
Nervousness	2 (2.8)	7 (9.6)	3 (4.4)	6 (8.1)	0 (0.0)
Tremor	0 (0.0)	5 (6.8)	0 (0.0)	2 (2.7)	0 (0.0)
Headache	3 (4.2)	4 (5.5)	2 (2.9)	2 (2.7)	3 (4.0)
Tachycardia	2 (2.8)	2 (2.7)	0 (0.0)	2 (2.7)	0 (0.0)
Leg cramps	0 (0.0)	2 (2.7)	0 (0.0)	0 (0.0)	1 (1.3)
Anxiety	0 (0.0)	2 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)
Dizziness	1 (1.4)	2 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)

*Events listed are those reported by 2% or more of patients in any treatment group.

not receive concomitant inhaled corticosteroids and who were receiving placebo: 0.63 mg levalbuterol and 1.25 mg levalbuterol arms when compared with racemic albuterol ($P = .006$ when comparing the combined levalbuterol groups and the combined racemic albuterol groups). There was a 0.13 and 0.31 L (7% and 15%) difference between the predose FEV₁ in subjects receiving 0.63 mg levalbuterol and 1.25 mg levalbuterol when compared with those receiving 1.25 mg and 2.5 mg racemic albuterol, respectively. Of note, the greatest increase in FEV₁ was in the 1.25 mg levalbuterol arm. Both racemic albuterol arms had FEV₁ values that were worse than the placebo group and their baseline values.

In regard to predose FEV₁ at study week 5, 1 week after active treatment had stopped and all patients had begun receiving single-blind placebo, similar results were observed despite the fact that the FEV₁ values for all treatment arms, including placebo, had increased. Similar to week 4, for patients not receiving concomitant inhaled corticosteroids, the mean change from baseline in FEV₁ for patients treated with 1.25 mg levalbuterol during the double-blind phase of the study was significantly better than either racemic albuterol arm (both $P < .015$), and the combined levalbuterol groups were significantly better than that of the combined racemic albuterol groups ($P = .045$). The same trend was noted as early as week 2; however, it did not reach statistical significance (data not shown).

Safety data

Twenty-two patients (6.1% of total) withdrew from the study because of adverse events: 3 (4.2%) in the 0.63 mg levalbuterol arm, 8 (11.0%) in the 1.25 mg levalbuterol arm, 2 (2.9%) in the 1.25 mg racemic albuterol arm, 4 (5.4%) in the 2.5 mg racemic albuterol arm, and 5 (6.7%) in the placebo arm. Serious adverse events occurred in only 8 (2.2%) patients (3 in the 0.63 levalbuterol arm; 1 each in the 1.25 mg levalbuterol, 1.25 mg racemic albuterol, and 2.5 mg racemic albuterol arms; and 2 in the placebo arm). There were no on-study deaths (1 patient who received placebo died 3 months after completing the study after an asthma attack).

Overall, study medication was well tolerated, with only 22.9% of all patients reporting any potentially drug-related adverse events and no significant differences across the treatment groups ($P = .18$). Potentially drug-related adverse events were reported by 16.7%, 31.5%, 20.6%, 27.0%, and 18.7% of patients in the 0.63 mg levalbuterol, 1.25 mg levalbuterol, 1.25 mg racemic albuterol, 2.5 mg racemic albuterol, and placebo arms, respectively (Table III). The events most commonly reported by patients were asthma-related and were similar across the treatment arms. The next most common events were nervousness, headache, tremor, and tachycardia. There was a dose-related incidence of β -adrenergic side effects, such as nervousness and tremor. The percentage of patients who reported nervousness or tremor in the combined low-dose groups (0.63 levalbuterol plus 1.25 mg racemic albuterol) compared with the combined high-dose groups (1.25 levalbuterol plus 2.5 mg racemic albuterol) was significantly lower ($P = .003$). The difference between the 0.63 mg levalbuterol arm and the 2.5 mg racemic albuterol arm was not significantly different ($P = .098$).

Significant, dose-related increases in mean ventricular heart rate relative to predose values were observed at week 4 after dosing with all active treatment arms in comparison with placebo ($P \leq .0001$). The 1.25 mg levalbuterol and the 2.5 mg racemic albuterol treatment arms demonstrated a similar increase in heart rate (ranging from 3.6 to 4.9 beats per minute, respectively; $P = .24$). The 0.63 mg levalbuterol and 1.25 mg racemic albuterol doses resulted in relatively minor increases in heart rate. Change in heart rate after dosing was significantly lower in the 0.63 mg levalbuterol arm than in the 2.5 mg racemic albuterol arm after both the first dose and at week 4 (Fig 4; $P \leq .03$).

Statistically significant increases in mean serum glucose (range, 2.4 to 10.3 mg/dL) occurred in all active treatment arms at all visits when compared with placebo ($P < .0414$). Elevations in mean serum glucose were more pronounced in the higher dose group than the lower dose group. Levalbuterol 0.63 mg had a less marked effect than racemic albuterol 2.5 mg, but this difference did not reach statistical significance (Fig 4).

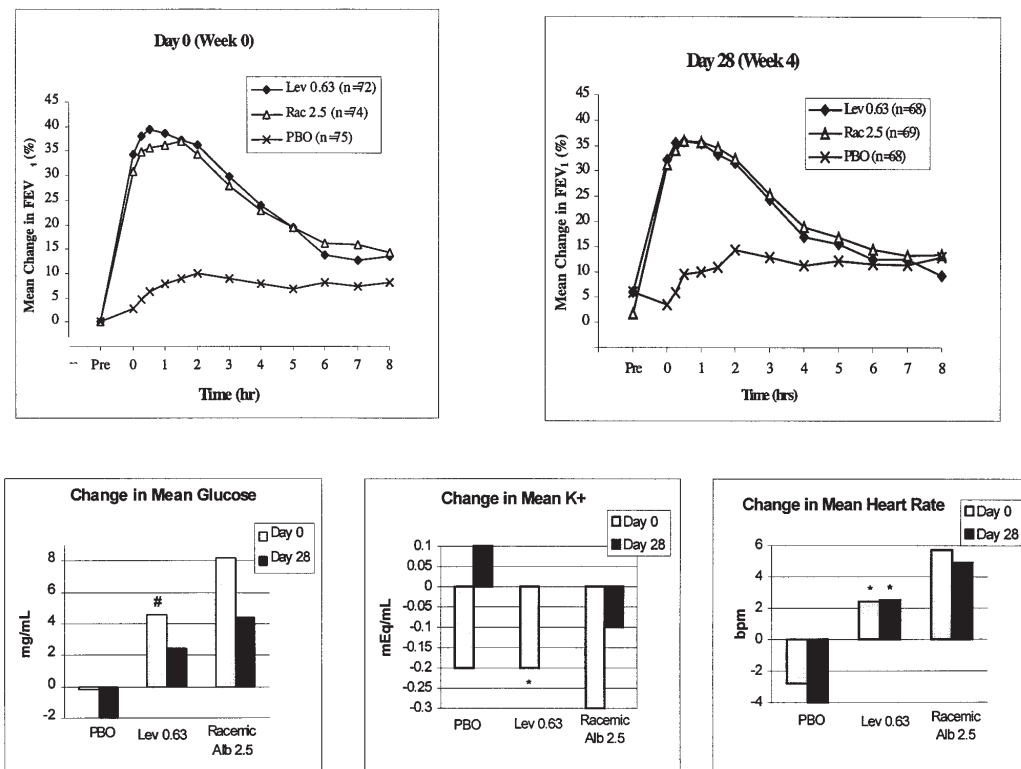


FIG 4. Summary of the key beneficial (bronchodilation) and adverse effect (heart rate at 15 minutes after dose, potassium and glucose 60 minutes after dose) properties of levalbuterol (Lev) 0.63 mg versus racemic albuterol (Racemic Alb) 2.5 mg on day 0 and on day 28. * $P < .05$ versus racemic albuterol 2.5 mg; # $P = .07$ versus racemic albuterol 2.5 mg.

Dose-related decreases in serum potassium values were also observed in the active treatment arms. Both 1.25 mg levalbuterol and 2.5 mg racemic albuterol produced significantly lower mean serum potassium values (decrease from baseline; range, -0.3 to -0.4 nmol/L) than the 0.63 mg levalbuterol dose at week 0 (Fig 4, $P < .018$). Although the same trend was evident at week 4, the difference was not significant.

Risk/benefit ratio

A summary of the key beneficial and adverse properties of equipotent doses of levalbuterol and racemic albuterol are compared in Fig 4. After both acute and chronic dosing, the bronchodilator response to 0.63 mg levalbuterol and 2.5 mg racemic albuterol was similar. Although β -adrenergic side effects were observed for both treatments, these side effects were consistently lower with 0.63 mg levalbuterol than with 2.5 mg racemic albuterol. These differences reached statistical significance for the increase in mean ventricular heart rate and for potassium decrease at week 0.

DISCUSSION

The effects of the (R)-enantiomer of albuterol, levalbuterol HCl, were compared with those of placebo and standard racemic albuterol in adolescent and adult

patients with moderate-to-severe asthma. The study was powered to determine differences between active treatments compared with placebo and was not designed to detect intertreatment differences. Although all of the active treatment arms experienced significant improvement in their FEV₁ values compared with placebo, the levalbuterol doses afforded better efficacy than equal doses of levalbuterol administered as part of the racemic mixture. These differences were not always statistically significant, but the rank order of efficacy was consistent at week 0, week 2, and week 4: levalbuterol 1.25 mg > levalbuterol 0.63 mg = racemic albuterol 2.5 mg > racemic albuterol 1.25 mg. The adverse effects of both levalbuterol and racemic albuterol were similar and appeared to be related to the amount of levalbuterol administered. This is supported by the results showing that the low-dose treatment groups had fewer β -adrenergic and total side effects than the high-dose treatment groups.

At lower doses, levalbuterol was an equipotent bronchodilator when compared with a much larger dose of racemic albuterol. Administration of 0.63 mg levalbuterol resulted in an improvement in lung function that was similar to 2.5 mg racemic albuterol and was associated with fewer total drug-related side effects, β -adrenergic side effects such as nervousness and tremor, and

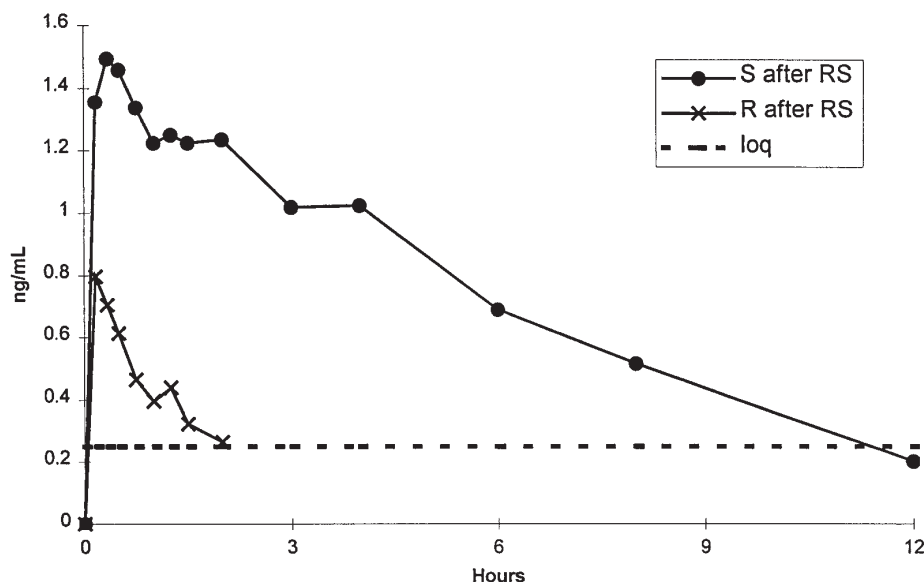


FIG 5. (R)- and (S)-albuterol plasma levels after inhalation of a single dose of 2.5 mg racemic albuterol.¹⁶ loq, Limit of quantitation.

fewer effects on heart rate, potassium, and glucose. At equal doses of the (R)-isomer, levalbuterol may be a more potent bronchodilator than racemic albuterol. Improvement in lung function was consistently, but not always, statistically significantly greater with 1.25 mg levalbuterol than 2.5 mg racemic albuterol, although the systemic effects were similar. The results observed regarding rescue medication use support the greater efficacy of levalbuterol and also raised the question of whether the efficacy results with levalbuterol would have been amplified had fewer patients self-administered rescue racemic albuterol.

That levalbuterol alone would improve pulmonary function more than equal doses of levalbuterol administered as part of a racemic mixture is a surprising and intriguing finding. It suggests that the S-albuterol contained within the racemic albuterol exerted deleterious effects on pulmonary function. There are 3 possible explanations for this. First, measurements of intracellular calcium in isolated airway smooth muscle cells have indicated that (S)-albuterol^{7,8} and racemic albuterol⁸ increase basal levels of intracellular Ca^{++} and induce cell shortening, and (S)-albuterol enhances the increase in intracellular calcium induced by carbachol.⁷ This is in direct contrast to the bronchodilator actions of levalbuterol that have been shown to decrease basal intracellular calcium^{7,8} and reduce the increase in calcium induced by carbachol.⁷ The increase in intracellular calcium caused by (S)-albuterol may hasten other adverse consequences. (S)-albuterol may cause an increase in calcium in the microvasculature that leads to endothelial cell disruption.¹⁷

Second, results of airway function studies have indi-

cated that the airway hyperresponsiveness produced by racemic albuterol resides with (S)-albuterol and that this induction is not a function of β_2 -receptor downregulation.^{10-12,18,19} Furthermore, exposure to racemic albuterol induces airway hyperresponsiveness to a variety of spasmogens or antigens in animals¹⁹ and humans,¹⁸ and this hyperresponsiveness persists longer than the bronchodilator effects of the compound.

Third, (S)-albuterol may have proinflammatory effects as gauged by eosinophil superoxide production in response to IL-5.¹³

The differential metabolism of levalbuterol and (S)-albuterol may contribute to these observed effects. (S)-albuterol is metabolized 10-fold more slowly, has a 5-fold greater AUC, a 2-fold higher C_{max} , and a longer elimination half-life than the therapeutic isomer, levalbuterol^{13,14,16,20} (Fig 5). On the basis of the pharmacokinetic profile of the racemic mixture, the potential exists for (S)-albuterol to exert its negative effects without being counterbalanced by the therapeutic effects of levalbuterol. In fact, (S)-albuterol has been detected in the blood of normal volunteers and patients for up to 24 hours after their last dose of racemic albuterol,¹⁶ demonstrating a potential for accumulation during chronic use. In addition, no interconversion of levalbuterol to (S)-albuterol has been observed in animal models or human subjects.^{14-16,21,22}

There has been considerable debate in recent years about the possible adverse consequences of regular or frequent β -agonist therapy.²³⁻²⁸ One issue in the debate is whether regular treatment with β -agonists worsens predose or trough lung function during chronic treatment. Predose lung function has been observed to decline in

some studies after regularly scheduled racemic albuterol treatment,²⁹⁻³¹ whereas it has remained essentially unchanged in others.^{25,32-34} However, the lack of significant improvement in predose lung function with racemic albuterol in the aforementioned studies is notable in light of the significant improvement in predose FEV₁ with levalbuterol or placebo in the study reported here. Significant improvement was associated only with levalbuterol and placebo treatment, particularly in the subgroup of patients not receiving concomitant inhaled corticosteroid therapy. This pattern has been previously reported.^{29,34} D'Alonzo et al²⁹ observed a small decline in predose FEV₁ relative to placebo after chronic treatment with albuterol. This difference was not apparent in the subgroup of patients using corticosteroids. Similarly, Pearlman et al³⁴ observed large differences in FEV₁ AUC responses to racemic albuterol between patients who were and were not treated with inhaled corticosteroids. The authors cited asthma severity as an important factor for the observed differences. The current study suggests that in patients unprotected by antiinflammatory treatment, racemic albuterol may have less efficacy. Corticosteroids are known to reduce airway hyperresponsiveness and to inhibit the production of cytokines, the recruitment of eosinophils, the release of inflammatory mediators, and microvascular leakage. Whether the adverse effects of (S)-albuterol are masked or prevented as a result of corticosteroid therapy and whether rescue racemic albuterol use by patients in the levalbuterol arms had any effect on masking an even larger improvement with levalbuterol compared with racemic albuterol on predose FEV₁ are questions for future studies.

This is the first study to compare the effects of chronic dosing of levalbuterol with racemic albuterol. The findings suggest 3 things: (1) Levalbuterol is a more potent bronchodilator when administered as the single enantiomer compared with the same amount of levalbuterol in a racemic mixture. (2) β -Adrenergic side effects are related to the levalbuterol dose. In support of this, 0.63 mg of levalbuterol provided comparable efficacy to 2.5 mg of racemic albuterol with reduced side effects. (3) Deterioration of predose lung function with chronic administration of racemic albuterol, but not levalbuterol administered as the pure enantiomer, may in part be a function of the administration of (S)-albuterol.

In summary, this study suggests that there may be a better therapeutic index for levalbuterol than racemic albuterol. The 0.63 mg levalbuterol dose ($\frac{1}{4}$ of the standard racemic dose) provided similar efficacy with reduced systemic β -agonist side effects compared with 2.5 mg of standard racemic albuterol. Levalbuterol 1.25 mg consistently provided better efficacy than 2.5 mg of standard racemic albuterol, with a similar safety profile. This difference was greatest in patients with a baseline FEV₁ value less than 60%, indicating that levalbuterol 1.25 mg may be particularly useful in patients with more severely compromised lung function. Racemic albuterol was associated with a decline in lung function compared with levalbuterol as assessed by morning FEV₁ before

dosing and after a 1-week washout. Additional studies are underway to further evaluate the decline in lung function that was observed in this study with racemic albuterol in patients with asthma.

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APPENDIX.

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