

Low-dose levalbuterol in children with asthma: Safety and efficacy in comparison with placebo and racemic albuterol

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Background: Racemic albuterol (RAC) is an equal mixture of (R)-albuterol and (S)-albuterol. Only the (R)-isomer, levalbuterol (LEV), is therapeutically active. Lower doses of LEV, devoid of (S)-albuterol, have demonstrated efficacy comparable to that of higher doses of the (R)-isomer administered as a component of RAC.

Objective: The purpose of this study was to determine whether LEV results in improved safety and efficacy in children.

Methods: Asthmatic children aged 4 to 11 years ($n = 338$; FEV₁, 40% to 85% of predicted) participated in this multicenter, randomized, double-blinded study and received 21 days of 3-times-a-day treatment with nebulized LEV (0.31 or 0.63 mg), RAC (1.25 or 2.5 mg), or placebo. The primary endpoint was FEV₁ (peak percent change). Adverse events, clinical laboratory test results, vital signs, and electrocardiograms were evaluated for safety.

Results: All active treatments significantly improved the primary endpoint in comparison with placebo ($P < .001$). Significant differences in FEV₁ were noted immediately after nebulization (median change, 2.0%, 19.0%, 18.1%, 12.4%, and 15.6% for placebo, LEV 0.31 and 0.63, RAC 1.25 and 2.5 mg, respectively; $P < .05$ vs placebo; $P < .05$ for LEV 0.31 and 0.63 vs RAC 1.25 mg). LEV 0.31 mg was the only treatment not different from placebo for changes in ventricular heart rate, QT_c interval, and glucose ($P > .05$). All active treatments decreased serum potassium (range, -0.3 to -0.6 ; $P < .002$ vs placebo), and RAC 2.5 mg caused the greatest change ($P < .005$ vs other actives). In a patient subset with severe asthma, a dose-response relationship was observed for levalbuterol, indicating that higher doses were more effective.

Conclusion: LEV was clinically comparable to 4- to 8-fold higher doses of RAC, and it demonstrated a more favorable safety profile. LEV 0.31 mg should be used as the starting dose in 4-11 year old children with mild to moderate persistent asthma. Patients with severe disease might benefit from higher doses. (*J Allergy Clin Immunol* 2001;108:938-45.)

Key words: Levalbuterol, racemic albuterol, (R)-albuterol, (S)-albuterol, asthma, pediatric, bronchodilator; FEV₁, β -agonist

The drug most commonly used to treat children with asthma is racemic albuterol (RAC).¹ Although asthma is the most widespread chronic disease of childhood (up to 80% of affected children present with symptoms before 5 years of age),² the optimal β_2 -agonist dose for children has not been determined. Pediatric asthma experts recommend use of the lowest effective dose to provide adequate clinical response while minimizing side effects.^{2,3} Despite a paucity of controlled clinical data to support this practice, many pediatricians reduce the dose of RAC for patients under the age of 12 years in hopes of decreasing β -mediated side effects.¹

RAC is composed of 2 isomers whose activities have been independently characterized in recent years. The (R)-albuterol isomer (hereafter referred to as *levalbuterol* [LEV]) has at least 100 times more potent binding at β_2 receptors than the (S)-albuterol isomer, and it appears to confer all of the bronchodilatory effects attributed to RAC.⁴ The role of (S)-albuterol has been reexamined in consequence of controversies surrounding deleterious effects of β_2 -agonists^{5,6} and the US Food and Drug Administration's mandate to quantify the risks of stereoisomeric drugs.⁷ (S)-albuterol, in contrast to LEV, has no bronchodilating activity and might have detrimental effects on the airways, including enhancement of calcium mobilization by smooth muscle cells,⁸ facilitation of acetylcholine release from dysfunctional presynaptic muscarinic autoreceptors,⁹ and enhancement of airway responsiveness to spasmogens.¹⁰⁻¹⁴ Thus, extensive evidence demonstrates that (S)-albuterol is not inert but might exacerbate airway reactivity and impair the control of asthma. Because of the relatively slower metabolic sulfation of (S)-albuterol in comparison with (R)-albuterol, plasma concentrations of (S)-albuterol are several-fold greater and remain in circulation much longer after the administration of RAC.^{15,16} Moreover, (S)-albuterol appears to be preferentially retained in the lungs in comparison with (R)-albuterol.¹⁷

In recent years, LEV (Xopenex), a β_2 -agonist solution free of (S)-albuterol and preservatives, has been available for the treatment or prevention of bronchospasm in patients aged 12 years and older. An improved safety and

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Abbreviations used

AE: Adverse event
bpm: Beats per minute
ECG: Electrocardiogram
HR: Heart rate
LEV: Levalbuterol
PK: Pharmacokinetic
RAC: Racemic albuterol

efficacy profile of LEV in comparison with RAC has been demonstrated in adults with asthma.¹⁸ In adult patients with more severe airways obstruction, LEV resulted in a greater recovery of airway function than that associated with RAC.¹⁸ A study in children aged 3 to 11 years demonstrated that single doses of LEV 0.31 mg and 0.63 mg produced FEV₁ reversibility comparable to that of RAC 2.5 mg and greater than that of RAC 1.25 mg and that it was associated with lower rates of β -mediated side effects (changes in ventricular heart rate [HR], glucose, and potassium) than the equipotent dose of RAC.¹⁹

This report describes a large, multicenter, randomized, double-blinded, placebo- and active-controlled study that evaluated the safety and efficacy of chronic treatment with nebulized LEV in 4- to 11-year-old patients with chronic asthma.

METHODS

This study was approved by local institutional review boards. Parents or legal guardians gave written informed consent before their children's participation. Key inclusion criteria were as follows: male or female, aged 4 to 11 years (inclusive); documented diagnosis of at least mild asthma for ≥ 60 days before screening; baseline FEV₁ within 40% to 85% of predicted with $\geq 15\%$ reversibility to RAC at screening. Key exclusion criteria were as follows: participation in an investigational study within 30 days of randomization; known sensitivity to study medications or their components; lower respiratory tract infection in the 2 weeks before randomization; clinically significant abnormality in the 12-lead electrocardiogram (ECG). Excluded medications were adrenergic bronchodilators, ipratropium bromide, nonprescription asthma medications, leukotriene inhibitors/antagonists, and corticosteroids (stable doses of inhaled corticosteroids initiated ≥ 60 days before randomization were permitted).

This multicenter, randomized, double-blinded, parallel-group study was designed to determine the safety and efficacy of LEV in comparison with placebo. RAC was included as an active control. The selection of doses was based on findings from previous clinical studies that indicated that a dose of LEV is comparable in efficacy to a 4-fold increased dose of RAC.^{18,19}

After screening, patients entered a 1-week, single-blinded, 3-times-a-day placebo run-in period. Eligible patients were then randomized to receive 21 days of 3-times-a-day double-blinded treatment with LEV 0.31 mg, LEV 0.63 mg, RAC 1.25 mg, RAC 2.5 mg, or placebo. Treatment was supplied in identical preservative-free unit dose vials (Sepracor Inc, Marlborough, Mass) that delivered 3 mL of blinded inhalation solution, administered by means of a PARI LC PLUS nebulizer and a DURA-NEB 3000 compressor (PARI Respiratory Inc., Richmond, Va). All patients received Ventolin MDI and Ventolin nebulers (GlaxoWellcome Inc,

Research Triangle Park, NC) as rescue medication. Ventolin nebulers were used only if the MDI provided inadequate symptom relief. Rescue and study medications were withheld before study visits (8 hours for MDI, 10 hours for the study drug, and 10 hours for Ventolin nebulers). Patients received the initial dose of study medication on the day of randomization (day 0) and returned to the clinic weekly for follow-up. Serial spirometry was performed in triplicate according to American Thoracic Society guidelines²⁰ after study medication on day 0 and day 21 at 15-minute intervals for the first 2 hours and then hourly up to 4 hours. On day 21, blood samples were collected in a subset of patients immediately before drug administration and then 15 minutes, 1 to 2 hours, and 5 to 7 hours after dose for analysis of drug levels and pharmacokinetic modeling.

The primary efficacy endpoint was FEV₁ (peak percent change from baseline) on day 21 after treatment. Baseline was defined as the FEV₁ on day 0 before the study drug was received. Secondary endpoints included changes in pulmonary function and percent of responders within 30 minutes after dose and time to peak improvement in FEV₁. Diary card data were collected to assess the use of rescue medication and asthma symptoms, including symptom-free days (days with an asthma symptom score of 0) and asthma control days (days when a patient had few or no symptoms, required ≤ 2 puffs per day of rescue medication, had no nocturnal awakenings, did not need unscheduled asthma-related medical care, and did not initiate oral corticosteroid rescue treatment). The Pediatric Asthma Caregiver's Quality of Life Questionnaire was administered at days 0 and 21. Patients were evaluated for adverse events (AEs), and physical examinations, clinical laboratory tests, and ECG recordings were done on days 0 and 21. ECG tracings were further analyzed for HR and the QT_c interval.

All analyses are presented for the entire intent-to-treat population, aged 4 to 11 years. The primary efficacy analysis consisted of an ANOVA model with effects for treatment, investigator, and treatment-by-investigator interaction. Because the primary endpoint data were not normally distributed, all efficacy data were rank-transformed and comparisons were made between the medians of each group. The Fisher least significant difference multiple comparison method was used for the primary efficacy endpoint and all secondary endpoints, and 2-sided tests were used for all hypothesis testing. To determine whether a difference existed among the LEV and placebo treatments, a 2-degrees-of-freedom contrast that included the 2 LEV-treated groups and the placebo group was constructed. Data for all treatment groups were included in the model, but the RAC groups were excluded from the contrast statement. If this contrast was statistically significant at the $P = .05$ level, then pairwise tests of each LEV group versus the placebo group were performed. A similar 2-degrees-of-freedom contrast between the 2 RAC groups and the placebo group was conducted; this was followed by pairwise tests of each RAC group versus the placebo group if the overall RAC contrast was statistically significant at the $P = .05$ level. Secondary efficacy analyses used this comparison method for the primary efficacy analysis and/or descriptive statistics. Post hoc tests included pairwise comparisons of the time to maximum response, the percent change in FEV₁, and the percent of responders immediately after dose.

The frequency and percentage of patients with AEs were tabulated overall, by treatment received, by severity, and by relationship. Safety data were normally distributed. An ANOVA model was used to analyze the change in HR and the change in QT_c interval on day 0 and day 21 through use of the same comparison method outlined for the primary efficacy parameter. Post hoc analyses examined overall symptom scores, asthma control days, and all pairwise comparisons for serum concentrations of potassium and glucose, HR, and the QT_c interval.

TABLE I. Patient demographics at baseline

	Placebo (n = 65)	LEV 0.31 (n = 70)	LEV 0.63 (n = 70)	RAC 1.25 (n = 67)	RAC 2.5 (n = 66)
Age (y)	8.2 (2.0)	8.7 (1.9)	8.6 (1.8)	8.7 (1.9)	8.5 (2.0)
Male: n (%)	36 (55.4)	41 (58.6)	41 (58.6)	37 (55.2)	42 (63.6)
Race*: n (%)					
Caucasian	41 (63.1)	49 (70.0)	38 (54.3)	38 (56.7)	38 (57.6)
Black	19 (29.2)	11 (15.7)	14 (20.0)	15 (22.4)	19 (28.8)
Hispanic	3 (4.6)	4 (5.7)	13 (18.6)	10 (14.9)	6 (9.1)
Concomitant medications					
Steroids: n (%)	31 (48)	37 (53)	38 (54)	33 (49)	31 (47)
LT modifiers: n (%)	4 (6)	4 (6)	4 (6)	3 (5)	4 (6)
FEV ₁ : mean (SD)					
Percent reversibility	26.4 (14.0)	28.8 (15.3)	27.8 (13.9)	23.9 (10.5)	27.4 (13.8)
Percent of predicted	74.0 (8.1)	72.0 (9.7)	74.0 (9.2)	74.4 (8.6)	73.3 (9.9)

Data presented are means (SD) unless otherwise noted; there were no significant differences among treatments for baseline demographics or lung function.

LT, Leukotriene.

*Data for Asian and other races not presented.

TABLE II. Airway function measurements

	Placebo	LEV 0.31	LEV 0.63	RAC 1.25	RAC 2.5	Overall P value
Day 0	n = 65	n = 70	n = 70	n = 67	n = 66	
FEV ₁ : Median peak percent change (Q1, Q3)	16.0 (8, 24)	27.0* (20, 40)	25.4* (18, 38)	24.2* (16, 32)	26.7* (16, 39)	<.001
Median time (min) to peak percent change (Q1, Q3)	118 (85, 194)	75* (31, 102)	83* (55, 104)	93* (74, 118)	90* (57, 120)	<.001
FEV ₁ : median percent change, Time 0 (Q1, Q3)	2.0 (-1, 8)	19.0*† (10, 28)	18.1*† (10, 27)	12.4* (5, 21)	15.6* (9, 27)	<.001
Percent responders at Time 0‡	12.3	62.9*†	56.5*	41.8*	54.6*	<.001
Day 21	n = 61	n = 64	n = 69	n = 65	n = 60	
FEV ₁ : Median peak percent change (Q1, Q3)	17.9 (11, 28)	24.9* (15, 36)	25.7* (17, 34)	22.3* (16, 33)	27.6* (14, 39)	.02
Median time (min) to peak percent change (Q1, Q3)	97 (74, 181)	77* (31, 106)	77* (30, 105)	75* (44, 105)	86* (48, 109)	<.001
FEV ₁ : Median percent change, Time 0 (Q1, Q3)	7.3 (-3, 17)	17.4* (7, 29)	15.9* (5, 25)	14.4* (6, 26)	16.6* (5, 28)	<.001
Percent responders at Time 0‡	31.2	56.3*	55.2*	47.6	54.2*	.02

* $P < .05$ vs placebo

† $P < .05$ vs RAC 1.25 mg.

‡Response defined as an improvement of $\geq 15\%$ from baseline FEV₁; Time 0 is the first FEV₁, completed immediately after nebulization; Q1 and Q3 are the 1st and 3rd quartiles.

RESULTS

Of the 398 enrolled patients, 338 (85%) successfully completed the single-blinded period and were randomized to treatment. Two to 6 patients in each treatment group (19 patients in all; 5.6%) discontinued treatment during the active treatment period; the most common reason for discontinuation was protocol deviation (6 patients; 1.8%). There were no discontinuations because of drug intolerance, and 319 (94.4%) of the 338 randomized patients completed the protocol.

Patient demographic characteristics were not significantly different among treatments, though the LEV 0.63 mg and RAC 1.25 mg groups had higher percentages of Hispanic subjects ($P > .17$; Table I). The mean patient age at screening was 8.5 years (range, 4–11 years). There were slightly more boys (58.3%) than girls. Caucasians constituted the largest racial group (60.4%). The majority

of patients had mild-to-moderate persistent asthma, 90% had allergic histories, approximately 50% were on concomitant steroids, and 6% were on leukotriene modifiers. There were no statistically significant differences among treatment groups for screening FEV₁, percent of predicted, percent reversibility, or concomitant asthma medications. During the study, predose FEV₁s were similar among the groups.

Efficacy results

All active treatments produced significant improvement in the primary endpoint, FEV₁ (peak percent change from baseline) in comparison with placebo on day 21 ($P \leq .019$; Table II). The effect on FEV₁ of LEV 0.31 mg was not significantly different from that of RAC 2.5 mg at either day 0 (median peak percent change, 26.95 and 26.66, respectively) or day 21 (median peak percent change, 24.94 and 27.59, respectively). There was no evidence of desensiti-

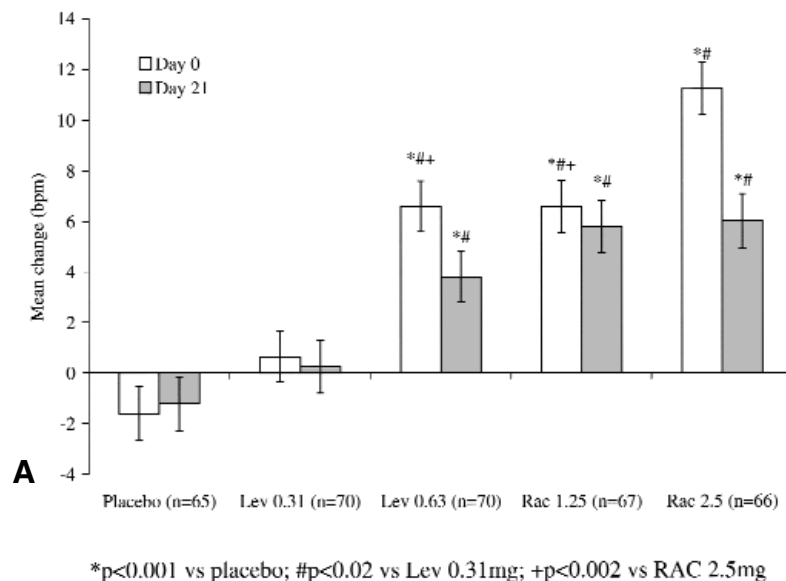


FIG 1. A, Mean change in ventricular HR 30 minutes after dose (least squares [LS] mean $\pm$ SEM).

zation to either LEV or RAC as measured by FEV₁ at day 21 in comparison with day 0. Similarly, there was a shorter median time to peak improvement in FEV₁ for all active treatment groups in comparison with placebo on days 0 and 21 ($P < .04$; Table II).

Clinically significant changes ($\geq 15\%$ median change from baseline FEV₁) occurred immediately after nebulization on days 0 and 21 for all groups except placebo and RAC 1.25 mg. Significantly more patients responded to active treatment in comparison with placebo on both days ($P < .02$; Table II), the exception being RAC 1.25 mg on day 21. On day 0, there were significantly more patients responding to LEV 0.31 mg (62.9%) than to RAC 1.25 mg (41.8%, $P = .012$) immediately after nebulization.

No significant differences were seen among the treatment groups for the variables overall asthma symptom assessment score, symptom-free days, and Quality of Life score (data not shown). Similarly, rescue medication use was comparable in all treatment groups over the course of the study (approximately 0.5 puffs per day for 1-2 days per week, on average). No differences among active treatments were detected in asthma control days during the first 14 days of double-blinded therapy. However, in the last 7 days (days 14-21), LEV 0.31 mg achieved a significantly greater change in asthma control days than LEV 0.63 mg and RAC 1.25 mg (median improvement, 1.6, 0.25, and 0 days for LEV 0.31 mg, LEV 0.63 mg, and RAC 1.25 mg, respectively; $P < .04$ for each comparison).

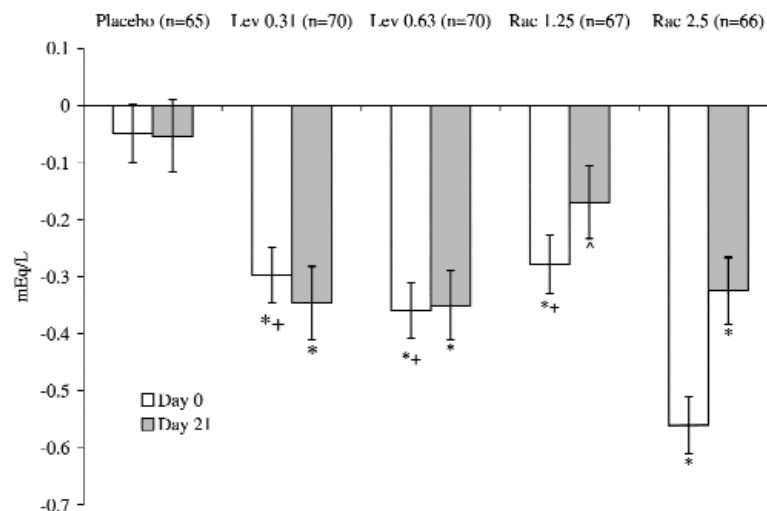
Safety results

There were no deaths or treatment-related serious AEs. One hundred forty-six of the 338 patients (43.2%) experienced a total of 299 AEs during the double-blinded period. In all, AEs were reported by more patients on the active

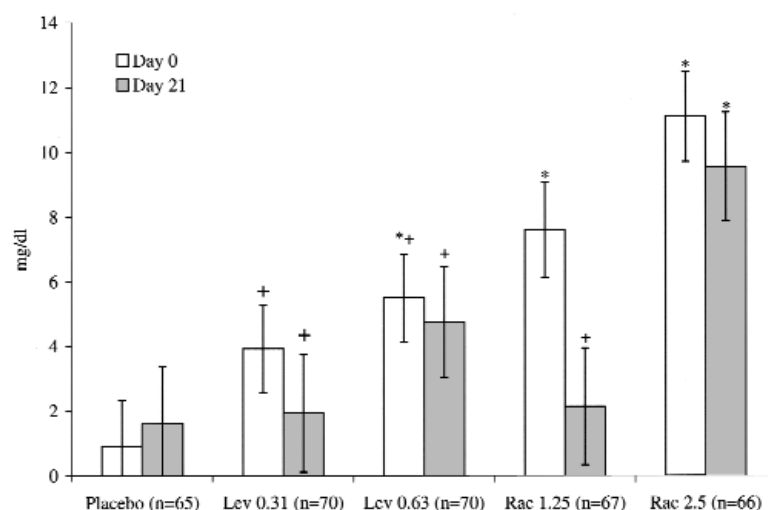
drug than on placebo (LEV 0.31 mg [42.9%], LEV 0.63 mg [52.9%], RAC 1.25 mg [34.3%], RAC 2.5 mg [51.5%], placebo [33.8%]). The most common AEs included fever, headache, asthma, pharyngitis, and rhinitis.

Changes in ventricular HR with LEV 0.31 mg were not different from those associated with placebo at any point during double-blinded treatment, whereas LEV 0.63 mg and the 2 RAC doses increased HR significantly (Fig 1, A). Thirty minutes after the first dose on day 0, LEV 0.31 mg induced a mean change in HR of 0.7 ± 8.2 beats per minute (bpm; $P = .12$ vs placebo); this compared with an increase of 11.3 ± 10.3 bpm by RAC 2.5 mg ($P < .001$ vs placebo; $P < .001$ vs LEV 0.31 mg). At day 21, the corresponding mean changes in HR were 0.2 ± 8.4 bpm with LEV 0.31 mg ($P = .331$ vs placebo) and 6.0 ± 9.4 bpm for RAC 2.5 mg ($P < .001$ vs placebo; $P < .001$ vs LEV 0.31 mg; Fig 1, A). RAC 2.5 mg consistently caused greater increases in HR than did either of the LEV doses, and post hoc analyses indicated that LEV 0.31 mg produced significantly smaller changes than all other active treatments ($P < .02$ for LEV 0.31 mg vs other active groups). In addition, 35% of subjects on RAC 2.5 mg had clinically significant tachycardia (defined as a ≥ 15 bpm increase in HR; Fig 2), and 35% had an HR ≥ 100 bpm at least once after RAC 2.5 mg; this compared with approximately 20% for all other active treatments and 6% for those receiving placebo (data not shown).

There were no changes attributable to LEV 0.31 mg in comparison with placebo on day 0 in the QT_c interval ($P = .474$ vs placebo; $P < .001$ for placebo vs other active treatment groups). In comparison with LEV 0.31 mg, RAC 2.5 mg caused a significantly greater prolongation of the QT_c on day 0 ($P < .001$), and this was nearly significant at day 21 ($P = .054$; data not shown).



B * $p < 0.002$ vs placebo; + $p < 0.005$ vs RAC 2.5mg; ^ $p < 0.04$ vs Lev 0.63mg



C * $p < 0.02$ vs placebo; + $p < 0.05$ vs RAC 2.5mg

FIG 1. B. Mean change in potassium 60 minutes after dose (LS mean $\pm$ SEM). **C.** Mean change in glucose 60 minutes after dose (LS mean $\pm$ SEM).

All active treatment groups showed a significant decrease in potassium levels in comparison with placebo at day 0 ($P < .002$; Fig 1, B), and more patients experienced a decrease of ≥ 0.8 mEq/mL after RAC 2.5 mg (25% vs 7%, 6%, and 5% after RAC 1.25, LEV 0.63, and LEV 0.31 mg, respectively). By day 21, all active treatments except RAC 1.25 mg were significantly different from placebo.

LEV 0.31 mg did not cause a significant change in serum glucose levels in comparison with placebo at the beginning or end of the active-treatment period ($P > .127$; Fig 1, C). RAC 2.5 mg caused significantly larger increases in serum glucose than LEV 0.31 mg and LEV 0.63 mg on both day 0 and day 21 ($P \leq .043$) and significantly greater increases than RAC 1.25 mg on day 21 ($P = .003$; Fig 1, C).

Pharmacokinetic results

A good fit between predicted and observed plasma concentrations was seen. The model predicted that exposure to (S)-albuterol was approximately 4-fold greater than exposure to (R)-albuterol at equivalent doses, which was also reflected in the apparent clearance of both enantiomers (ie, 0.63 mg of (R)-albuterol vs 1.25 mg of RAC). The model also indicated that no obvious effect of (S)-albuterol was observed on the clearance of (R)-albuterol (Table III).

DISCUSSION

RAC is a 50:50 mixture of 2 isomers, (R)-albuterol

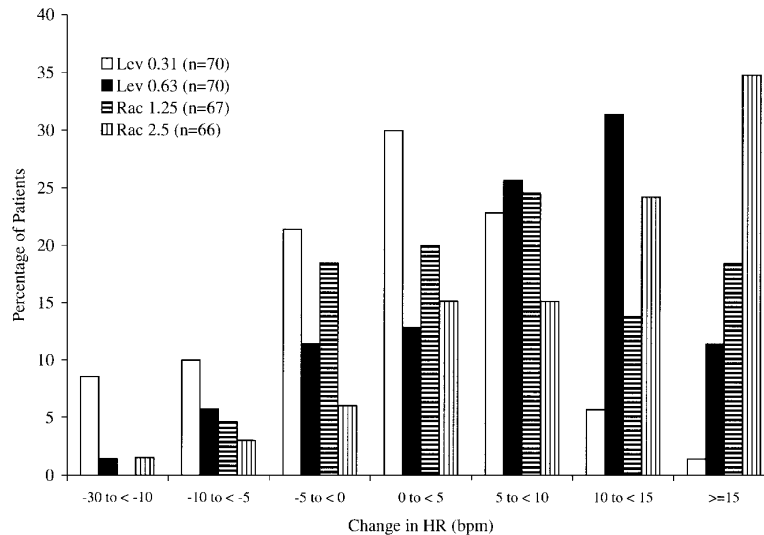


FIG 2. Distribution of patient response (mean change in ventricular HR 30 minutes after dose).

TABLE III. Model derived population pharmacokinetic parameters of (R)-albuterol and (S)-albuterol in pediatric subjects

	LEV 0.31 (n = 67)	LEV 0.63 (n = 67)	RAC 1.25 (n = 65)		RAC 2.5 (n = 63)	
	(R)-albuterol	(R)-albuterol	(R)-albuterol	(S)-albuterol	(R)-albuterol	(S)-albuterol
CL/F (L/hr)	240 (53.6)	262 (56.7)	263 (58.7)	67.4 (22.0)	259 (48.8)	62.3 (19.7)
T _{1/2} (hr)	6.45 (1.46)	6.40 (1.18)	6.87 (4.53)	6.83 (3.80)	6.33 (0.866)	7.90 (4.59)
AUC (ng*hr/mL)	1.36 (0.352)	2.55 (0.734)	2.65 (1.53)	10.5 (3.96)	5.02 (1.19)	23.0 (11.2)
C _{max} (ng/mL)	0.303 (0.108)	0.521 (0.191)	0.553 (0.295)	1.26 (0.734)	1.08 (0.471)	2.30 (1.12)

Data presented are means (SDs).

CL, Apparent clearance; F, apparent bioavailability; T_{1/2}, apparent terminal-phase half-life; AUC, area under the curve; C_{max}, maximum plasma concentration.

(LEV) and (S)-albuterol. Importantly, only LEV confers the bronchodilatory effects of RAC,²¹ whereas the pharmacologic properties of the distomer, (S)-albuterol, cause the destabilization of the airways in asthma.⁸⁻¹⁴ The availability of the single isomer has provided a means by which to examine the hypothesis that administration of LEV, or (R)-albuterol, in the absence of (S)-albuterol results in increased efficacy and greater safety. Indeed, clinical trials in adults and in children more than 12 years of age have demonstrated that LEV produces bronchodilation comparable to that associated with much higher doses of RAC.¹⁸ These findings were corroborated in children aged 3 to 11 years in whom single doses of LEV 0.31 mg and 0.63 mg produced FEV₁ improvements comparable to those associated with RAC 2.5 mg and better than those associated with RAC 1.25 mg, with smaller changes in HR, glucose, and potassium levels.¹⁹

This article describes findings after regular, chronic treatment with nebulized β -agonists over a 21-day period. This clinical model was chosen to determine the safety and efficacy of 2 doses of levalbuterol, and it was intended to mimic actual patient use. Although the Expert Guidelines recommend that β -agonists be used as needed, chronic use is still common. Twenty-five percent to 33% of patients with mild asthma, 53% of patients

with moderate persistent asthma, and 73% of patients with severe persistent asthma report chronic use of β -agonists.²² The majority of asthma medications prescribed by pediatricians and primary care physicians are β -agonists, with short-acting bronchodilators accounting for 39% and 58% of asthma medications prescribed by primary care physicians and pediatricians, respectively.²³

In the present study, lower doses of LEV were highly effective over 3 weeks of regular use with little effect on HR in comparison with RAC. All active treatment groups showed efficacy when compared with placebo. RAC had dose-dependent effects on spirometry and symptom endpoints that were accompanied by the expected dose-dependent β_2 -mediated side effects, including tachycardia, QT_c prolongation, decreased serum potassium, and increased serum glucose. In contrast, the 2 LEV groups showed no significant differences between the doses studied with regard to spirometry endpoints, and the lower LEV dose was as efficacious as an 8-fold higher RAC dose. Reversibility was rapid and sustained and not significantly different from that for RAC doses that contained 2- and 4-fold more (R)-albuterol. These data suggest that LEV might represent a more effective β_2 -agonist rescue treatment than RAC for an acute asthma attack. These observations are also in agreement with

previous studies which indicate that administration of lower doses of the pure (R)-isomer, in the absence of (S)-albuterol, results in efficacy that is clinically comparable to that of higher doses of the racemate.

Although the study was not designed to assess the dose-response relationship or relative potency of LEV in comparison with RAC, a previous study of LEV demonstrated a dose-dependent response in patients with more severe disease.¹⁸ The current study included patients with FEV₁ values of 40% to 85% of predicted, but a majority of patients enrolled had mild asthma, making differentiation between the levalbuterol doses more difficult. When patients with FEV₁ ≤60% predicted at baseline (n = 30) were examined post hoc, a numeric dose response was evident (FEV₁ peak change percent predicted, 22%, 35%, 17%, and 35% for LEV 0.31, LEV 0.63, RAC 1.25, and RAC 2.5 mg, respectively).

Population pharmacokinetic (PK) analysis of subjects from this study revealed 4-fold higher (S)-albuterol levels in plasma in comparison with (R)-albuterol. In other studies, (S)-albuterol has been shown to have a longer half-life than LEV, persisting for up to 10 hours after a single dose,¹⁵ to accumulate with repeated dosing,¹⁶ and to be retained in the lungs.¹⁷ No evidence of interconversion of (R)-albuterol to (S)-albuterol was noted, and no effect of (S)-albuterol on the PK profile of (R)-albuterol was found.^{15,16} These data suggest that the adverse effects of (S)-albuterol would be most pronounced with chronic use and are likely due to intrinsic properties of the isomer itself rather than to a change in the clearance of LEV because of the presence of (S)-albuterol.

A particularly important requirement for pediatric patients is that an agent used for asthma therapy not cause untoward side effects. RAC 2.5 mg induced a median increase in HR of 12 bpm after the first dose; this compared with just 2 bpm with LEV 0.31 mg. In addition, 35% of patients experienced clinically significant tachycardia (≥15 bpm increase in ventricular HR) after RAC 2.5 mg; this compared with 3%, 1%, 11%, and 18% of patients after placebo, LEV 0.31, LEV 0.63 mg, and RAC 1.25, respectively. LEV 0.31 mg was indistinguishable from placebo with regard to change in HR, serum glucose, and QT_c interval at day 0. Furthermore, a significantly smaller effect of LEV 0.31 mg on serum potassium in comparison with RAC 2.5 mg was observed. Because β-mediated side effects are related to the amount of (R)-albuterol, these decreases were expected.

Although RAC 2.5 mg is the approved label dose²⁴ and is recommended by the NHLBI² and in AAAAI guidelines,³ we sought in this study to determine whether a smaller dose would maintain efficacy and reduce adverse effects. Reducing the RAC dose from 2.5 to 1.25 mg decreased effectiveness (Table II). This is consistent with the results of other clinical trials.^{18,19,25} Although there was an associated decrease in the β₂-mediated side effects, RAC 1.25 mg produced the lowest peak percent change in FEV₁ among the active treatments, the longest median time to peak change at day 0, and the lowest median changes and percentage of responders within 30

minutes after nebulization; in addition, it was generally less efficacious than LEV 0.31 mg. It is common for adults, children, and physicians to decrease the dose or regimen of RAC to reduce the side effects.¹ However, reducing the dose of RAC to 1.25 mg compromises efficacy and does not diminish the untoward effects of RAC to an extent equal to those of LEV 0.31 mg.

The results of the PK analysis indicated that a levalbuterol dose of 0.31 mg in children aged 4 to 11 years provided exposure parameter estimates similar to those of a dose of 0.63 mg in adults (0.63 mg is the recommended starting dose for adult patients). A levalbuterol dose of 0.63 mg in children aged 4 to 11 years provided exposure parameter estimates similar to those of a dose of 1.25 mg in adults (data not shown).

In summary, in comparison with RAC, a much smaller dose of LEV achieved bronchodilation that was comparable in magnitude. LEV 0.31 mg produced bronchodilation equivalent to that associated with RAC 2.5 mg and was indistinguishable from placebo for most β₂-adrenoceptor-mediated side effects. On the basis of these results and the PK data, it is suggested that 0.31 mg levalbuterol be used as the starting dose for children aged 4 to 11 years. Patients with more severe disease or those who do not respond optimally to the 0.31-mg dose might benefit from higher doses. LEV represents a new, safe, and effective alternative for bronchodilation in asthmatic patients aged 4 to 11 years and has a more favorable therapeutic index than the standard or reduced dose of RAC.

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