

The safety and efficacy of nebulized levalbuterol compared with racemic albuterol and placebo in the treatment of asthma in pediatric patients

Sandra M. Gawchik, DO,^a Consuelo L. Saccar, PharmD,^a Michael Noonan, MD,^b
David S. Reasner, PhD,^c and Sidney S. DeGraw, MS, MPhil^c *Chester, Pa, Portland, Ore,*
and Marlborough, Mass

Background: Limited dose-response information is available for nebulized β_2 -agonists, especially in young children.

Objective: The purpose of this study was to determine the safety and efficacy of increasing doses of nebulized levalbuterol (Xopenex; the pure R-isomer of racemic albuterol) and racemic albuterol compared with placebo in the treatment of asthma in pediatric patients.

Methods: In this randomized, double-blind, crossover study, children (aged 3 to 11 years) with asthma (resting FEV₁ 50% to 80% of predicted normal [Polgar's] values) were treated with either levalbuterol, racemic albuterol, or placebo. Eligible subjects underwent a screening visit followed by 4 treatment visits. At each treatment visit, serial pulmonary function tests were completed before and after the treatment; plasma was collected to determine enantiomer levels, and safety was evaluated.

Results: Five 3- to 5-year-old patients and twenty-eight 6- to 11-year-old patients completed the study, and a total of 87 doses of levalbuterol were administered. In the 6- to 11-year-old group, all doses of levalbuterol were significantly greater than placebo in peak change and percent peak change in FEV₁ and area under the FEV₁ versus time curve ($P < .05$). The FEV₁ values over the 8-hour study period were similar for levalbuterol 0.31 and 0.63 mg and racemic albuterol 2.5 mg and were greatest after levalbuterol 1.25 mg. Median plasma levels of R-albuterol depended on dose and were 0.4, 0.7, 1.2, and 1.0 after levalbuterol 0.31 mg, 0.63 mg, and 1.25 mg and racemic albuterol 2.5 mg, respectively. All patients in the 2.5-mg racemic albuterol arm had measurable plasma levels of S-albuterol, although S-albuterol levels were undetectable in most patients in the levalbuterol arms. In a few patients who received levalbuterol, S-albuterol levels were detected, which was likely because of the use of racemic albuterol as a concomitant medication. All active treatments were well tolerated. β -Mediated changes in heart rate, potassium, and glucose were dose dependent for all active treatment groups.

Conclusion: Levalbuterol caused a significantly greater increase in FEV₁ than placebo, and FEV₁ values were comparable with or better than those observed with racemic

albuterol. β -Mediated side effects were lower for an equipotent dose of levalbuterol when compared with racemic albuterol.

Treatment with levalbuterol resulted in plasma levels that were dose dependent and had an approximate correlation with pharmacodynamic parameters. (*J Allergy Clin Immunol* 1999;103:615-21.)

Key words: Levalbuterol, pediatric, asthma, FEV₁, racemic albuterol, bronchodilator, β_2 -agonist, inhalation solution, S-albuterol, R-albuterol

Levalbuterol is the pure R-isomer of racemic albuterol. Racemic albuterol is manufactured by a method that results in a 50:50 mixture of R-albuterol and S-albuterol (R,S-albuterol). Levalbuterol is synthesized by a manufacturing process based on resolution of R,S-benzylalbuterol to prepare an optically pure form of the stereoisomer R-albuterol.¹ Levalbuterol is known to be responsible for the bronchodilator effects of the racemate, and S-albuterol has been considered biologically inert.²

Many studies have indicated that there is a potential for deleterious effects of S-albuterol, however. Results from an in vitro study of cyclic adenosine monophosphate production and binding to human β -adrenergic receptors demonstrated that levalbuterol is 2-fold more potent than racemic albuterol and 90- to 100-fold more potent than S-albuterol.³ In airway smooth muscle cells, levalbuterol decreased intracellular calcium concentrations, although S-albuterol and racemic albuterol increased intracellular calcium and induced cell shortening.^{4,5} In isolated guinea pig airways, levalbuterol and racemic albuterol were 100-fold more potent against all spasmogens. Preincubation with levalbuterol or racemic albuterol decreased carbachol-induced contractions, but S-albuterol enhanced these contractile responses.⁶ In humans, S-albuterol has been shown to increase bronchial responsiveness to methacholine 3 hours after treatment; levalbuterol decreased hyperresponsiveness, and racemic albuterol had no effect.⁷ Levalbuterol 0.63 mg has been shown to be as effective as 2.5 mg of racemic albuterol, with fewer β -mediated side effects in patients age 12 years or older with moderate-to-severe asthma.⁸ Of interest, in the latter study, after 4 weeks of therapy racemic albuterol decreased pretreatment lung function compared with both placebo and levalbuterol, suggesting a deleterious effect of the S-albuterol isomer.

From ^aAsthma and Allergy Research Associates, Chester; ^bAllergy Associates, PC, Portland; and ^cSepracor Inc, Marlborough.

Supported by Sepracor Inc.

Received for publication June 2, 1998; revised Oct 26, 1998; accepted for publication Oct 26, 1998.

Reprint requests: Sandra M. Gawchik, DO, Asthma and Allergy Research Associates, President's House, 1 Medical Center Blvd, Chester, PA 19013.

Copyright © 1999 by Mosby, Inc.

0091-6749/99 \$8.00 + 0 1/1/95463

TABLE I. Subject disposition

Disposition	ITT population (n)	Age group		
		2-5 y	6-9 y	10-11 y
Randomized (%)	43 (100)	7 (16.3)	21 (48.8)	15 (34.9)
Completed (%)	33 (76.7)	5 (11.6)	14 (32.6)	14 (32.6)
Discontinued (%)	10 (23.3)	2 (4.6)	7 (16.3)	1 (2.3)
Adverse event	5	1	4	
Protocol violation	4		3	1
Voluntary withdrawal	1	1		

ITT, Intent to treat.

Abbreviation used

AUC: Area under the curve (L • h)

This study was designed to investigate the safety and efficacy of levalbuterol and racemic albuterol in the reversal of bronchoconstriction in subjects with asthma between the ages of 2 and 11 years and to measure levalbuterol plasma levels after patients received a range of treatments.

METHODS**Participants**

The study was conducted at 2 centers between October 1996 and February 1997. Children between the ages of 2 and 11 years were eligible if they had a history of asthma for 6 months or more, a resting FEV₁ between 50% and 80% of predicted normal (Polgar's⁹) values, 3 consecutive FEV₁ values that varied by less than 10%, and reversibility of 12% or more within 30 minutes after 2.5 mg of racemic albuterol was administered through nebulization. Children were not eligible if they had an upper or lower respiratory infection within 15 days of the baseline visit; were taking theophylline, methylphenidate hydrochloride, monoamine oxidase inhibitors, or tricyclic antidepressants; received antibiotic treatment within 72 hours of the baseline visit; received treatment with an investigational drug or systemic steroid within 30 days or astemizole within 90 days of the baseline visit; or had a history of hypersensitivity or allergic reaction to racemic albuterol. Subjects were able to continue to use their routine asthma medications during the study, but specific washout periods were established before study visits. Racemic albuterol was withheld for 8 hours or more before testing on study days. This study was reviewed and approved by a qualified institutional review board, and written informed consent and patient assent were obtained before any study-specific procedures were conducted.

Design

This was a randomized, double-blind, single-dose, crossover study with a 7 × 4 balanced incomplete block design based on Patterson's squares, as presented by Jones and Kenward.¹⁰ Eligible subjects underwent a screening visit consisting of a physical examination, assessment of vital signs, a 12-lead electrocardiogram, collection of blood and urine for analysis, and baseline pulmonary function testing. Those who qualified were randomly assigned to treatment sequences and administered a single dose of the study drug at 4 treatment visits, which were scheduled 2 to 8 days apart. Before and after the administration of the study drug, vital signs were recorded; a 12-lead electrocardiogram was obtained (30 min-

TABLE II. Subject demographics

Demographics	ITT population (n = 33)	Efficacy population (n = 28)
Mean age (y)	8.3 ± 2.3	9.4 ± 1.3
Range (y)	3-11	6-11
Male (%)	22 (51.2)	14 (50)
Female (%)	21 (48.8)	14 (50)
Race		
White (%)	34 (79.1)	22 (78.6)
Black (%)	8 (18.6)	6 (21.4)
Other (%)	1 (2.3)	0
Height (cm)	134.0 ± 15.1	141.2 ± 9.1
Weight (kg)	34.8 ± 13.5	39 ± 12.4
FEV ₁ % predicted	69.5 ± 8.7	68.9 ± 9.7
Percent reversibility	30.5 ± 13.4	28.2 ± 12.6

ITT, Intent to treat.

utes after the treatment); blood was collected for analysis (15 and 60 minutes after the treatment); and serial pulmonary functions were tested (immediately after the treatment, at 15, 30, 45, 60, 90, and 120 minutes and then hourly for 6 or more hours after the treatment). Patients were seen for a final visit within 48 hours of the last treatment visit.

The study drug was provided in identical unit dose vials by Sepracor, Inc, and was administered as a single dose with a PARI LC PLUS nebulizer and a DURA-NEB 2000 Portable compressor (Pari Respiratory Equipments Inc, Richmond, Va). Levalbuterol inhalation solutions contained levalbuterol in 0.9% saline solution, without preservative, in 3 mL volumes in the doses of 0.16 mg, 0.31 mg, 0.63 mg, and 1.25 mg. Racemic albuterol contained R,S-albuterol sulfate in 0.9% saline solution, without preservative, in 3 mL volumes in the doses of 1.25 mg and 2.5 mg. The placebo solution was 0.9% saline solution in 3 mL volumes. Medication was given at the same time of day (1 hour) on each treatment visit. To maintain blinding, medication was dispensed by an individual who was not responsible for subject care or assessment.

Pulmonary function tests were performed in triplicate at each time point, and the largest FEV₁ was used.¹¹ The primary efficacy endpoint was the peak change in FEV₁ relative to the pretreatment value (peak change in FEV₁ [ΔFEV₁]). Secondary endpoints were the peak percent ΔFEV₁ relative to pretreatment and the area under the curve (L • h) (AUC).

Safety was assessed by incidence of adverse events and changes in vital signs, electrocardiogram parameters, laboratory tests, and physical examinations. Adverse events occurring between visits were assigned to the previous treatment.

Levalbuterol (R-albuterol) and S-albuterol plasma concentrations were measured 15 minutes after the drug administration. Blood samples were collected and centrifuged within 30 minutes, and then plasma was harvested, frozen at -20°C, and analyzed in a central laboratory.

Statistical analysis

The primary analysis was based on differences relative to placebo, and the study was powered to detect these differences. Treatment groups were compared with placebo for differences in peak ΔFEV₁, peak percent ΔFEV₁, and AUC based on an ANOVA model for crossover designs. If the treatment effect was significant at the .05 level, pairwise comparisons were presented along with the dose-response testing of levalbuterol and racemic albuterol. The dose-response hypothesis testing was performed with Holm's sequential-

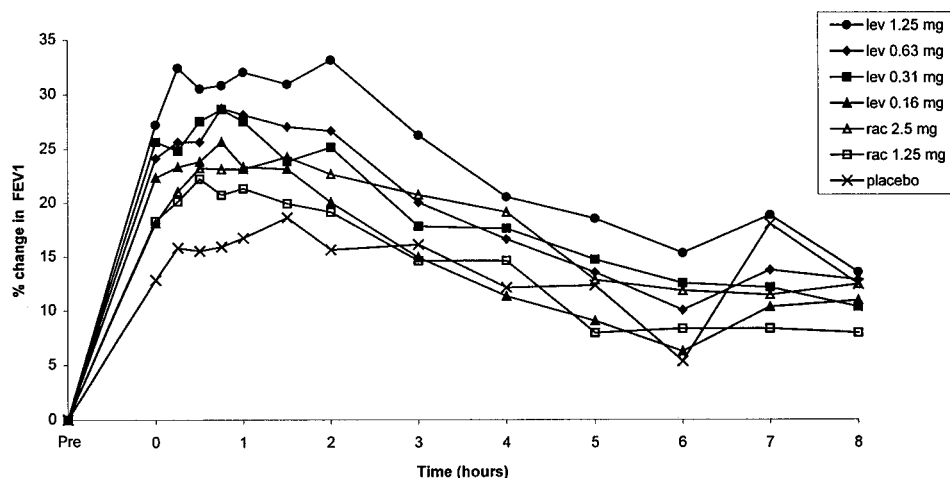


FIG 1. Mean percent change in FEV₁ over time after exposure to levalbuterol (*lev*), racemic albuterol (*rac*), or placebo in patients aged 6 to 11 years.

TABLE III. Changes in the FEV₁ by treatment for patients aged 6 to 11 years

	Levalbuterol				Racemic albuterol		Placebo (n = 16)
	0.16 mg (n = 16)	0.31 mg (n = 16)	0.63 mg (n = 16)	1.25 mg (n = 16)	1.25 mg (n = 16)	2.5 mg (n = 16)	
ΔFEV ₁ (L)							
Mean (SD)	0.39* (0.19)	0.42* (0.24)	0.41* (0.22)	0.51* (0.28)	0.35* (0.19)	0.40* (0.18)	0.37 (0.22)
LSM	0.40*	0.41*	0.41*	0.48*	0.40*	0.48*	0.28
Range	0.19-0.66	0.11-1.02	0.17-0.84	0.18-1.04	0.10-0.66	0.15-0.74	0.06-0.90
Peak % ΔFEV ₁							
Mean (SD)	28.7* (16.9)	30.6* (19.3)	31.1* (24.7)	36.8* (22.5)	24.6* (22.5)	27.9* (16.2)	26.2 (15.6)
LSM	28.4*	28.8*	30.8*	35.3*	28.8*	34.6*	19.1
Range	8.7- 51.7	6.2- 67.5	10.8- 98.7	9.0- 85.3	5.5- 78.5	8.6- 69.2	3.8- 52.6
AUC FEV ₁							
Mean (SD)	9.3* (1.2)	9.8* (1.3)	9.4* (1.9)	10.3* (1.1)	9.1 (1.4)	9.5* (1.3)	8.7 (1.7)
LSM	9.3*	9.6*	9.6*	10.1*	9.1	9.9*	8.4
Range	6.5-11.3	6.7-11.9	5.2- 12.5	8.5- 12.1	5.5- 11.5	7.3- 12.5	4.6- 10.7

LSM, Least square means.

**P* < .05 vs placebo.

ly rejective Bonferroni procedure, which adjusted the type I error for simultaneous hypotheses.

RESULTS

Forty-three subjects were enrolled: 7 subjects were aged 3 to 5 years, and 36 subjects were aged 6 to 11 years. Five subjects were discontinued because of adverse events unrelated to the study drug, 4 subjects were discontinued because of protocol violations, and 1 subject was discontinued for personal reasons (Table I). Thirty-three subjects completed the study: 5 subjects in the 2- to 5-year age group and 28 subjects in the 6- to 11-year age groups (14 subjects aged 6 to 9 years and 14 subjects aged 10 to 11 years). Patterson's squares¹⁰ require that at least 14 subjects per age group complete the study for the squares to be balanced for carry-over and for the planned analysis to be performed. Therefore data from the 6- to 11-year-old group was used in the

efficacy analyses, but the data from the 3- to 5-year-old group was excluded from the efficacy analysis because of incomplete enrollment for this age group. All patients who received at least 1 dose of study drug were included in the safety analysis.

The average age of the efficacy population was 9.4 ± 1.3 years, and one half of the study population was male. Approximately 80% were white, with an average FEV₁ approximately 70% of predicted value (Table II).

Treatment with all doses of levalbuterol and racemic albuterol 2.5 mg was significantly better than administration of placebo in mean peak ΔFEV₁, peak percent ΔFEV₁, and AUC. Racemic albuterol 1.25 mg was not significantly better than placebo in AUC but was better in peak ΔFEV₁ and peak percent ΔFEV₁ (Table III). The FEV₁ values over the 8-hour study period were similar for levalbuterol 0.31 and 0.63 mg and racemic albuterol 2.5 mg, with the largest improvements occurring at all

TABLE IV. Summary of R-albuterol and S-albuterol plasma levels for all patients

	Levalbuterol				Racemic albuterol		
	0.16 mg (n = 23)	0.31 mg (n = 20)	0.63 mg (n = 22)	1.25 mg (n = 22)	1.25 mg (n = 20)	2.5 mg (n = 20)	Placebo (n = 23)
R-albuterol level (ng/mL)							
Mean (SD)	0.4 (0.15)	0.5 (0.24)	0.8 (0.41)	1.4 (0.73)†	0.6 (0.21)	1.1 (0.39)	0.3
Median	0.3	0.4	0.7	1.2	0.6	1.0	N/A
Min, max	0.3, 0.6	0.3, 0.9	0.3, 1.9	0.5, 3.1	0.3, 1.0	0.4, 1.7	N/A
n* (%)	7 (35)	12 (71)	21 (100)	18 (95)	15 (88)	19 (100)	1 (5)
BQL*	13	5	0	1	2	0	19
S-albuterol level (ng/mL)							
Mean (SD)	0.8 (0.37)	1.4 (1.05)	1.0 (1.44)	1.9 (1.62)	1.3 (0.61)	2.7 (1.11)	0.7
Median	0.7	1.7	0.5	1.6	1.4	2.3	0.5
Min, max	0.6, 1.4	0.4, 2.8	0.3, 4.8	0.4, 4.4	0.3, 2.3	0.8, 5.0	0.3, 1.1
n* (%)	4 (20)	5 (29)	9 (43)	5 (25)	14 (82)	19 (100)	3 (14)
BQL*	16	12	12	15	3	0	18

*The overall potential sample size is given in the column header; the number of quantifiable values is given as *n*; the number of subjects with values below the quantifiable limit (BQL; <0.25 ng/mL) is indicated. It was not possible to test some samples because of insufficient sample volume for retesting.

†Mean excludes 1 outlier (patient with plasma level of 14.3 ng/mL of R-albuterol).

time points after the administration of levalbuterol 1.25 mg (Fig 1).

There were no significant differences between treatment groups, but trends were noted in the comparison of peak ΔFEV_1 between levalbuterol 1.25 mg and levalbuterol 0.16 mg and between levalbuterol 1.25 mg and racemic albuterol 1.25 mg ($P < .055$). The mean peak percent ΔFEV_1 after active treatment ranged from 26.2% in the placebo group to 36.8% in the levalbuterol 1.25 mg group. In the analysis of AUC, all active treatments except racemic albuterol 1.25 mg were significantly better than placebo. Treatment with levalbuterol 0.31 and 0.63 mg resulted in AUCs greater than or comparable with racemic albuterol, and the greatest AUC occurred after treatment with levalbuterol 1.25 mg (Table III). Treatment with 0.31 mg, 0.63 mg, and 1.25 mg levalbuterol doses produced greater or equivalent improvements in mean percent ΔFEV_1 than both doses of racemic albuterol over the 8-hour study period (Fig 1).

Plasma levels of levalbuterol (R-albuterol) were detectable in most patients after administration of levalbuterol 0.31 mg, 0.63 mg, and 1.25 mg and both doses of racemic albuterol (Table IV). Plasma levels of individual enantiomers increased with increasing dose, and R-albuterol levels were similar for levalbuterol 1.25 mg and racemic albuterol 2.5 mg (median, 1.2 ng/mL and 1.0 ng/mL, respectively) and levalbuterol 0.63 mg and racemic albuterol 1.25 mg (median, 0.7 ng/mL and 0.6 ng/mL, respectively). S-albuterol was quantifiable in 82% and 100% of the patients who received treatment with racemic albuterol 1.25 mg and 2.5 mg, respectively. S-albuterol was also detectable in 20% to 43% of the patients who received levalbuterol and 14% of the patients who received placebo. All of the patients who received levalbuterol and placebo in whom S-albuterol levels were detected used concomitant racemic albuterol during the study.

Safety

Therapy was well tolerated, and all adverse events reported were mild or moderate in severity. A total of 49 adverse events were reported in 22 subjects (51.2%). No significant differences across treatment groups were seen in the incidence of total adverse events, and the most common events were a worsening of asthma (19 events reported by 11 patients), asthma increase (5 events reported by 5 patients), and headache (5 events reported by 5 patients). The most frequent potentially related adverse event (either a definite, probable, possible, or unknown relationship to treatment) was worsening of asthma symptoms (17 events reported by 10 patients). There was no relationship between dose level and the number of potentially related adverse events within the levalbuterol treatment group (5, 1, 5, and 2 events for 0.16 mg, 0.31 mg, 0.63 mg, and 1.25 mg levalbuterol, respectively, compared with 12 events for placebo).

Five subjects were discontinued because of adverse events of asthma exacerbations; 4 of these events were associated with upper respiratory infections. One event each of asthma exacerbation occurred after treatment with levalbuterol 0.16 mg, levalbuterol 0.63 mg, racemic albuterol 1.25 mg, racemic albuterol 2.5 mg, and placebo. No serious adverse events were reported.

No significant changes in vital signs were detected in blood pressure, respiratory rate, or body temperature. β -Mediated side effects were dependent on the levalbuterol dose, whether administered as the single enantiomer or as racemic albuterol. Ventricular heart rate was elevated 30 minutes after treatment with all active drugs (Table V). Levalbuterol 0.63 mg resulted in changes similar to those seen in both racemic albuterol groups. Changes in the corrected Q-T interval were 3.3 ms, 4.3 ms, 6.6 ms, and 11.4 ms after 0.16 mg, 0.31 mg, 0.63 mg, and 1.25 mg levalbuterol, respectively, compared with 4.2 ms, 7.6

TABLE V. Mean change in β -mediated events relative to before treatment for all patients

	Levalbuterol				Racemic albuterol		Placebo (n = 23)
	0.16 mg (n = 23)	0.31 mg (n = 20)	0.63 mg (n = 22)	1.25 mg (n = 22)	1.25 mg (n = 20)	2.5 mg (n = 20)	
Glucose (mg/dL)	14.8	-0.5	21.2	30.5	16.2	19.6	5.9
Change (%)	18	-0.53	24.6	35.6	18.8	23.6	6.6
Potassium (mEq/L)	-0.2	-0.2	-0.5	-0.5	-0.4	-0.6	-0.1
Change (%)	-4.7	-4.8	-11.9	-12.2	-9.5	-13.95	-2.3
Ventricular heart rate (bpm)	0.4	6.0	10.8	15.9	10.6	10.2	-0.1
Change (%)	0.46	7.3	13.2	19.2	13.2	12.1	0.12

ms, and 1.3 ms after 1.25 mg and 2.5 mg racemic albuterol and placebo, respectively. Small increases in the corrected Q-T interval are expected with β -agonists, and the magnitude of the changes found in this study were not clinically significant.

Potassium levels showed a slight decrease 60 minutes after the treatment, with a mean change of -0.6 mEq/L with racemic albuterol 2.5 mg and -0.5 mEq/L with levalbuterol 1.25 mg and 0.63 mg groups (Table V). The smallest decreases were seen with levalbuterol 0.16 mg and 0.31 mg and placebo. Glucose levels were increased 60 minutes after the administration of all active treatments, with the exception of levalbuterol 0.31 mg (Table V). Racemic albuterol 2.5 mg and levalbuterol 0.63 mg resulted in comparable increases in glucose (19.6 mg/dL and 21.2 mg/dL, respectively), and the largest increase was seen in the levalbuterol 1.25 mg group.

DISCUSSION

In this study the efficacy of levalbuterol and racemic albuterol were compared with that of placebo in pediatric patients aged 6 to 11 years who had asthma. These results demonstrated that levalbuterol was better than or comparable to racemic albuterol at improving pulmonary function at dosages lower than racemic albuterol. Levalbuterol 0.31 mg and 0.63 mg, 12% and 25% of the racemic albuterol dose, produced efficacy comparable to racemic albuterol 2.5 mg and better than racemic albuterol 1.25 mg over an 8-hour period. The rank order of efficacy over the study period was levalbuterol 1.25 mg greater than levalbuterol 0.63 mg equaled levalbuterol 0.31 mg equaled racemic albuterol 2.5 mg greater than levalbuterol 0.16 mg greater than racemic albuterol 1.25 mg greater than placebo. The onset of action was evident immediately after nebulization, and all levalbuterol treatments resulted in mean improvements in FEV₁ that were greater than both doses of racemic albuterol at this time. Clinically significant improvements (defined as an increase in FEV₁ of 15% or more above baseline) were maintained for 3 hours after the administration of racemic albuterol 1.25 mg, for 4 hours after the administration of levalbuterol 0.31 mg and 0.63 mg and racemic albuterol 2.5 mg, and for at least 6 hours after the administration of levalbuterol 1.25 mg (Fig 1). These results are similar to those obtained in a large (n =

362) 4-week study in adolescents and adults with asthma after the use of levalbuterol 0.63 mg and 1.25 mg and racemic albuterol 1.25 mg and 2.5 mg. This study demonstrated that levalbuterol 0.63 mg and racemic albuterol 2.5 mg were equipotent, with a rank order of levalbuterol 1.25 mg > levalbuterol 0.63 mg = racemic albuterol 2.5 mg > racemic albuterol 1.25 mg.⁸

The incidence of β -mediated side effects was related to the levalbuterol dose and was lowest in the levalbuterol 0.16 mg and 0.31 mg groups. Increases in heart rate occurred in the first 30 minutes and thereafter stabilized or declined. This response is similar to those responses reported in 4- to 12-year-old subjects after treatment of acute asthma with 2.5 mg of nebulized albuterol (Ventolin).¹² In that study tremor was reported by 57% of the subjects; in contrast, tremor was not reported by any subject in this study. Decreases in serum potassium were seen 60 minutes after dosing with levalbuterol and racemic albuterol, with the largest changes after racemic albuterol 2.5 mg and the 2 highest levalbuterol groups (0.63 mg and 1.25 mg). Plasma glucose levels were increased 60 minutes after treatment for all treatment groups except levalbuterol 0.31 mg. Reducing the amount of β -agonist administered by reducing the amount of levalbuterol per treatment appears to have a beneficial effect in β -mediated side effects.

R-albuterol plasma levels were dependent on the dose of levalbuterol administered, and these levels were comparable for the single enantiomer levalbuterol or racemic albuterol groups. Although no formal statistical analyses were completed, there appeared to be a correlation between levalbuterol plasma levels and both FEV₁ and β -mediated side effects. If these results are confirmed, this would be the first time that levalbuterol plasma levels had a correlation with pharmacodynamic parameters. In previous reports of nebulized racemic albuterol in children, pharmacokinetic data is minimal, and studies were not well controlled.^{13,14} In 1 report that included 33 children up to the age of 17 years, there was no correlation between albuterol levels and pharmacodynamic parameters, possibly because R-albuterol and S-albuterol could not be distinguished in the plasma assay and only the R-albuterol molecule had therapeutic activity.¹⁴

Plasma levels of S-albuterol were detectable in almost all subjects in the racemic albuterol group (82% to 100% for low- and high-dose racemic albuterol, respectively).

Not unexpectedly, S-albuterol was detected in 20% to 43% of subjects in the placebo and levalbuterol groups. This was due to the concomitant use of racemic albuterol between visits that was allowed per protocol. There are 2 main reasons to support this. First, patients were instructed not to take racemic albuterol for at least 8 hours before a visit, and although this was adequate for washout of R-albuterol, it was not adequate for S-albuterol because of its long half-life.¹⁵⁻¹⁷ Because of its slow metabolism, S-albuterol is detectable for up to 12 hours after the administration of single doses and up to 24 hours after the administration of multiple doses of racemic albuterol.¹⁷ Second, preclinical and clinical studies have shown that interconversion of R-albuterol to S-albuterol, and vice versa, does not occur in vivo.^{15,17-20}

This study compares favorably with other well-controlled studies examining the effects of nebulized short-acting β_2 -agonists in children with asthma who are less than 12 years of age because it adds important new information. In addition to the measurement of plasma levels of levalbuterol, other useful information was obtained. For example, other studies examined children who had acute attacks of asthma^{12,14,21}; this study was conducted in patients with chronic, stable asthma. FEV₁ was used as the outcome as opposed to peak expiratory flow or other nonstandard or more subjective measures.^{12,22,23} FEV₁ assessments were made over a period of 8 hours so that the duration of drug effect could be measured compared with other studies in which pulmonary function was measured for only 1 hour or less^{12,22-25} or for 3 hours.^{14,21}

This study evaluated 4 doses of levalbuterol and 2 doses of racemic albuterol in 43 children with chronic stable asthma in a randomized, double-blind, placebo-controlled crossover manner. The children received a total of 87 doses of levalbuterol and 40 doses of racemic albuterol. Other studies were not blinded to treatment,¹² had only single blinding or blinding status was unknown,^{24,25} included only 1 dose of racemic albuterol,^{22,23,25} or studied small numbers of subjects (10 patients,^{24,25} 14 patients,²³ and 19 patients²²).

The study reported here administered single doses of levalbuterol to children on separate days, but should be predictive of their response with multiple doses administered chronically. This statement is supported by the results obtained from children aged 12 to 17 years and adults aged 18 years and above in the study by Nelson et al.⁸ In this study the efficacy and safety of nebulized levalbuterol given 3 times per day for 28 days in 362 subjects was shown to be as good or better than results obtained with racemic albuterol. In addition, other studies have demonstrated that results obtained with single doses of bronchodilators are accurate predictors of efficacy and safety when long-term use in children is evaluated. In a study in 65 children aged 6 to 9 years with asthma, efficacy, as measured by a 20% increase in FEV₁ after a single dose of racemic albuterol syrup, was comparable to the efficacy seen after 4 weeks of daily treatment.²⁶ Another dose-ranging study in 204 children with asthma compared the efficacy of racemic albuterol as an

aerosol by metered-dose inhaler or as a dry powder with a 12-week 4 times daily regimen. The results of pulmonary function testing performed on the first day of treatment and after 12 weeks of treatment were consistent and duplicated those of a 25-patient, single-dose study reported in the same article.²⁷

In summary, levalbuterol 0.16 mg, 0.31 mg, 0.63 mg, and 1.25 mg and racemic albuterol 1.25 mg and 2.5 mg produce significantly greater improvements in FEV₁ than placebo. Patients treated with levalbuterol 0.31 mg and 0.63 mg and racemic albuterol 2.5 mg maintained clinically significant improvements for 4 hours, although the effect of levalbuterol 1.25 mg was apparent for at least 6 hours. Administration of lower doses of levalbuterol, the active isomer of racemic albuterol, was as effective as the currently recommended dose of racemic albuterol in improving FEV₁ in pediatric patients with asthma.

We thank the parents of the enrolled children; the study coordinators; PPD Pharmaco, Inc, for the conduct of the study, management and analysis of the data, and the preparation of the study report; and Lynn Traxler for her contribution to the study design, analysis, and reporting.

REFERENCES

1. Bakale RP, Wald SA, Butler HT, et al. Albuterol. *Clin Rev Allergy Immunol* 1996;14:7-36.
2. Hartley D, Middlemiss D. Absolute configuration of the optical isomers of salbutamol. *J Med Chem* 1971;14:895-9.
3. Penn RB, Frielle T, McCullough JR, Aberg G, Benovic J. Comparison of R-, S-, and RS-albuterol interaction with human β_1 - and β_2 -adrenergic receptors. *Clin Rev Allergy Immunol* 1996;14:37-45.
4. Yamaguchi H, McCullough J. S-Albuterol exacerbates calcium responses to carbachol in airway smooth muscle cells. *Clin Rev Allergy Immunol* 1996;14:47-55.
5. Mitra S, Ugur M, Ugur O, Goodman HM, McCullough JR, Yamaguchi H. S-albuterol increases intracellular free calcium by muscarinic receptor activation and a phospholipase C-dependent mechanism in airway smooth muscle. *Mol Pharmacol* 1998;53:347-54.
6. Johansson F, Rydberg I, Aberg G, Andersson RGG. Effects of albuterol enantiomers on in vitro bronchial reactivity. *Clin Rev Allergy Immunol* 1996;14:57-64.
7. Perrin-Fayolle M, Blum P, Morley J, Grosclaude M, Chambe M. Differential responses of asthmatic airways to enantiomers of albuterol. *Clin Rev Allergy Immunol* 1996;14:139-47.
8. Nelson H, Bensch G, Pleskow W, et al. Improved bronchodilation with levalbuterol compared to racemic albuterol in patients with asthma. *J Allergy Clin Immunol* 1998;102:943-52.
9. Polgar G, Promodhat V. Pulmonary function testing in children: techniques and standards. Philadelphia: WB Saunders; 1971. p. 272.
10. Jones B, Kenward M. Design and analyses and for three or more treatments: design and analysis of cross-over trials. New York: Chapman & Hall; 1990. p. 189-241.
11. Crapo R, Hankinson J, Irvin C. Standardization of spirometry. *Am J Respir Crit Care Med* 1995;152:1107-36.
12. Oberklaid F, Mellis C, Le Souef P, Geelhoed G, Maccarrone A. A comparison of a bodyweight dose versus a fixed dose of nebulised salbutamol in acute asthma in children. *Med J Aust* 1993;158:751-3.
13. Penna AC, Dawson KP. Nebulized salbutamol (albuterol): systemic absorption could be important in achieving bronchodilatation. *J Asthma* 1993;30:105-7.
14. Schuh S, Reider M, Canny G, et al. Nebulized albuterol in acute childhood asthma: comparison of two doses. *Pediatrics* 1990;86:509-13.
15. Walle T, Eaton EA, Walle UK, Pesola G. Stereoselective metabolism of RS-albuterol in humans. *Clin Rev Allergy Immunol* 1996;14:101-13.
16. Tan YK, Soldin SJ. Analysis of S-albutamol enantiomers in human urine

- by chiral high-performance chromatography and preliminary studies related to the stereoselective disposition kinetics in man. *J Chromatogr* 1987;422:187-95.
17. Gumbhir-Shah K, Kellerman D, DeGraw S, Koch P, Jusko W. Pharmacokinetic-pharmacodynamic characteristics and safety of inhaled albuterol enantiomers in healthy volunteers. *J Clin Pharmacol* 1998 (in press).
 18. Boulton D, Fawcett JP. Enantioselective disposition of salbutamol in man following oral and intravenous administration. *Br J Clin Pharmacol* 1996;41:35-40.
 19. Auclair B, Fried K, Wainer I, Jerussi T, Koch P, Ducharme M. A population analysis of nebulized R-albuterol in dogs using a novel mixed gut-lung absorption PK-PD model [abstract]. *FASEB J* 1998;12:A142.
 20. Fried K, Koch P, Wainer I. Determination of the enantiomers of albuterol in human and canine plasma by enantioselective high-performance liquid chromatography on a teicoplanin-based chiral stationary phase. *Chirality* 1998;10:484-91.
 21. Schuh S, Parkin P, Rajan A, et al. High- versus low-dose, frequently administered, nebulized albuterol in children with severe, acute asthma. *Pediatrics* 1989;83:513-8.
 22. Bannister O. The effectiveness of nebulized salbutamol in the management of acute asthma in children. *Physiotherapy* 1980;66:144-6.
 23. Groggins R, Milner A, Stokes G. Bronchodilator effects of clemastine, ipratropium bromide, and salbutamol in preschool children with asthma. *Arch Dis Child* 1981;56:342-4.
 24. Blackhall M, Dauth M, Mahoney M, O'Donnell S. Inhalation of fenoterol (berotec) by asthmatic children: a clinical comparison with salbutamol, orciprenaline and isoprenaline. *Med J Aust* 1976;2:439-44.
 25. Hughes D, Mindorff C, Levison H. The immediate effect of sodium cromoglycate on the airway. *Ann Allergy* 1982;48:6-8.
 26. Wolfe J, Shapiro G, Ratner P, et al. Comparison of albuterol and metaproterenol syrup in the treatment of childhood asthma. *Pediatrics* 1991;88:312-9.
 27. Kemp J, Furukawa C, Bronsky E, et al. Albuterol treatment for children with asthma: a comparison of inhaled powder and aerosol. *J Allergy Clin Immunol* 1989;83:697-702.

Correction

The following correction applies to an abstract that appeared in volume 103, number 1, part 2, p. S60, 1999, of The Journal.

231 Effect of Immunotherapy (IT) on Allergen-Induced Late Phase Skin Responses (LPR) and Associated Cell Infiltration Three Years after Withdrawal of Treatment. *EM Varga, K Nouri-Aria, F O'Brien, SM Walker, MR Jacobson, SR Durham*, National Heart and Lung Institute, London, UK.

In 40 patients with summer hayfever grass pollen IT was effective and inhibited late cutaneous responses and associated T cell infiltration (Varney et al. *J Clin Invest* 1993;92:644-651). In order to evaluate the effect of IT withdrawal on these parameters following 4 years treatment, the remaining 32 patients received double-blind either continued IT (IT-a) or placebo (IT-p) monthly injections for a further 3 years. Matched IT-naïve patients were studied in parallel. Subjects received intradermal allergen (*Phleum pratense* 3BU) and a control challenge with diluent followed by trephine biopsies (3mm) at 24hr. Immunohistology of 6µm sections from 4% paraformaldehyde fixed biopsies (APAAP technique) was used to assess cell phenotype and activation markers for CD3+T-cells CD25+ activated cells, CD68+ macrophages, EG2+ eosinophils and tryptase+ mast cells. Median values were as follows:

Cells/mm ²	IT-a (n = 12)		IT-p (n = 13)		IT-naïve (n = 11)	
	C	Ag	C	Ag	C	Ag
CD3	20	39	22	40*	20	139**
CD25	6	6	4	11	3	36**
CD68	6	16**	3	40**	22	74*
EG2	0	21**	0	110**	0	64**
Tryptase	73	51	83	64*	56	3

P values refer to Allergen (Ag) vs Diluent (C) sites (Wilcoxon matched pairs test). * p<0.05 ** p<0.01. LPR sizes were not different (p=0.19) between IT-a and IT-p whereas both were lower (p=0.0001; p=0.0002) than the IT-naïve group. In patients with summer hayfever grass pollen IT resulted in a prolonged reduction in the late skin response and associated dermal infiltration of CD3+ T-lymphocytes and CD25+ cells which persisted for three years following withdrawal of treatment.