

Clinical experience with levalbuterol

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Although racemic albuterol is an effective bronchodilator, regular use has been associated with some loss of bronchodilator potency, decreased protection against bronchoprovocation, increased sensitivity to allergen challenge, and increased sensitivity to some bronchoconstrictor stimuli. In experimental animals racemic albuterol has produced bronchial hyperresponsiveness, which could also be induced by administration of (S)-albuterol. These findings suggest that the pure or homochiral formulation of (R)-albuterol (levalbuterol) might be more effective as a bronchodilator than the racemic form. Single doses of levalbuterol provided more prolonged protection against methacholine challenge than the racemate, whereas (S)-albuterol significantly increased sensitivity to methacholine. In a 4-week study in adults, equivalent amounts of pure levalbuterol provided greater bronchodilation than did similar amounts of levalbuterol given as racemic mixtures. Furthermore, after 4 weeks, the baseline morning FEV₁ was lower in those receiving the racemate than in those receiving placebo or levalbuterol. In a single-dose study in children, the same conclusion regarding greater bronchodilation with pure levalbuterol compared with the same amount of levalbuterol in a racemic mixture was confirmed. These studies appear to confirm the greater efficacy of pure levalbuterol over a similar amount in a racemic mixture. This implies a deleterious effect of (S)-albuterol on both the acute bronchodilator response and baseline airway caliber, the exact mechanism of which will require further investigation. (*J Allergy Clin Immunol* 1999;104:S77-84.)

Key words: Racemic albuterol, levalbuterol, isomers, bronchodilation, nebulization, asthma, pediatric asthma

Racemic albuterol is a highly effective bronchodilator agent. Whether delivered from a nebulizer or from a metered dose inhaler (MDI), racemic albuterol rapidly induces maximal or near maximal bronchodilation in the airways of patients with asthma.^{1,2} In asthmatic airways, resolution of airway obstruction by racemic albuterol is determined predominantly by relaxation of airway smooth muscle.

Reduction of bronchodilator efficacy, termed subsensitivity or tolerance, has been reported during regular use of racemic albuterol^{3,4} and a similar effect was observed after regular use of racemic terbutaline by asthma patients.⁵ Subsensitivity is particularly evident when there has been a preceding avoidance of β -agonist use (washout) and is more apparent by reduction of the duration than the peak of the bronchodilator response.

Abbreviations used

max:	Time to maximum concentration
AUC:	Area under the curve
MDI:	Metered dose inhaler
EPO:	Eosinophil peroxidase

Although reduced bronchodilator efficacy has not been detected in all studies,^{6,7} loss of bronchoprotection has been detected with regularity.⁷ Loss of bronchoprotection against both allergen and methacholine challenges becomes apparent during regular use of racemic albuterol.⁸ However, even when this tolerance develops there remains a considerable functional β -agonistic effect.⁹

Racemic albuterol and airway hyperresponsiveness

It has been reported that regular exposure to racemic albuterol will facilitate allergic bronchospasm in laboratory animals.¹⁰ Guinea pigs given an infusion of racemic albuterol were initially protected against allergen induced bronchospasm. However, after 48 hours of continuous infusion of albuterol, the animals collapsed and died after inhalation of the antigen.¹⁰ Because the airways of similarly treated animals have been demonstrated to be hyperresponsive to a range of bronchoconstrictor stimuli, it is reasonable to suggest that airway hyperreactivity underlay the heightened susceptibility to antigen.¹¹

It has been demonstrated that subjects who use racemic albuterol regularly have an increased airway immediate⁸ and late¹² responsiveness to allergen but not to methacholine.^{8,13} The exaggerated late response to allergen is accompanied by transiently higher eosinophil levels in the sputum¹²; there is no evidence that long-term treatment with racemic albuterol increases eosinophilic infiltrate in the airways. However, (S)-albuterol has been shown in isolated human eosinophils to augment of both superoxide (statically significant¹⁴) and EPO (dose-trend¹⁵) responses, indicating that (S)-albuterol might have a potential detrimental effect on cellular activation. Levalbuterol and racemic albuterol inhibited superoxide generation and EPO release, results consistent with other studies denoting in vitro anti-inflammatory effects of racemic β -agonists.

Isomers of albuterol and airway responsiveness

The effect of β_2 -agonist isomers on airway responsiveness first became of interest when it was recognized

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that hyperreactivity of guinea pig airways could result from acute infusion of racemic isoproterenol.¹⁶ As activation of β -adrenoceptors by (R)-isoproterenol reduces airway responsiveness, the possibility had to be considered that (S)-isoproterenol might be responsible for the anomalous reaction of airways to racemic isoproterenol. Although (S)-isoproterenol neither relaxes nor contracts airway smooth muscle, intravenous infusion nevertheless amplified bronchoconstrictor responses of intact airways to histamine.¹⁶ Subsequently, analogous findings have been reported in guinea pigs for (S)-albuterol, which closely replicates the anomalous actions of racemic albuterol by evoking a more pronounced hyperresponsiveness to bradykinin and LTC₄ than to histamine.^{10,17,18} The cellular and subcellular mechanisms, which enable β_2 -agonist distomers (less active isomers) to induce hyperreactivity of the airways have yet to be established with certainty, but, most probably, they lead to an influx of calcium ions into the cytosol, a process that will counter adenyl cyclase activation due to activation of β -adrenoceptors.^{19,20}

Clinical studies in adults

On the basis of these preclinical studies, (S)-albuterol might be expected to induce untoward effects in asthmatic airways. And, as a corollary, bronchoprotective and bronchodilator effects of homochiral (pure) levalbuterol should prove more effective than an equal dose of levalbuterol as a constituent of racemic albuterol.

This proposition has been tested in a study of asthmatic volunteers with mild airway obstruction. Sensitivity to methacholine was determined 20 minutes and 3 hours after inhalation of racemic albuterol (200 mg), levalbuterol (100 mg), (S)-albuterol (100 mg), or vehicle and compared with pretreatment levels.²¹ Increased and more protracted protection followed inhalation of levalbuterol as compared with racemic albuterol, whereas decreased protection as compared with vehicle followed inhalation of (S)-albuterol.

In light of these findings, it is important to ascertain whether levalbuterol has a corresponding advantage over racemic albuterol as a bronchodilator. Hence, bronchodilator effects have been defined for levalbuterol, racemic albuterol, or vehicle both in adults and in children with chronic moderate to severe asthma.^{23,23}

Levalbuterol in adult asthmatics

Nonsmoking male or female subjects ($n = 424$) (>12 years of age) with a history (>6 months) of chronic, stable asthma were studied.²² On withholding short-acting β -agonists (for at least 8 hours), moderate to severe airflow limitation could be demonstrated as FEV₁ between 45% and 70% of that predicted for age, sex, height, and race. All subjects experienced an improvement in FEV₁ of at least 15% after inhalation of nebulized racemic albuterol (2.50 mg). All were using regular albuterol and some additionally used other medications for control of

asthma or allergic rhinitis. Use of inhaled or intranasal glucocorticosteroids, sodium cromoglycate, or nedocromil sodium did not preclude inclusion if these medications were used regularly throughout the study. Albuterol and supplementary medications were withheld for an appropriate period before spirometric studies. Subjects needing oral steroids for exacerbation of asthma were excluded if a high dose (>60 mg/d) or prolonged use (>5 days) were used in therapy. All subjects were provided with racemic albuterol (MDI) for relief of asthma symptoms.

Subjects were randomly assigned to receive nebulized levalbuterol (0.63 mg), levalbuterol (1.25 mg), racemic albuterol (1.25 mg), racemic albuterol (2.50 mg), or vehicle 3 times daily for 4 weeks. Pulmonary function was evaluated in the clinic after the first dose (week 0) and after 2 and 4 weeks, by measurement of FEV₁ before nebulization, on completion of nebulization, after 15, 30, 60, 90, and 120 minutes, and at hourly intervals thereafter for 4 hours. Area under the curve (AUC) defined by these serial measurements and use of racemic albuterol by MDI throughout the 4 weeks of the study provided supplementary response indexes. Vital signs were recorded in parallel with pulmonary function tests, and blood samples were collected for determination of glucose and electrolyte concentrations 1 hour after termination of nebulization. One would empirically expect 0.63 and 1.25 mg levalbuterol to be equivalent to 1.25 and 2.50 mg racemic albuterol, respectively.

Of the 424 subjects enrolled, 62 were excluded before random assignment, and, of the remainder, 328 completed the study. Subjects in each treatment group had comparable pulmonary function at baseline: mean predicted FEV₁ being 60% (range 44% to 77%) and mean reversibility to nebulized racemic albuterol being 40% (range 15% to 115%). A proportion (37% to 60%) of subjects in each group used inhaled glucocorticosteroids regularly, but use of cromolyn sodium or nedocromil was infrequent. A substantial proportion (43% to 57%) of subjects in each group had severe asthma as defined by a baseline FEV₁ less than 60% of their predicted value.

Substantial bronchodilation resulted from exposure to either racemic albuterol or levalbuterol and was maintained (FEV₁ $>15\%$) for at least 5 hours, whether measured after the first dose (Figure 1) or after 4 weeks of regular treatment (Figure 2). At the initial evaluation and also at 4 weeks, mean maximal increase in FEV₁ was significantly ($P < .001$) greater for all treatment groups than for placebo vehicle (Figures 1 and 2). The largest and most protracted increase (whether maximal FEV₁ or cumulative response over 6 hours) was observed in subjects receiving levalbuterol (1.25 mg) and the smallest and least sustained response was observed in subjects receiving racemic albuterol (1.25 mg). Levalbuterol (0.63 mg) and racemic albuterol (2.50 mg) evoked bronchodilation with maximal values and duration that were closely comparable. In subjects with more severe asthma (baseline FEV₁ $<60\%$ of predicted), a significantly ($P < .05$) greater maximal bronchodilation was observed in groups receiving levalbuterol when compared with

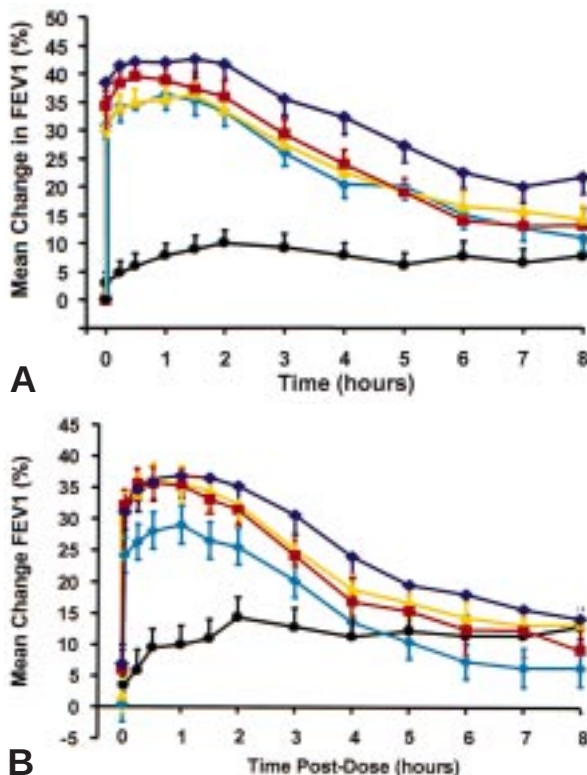


FIG. 1. Mean percent change (mean $\pm$ SEM) from baseline in FEV₁ after first dose (week 0, *top panel*) and after 4 weeks (week 4, *bottom panel*) of study treatment. Week 0 mean peak FEV₁ change (liters) was $P < .001$ greater than placebo, for all treatment groups. In addition, combined FEV₁ values for both of levalbuterol doses was greater than both racemic albuterol active treatments ($P = .023$), as were the area under the curve values ($P = .023$). At week 4 (*lower panel*), the peak FEV₁ of both levalbuterol groups was not significantly different ($P = .13$) from both racemic doses nor was the over all area under the curve (.14). Placebo (black circles), 1.25 mg racemic albuterol (aqua diamonds), 2.50 mg racemic albuterol (yellow triangle), 0.63 mg levalbuterol (red square), 1.25 mg levalbuterol (purple diamond).

groups receiving racemic albuterol. For all analyses based on recordings of FEV₁, the rank order for efficacy was levalbuterol (1.25 mg) more than levalbuterol (0.63 mg) = racemic albuterol (2.50 mg) more than racemic albuterol (1.25 mg). The mean change from study baseline in predose FEV₁ (liters) after 4 weeks of treatment in the subset of patients who were not taking concurrent corticosteroid therapy (Figure 3) was 0.13 L and 0.31 L, respectively, for 0.63 and 1.25 mg levalbuterol. The racemic albuterol treatment groups were below baseline predose values.

More than 95% of subjects used racemic albuterol MDIs during the period of study.²² If compared with use before random assignment, subjects who received vehicle used MDIs significantly ($P = .019$) more during the study, whereas subjects who regularly used levalbuterol (1.25 mg) required significantly ($P < .001$) less racemic medication by MDI. This latter outcome can be contrasted with the marginal significance ($P = .056$) of the reduction

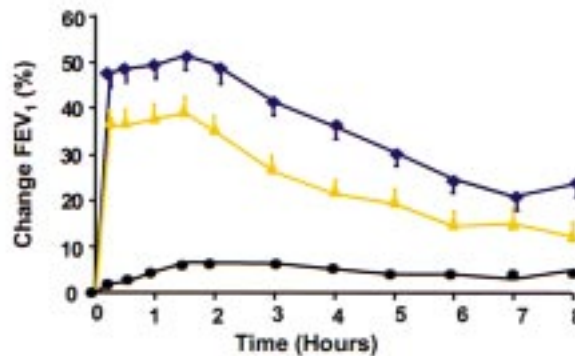


FIG. 2. Mean percent change (mean $\pm$ SEM) in FEV₁ first dose in a subgroup of patients with pretreatment FEV₁ of 60% or less of predicted normal value. The 1.25 mg levalbuterol group ($n = 36$) showed a significantly greater peak FEV₁ ($P = .0024$) over the 2.5 mg racemic albuterol group ($n = 38$) and placebo ($n = 34$). Mean peak change, $P = .0476$, levalbuterol versus racemic albuterol. Placebo (black circles), 1.25, 2.50 mg racemic albuterol (yellow triangle), 1.25 mg levalbuterol (purple diamond).

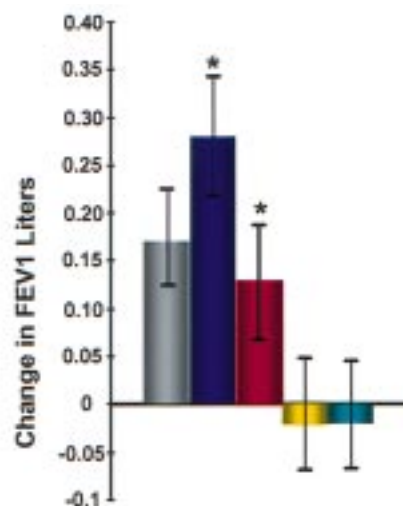


FIG. 3. Mean change from study baseline (mean $\pm$ SEM) in pre-dose FEV₁ (liters) after 4 weeks of treatment for subgroup of patients who were not taking concurrent inhaled corticosteroid therapy. All patients: $P = .41$ across all treatments; inhaled corticosteroid-free patients: $P = .006$, levalbuterol versus racemic albuterol. Placebo (gray bar), 1.25 mg racemic albuterol (yellow bar), 2.50 mg racemic albuterol (aqua bar), 0.63 mg levalbuterol (red bar), 1.25 mg levalbuterol (blue bar).

in MDI usage by subjects receiving racemic albuterol (2.50 mg).

After regular treatment, the same group mean FEV₁ values recorded immediately before nebulization at 4 weeks differed from those at baseline. In groups who had received levalbuterol (1.25 mg or 0.63 mg) or vehicle, there was an incremental improvement (FEV₁) of approximately 0.1 L, whereas no increase was detected in groups exposed regularly to racemic albuterol 2.50 mg or 1.25 mg. In those subjects who were not using inhaled

TABLE I. Changes from pre-treatment values for serum potassium and serum glucose (at 60 minutes) and ventricular beat frequency (at 15 minutes) after completion of initial inhalation of nebulised albuterol or placebo

Response parameter	Units	Incremental increase				Vehicle
		R-albuterol (0.63 mg)	R-albuterol (1.25 mg)	Racemic albuterol (1.25 mg)	Racemic albuterol (2.5 mg)	
Serum potassium	nmol/L	-0.2	-0.3	-0.3	-0.3	-0.2
Serum glucose	mg/dL	4.6	10.3	4.0	8.2	-0.2
Ventricular beat frequency	beats/min	2.3	6.7	2.5	5.7	-3.0

TABLE II. Changes from pretreatment values for serum potassium and serum glucose (at 60 minutes) and ventricular beat frequency (at 15 minutes) after completion of inhalation of nebulised albuterol or placebo after regular treatment for 4 weeks

Response parameter	Units	Incremental increase				Vehicle
		R-albuterol (0.63 mg)	R-albuterol (1.25 mg)	Racemic albuterol (1.25 mg)	Racemic albuterol (2.5 mg)	
Serum potassium	nmol/L	-0.0	-0.1	0.1	-0.1	0.1
Serum glucose	mg/dL	2.4	4.2	2.6	4.4	-2.0
Ventricular beat frequency	beats/min	2.5	3.6	3.6	4.9	-4.0

glucocorticosteroids, these differences were accentuated, such that FEV₁ increased by 0.13 L with 0.63 mg levalbuterol and 0.31 L with 1.25 mg levalbuterol, representing 7% and 15% increases, respectively, over baseline FEV₁. These increases may be contrasted with the reductions of 3% and 5% that were observed in groups who had regularly used 1.25 mg or 2.50 mg doses of racemic albuterol. One can further contrast the 0.31 L improvement in lung function achieved with levalbuterol is comparable to the 0.25 to 0.28 L seen with budesonide in other studies.^{24,25}

As anticipated, initial exposure of subjects to these formulations of isomeric or racemic albuterol induced appreciable changes in serum potassium and blood glucose concentrations and to an increased ventricular beat frequency. These effects were related to corresponding dose of levalbuterol either given as a racemate or as the single isomer levalbuterol (Table I).

After 4 weeks of continuous treatment, these effects declined in magnitude, as did differences between levalbuterol and the racemate (Table II). Throughout the period of study the overall incidence of nervousness and tremor were slightly greater (15% vs 11%) for levalbuterol (1.25 mg) than for racemic albuterol (2.50 mg).

Levalbuterol in children with asthma

Fourteen boys and 14 girls, 6 to 11 years old (9.4 ± 1.3 years) and with a history (6 months) of chronic, stable asthma, were studied.²³ All used racemic albuterol regularly and, if β -agonists were withdrawn (for 8 hours), experienced moderate to severe airflow limitation with FEV₁ consistently between 50% and 80% of predicted values²⁶ and improved (12%) within 30 minutes of inhalation of nebulized racemic albuterol (2.50 mg). A proportion of subjects used supplementary drugs for control of asthma, and these drugs were withheld appropriately before laboratory studies.

Subjects received nebulized levalbuterol (0.16 mg, 0.31 mg, 0.63 mg, or 1.25 mg), racemic albuterol (1.25 mg, 2.50 mg), or vehicle (0.9% saline). To allow double blind, single-dose, crossover comparisons, a balanced incomplete (7×4) block design was derived from Patterson's squares.²⁷ Subjects were assigned randomly to receive single doses of sequential test materials on successive visits, scheduled 2 to 8 days apart. Measurements of FEV₁ were made on completion of nebulization and after 15, 30, 45, 60, 90, and 120 minutes, as well as hourly for 6 or more hours. Before and after administration of test material, vital signs were recorded, a 12-lead electrocardiogram was obtained (at 30 minutes), and blood was collected for analysis (at 15 and 60 minutes). Treatment groups were compared with placebo for differences in peak FEV₁, percent peak change in FEV₁, and AUC by analysis of variance. If a treatment effect was significant (<.05 level), paired comparisons used Holm's sequentially rejective Bonferroni procedure, which adjusted the type I error for simultaneous hypotheses.

Whether measured as peak FEV₁ or as cumulative AUC, bronchodilator responses to levalbuterol (1.25 mg, 0.63 mg, 0.31 mg, and 0.16 mg) and racemic albuterol (2.50 mg) were significantly greater than vehicle. Peak FEV₁ of the bronchodilator response to racemic albuterol (1.25 mg) was significantly greater than vehicle but, when measured as AUC, the bronchodilator response failed to achieve significance (Table III). The bronchodilator response at all time points was greatest after inhalation of levalbuterol (1.25 mg), and the bronchodilator responses to levalbuterol (0.31 mg and 0.63 mg) were closely similar to those of racemic albuterol (2.50 mg). Overall, levalbuterol (0.31 mg, 0.63 mg, and 1.25 mg) produced greater or equivalent bronchodilation than either dose of racemic albuterol over the 8-hour study period (Table III).

There were 49 adverse events in 22 subjects (51.2%) but there were no significant differences between groups. Side effects that can be attributed to activation of extra-

TABLE III. Changes in the FEV₁ by Treatment for patients 6 to 11 years of age

	Levalbuterol			Racemic albuterol			Vehicle
	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)	(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 values were derived from sequential testing by use of Holms sequentially rejective Bonferroni procedure.

*P < .05 vs vehicle.

TABLE IV Mean change in β-mediated events expressed as a percentile of predose estimates

	Levalbuterol			Racemic albuterol			Vehicle
	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)	(n = 23)
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 HR (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%

pulmonary β-adrenoceptors were dependent on the levalbuterol dose, whether administered as the single isomer or as racemic albuterol (Table IV).

DISCUSSION

Studies in children and adults have demonstrated that inhalation of nebulized levalbuterol produced significantly greater bronchodilation than when administered as an equal dose as racemate, in which levalbuterol coexists with an equal quantity of the distomer (nearly inactive isomer) (S)-albuterol. Differences between the homochiral (pure) and racemic formulations of albuterol were evidenced both as greater amplitude and as longer duration of bronchodilation. These differences were manifest upon first administration and remained in evidence after 4 weeks of regular usage of these formulations of albuterol. Such an outcome implies that (S)-albuterol opposes, or impairs, the capacity of levalbuterol to achieve bronchodilation after activation of β₂-adrenoceptors.

The capacity of racemic albuterol to relax airway smooth muscle and to inhibit expression of airway hyperactivity resides predominantly, or possibly exclusively, with the eutomer levalbuterol.²⁰ Levalbuterol binds to β₂-adrenoceptors and thereby accelerates the formation of

intracellular cyclic adenosine monophosphate, an effect that is not mimicked, or otherwise influenced, by the presence of (S)-albuterol.²⁰ Hence the greater capacity of levalbuterol to reduce airway obstruction implies that (S)-albuterol must be promoting or facilitating contraction of airway smooth muscle and thereby opposing the bronchodilator action of levalbuterol. Three mechanisms might contribute to such an effect of (S)-albuterol: intensification of tolerance to levalbuterol; diminished activation of β₂-adrenoceptors by levalbuterol; increased sensitivity to bronchoconstrictors; and/or enhanced contractility of airway smooth muscle.

Subsensitivity or tolerance describes a loss of efficacy that can follow excessive or sustained exposure to a β₂-agonist. For β₂-adrenoceptors, regular exposure to racemic albuterol can result in subsensitivity not only in bronchodilation^{3,4} but also in peripheral blood leukocytes,²⁸ skeletal muscles, and cardiac β₂-adrenergic receptors.²⁹ In studies of levalbuterol, a significant difference between bronchodilator responses to levalbuterol and racemic albuterol became evident on first administration. By definition, such a difference could not be attributed to β₂-adrenoceptor downregulation. Nor is it likely to have been determined by some systemic variation in β₂-adrenoceptor sensitivity because no corresponding difference was evident for serum potassium,

blood glucose, or increased ventricular beat frequency. After 4 weeks of continuous use, changes of serum potassium were no longer evident and the increases of blood glucose and of ventricular beat frequency were blunted. These changes are consistent with a slight β_2 -adrenoceptor downregulation and might account for the diminished bronchodilator response of levalbuterol or racemic albuterol when either is used regularly. However, a persisting difference between bronchodilator responses to equivalent doses of levalbuterol and racemic albuterol cannot be so explained because both formulations have an identical content of levalbuterol and hence would be expected to affect receptor downregulation to an equal extent.

Measurement of the plasma concentrations of albuterol isomers in normal volunteers after administration of either racemic albuterol (2.50 mg) or levalbuterol (1.25 mg) by nebulization did not reveal differences in maximal or cumulative AUC (area under curve) concentrations of levalbuterol after either single or repetitive administrations. Levalbuterol (t_{max} circa 1 ng/mL at 20 minutes) was more rapidly absorbed and more rapidly eliminated than (S)-albuterol (t_{max} circa 1.8 ng/mL at 60 minutes) so that, after repetitive administration, the concentration of (S)-albuterol in plasma could considerably exceed that of levalbuterol.³⁰ Because the bulk of nebulized racemic albuterol will have been deposited on the oropharynx and swallowed, observed differences in serum concentrations of isomers can be presumed to reflect absorption from the gut to a much greater extent than airway epithelium. Whether metabolized in gut and liver or in the airway epithelium, it is evident that levalbuterol will be metabolized more rapidly than (S)-albuterol.^{31,32} As a consequence, there will be selective loss of levalbuterol during regular use of racemic albuterol and the persistence of (S)-albuterol in plasma will lead to a concentration differences between the two isomers of 5-fold to 7-fold. Despite these large differences in concentration, the presence of (S)-albuterol does not modify β_2 -adrenoceptor activation by levalbuterol.³³

That (S)-albuterol is pharmacologically active has been recognized ever since it was reported to be more potent than levalbuterol in reducing intraocular pressure in the rabbit.³⁴ Exposure of human isolated bronchus to (S)-albuterol resulted in augmented contractile responses to histamine and leukotriene C₄.³⁵ This finding is in accord with the clinical evidence of increased sensitivity to inhaled methacholine after inhalation of (S)-albuterol by asthmatic individuals.²¹ On the basis of these laboratory and clinical findings, it can be anticipated that the net effect of inhalation of racemic albuterol will be determined by the ease with which induction of hyperreactivity by (S)-albuterol can be eclipsed by the consequences of β_2 -adrenoceptor activation by levalbuterol. Interaction between processes that reduce airway obstruction and processes that promote airway obstruction can be expected to foreshorten bronchodilation as well as reducing the amplitude of the response because (S)-albuterol will persist over many hours and will continue to influence airway

responsiveness when bronchodilator effects of levalbuterol have waned. The mismatch will be amplified further when use of racemic albuterol is repetitive. Foreshortened and diminished bronchodilator responses have been noted during regular use of racemic β_2 -agonists. Although most pronounced for isoproterenol,^{36,37} similar effects have been noted after regular use of metaproterenol³⁶ or fenoterol³⁷ as well as albuterol.^{3,4} It can be presumed that this phenomenon accounts for the progressive reduction observed in FEV₁ recorded immediately before nebulization in those subjects who had used racemic albuterol regularly. It is significant therefore that this decline in FEV₁ was not observed with levalbuterol.

An association between regular or excessive use of inhaled isoproterenol and death from asthma in children was reported some time ago.³⁸ More recently, an analogous situation has arisen, after recognition of a relation between death or near-death from asthma and the amount of prescribed β_2 -adrenoceptor.³⁹ Although final analysis suggested that the increased use of β -agonists was a marker for poorly controlled asthma, the latter was most probably the cause for the excess asthma mortality rates.⁴⁰ The difference between bronchodilator actions of levalbuterol in the presence and absence of (S)-albuterol could explain the proposed association between regular use of racemic albuterol and exacerbation of asthma. Thus increased susceptibility to constrictor stimuli and impaired bronchodilation that might stem from receptor downregulation would be compounded by the pharmacologic actions of (S)-albuterol, which accumulates disproportionately when racemic albuterol is being used repetitively and excessively.

Attempts to detect anomalous hyperreactivity after regular use of racemic albuterol have usually relied on tests with methacholine and have revealed either unchanged sensitivity⁴¹ or modestly increased sensitivity⁴² of uncertain clinical significance. Inhalation of hypertonic saline as a stimulus to sputum expectoration had effects on airflow that were inconsequential in mild asthma yet produced airway obstruction in subjects with severe asthma when airway obstruction had a magnitude (up to 42% fall in FEV₁) that was directly proportional to the quantity of β_2 -agonist used in the preceding 24 hours.⁴³ Even in mild asthma, substantial anomalous effects can be detected. Thus inhalation of small aliquots of 10% ethanol typically had no discernible influence on airflow in subjects with mild asthma. However, after regular use of albuterol for 1 week, exaggerated airway responsiveness to bradykinin and, in some patients, profound overt bronchospasm (FEV₁ reduced by 1.5 L) followed inhalation of a quantity of ethanol that would be innocuous in normal subjects or in asthmatic subjects who are not exposed regularly to racemic albuterol.⁴⁴

Over the last decade, a substantial body of preclinical evidence has been assembled to implicate distomers of β_2 -agonists in causing anomalous effects of racemic β_2 -agonists during asthma therapy.¹⁹ Clinical evidence has largely been consistent with expectations from preclinical findings and supportive of the viewpoint that β_2 -ago-

nist distomers are counterproductive in asthma therapy. As these studies progress into clinical settings it becomes possible to define the actions of distomers such as (S)-albuterol with greater precision. An incisive example is the capacity of racemic albuterol to exaggerate eosinophilic infiltration into asthmatic airways during allergic reactions. This finding has prompted study of the isomers to reveal that whereas levalbuterol will suppress activation of human eosinophils, (S)-albuterol will augment activation of these cells.¹⁴ As well as providing a basis for the paradoxical phenomena of airway hyperresponsiveness and enhanced airway obstruction during regular treatment with racemic albuterol, these observations raise the possibility that levalbuterol may have appreciable anti-inflammatory potential. Extension of these clinical findings is therefore awaited with interest because the use of albuterol in the management of clinical asthma may be modified as a consequence.

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