

A cumulative dose study of levalbuterol and racemic albuterol administered by hydrofluoroalkane-134a metered-dose inhaler in asthmatic subjects

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Background: The short-acting β_2 -agonists levalbuterol and racemic albuterol are available for administration through a hydrofluoroalkane-134a (HFA) metered-dose inhaler (MDI).

Objective: This study compared the short-term safety and efficacy of cumulative doses of levalbuterol HFA MDI and racemic albuterol HFA MDI in asthmatic subjects.

Methods: This was a randomized, modified-blind, active-controlled, multicenter, 2-way crossover study. Subjects ($n = 49$) were randomized to 16 cumulative doses ($1\times$, $2\times$, $4\times$, $8\times$, and $16\times$) of levalbuterol ($45\ \mu\text{g}$ per dose) or racemic albuterol ($90\ \mu\text{g}$ per dose) administered over a 2-hour period. After a 7-day washout period, subjects were crossed over to the other treatment. After each dose, safety outcomes and pulmonary function were assessed.

Results: Heart rate and (R)-albuterol exposure increased for both racemic albuterol HFA and levalbuterol HFA. For cumulative doses of $8\times$ or greater, racemic albuterol HFA treatment had greater increases in mean heart rate than levalbuterol HFA (least-squares mean [$\pm$ SD] difference at the $8\times$ dose was 2.8 beats/min [95% CI, 0.3 - 5.3] and at the $16\times$ dose was 3.5 beats/min [95% CI, 0.6 - 6.4]). (R)-albuterol plasma levels ranged from 10% to 18% higher after racemic albuterol HFA MDI dosing versus after levalbuterol HFA MDI. FEV_1

improvements were similar for both treatments. The relative potencies of the 2 therapies, based on FEV_1 , were similar (ratio, 1.1 [90% CI, 0.9 - 1.2]; Finney method).

Conclusion: In this study single-day cumulative dosing of asthmatic subjects with levalbuterol HFA MDI or racemic albuterol HFA MDI resulted in similar improvements in FEV_1 and tolerability. Plasma (R)-albuterol levels and mean heart rate were less with levalbuterol HFA MDI. (*J Allergy Clin Immunol* ■■■■;■■■:■■■-■■■.)

Key words: Asthma, safety, efficacy, relative potency, cumulative dose, levalbuterol HFA MDI, racemic albuterol HFA MDI

Short acting β_2 -agonists play a major role in the management of asthma as a result of their ability to promote bronchodilation and prevent bronchoconstriction associated with exercise or a challenge with an agent, such as cold air or histamine.¹ Metered-dose inhalers (MDIs) are the most commonly used delivery system for β_2 -agonists.² Until recent years, most MDIs used chlorofluorocarbon propellants. However, the Montreal Protocol on Substances that Deplete the Ozone Layer³ called for an elimination of chlorofluorocarbon production by 2008, thus leading to the development of hydrofluoroalkane-134a (HFA)-propellant MDIs.

Levalbuterol and racemic albuterol are 2 commonly prescribed short-acting β_2 -agonists used for the treatment of asthma. Racemic albuterol is an equal mixture of (R)- and (S)-albuterol enantiomers, with the (R)-albuterol enantiomer (levalbuterol) being responsible for bronchodilation and the bronchoprotective properties of the drug.^{4,5} The clinical effects of the (S)-albuterol isomer are unclear.^{4,6,7}

In a study in asthmatic children (4-11 years of age), levalbuterol HFA MDI ($45\ \mu\text{g}$) and racemic albuterol HFA MDI ($90\ \mu\text{g}$) had similar efficacy, although fewer total adverse events were observed in levalbuterol HFA MDI-treated subjects, including asthma exacerbations and respiratory adverse events.⁸ In older subjects with asthma, possible treatment differences between the 2 preparations have not been well studied. This study compared the tolerability, airway function efficacy, and relative potency of cumulative single-day dosing with levalbuterol HFA MDI and racemic albuterol HFA MDI in subjects 12 years of age or older with asthma.

METHODS

Study design

This was a randomized, double-blind, active-controlled, multicenter (8 sites), 2-way crossover, single-day cumulative dosing study to investigate the

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Disclosure of potential conflict of interest: K. Tripp has been an employee of and served as a consultant for Sepracor. W. K. McVicar has been an employee and stockholder of Sepracor. P. Nair has served as an investigator for GlaxoSmithKline Canada, Cepion, Inc, and Topigen, Inc, and has served as an expert witness for the Health Canada Appeal Panel. J. Corren has served as a researcher for Schering-Plough, GlaxoSmithKline, Sepracor, Aventis, Genentech, Boehringer Ingelheim, and Amgen and has served as an expert witness regarding mold allergies. W. W. Pleskow has served on the speakers' bureau for Sepracor and Alcon, has served as the principal investigator for Altana, Abbott Laboratories, Schering-Plough, Alcon, Neopointe, MedaCorp, Apotek, SkyePharma, Allmiral, Novartis, and Medicinova. R. A. Baumgartner, J. P. Hanrahan, and E. Goodwin are employees of Sepracor.

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Abbreviations used

HFA: Hydrofluoroalkane-134a
LS mean: Least-squares mean
MDI: Metered-dose inhaler

safety, efficacy, and relative potency of levalbuterol HFA MDI (lot no. 020539; Sepracor, Inc, Marlborough, Mass) and racemic albuterol HFA MDI (lot no. GDE018A; Schering-Plough, Deerfield, Ill) in subjects with stable asthma. The study was performed according to the principles of Good Clinical Practice, the International Conference on Harmonization, and the Declaration of Helsinki. The appropriate review boards approved the protocol, and written informed consent was obtained from subjects.

Study subjects

Subjects were eligible if they were 12 years of age or older, had physician-diagnosed asthma for at least 6 months before enrollment, and were clinically stable with baseline FEV₁ values of 45% or greater and 75% or less of predicted value. To be eligible, subjects must have used a β -adrenergic agonist, anti-asthma anti-inflammatory medication, and/or over-the-counter asthma medication for at least 6 months. Subjects were also required to demonstrate 15% or greater reversibility of airflow obstruction within 15 to 30 minutes after being administered 180 μ g of racemic albuterol. Subjects were ineligible if they had a history of hospitalization for asthma within 4 weeks of starting the study, had diagnosed life-threatening asthma (requiring intubation, associated with hypercapnia, respiratory arrest, or associated with hypoxic seizures) within 12 months, or had a clinically significant respiratory tract infection within 3 weeks before visit 1 (see below). Subjects were not eligible if they used inhaled corticosteroids, systemic corticosteroids, or both within 21 days of visit 1.

Protocol

The study had 4 clinic visits. At the screening visit (visit 1), all baseline values were obtained. This was followed by a 7-day period to wash out excluded medication. Disallowed medication included β_2 -adrenergic bronchodilators (except rescue medication), nonprescription asthma medication, ipratropium bromide, and inhaled corticosteroids, systemic corticosteroids, or both. Open-label pirbuterol acetate (0.2 mg per actuation; Maxair; Graceway Pharmaceuticals, Bristol, Tenn) MDI was used as rescue medication, which was withheld for at least 7 hours before all study visits. There were 2 treatment visits (visits 2 and 3). At visit 2, subjects were randomized to one of 2 single-day cumulative dosing treatments: either levalbuterol HFA MDI or racemic albuterol HFA MDI. After a 7-day washout period, subjects were crossed over to the other treatment. On the treatment day visits, subjects who were administered study drug had vital signs, potassium and glucose serum levels, electrocardiograms, (R)- and (S)-albuterol plasma concentrations, serial spirometric results, and adverse events evaluated. The final visit (visit 4) occurred about 3 days after visit 3. At this visit, vital signs, serum potassium and glucose levels, electrocardiograms, spirometric results, and adverse events were similarly assessed. Diary cards and medical event calendars were dispensed at each visit for the daily recording of concomitant medication and adverse events.

At visits 2 and 3, 16 cumulative doses of levalbuterol or racemic albuterol (45 μ g and 90 μ g each actuation for levalbuterol and racemic albuterol, respectively) were administered with an MDI without a spacer device. For this analysis, the levalbuterol HFA and racemic albuterol HFA doses were standardized to the amount of (R)-albuterol administered (eg, 90 μ g of racemic albuterol contains 45 μ g of [R]-albuterol). Study drug doses were administered as 1 actuation at 0 and 30 minutes, 2 actuations at 60 minutes, 4 actuations at 90 minutes, and 8 actuations at 120 minutes. Dosing was started in the morning at approximately the same time (± 1 hour) on each visit day. Study personnel who were not responsible for other study procedures performed in-clinic dosing. Dosing occurred in a separate room away from the pulmonary function testing, and no other study personnel were present.

Subjects were blinded to treatment by the use of blindfolds. Study subjects and personnel performing the assessments were thus blind to the treatment received. Randomization occurred separately within each site by using permuted blocks of 4, and the randomization was controlled by the investigator at each site. Inhalers were primed before initiation of the cumulative dosing regimen to ensure optimal drug delivery.

Heart rate and blood pressure were recorded at every clinic visit before dosing, 15 minutes after each cumulative dose, and every 30 minutes for 8 hours after the final dose. Serum was collected for evaluation of potassium, glucose, and both (S)- and (R)-albuterol concentrations before dosing at each clinic visit; immediately before each cumulative dose; and at 30 minutes and 4, 6, and 8 hours after the final dose on both treatment days. Electrocardiograms were evaluated before dosing at all clinic visits, 20 minutes after each cumulative dose, and at 40 minutes and 1, 6, and 8 hours after the final dose at visits 2 and 3. Spirometric measurements were taken before dosing, 25 minutes after each cumulative dose, and hourly for 8 hours after the final dose. Adverse events, rescue medication, and asthma exacerbations were recorded at each clinic visit and the telephone evaluation.

Statistical analysis

The intent-to-treat population included all randomized subjects who received at least 1 dose of blinded study medication and was used for the analysis of all efficacy and safety data. The primary end point was a safety comparison between the cumulative dosing of levalbuterol HFA MDI and racemic albuterol HFA MDI with respect to changes in heart rate, blood pressure, and potassium and glucose serum concentrations. Secondary safety end points were adverse events and rescue medication use. Other secondary end points included spirometric measurements and (R)- and (S)-albuterol plasma levels.

For changes in heart rate (derived from electrocardiography), blood pressure, potassium and glucose serum levels, and percent predicted FEV₁, the estimate for the least-squares (LS) mean (the LS mean is an adjusted mean for parameters in the statistical model, see below), the standard error (SE) of the LS mean, the LS mean difference, and the 95% CI of the LS mean difference were calculated by fitting a mixed effects model with the change in a given parameter as the dependent variable. Independent variables included sequence, treatment, period, log(dose), and the log(dose)-by-treatment interaction as fixed effects and subject within sequence, treatment-by-subject within sequence, log(dose)-by-subject within sequence, and log(dose)-by-treatment-by-subject within sequence as random effects. Concentrations of (R)- and (S)-albuterol were summarized before and during cumulative dosing and during the 8-hour postdose follow-up period. The relationship between each time-matched heart rate and FEV₁ value versus the (R)-albuterol concentration was examined by using descriptive statistics.

The slope-ratio method was used, as described by Finney, to assess the relative potency of the 2 treatments with respect to spirometric measures.⁹ A random coefficient model contained sequence, period, and treatment-by-log(dose) interaction, and a random subject effect was fit. The relative potency was determined by calculating the ratio of the slopes, β_T/β_S , where β_T is the slope associated with the levalbuterol HFA dose and β_S is the slope associated with racemic albuterol HFA dose. By using this method, a slope ratio of 1 is considered to indicate similar relative potency. The 90% CI for the ratio of the slope was calculated by using Feiller's theorem.⁹ Two inhaled formulations have been considered by some to be bioequivalent if the 90% CI of the relative potency is between 0.67 and 1.5.¹⁰ Pulmonary function and the frequency of adverse events and rescue medication use were summarized overall by treatment, cumulative dose level, and washout period.

RESULTS

Of 49 subjects with mild-to-moderate asthma enrolled in this study, 22 were randomized to the levalbuterol HFA/racemic albuterol HFA sequence and 27 to the reverse sequence (Table 1). Forty-three (88%) of the 49 subjects completed the study. Reasons for discontinuation included adverse events (n = 1),

abnormal electrocardiographic measurements ($n = 4$; 3 subjects after first-day dosing with levalbuterol HFA MDI and 1 subject after first-day dosing with racemic albuterol HFA MDI), and protocol violation ($n = 1$).

Safety, disease control, and adverse events

Mean $\pm$ SD predose heart rate was similar for the levalbuterol HFA MDI and racemic albuterol HFA MDI (levalbuterol, 73.6 ± 12.3 beats/min; racemic albuterol, 71.0 ± 8.8 beats/min). Mean heart rate demonstrated stepwise increases with both levalbuterol HFA MDI and racemic albuterol HFA MDI treatment after each dose (Fig 1), although mean heart rate decreased at the $1\times$ dose level compared with the baseline value. The increase in mean heart rate observed was greater for racemic albuterol HFA MDI at each dose level. Heart rate treatment differences were significant for doses at or greater than $8\times$ cumulative actuations (LS mean differences in change in heart rate for racemic albuterol HFA MDI vs levalbuterol HFA MDI treatment were 2.8 beats/min after the $8\times$ dose (95% CI, 0.3-5.3) and 3.5 beats/min after the $16\times$ dose (95% CI, 0.6-6.4).

Mean $\pm$ SD predose serum potassium level was not different between levalbuterol HFA MDI and racemic albuterol HFA MDI (levalbuterol, 4.31 ± 0.43 mEq/L; racemic albuterol, 4.32 ± 0.46 mEq/L). The normal range of serum potassium level is 3.3 to 4.7 mEq/L. Serum potassium concentrations decreased after dosing for both treatments, particularly after $8\times$ and $16\times$ cumulative actuations (Fig 2, A). After $16\times$ cumulative actuations, LS mean $\pm$ SE serum potassium concentrations decreased by -0.20 ± 0.07 mEq/L for levalbuterol HFA and -0.30 ± 0.07 mEq/L for racemic albuterol HFA from predose levels. The predose level of glucose was also similar between levalbuterol HFA MDI and racemic albuterol HFA MDI (mean $\pm$ SD, 93.3 ± 20.3 and 95.3 ± 18.2 , respectively). The normal range of serum glucose is 80 to 100 mg/dL. The LS mean ($\pm$ SE) glucose levels increased after $8\times$ and $16\times$ cumulative actuations for both treatments (Fig 2, B). Treatment differences for changes in serum potassium or glucose concentrations were not significant. No subjects used rescue medication during the assessment period during visits 2 and 3.

No patients experienced an asthma exacerbation or a serious adverse event during the study period. Five adverse events were reported (racemic albuterol: back pain [$n = 1$], chest pain [$n = 1$], and headache [$n = 1$]; levalbuterol: dizziness [$n = 1$] and hypertension [$n = 1$]).

Pharmacokinetic results

The median (R)-albuterol plasma concentration increased for both treatments during the dosing regimen and continued to increase for at least 30 minutes after the last cumulative dose (Table II and Fig 1). Eight hours after the final dose, the median (R)-albuterol levels decreased but remained at greater than predose values: 0.14 ng/mL (interquartile range, 0.11-0.18) for levalbuterol HFA MDI treatment and 0.17 ng/mL (interquartile range, 0.15-0.20) for racemic albuterol HFA MDI treatment. The mean $\pm$ SD ratio of the (R)-albuterol plasma level after each levalbuterol cumulative dose to the (R)-albuterol plasma level after each racemic albuterol cumulative dose ranged from 0.82 ± 0.25 to 0.90 ± 0.42 , indicating that (R)-albuterol exposure was from 10% to 18% lower for levalbuterol HFA MDI treatment compared with that for racemic albuterol HFA MDI (Table II). For

TABLE I. Demographic and baseline characteristics

Characteristic	Total (n = 49)
Age (y), mean (SD)	29.6 (11.4)
Female sex, n (%)	26 (53.1)
Race, n (%)	
White	45 (91.8)
Black	3 (6.1)
Asian	1 (2.0)
Percent predicted FEV ₁ , mean (SD)	66.5 (7.5)
FEV ₁ percent reversibility, mean (SD)	29.7 (13.5)
Screening FEV ₁ (L), mean (SD)	2.5 (0.5)
Concomitant medication, n (%)	
Montelukast sodium	7 (14.3)
Flunisolide	1 (0.2)
Fluticasone propionate	3 (6)
Mometasone furoate	1 (0.2)

the majority of the cumulative doses, the ratio was significantly different than 1, indicating the serum (R)-albuterol concentrations of the 2 medications were not equivalent.

The (S)-albuterol serum concentration also increased with each cumulative dose of racemic albuterol HFA MDI (Fig 1). The median plasma levels increased from zero before the first actuation ($1\times$) to 3.11 ng/mL (interquartile range, 2.23-3.64) 30 minutes after the $16\times$ cumulative actuation. The median (S)-albuterol concentration decreased 8-hours after the final dose of racemic albuterol HFA MDI but remained at greater than predose values (1.10 ng/mL [interquartile range, 1.0-1.24]) and more than 5-fold greater than the median (R)-albuterol plasma levels at this time. The median levels of (S)-albuterol for levalbuterol HFA MDI treatments were less than the level of detection for the assay (0.002 ng/mL) throughout the cumulative dosing regimen (Fig 1).

Spirometric measurements

Before dosing, FEV₁ values were similar between levalbuterol HFA MDI and racemic albuterol HFA MDI (mean $\pm$ SD: 2.48 ± 0.48 and 2.50 ± 0.54 , respectively). The mean $\pm$ SD percentage change in FEV₁ values improved from before dosing after each cumulative dose to a similar extent for both treatments (Fig 3) and remained greater than baseline values for 8 hours after the final dose (for levalbuterol HFA MDI, $19.3\% \pm 11.5\%$; for racemic albuterol HFA MDI, $20.3\% \pm 12.5\%$). The LS mean percent predicted FEV₁ value at 25 minutes after each cumulative dose increased similarly for both preparations (Table III).

The slope ratio and the 90% CI (see the Methods section) based on the mean percentage change in FEV₁ between HFA MDI and racemic albuterol HFA MDI was calculated to evaluate the relative potency of the 2 therapies. The ratio (levalbuterol HFA MDI/racemic albuterol HFA MDI) of the slopes was 1.1 (90% CI, 0.9-1.2). Based on defined equivalence criteria (see the Methods section), the 2 treatment regimens were bioequivalent with respect to improvement in FEV₁.

DISCUSSION

This is the first published study to compare the efficacy and safety of levalbuterol HFA MDI with that of racemic albuterol HFA MDI over a cumulative dosing regimen in subjects with asthma and to use a cumulative dose design to determine the relative potency of 2 treatments by using the Finney method.⁹ The study showed that single-day cumulative dosing of asthmatic

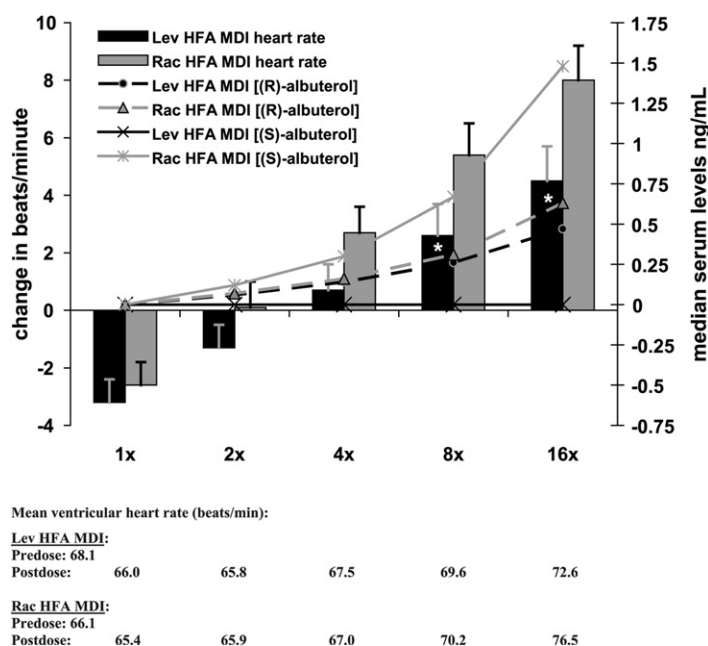


FIG 1. Mean change in ventricular heart rate per cumulative dose and (R)- and (S)-albuterol plasma concentration. Columns indicate the change in mean heart rate, and dashed and solid lines indicate the median (R)- or (S)-albuterol plasma concentration. Asterisks denote significant differences between heart rates after cumulative dosing with levalbuterol (Lev) HFA MDI and racemic albuterol (Rac) HFA MDI, and SEs are indicated.

subjects with levalbuterol HFA MDI or racemic albuterol HFA MDI resulted in similar improvement in FEV₁ and tolerability. Plasma (R)-albuterol levels and increases in mean heart rate were greater for racemic albuterol than levalbuterol treatment. Differences in mean heart rate, however, were small and unlikely to be clinically meaningful for most patients.

The safety profile for the 2 therapies differed over the cumulative dosing interval. Increases in mean heart rate were slightly greater for subjects administered racemic albuterol HFA MDI than for those treated with levalbuterol HFA MDI and were significantly increased at the higher cumulative doses (8× and 16×). Similarly, (R)-albuterol plasma levels were 10% to 18% higher for racemic albuterol HFA MDI compared with levalbuterol HFA MDI after each cumulative dose. For both therapies, increases in (R)-albuterol exposure paralleled increases in heart rate (Fig 1), which is consistent with the pharmacologic effects of β_2 -agonists.⁶ The higher heart rate after racemic albuterol HFA MDI versus levalbuterol HFA MDI likely reflects the greater systemic (R)-albuterol concentration and resulting cardiac adrenergic receptor stimulation. The difference in plasma concentrations between the 2 treatments (which have 45 μ g per actuation of the [R]-albuterol moiety) suggests that drug delivery or local airway properties, oral metabolism properties, or both might differ between the 2 therapies. These factors are not well understood but could relate to solution formulation, emitted MDI dose, particle size, or local absorption and metabolism differences. Consistent with prior reports^{8,11,12} for subjects receiving racemic albuterol HFA, the (S)-albuterol plasma concentration reached at least a 4-fold higher level than the (R)-albuterol plasma concentration. These high levels of (S)-albuterol in the subjects administered racemic albuterol were not associated with impaired bronchodilatory response in this study. There was also no

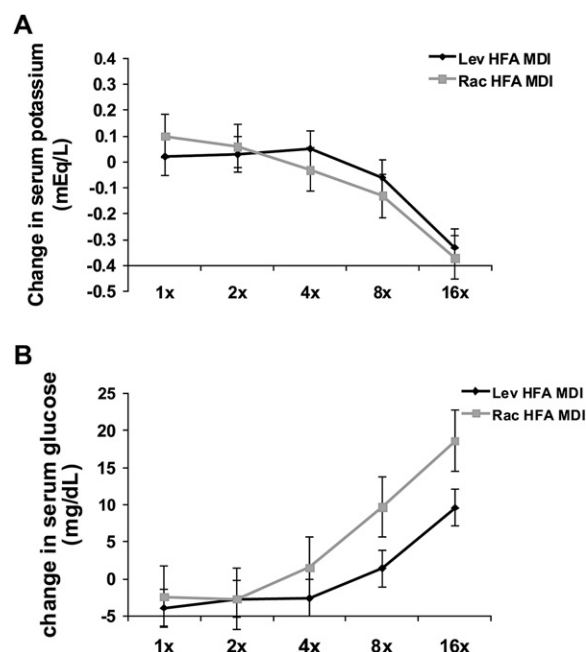


FIG 2. A, Mean change in serum potassium levels from before dosing to after each cumulative dose. B, Mean change in serum glucose levels from before dosing to each cumulative dose. SEs are indicated. Lev, Levalbuterol; Rac, racemic albuterol.

difference between the therapies with respect to mean changes in serum potassium and glucose levels.

A decrease in heart rate from baseline values was detected for the first several cumulative doses of both levalbuterol HFA MDI

TABLE II. Plasma concentration of (R)-albuterol

	Levalbuterol, median (min-max; n = 47)	Racemic albuterol, median (min-max; n = 45)	Ratio of levalbuterol (R)- to racemic albuterol (R)-, mean (SD)	95% CI of ratio (P value)
Before 1× dose	BLQ (BLQ-0.26)	BLQ (BLQ-0.22)	ND	
Before 2× dose	0.06 (BLQ-0.17)	0.07 (0.02-0.32)	0.84 (0.44)	0.69-0.99 (.04)
Before 4× dose	0.14 (0.03-0.36)	0.16 (0.03-0.30)	0.90 (0.42)	0.76-1.04 (.16)
Before 8× dose	0.26 (0.07-1.48)	0.31 (0.07-0.63)	0.87 (0.34)	0.76-0.98 (.03)
Before 16× dose	0.47 (0.13-1.09)	0.63 (0.15-1.18)	0.82 (0.25)	0.74-0.90 (<.0001)
30 min after last dose	0.91 (0.25-2.20)	1.14 (0.30-3.76)	0.82 (0.25)	0.73-0.90 (<.0001)

BLQ, Below limit of quantitation (0.002 ng/mL); ND, not done.

and racemic albuterol HFA MDI. After each dose, subjects took at least 4 deep inhalations (1 for drug and 3 for pulmonary measurements). Deep inspiration and bronchodilation caused by the drug might have improved ventilation-perfusion matching, which could reduce the requirement for cardiac output. Alternatively, subjects might have been anxious before treatment, resulting in high baseline heart rates. This decrease in heart rate might not be medication related because a prior cumulative dose study detected a similar decrease in heart rate after the first few cumulative doses of placebo.⁴

FEV₁ values improved similarly for subjects administered levalbuterol HFA MDI and racemic albuterol HFA MDI over the cumulative dosing regimen, which is consistent with a report that evaluated the efficacy of these 2 therapies in asthmatic children aged 4 to 11 years.⁸ A prior cumulative dose study comparing levalbuterol and racemic albuterol delivered by means of nebulization reported similar improvements in FEV₁, changes in heart rate, and serum potassium concentration for the 2 treatments.⁴ This previous study also reported a similar therapeutic ratio for the 2 treatments.

Several design features of this study must be taken into account when considering these results. Although useful in comparing the relative potency of bronchodilation in the 2 treatments, the dosing regimen used in this study is not recommended in the prescribing information of either product. Nonetheless, cumulative (or stacked) doses of inhaled β -agonists are commonly used as part of a treatment approach for reversing bronchospasms in acute asthma exacerbations. Responses after cumulative dosing can differ from those after noncumulative dosing. A response curve with cumulative dosing does not plateau, which is in contrast to a design in which the same number of actuations are delivered at a single dosing time.^{13,14} It is possible that bronchodilation from earlier doses might affect the delivery or pharmacologic effects of subsequent doses.^{13,14} It is also more difficult in a cumulative dose design to segregate the effects of dose from time on the observed degree of FEV₁ improvement (bronchodilation). The asthmatic subjects in this study were required to have pulmonary function compromise (FEV₁ 45% to 75% of predicted value) that would, based on recent guidelines, necessitate inhaled corticosteroids or other controller therapy. These inclusion criteria were designed to optimize the study's ability to detect cumulative dosing efficacy and safety differences between treatments. We did not assess the effect of concomitant controller therapies on the outcomes observed in this study.

Several experimental designs have been used to compare the clinical efficacy and safety between inhaled medications.¹⁰ Assessment of the relative potency of 2 compounds should compare a range of doses that are clinically relevant and that are on the

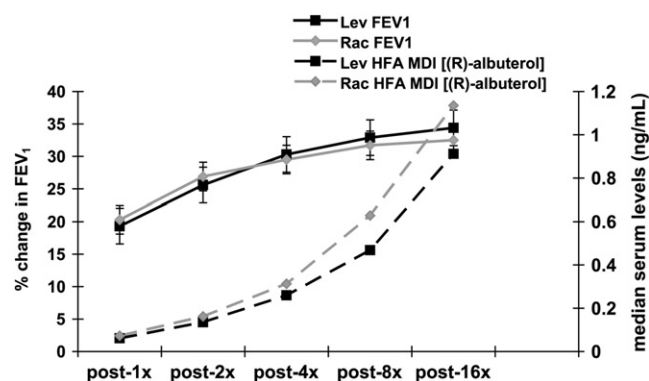


FIG 3. Mean percentage change in FEV₁ from before dosing to after each cumulative dose and median (R)-albuterol plasma concentration. Solid lines indicate the change in FEV₁, and dashed lines indicate the changes in (R)-albuterol concentration. SEs are indicated. Lev, Levalbuterol; Rac, racemic albuterol.

steep part of the dose-response curve for the 2 compounds of interest.^{10,15} If treatment comparisons are conducted on the plateau portion of the dose-response curve, then one of the assumptions of Feiller's methodology⁹ to evaluate bioequivalence is violated. Marketed doses of drugs are determined to achieve clinically meaningful effects while minimizing adverse events, with higher doses likely increasing side effects.¹⁶ This places many marketed doses of medications on the plateau portion of the dose-response curve. In this study doses were limited by the amount of drug delivered in a single actuation of the marketed devices (45 μ g for levalbuterol HFA MDI and 90 μ g for racemic albuterol HFA MDI) and thus might have been beyond the steep portion of the dose-response curve. Ideal bioequivalence trial design might therefore require both noncumulative dose studies and the ability to assess doses less than those delivered by a single actuation.

In summary, this cumulative dosing study suggests similar relative bronchodilator potency of levalbuterol HFA MDI and racemic albuterol HFA MDI at doses between 1× and 16× actuations. Tolerability of both treatments was similar, although heart rate increases were greater with racemic albuterol HFA MDI.

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TABLE III. Percent predicted FEV₁ from before dosing to 25 minutes after each cumulative dose

	Levalbuterol (mean [SD]), n = 47	Racemic albuterol (mean [SD]), n = 45		
Before dosing	67.2 (6.3)	67.5 (6.8)		
	LS mean (SE)	LS mean (SE)	LS mean difference	95% CI
After 1× dose	80.8 (1.8)	81.2 (1.8)	−0.4	−2.3-1.6
After 2× dose	83.4 (1.8)	83.2 (1.8)	0.1	−1.7-2.0
After 4× dose	85.9 (1.9)	85.3 (1.9)	0.6	−1.1-2.4
After 8× dose	88.5 (2.0)	87.3 (2.0)	1.1	−0.7-3.0
After 16× dose	91.0 (2.1)	89.3 (2.1)	1.6	−0.4-3.6

Steven (Allergy, Asthma, and Sinus Center, Greenfield, Wis), and their research coordinators who participated in the clinical study.

Clinical implications: Bronchodilation and clinical tolerability were similar for stacked drug dosing of levalbuterol HFA and racemic albuterol HFA, although heart rate increases might be less with levalbuterol HFA.

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