

Levalbuterol and racemic albuterol: Are there therapeutic differences?

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In a 1998 report in the JACI, Nelson et al¹ concluded that levalbuterol (the generic name for R-albuterol administered as a single enantiomer) had a better therapeutic ratio than racemic albuterol (which contains both the R- and S-enantiomers of albuterol). The following year, Gawchik et al² likewise concluded that levalbuterol had fewer β -agonist-mediated side effects than racemic albuterol when administered in doses that produce similar efficacy. Handley et al³ also reported that nebulized levalbuterol, in doses yielding comparable bronchodilation, had fewer β -agonist-mediated side effects than nebulized racemic albuterol (R,S-albuterol). All 3 reports implied that levalbuterol had a therapeutic advantage over racemic albuterol because less R-albuterol was required to produce the same degree of efficacy when administered as levalbuterol than when administered in a racemic formulation. Negative effects of the S-enantiomer were proposed as the explanation for this. The lower dose of R-albuterol (levalbuterol), in turn, resulted in fewer systemic effects for the same degree of bronchodilator efficacy (ie, a better "therapeutic ratio").

However, in a report appearing in this month's issue of the Journal, Lötvall et al⁴ arrived at a different conclusion. They failed to find any difference between the therapeutic ratios for levalbuterol and the racemic formulation. Specifically, they found that all pharmacologic effects of racemic albuterol reside with levalbuterol (the R-enantiomer) and that the S-albuterol was clinically inactive. Why the difference, and which conclusion should guide therapeutic decision-making?

Concerns about potential adverse effects of S-albuterol were first supported by results obtained from preclinical animal and in vitro models.⁵⁻⁷ These studies, previously reviewed in the pages of this Journal,⁸⁻¹⁰ indicated that S-albuterol had proinflammatory effects,

increased airway smooth muscle responsiveness to LTC₄ and histamine, and acted in opposition to the airway protective effects of R-albuterol (levalbuterol) against antigen-induced bronchospasm.

On the basis of these preclinical studies, clinically relevant adverse effects of S-albuterol in human beings were postulated.¹⁰ These included the following: diminution of the efficacy of R,S-albuterol by working in opposition to the bronchodilator and bronchoprotective effects of R-albuterol; the development of tolerance to beneficial effects of R,S-albuterol with repeated use, based on the preferential accumulation of S-albuterol versus R-albuterol in the lung; increased airway responsiveness, possibly due to proinflammatory effects of S-albuterol; and the potential for producing paradoxical bronchospasm. The potential for these clinically important adverse effects from S-albuterol provided the rationale for clinical development of a nebulized formulation of relatively pure R-albuterol (levalbuterol) and its marketing under the trade name Xopenex.

Because the conclusions of Lötvall et al⁴ in this issue of the Journal conflict with those in the other publications noted above,¹⁻³ it is appropriate to reexamine the weight of evidence from all of the published clinical trials that have attempted to test the hypothesized adverse effects of S-albuterol and the associated potential benefits of using levalbuterol rather than racemic albuterol.

Hypothesis: S-albuterol works in opposition to the bronchodilator and bronchoprotective effects of R-albuterol

If true in human beings, this adverse effect of S-albuterol would cause R-albuterol, administered as levalbuterol, to be significantly more potent than an equal amount of R-albuterol given in the racemic formulation. Let us first look in more detail at the studies whose conclusions supported this hypothesis. The study by Nelson et al evaluated the bronchodilator effects of the levalbuterol and racemic formulations in 362 adolescent and adult subjects treated with levalbuterol, racemic albuterol, or placebo 3 times daily for 4 weeks. Two doses of each formulation were given: 630 and 1250 μ g of levalbuterol and 1250 and 2500 μ g of the racemate. These doses were matched to deliver the same quantities of R-albuterol (ie, 630 and 1250 μ g). The mean peak change in FEV₁ from baseline that occurred with the active regimens ranged from approximately 35% to 42%. Given the mean baseline FEV₁ of approximately 60% of predicted, this is consistent with postbronchodilator values that differed very

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little, averaging from approximately 81% to 85% of predicted for each of the active regimens. Although the mean differences between active regimens were small, a statistically significant difference was found between levalbuterol and the racemic preparation after the first dose, though not after 4 weeks of 3-times-a-day treatment.

In a study of 43 children, Gawchik et al² compared 4 single doses of levalbuterol, ranging from 160 to 1250 μ g, with 1250- and 2500- μ g doses of the racemic formulation. Although all regimens provided a significant bronchodilator effect in comparison with placebo, no significant difference in bronchodilator effect could be demonstrated between any of the active regimens.

The report of Handley et al³ compared several doses of levalbuterol, ranging from 310 to 1250 μ g, with a 2500- μ g dose of the racemic formulation. No significant differences between active regimens were reported among the 20 adult subjects.

Authors of all 3 of these studies¹⁻³ found similar bronchodilatation for the 630- μ g dose of levalbuterol and the 2500- μ g dose of racemic albuterol. This has been taken to indicate that levalbuterol as the single enantiomer has a better therapeutic index by being more effective and having less potential for adverse effects in the absence of the S-enantiomer.

However, none of these studies provides strong support for the hypothesis that R-albuterol is more potent when administered as levalbuterol than when administered in the racemic formulation. In fact, the results of each of these studies violate the basic validity criteria that apply to investigations intended to compare the potencies of formulations.^{12,13} Such violation occurs in more than one way, but the most important is this: none of these studies was able to demonstrate a significant dose-response relationship. Stated another way: If these studies cannot detect differences between different doses of the *same* formulation, then they clearly are inadequate to evaluate and quantitate differences between *different* formulations.

Rigorous methods for comparing and estimating differences in potency of inhaled β -agonist formulations have been published.^{12,14-16} These methods use bioassay study design and statistical analyses to estimate differences in potency and are capable of making such estimates with a high degree of precision. The study by Löt-vall et al,⁴ reported in this issue of the Journal, is the first to use statistical bioassay methodology to estimate the relative potency of levalbuterol and racemic albuterol. The authors examined the results of progressively increasing doses of R- or S-albuterol ranging from 625 to 3200 μ g as the individual enantiomers and combined in the racemic formulation. The potency ratio that they calculated for R-versus R,S-albuterol was 1.9, indicating that each microgram of levalbuterol was equivalent to 1.9 μ g of racemic albuterol. The 95% CI encompassed a relative potency of 2, as would be expected if all pharmacologic effects of racemic albuterol were entirely from the R-enantiomer. In other words, the pharmacologic activity of the R-enantiomer was the same when the single enantiomer (levalbuterol) was used as when the S-enantiomer was

also present, as in the racemic formulation. Although this study can be criticized for using a cumulative-dose design, which confounds the effects of time and dosing,¹⁷ the authors' approach nonetheless provides the most reliable estimates of differences in potency between levalbuterol and racemic albuterol available to date.

Several other studies that have tested this hypothesis using albuterol-induced protection against methacholine challenge. Perrin-Fayolle,¹⁸ in a brief report published as a letter in *The Lancet*, described enhanced protection against methacholine challenge when levalbuterol (identified as D-salbutamol in the report) was administered as the single enantiomer in comparison with racemic albuterol and reported that S-salbutamol (identified as L-salbutamol in the report) increased airway sensitivity to methacholine. However, the differences observed between levalbuterol and the racemic formulation were not statistically significant, and others have failed to find any evidence of a difference in bronchoprotective or bronchodilator effect between R-albuterol given alone and R-albuterol given at the equivalent dose in the racemic formulation.^{19,20}

The weight of evidence thus supports neither the concept that S-albuterol works in opposition to the bronchodilator and bronchoprotective effects of R-albuterol nor the concept that there is any difference in R-albuterol potency when it is administered as a single enantiomer rather than in a racemic formulation.

Hypothesis: S-albuterol is responsible for development of tolerance to the beneficial effects of R,S-albuterol

If true in human beings, this would cause the tolerance after repeated administration of levalbuterol to be absent or at least smaller in magnitude than that associated with racemic albuterol. Only a study by Cockcroft et al²¹ addresses this hypothesis. They administered R-albuterol alone, S-albuterol alone, racemic albuterol (all enantiomers in equimolar doses), or placebo for 6 days. On days 0 and 7, they evaluated the protective effect of the R-albuterol on methacholine responsiveness. They found a significant and equivalent degree of tolerance after R-albuterol and racemic albuterol treatment but not after S-albuterol or placebo treatment. This does not support the hypothesis that S-albuterol is involved in the induction of tolerance to bronchoprotective effects of albuterol and argues against the suggestion that less tolerance develops when R-albuterol is administered as the single enantiomer (levalbuterol) than when it is administered in a racemic formulation.

Hypothesis: S-albuterol increases airway hyperresponsiveness

If true, this would result in less hyperresponsiveness after administration of levalbuterol than after administration of the racemic formulation. The study by Nelson et al showed that after 4 weeks of treatment there was a small increase in baseline FEV₁ with placebo or leval-

buterol but not with racemic albuterol. This was statistically significant only in a subgroup of subjects using inhaled corticosteroids. The authors suggested that this might have been due to an increase in airway responsiveness caused by the S-enantiomer.

Four studies have directly tested this hypothesis using bronchoprovocation techniques.¹⁸⁻²¹ The brief report of Perrin-Fayolle¹⁸ indicated a significantly lower PC₂₀ FEV₁ to methacholine 3 hours after treatment with S-albuterol in comparison with placebo. However, the other 3 studies failed to find changes in responsiveness to methacholine or adenosine monophosphate from inhalation of single^{19,20} or multiple²¹ doses of S-albuterol.

Thus evidence in support of the hypothesis that S-albuterol increases airway hyperresponsiveness is at best inconclusive.

Hypothesis: S-albuterol is responsible for inducing some or all of the paradoxical bronchospasm seen with racemic albuterol

If true, this would result in a lower incidence of paradoxical bronchospasm after treatment with R-albuterol than after treatment with R,S-albuterol. Unfortunately, there are no studies that directly test this hypothetical adverse effect of S-albuterol.

Hypothesis: S-albuterol itself causes some of the systemic effects seen with inhaled albuterol

No authors of published preclinical studies or of papers that reviewed these studies have actually posed this hypothesis. Nonetheless, 2 other groups of authors have addressed this issue in normal volunteers.^{22,23} In addition, the current report by Lötvall et al⁴ addresses the issue in subjects with asthma. All of these reports concluded that all observed systemic effects of racemic albuterol are due to the R-enantiomer.

So where are we now regarding a basis for decision-making? Although the preclinical data remain intriguing, available clinical data provide little support for the routine use of levalbuterol over the racemic formulation. Perhaps adverse effects of S-albuterol can be demonstrated in more severely ill asthmatic patients seen in the emergency room or intensive care unit when much larger doses are given for sustained periods. Studies in these clinical settings using appropriate methodology would be of interest.

For now, however, we have to deal with the data at hand concerning the potential benefits and costs of using pure R-albuterol over the traditional racemic formulation. Taken as a whole, the available data provide no evidence that levalbuterol is any safer or more effective than doses of racemic albuterol that contain equimolar doses of R-albuterol. Similar views have been expressed by others.^{24,25} Thus there appears to be no compelling reason to use levalbuterol rather than any other preservative-free albuterol aerosol. Considering the greater cost that is

TABLE I. Range of costs per usual dose for different formulations of albuterol aerosol preparations taken from 4 major online-pharmacy Web sites

Produce	Price range per dose (US \$)
Xopenex (0.63 or 1.25 mg/3 mL)	1.91 - 2.17
Albuterol (2.5 mg/3 mL)	0.80 - 0.88
Albuterol MDI (200 inhalations, 2 inhalations/dose)	0.14 - 0.20

currently associated with Xopenex (Table I), routine use of this product has the potential to increase the cost of asthma care without identified benefit.

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