Levalbuterol in the Treatment of Patients With Asthma and Chronic Obstructive Lung Disease

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Effective asthma control requires long-term (anti-inflammatory) controller medications for patients with mild-persistent to severe-persistent disease, and quick-relief bronchodilator medication for all patients with asthma to control intermittent symptoms of cough, wheeze, and bronchoconstriction, as well as acute exacerbations. For patients with chronic obstructive pulmonary disease, quick-relief and long-acting bronchodilators are primarily used in the maintenance and treatment of associated symptoms, including shortness of breath. For many years, the most widely used bronchodilator has been racemic (R, S)-albuterol, a short-acting β2-adrenergic agonist, commonly dispensed as an inhaled aerosol or solution.

Until the introduction of levalbuterol inhalation solution (Xopenex) in 1999, all marketed forms of albuterol (including Ventolin and Proventil brands) were racemic mixtures composed of a 1:1 ratio of (R)- and (S)-stereoisomers. Administered as a proportionally equivalent nebulized dose, levalbuterol [(R)-albuterol] provides greater bronchodilation than racemic albuterol and, in the appropriate clinical setting, offers the possibility for improving clinical outcomes in patients with asthma and other obstructive airway diseases. Additionally, levalbuterol can be given at lower doses than racemic albuterol to provide comparable bronchodilation, with the potential for reduced β-mediated adverse effects in adults and children. Only since the past decade has the technology to separate stereoisomers become available, and thus the biologic activities of the albuterol stereoisomers had not been established.

Binding studies have demonstrated that (R)-albuterol binds to the β2-adrenergic receptor with a high affinity, whereas (S)-albuterol binds with 100-fold less affinity than (R)-albuterol. Other evaluations have suggested that (R)-albuterol possesses the bronchodilatory, bronchoprotective, and ciliary-stimulatory properties of racemic albuterol, while (S)-albuterol does not contribute beneficially to the therapeutic effects of the racemate and was originally assumed to be inert. However, preclinical evaluations have shown that (S)-albuterol has effects that work in opposition to (R)-albuterol and may diminish the therapeutic effects of (R)-albuterol.

Asthma is a prevalent and costly condition. As many as 15 million Americans, one third of whom are children, have asthma. In addition to the direct costs associated with asthma treatment, which are estimated to be more than $7 billion annually, there are significant indirect costs associated with the condition, such as time lost from school or work and reduced quality of life. The psychosocial toll of asthma can be substantial, especially in families with young children who have frequent exacerbations or night awakenings due to poorly controlled symptoms.

Like asthma, the burden of chronic obstructive pulmonary disease (COPD) is also considerable. Approximately 16 million Americans have COPD, a disease that is most prevalent in Caucasians older than 45 years of age. The direct costs of COPD are significant, with approximately $30 billion spent during 2000 in the United States alone, most of which can be attributed to monies spent on hospital and inpatient care.

Despite the recent development of new maintenance therapeutics for long-term control of asthma (leukotriene receptor antagonists and modifiers, anti-IgE), short-acting β2-agonists are still the quick-relief medications of choice to provide bronchodilation and to alleviate symptoms of cough, wheeze, and chest tightness, regardless of the patient’s asthma severity (Table).

For treatment of patients with COPD, β2-agonists are recommended both on a regular schedule and as needed to improve patients’ pulmonary function, depending on disease progression (phases I through III).

Racemic albuterol [(R, S)-albuterol], a selective β2-agonist and the most commonly prescribed short-acting β-agonist in the United States, has become the foundation for symptom management of asthma and other obstructive airway diseases, including COPD. Despite physicians’ and patients’ reliance on racemic albuterol, some questions have been raised and some dismissed regarding the negative effects of its regular and excessive use by patients. Results of recent research using animals and cellular models has substantiated...
ated these clinical concerns\textsuperscript{13-15} and suggested some problems associated with the drug may stem from (S)-albuterol, which is found in the racemic mixture.\textsuperscript{16}

Clinical studies addressing the activity of levalbuterol [(R)-albuterol], which formed the basis for the US Food and Drug Administration’s approval of the product,\textsuperscript{17} were designed to investigate its safety and efficacy compared with placebo and included racemic albuterol as an active control. Although they were neither designed nor powered to demonstrate statistically significant differences between active treatments,\textsuperscript{18,19} results obtained from these large clinical studies have suggested that equal amounts of (R)-albuterol administered as a single isomer provide greater bronchodilation than (R)-albuterol administered as a racemate, while reduced amounts of (R)-albuterol administered as a single isomer provide comparable bronchodilation with reduced /H9252-mediated adverse effects compared with the standard dose of racemic albuterol.\textsuperscript{18,19} It is important that primary care physicians are aware of recent data regarding racemic albuterol and the therapeutic alternative, levalbuterol. This article reviews recent levalbuterol trials and discusses the use of \(\beta\)-agonists for treating patients with respiratory distress.

A Medline search was performed to identify large, randomized, controlled clinical trials that included both levalbuterol and the active comparator racemic albuterol. Other relevant studies in pediatric and adult patient populations were included for discussion. In evaluating the historic clinical use of \(\beta\)-agonists, single-isomer drug development, and preclinical studies regarding albuterol stereoisomers, both recent and older “landmark” references have been cited.

### Racemic Albuterol

Albuterol is manufactured as a racemic mixture, containing equal parts of its stereoisomers, (S)-albuterol and (R)-albuterol (Figure 1). The ability to separate stereoisomers derived from a racemic mixture is relatively new. Thus, in 1992, the Food and Drug Administration adopted guidelines similar to those already established in Canada, Europe, and Japan mandating that pharmaceutical companies characterize the properties of individual isomers within racemic mixtures in new drug applications.\textsuperscript{20} This policy has created a foundation for the development of single-isomer drugs in the United States and other countries.

Studies examining the individual biological characteristics of (R)- and (S)-albuterol stereoisomers have been performed: in vitro binding experiments have demonstrated that, like naturally occurring (R)-epinephrine, (R)-albuterol is a potent ligand for the \(\beta_2\)-adrenergic receptor, having approximately 100 times greater receptor affinity than (S)-albuterol.\textsuperscript{21} Additionally, (R)-albuterol contributes all the clinical bronchodilator activity

<table>
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<td>Classification of Asthma Severity and the Corresponding Step Therapies\textsuperscript{6}</td>
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<tr>
<th>Symptoms</th>
<th>Nighttime symptoms</th>
<th>Lung function* FEV\textsubscript{1}</th>
<th>Peak flow variability*</th>
<th>Classification of asthma severity</th>
<th>Quick-relief bronchodilator medication</th>
<th>Long-term controller medication</th>
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<tr>
<td>(\leq \text{2/wk})</td>
<td>(\leq \text{2/mo})</td>
<td>(\geq \text{80}%)</td>
<td>(&lt; \text{20}%)</td>
<td>Step 1. Mild intermittent</td>
<td>As needed</td>
<td>None</td>
</tr>
<tr>
<td>(&gt; \text{2/wk})</td>
<td>(&gt; \text{2/mo})</td>
<td>(\geq \text{80}%)</td>
<td>(20%-30%)</td>
<td>Step 2. Mild persistent</td>
<td>As needed</td>
<td>Single anti-inflammatory agent</td>
</tr>
<tr>
<td>Daily symptoms</td>
<td>(&gt; \text{1/wk})</td>
<td>(&gt;60%) and (&lt; \text{80}%)</td>
<td>(&gt; \text{30}%)</td>
<td>Step 3. Moderate persistent</td>
<td>As needed</td>
<td>ICS; add LABA if needed</td>
</tr>
<tr>
<td>Continual symptoms</td>
<td>Frequent</td>
<td>(\leq \text{60}%)</td>
<td>(&gt; \text{30}%)</td>
<td>Step 4. Severe persistent</td>
<td>As needed</td>
<td>Multiple controller medications; add oral steroid if needed</td>
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\*Peak flow differences measured according to the predicted or expected value for patient’s height and weight.

ICS indicates inhaled corticosteroid; LABA, long-acting \(\beta\)-agonist.
of the racemate. In vitro and in vivo experimental models have shown that (S)-albuterol has activity and may work in opposition to (R)-albuterol by promoting bronchoconstriction, as well as various proinflammatory responses, including immune cell proliferation and cytokine production. In light of clinical observations that suggest racemic albuterol and other β-agonists can paradoxically exacerbate asthma and possibly contribute to the mortality associated with the disease, these preclinical findings should warrant clinical consideration. Of additional concern is the fact that (S)-albuterol is metabolized and eliminated tenfold more slowly than (R)-albuterol, resulting in the relative accumulation of the (S)-isomer over (R)-albuterol and its sustained presence in the plasma and lung tissue of patients after the (R)-isomer has been cleared.

Clinical Activity of Single-Isomer Levalbuterol

A 4-week, randomized, double-blind, parallel-group study evaluated 362 patients aged 12 years and older with moderate to severe asthma (forced expiratory volume in 1 second [FEV₁] between 45% and 70% of predicted). In this study, subjects were randomly assigned to receive nebulized levalbuterol (0.63 mg or 1.25 mg), equivalent amounts of (R)-albuterol administered as racemic albuterol (1.25 mg or 2.5 mg), or placebo three times daily for 4 weeks. The mean percent change in FEV₁ after the first dose was significantly greater in the combined levalbuterol group than in the combined racemic albuterol group. There were similar, though statistically non-significant, improvements in FEV₁ measured at week 4 in the groups receiving levalbuterol compared with those receiving racemic albuterol. The greatest mean percent change in FEV₁ and the longest duration of improvement were seen in patients treated with levalbuterol 1.25 mg, whereas the smallest mean percent change in FEV₁ and the shortest duration of improvement were seen in patients treated with racemic albuterol 1.25 mg (Figure 2). Patients receiving levalbuterol 0.63 mg had improvements in FEV₁ comparable to those receiving racemic albuterol 2.5 mg, but had significantly lower increases in ventricular heart rates. A post hoc analysis of serial pulmonary function data pooled from 4 randomized, double-blinded levalbuterol studies using racemic albuterol as an active comparator has shown that, after the first dose, levalbuterol 1.25 mg produced significantly greater bronchodilation than racemic albuterol 2.5 mg, as measured by area under the curve for the normalized mean percent change in FEV₁ versus time curve (P < .05).

Additionally, compared with patients receiving placebo, those receiving levalbuterol 1.25 mg had a reduced need for rescue medication (racemic albuterol metered dose inhaler) between regularly scheduled treatments by an average of 2.2 puffs per day. Corticosteroid-naïve patients who received levalbuterol or placebo had a mean 300-mL improvement in baseline pulmonary function during the 4-week study. In contrast, corticosteroid-naïve patients receiving racemic albuterol demonstrated slightly reduced baseline pulmonary function after 4 weeks of treatment. This phenomenon of reduced
pulmonary function has been observed in other, but not all, studies of prolonged use of racemic albuterol.\textsuperscript{9,10}

Another multicenter, double-blind study evaluated 338 pediatric subjects aged 4 to 11 years (FEV\textsubscript{1} 40\% to 85\% of predicted) who were randomized to receive nebulized levalbuterol (0.31 mg or 0.63 mg), racemic albuterol (1.25 mg or 2.50 mg), or placebo three times daily for 21 days.\textsuperscript{19} Patients in all active treatment groups, including levalbuterol 0.31 mg and 0.63 mg, showed significant improvement in FEV\textsubscript{1} compared with those administered placebo (overall \( P < .001 \)), producing mean peak percent changes for placebo, levalbuterol 0.31 mg and 0.63 mg, and racemic albuterol 1.25 mg and 2.50 mg of 2.0\%, 19.0\%, 18.1\%, 12.4\%, and 15.6\%, respectively. The 0.31-mg dose of levalbuterol was the only active treatment that did not differ from placebo with respect to changes in heart rate (\( P > .05 \)). Although this study was prospectively designed to compare racemic albuterol and levalbuterol to placebo and not to each other, the data show that levalbuterol was the only active treatment that did not differ from placebo with respect to changes in heart rate (\( P > .05 \)).

Levalbuterol is currently available as an inhalation solution, with a labeled indication for the treatment and prevention of bronchospasm in adults, adolescents, and children 6 years of age and older with reversible obstructive airways disease. The recommended dose is levalbuterol 0.31 mg three times daily for children 6 to 11 years and 0.63 mg three times daily for adults and children 12 years and older. A higher dosage (1.25 mg three times daily) can be administered to patients 12 years of age and older who have more severe asthma or do not respond adequately to a dose of 0.63 mg. A levalbuterol hydrofluoroalkane metered dose inhaler formulation is currently under development.

Because levalbuterol costs more than racemic albuterol, which is available in generic formulations, health care professionals have questioned whether the clinical benefits outweigh the higher acquisition cost, and some have suggested that they may not.\textsuperscript{30} However, it is important to not only consider the drug acquisition costs, but also the impact a drug may have on the total cost of care. For example, in a double-blind, randomized clinical trial among children aged 1 to 18 years treated for asthma exacerbations in an emergency department, there was a 9.4\% absolute reduction in the hospital admission rate (20\% relative reduction) among children treated with levalbuterol 1.25 mg (36\%, 101 of 278 children), compared with those treated with racemic albuterol 2.5 mg (45\%, 122 of 269 children) that was statistically significant (\( P < .02 \)).\textsuperscript{31}

Similarly, a retrospective chart review of more than 700 patients presenting to the emergency department with asthma exacerbations found that levalbuterol (1.25 mg) used in place of racemic albuterol (2.5 mg) resulted in statistically significant reductions in hospital admissions (15.1\% admissions with racemic albuterol versus 4.7\% admissions with levalbuterol; \( P = .0016 \)).
Another retrospective study among patients hospitalized with asthma or COPD showed that levalbuterol administered 1.25 mg every 8 hours and as needed, used in place of racemic albuterol administered 2.5 mg every 4 hours and as needed, shortened lengths of hospital stay by 16%, or 0.91 days (P = .058).33 On average, patients receiving levalbuterol were administered 38% fewer nebulized treatments (ipatropium bromide and β-agonist treatments) per hospital stay (19 ± 12.7 treatments for levalbuterol, and 30.8 ± 24 treatments for racemic albuterol), as well as 60% fewer ipatropium bromide treatments. Furthermore, despite less frequent dosing of levalbuterol than racemic albuterol, fewer levalbuterol patients required rescue medications of any kind between regularly scheduled doses. Total hospital costs for patients receiving levalbuterol compared to racemic albuterol were lower (P = .1); on average, levalbuterol therapy reduced the cost of care for both asthma and COPD patients by approximately $600.33 Thus, these study results suggest a possibility for reduced hospital admissions, less frequent bronchodilator treatments, and an overall cost savings with the use of levalbuterol in place of racemic albuterol in acute care settings. When considered in the context of data taken from large outpatient studies in adults and children with asthma, the use of levalbuterol in place of racemic albuterol may also provide greater clinical benefits in ambulatory patients.

Racemic albuterol has been an important bronchodilatory agent for obstructive airway diseases in both emergent and ambulatory treatment settings for many years. However, large, well-controlled clinical studies performed in adults with asthma have shown that nebulized levalbuterol 1.25 mg produces greater bronchodilation than the standard 2.5-mg dose of racemic albuterol, while levalbuterol 0.63 mg results in bronchodilation that is similar to that provided by racemic albuterol 2.5 mg but with fewer β-mediated side effects.18 Additionally, studies in children with asthma have shown that 0.63- and 0.31-mg doses of levalbuterol produce bronchodilation that is comparable to that experienced by patients treated with racemic albuterol 2.5 mg and 1.25 mg.19 Lower dosing of the (R)-albuterol isomer to patients with the use of levalbuterol provides comparable or superior bronchodilation as racemic albuterol, with the potential for fewer β-mediated side effects. Both clinical trials and preclinical experiments have suggested that the inclusion of (S)-albuterol in racemic albuterol provides no clinical benefit and may oppose some of the therapeutic benefits of the (R)-isomer (levalbuterol).

References


