The Cost Effectiveness of Levalbuterol Versus Racemic Albuterol

Campion Quinn, MD, FACP, MHA

Abstract

Albuterol is a selective β_2-agonist that is widely used in the prevention and treatment of reactive airway disease. It is formulated as a racemic mixture containing equal parts of the R- and S-isomers. The therapeutic activity of albuterol is due entirely to the R-isomer, whereas the S-isomer may actually have detrimental effects. Because the slowly metabolized S-isomer tends to accumulate in the body, there has been concern that chronic use of racemic albuterol might lead to loss of effectiveness and clinical deterioration, with potentially serious health and cost consequences. Levalbuterol is a formulation containing only the R-isomer of albuterol, and clinical trials have demonstrated that it offers therapeutic advantages over racemic albuterol. The cost effectiveness of levalbuterol derives mainly from reduced need for acute medical care and hospitalization.

(Am J Manag Care. 2004;10:S153-S157)

Asthma is a serious, common, and growing health problem in the United States. During the period 2000-2001, 20.3 million Americans, including 6.3 million children and adolescents, reported having asthma. In these patients, the annual toll attributed to asthma included 12 million acute attacks, over 10 million outpatient visits of which almost 2 million were to emergency departments, almost a half-million hospitalizations, and nearly 5000 deaths.[1]

Moreover, the burden of asthma has been growing steadily in all age/sex/ethnic groups. The age-adjusted prevalence rose from 30.7 per 1000 in 1980 to 53.8 per 1000 as the 2-year average for 1993-1994—a 75% increase. Among children aged 5 to 14 years, the overall prevalence is higher and the increase since 1980 has been steeper.[2] A study examining health claims and prescription data for the year 1987 noted the following: when compared to a cohort of nonasthmatic children, children with asthma accounted for 3.1 times as many prescriptions, 1.9 times as many outpatient visits, 2.2 times as many emergency department visits, 3.5 times as many hospitalizations, and 2.8 times the mean total medical expenditure.[3] For the American population in general, total annual asthma-related costs were estimated at $11.3 billion in 1992 and $14 billion in a 2002 report.[4] Asthma accounts for 14 million lost school days for pediatric patients and 14.5 million lost work days for adults.[5]

Costs associated with hospitalizations are the most expensive element in acute asthma management. One positive development is that the rate of hospitalization is decreasing; therefore, the cost of hospitalization represents a declining percentage of total direct medical expenditures.[6] This change is due, in large measure, to improved pharmacotherapy.

One class of drugs—short-acting β_2-agonists—has emerged as the mainstay of acute asthma management. Albuterol has been the most widely used agent of this class.

In this report, we compare the β_2-agonists levalbuterol and albuterol in terms of pharmacology, clinical profile, and cost effectiveness.

Beta-Agonists: A History of Increasing Refinement of Pharmacologic Effects

Beta-adrenergic agonist activity has numerous therapeutic benefits in asthma management, including relaxation of bronchial smooth muscle, reduction in airway reactivity to spasmogens, decreased inflammation, diminished mucosal edema, and improved mucociliary activity to remove allergens and clear the airways.

The first commercial product offering β-agonist activity was synthetic epinephrine.

Although it is therapeutically effective, it also produces α-adrenergic effects such as increased heart rate, hypertension, and agitation. Eventually, its clinical role in asthma treatment was restricted to emergency care for acute episodes.

Isoproterenol offered β-agonist activity without α activity, but it nevertheless incurred a substantial risk of cardiac side effects. The reason is that its β activity is nonselective—β_2 activity provides the therapeutic effects in asthma treatment, whereas β_1 activity causes increases in heart rate and contractility.[7]

Albuterol was the first agent offering selective β_2 activity. However, like all the earlier synthetic β-agonists, albuterol is a racemic mixture of R- and S-enantiomers. Although the R- and S-isomers are chemically identical, they may have profoundly different physiologic effects. The therapeutic effects in relieving asthma are delivered entirely by the R-isomer of albuterol.

This process of increasing refinement of pharmacologic effect reached what may be its logical conclusion with levalbuterol, a selective β_2-agonist formulated as the pure R-isomer. In 1999, levalbuterol was approved in doses of 0.63 and 1.25 mg for patients aged 12 years and up; in 2002, it was approved in doses of 0.31 and 0.63 mg for children aged 6 through 11.

Pharmacology

The binding of the R-isomer of a β_2-agonist to airway smooth muscle receptors activates adenylcyclase and increases cyclic adenosine monophosphate, with 2 effects: (1) lowering of intracellular calcium, leading to muscle relaxation; and (2) inhibiting the release of inflammatory mediators from airway mast cells. These bronchodilatory and protective effects occur throughout the airway system, regardless of the spasmogenic trigger.

The S-isomer of racemic albuterol was long assumed to be pharmacologically inert. However, evidence now suggests that it may cause bronchoconstriction, increased airway hyperreactivity, and increases in eosinophil activity and histamine production. These effects compromise the therapeutic activity of the R-isomer, as demonstrated by research showing that levalbuterol is more effective than racemic albuterol in doses containing the same amount of the R-isomer.[8]

In addition, because metabolism of the S-isomer is much slower than that of the R-isomer, ongoing treatment with racemic albuterol can lead to an accumulation of the S-isomer. The potential clinical result would be gradually diminishing effectiveness, marked by shorter intervals between treatments, a smaller response to treatment, and even a risk of paradoxical bronchospasm. However, clinical studies have shown inconsistent results concerning detrimental effects from chronic use of racemic albuterol.

Levalbuterol is not free of side effects. β_2-receptors are found mainly in the vascular system. The main clinical effect of β_2-agonist activity on the cardiovascular system is peripheral vasodilation, which may cause a reflex increase in heart rate; however, the therapeutic improvement in pulmonary function may have the effect of reducing heart rate,[7] and the effects of an agonist at these sites are dose-dependent with both levalbuterol and racemic albuterol.

Clinical and Cost Effectiveness

The literature directly comparing levalbuterol and racemic albuterol in terms of cost effectiveness is limited but compelling. Cost effectiveness can also be inferred from clinical data showing a reduced need for hospitalization (**Table**). Although medication accounts for the greatest portion of direct medical costs for asthma management on a population basis,[6] those patients who require hospitalization incur greatly increased costs.

In a randomized, double-blind trial, Milgrom et al[9] treated 338 asthmatic children (ages 4-11, FEV_1 [forced expiratory volume in 1 second] 40%-85% of expected normal) with 3-times-daily doses of nebulized levalbuterol (0.31 or 0.63 mg), racemic albuterol (1.25 or 2.5 mg), or placebo for 21 days. Immediately after nebulization, median improvements in FEV_1 were 2% with placebo, 19% and 18.1% with levalbuterol 0.31 and 0.63 mg, and 12.4% and 15.6% with racemic albuterol 1.25 and 2.5 mg.

Both doses of levalbuterol provided greater bronchodilation compared with racemic albuterol 1.25 mg (P <.05), and higher doses of levalbuterol were more effective in the subset of patients with more severely depressed FEV_1 at baseline.

In an open-label dose-escalation trial, Nowak et al[10] sequentially assigned 91 asthmatic patients (mean age 33, median baseline FEV_1 1.2 L or 39% of predicted) to levalbuterol 0.63, 1.25, 2.5, 3.75, or 5.0 mg, or racemic albuterol 2.5 or 5.0 mg; treatments were given in 3 nebulized doses, 20 minutes apart. Median improvement in FEV_1 after the first dose was 56% with levalbuterol 1.25 mg versus 5% and 14% with racemic albuterol 2.5 and 5.0 mg. Better results were observed with levalbuterol 1.25, 2.5, and 5.0 mg (final median FEV_1 2.1-2.3 L) than with levalbuterol 0.63 and 3.75 mg and both doses of racemic albuterol (1.5-1.8 L; the relatively poor performance of the 3.75-mg formulation of levalbuterol is difficult to explain). In patients with very low baseline FEV_1, the improvement was 10 times greater with levalbuterol than with racemic albuterol (75% vs 3.2%-7.5%), which is important because lack of improvement in FEV_1 is associated with an increased likelihood of hospitalization.

In children with asthma, FEV_1 values were comparable after treatment with levalbuterol 0.31 and 0.63 mg and racemic albuterol 2.5 mg; in children treated with levalbuterol 1.25 mg, FEV_1 values were superior to those in children treated with racemic albuterol.[11] Another retrospective comparative study showed that the rate of hospitalization following treatment for acute asthma was significantly lower with levalbuterol than with racemic albuterol (5% vs 15%; P <.002).[12]

Both levalbuterol and racemic albuterol are generally well tolerated by asthmatic patients.[8] Some reports indicate that levalbuterol has fewer β_2-mediated side effects.[9,11]

The cost effectiveness of averting hospitalization for asthma was demonstrated dramatically in the double-blind study by Carl et al,[13] in which 482 children aged 1 to 18 years were assigned to levalbuterol 1.25 mg or racemic albuterol 2.5 mg administered every 20 minutes to a maximum of 6 doses in 2 hours. Patients having an inadequate response after 2 hours would then be admitted. There were significantly fewer hospitalizations with levalbuterol than with racemic albuterol (37% vs 45%; P = .02), and the number needed to treat with levalbuterol to avert a hospitalization was 10.6 patients. At the study institution (an urban tertiary-care children's hospital), a 9% reduction in the annual average of 1000 hospitalizations for asthma would save $180 000 minus the additional drug acquisition costs for levalbuterol ($1.25/vial x 4 vials/patient = $5/patient).

Another noteworthy cost-effectiveness analysis was a retrospective study by Truitt et al.[14] Among patients hospitalized for asthma or chronic obstructive pulmonary disease (COPD), charts were reviewed from 125 patients treated with racemic albuterol 0.5 mg at 4-hour intervals (July-December 1998) and from 109 patients treated with levalbuterol 1.25 mg at 8-hour intervals (July-December 1999). Injected corticosteroids were given to almost all patients; all COPD patients and asthma patients with infection also received antibiotics, and ipratropium was used as needed. Medication and other hospital costs were calculated using Medicare reimbursement rates and 1999 Red Book listings of wholesale drug costs. The goal was to assess the amount and cost of treatment needed to achieve comparable therapeutic benefit (improvement in FEV_1 sufficient for discharge) with each drug.

Table. Key Cost-effectiveness Trials of Levalbuterol Versus Racemic Albuterol

Investigators	Conclusions
Milgrom et al, 2001[9]	Levalbuterol was as effective as 4-fold to 8-fold higher doses of racemic albuterol
Nowak et al, 2004[10]	Less need for hospital admission with levalbuterol than with racemic albuterol
Carl et al, 2003[13]	Fewer hospitalizations and calculated substantial cost savings with levalbuterol versus racemic albuterol
Truitt et al, 2003[14]	Shorter hospital stay, lower risk of rehospitalization, and lower cost with levalbuterol versus racemic albuterol

The lower mean number of treatments with levalbuterol versus racemic albuterol (19.0 vs 30.8; P <.001) was partly due to protocol-mandated differences in the dosing schedules. (A published letter challenged the study on this basis and also for using average wholesale prices, which may be different from what hospitals actually pay. The study investigators responded that the need for more frequent dosing with racemic albuterol than with levalbuterol to achieve an adequate clinical response was the very point of the study, and that average wholesale prices are standard in cost analyses.[15]) However, the protocol did not account for the fact that the mean duration of β_2-agonist treatment was 29% shorter with levalbuterol than with racemic albuterol (5.5 vs 3.9 days), or that patients receiving levalbuterol versus racemic albuterol required fewer adjunctive treatments with ipratropium (mean 9.4 vs 23.2; P <.001) and had a lower 30-day rehospitalization rate (mean 5.7% vs 16.4%; P = .01). This difference was noted mainly in the subset of patients with COPD, and other factors may have affected the risk of readmission. Overall costs for delivering nebulized medications were significantly lower with levalbuterol than with racemic albuterol (for all patients $61 vs $112, P <.001; among asthma patients, $44 vs $99, P <.005). Total hospital costs were numerically lower (for all patients $2756 vs $3225, P = .11; among asthma patients, $1856 vs $2503). Regression analysis controlling for baseline FEV_1, diagnosis, and ipratropium use showed that levalbuterol was associated with a 0.9-day shorter stay (P = .015), a 67% lower rate of rehospitalization (P = .056), and total cost savings of $556 per patient ($P$ = .013).

The Economics of Asthma Care

Assessing the costs of asthma and its treatment, and the cost effectiveness of specific therapies, is a daunting task. A review by Sculpher and Price[16] outlines several of the difficulties, starting with the fact that looking at total direct and indirect costs does not address the disproportionate share of costs incurred by patients with severe asthma or the unnecessary costs attributable to suboptimal management. Moreover, published reports employ such a variety of methods, outcome measures, and definitions that their findings are difficult to compile and compare. Finally, most cost-effectiveness data emerge from short-term studies of clinical efficacy, safety, and tolerability, and such findings are not necessarily predictive of long-term outcomes.

In an attempt to sort out the numerous variables that must be considered in all clinical-economic evaluations of drugs, Eisenberg and colleagues[17] proposed a 3-dimensional model: (1) type of analysis (cost identification, cost effectiveness, cost benefit); (2) point of view (patient, clinician, insurer, society); and (3) types of outcome measures (direct and indirect costs, morbidity and mortality, intangible or unquantifiable results). For example, quantifiable clinical outcomes are usually of most interest to physicians, less readily quantifiable outcomes such as quality of life reflect the patient's point of view, while cost-effectiveness analyses aimed at obtaining the best clinical outcome at the lowest cost are of greatest concern to managed care, insurers, and government.

Applying this model to asthma, the economic comparison of levalbuterol versus racemic albuterol involves cost-effectiveness analysis from the point of view of the clinician and the insurer, with the focus on direct medical costs. Yet further definition is necessary; for example, pharmacy services may focus only on drug acquisition costs, but the overall cost to the medical facility and insurer may be more strongly affected by such clinical outcomes as needed for hospitalization. In the previously cited pediatric study,[13] the number needed to treat (with levalbuterol instead of racemic albuterol) to avert a hospitalization was only 10.6 patients; the incremental cost of levalbuterol for such a small number of patients is minuscule compared with the cost of a single hospitalization.

Most studies that reflect the interests of the clinical audience have focused on objective measures of efficacy, such as FEV_1. However, efficacy in the ideal setting of a well-designed clinical trial is not the same as effectiveness in the real-world setting of actual clinical practice. For example, how

should a worsening FEV_1 be interpreted in clinical practice? Assuming adequate adherence to treatment, it may be difficult to determine whether the patient's condition is becoming more severe or the drug is losing its effectiveness. With the latter possibility, loss of effectiveness may be an intrinsic problem with the drug or the result of something else happening in that patient, such as a drug interaction that induces increased metabolism of the asthma medication.

Just as it is difficult to gauge the overall therapeutic worth of an asthma drug from changes in FEV_1 in a short-term controlled clinical trial, it is difficult to assess a drug's cost effectiveness by looking only at direct medical expenditures recorded in that same trial. A working group from the National Heart, Lung, and Blood Institute reviewed the role of health economics in planning optimal asthma management strategies, and offered a set of recommendations for future research, including adoption of standardized definitions and outcome measures, a focus on long-term effectiveness rather than short-term efficacy, and controls for such variables as patients' age and socioeconomic status, and the duration and severity of asthma.[18]

Conclusion

From the evidence currently available, it appears that levalbuterol represents a clinically important advance over racemic albuterol. The advantage in clinical efficacy (ie, improved respiratory performance) is matched by an advantage in cost effectiveness, which leads to a reduction in the need for hospitalization. Long-term follow-up in the clinical practice setting may determine the degree to which these short-term advantages are maintained.

REFERENCES

1. Asthma Prevalence, Health Care Use, and Mortality, 2000-2001. National Center for Health Statistics, Centers for Disease Control and Prevention.

2. Data Fact Sheet: Asthma Statistics. National Heart, Lung, and Blood Institute, National Institutes of Health; January 1999.

3. Lozano P, Sullivan SD, Smith DH, Weiss KB. The economic burden of asthma in US children: estimates from the National Medical Expenditure Survey. *J Allergy Clin Immunol.* 1999;104:957-963.

4. Morbidity & Mortality: 2002 Chart Book on Cardiovascular, Lung, and Blood Diseases. National Heart, Lung, and Blood Institute, National Institutes of Health, May 2002.

5. Surveillance for Asthma—United States, 1980-1999. Morbidity and Mortality Weekly Report Surveillance Summaries, Centers for Disease Control and Prevention, March 29, 2002.

6. Weiss KB, Sullivan SD. The health economics of asthma and rhinitis. I. Assessing the economic impact. *J Allergy Clin Immunol.* 2001;107:3-8.

7. Hoffman BB. Catecholamines, sympathomimetic drugs, and adrenergic receptor antagonists. In: Hardman JG, Limbird LE, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics.* 10th ed. New York, NY: McGraw-Hill; 2001.

8. Nelson HS, Bensch G, Pleskow WW, et al. Improved bronchodilation with levalbuterol compared to racemic albuterol in patients with asthma. *J Allergy Clin Immunol.* 1998;102:943-952.

9. Milgrom H, Skoner DP, Bensch G, Kim KT, Claus R, Baumgartner RA, Levalbuterol Pediatric Study Group. Low-dose levalbuterol in children with asthma: safety and efficacy in comparison with placebo and racemic albuterol. *J Allergy Clin Immunol.* 2001;108: 938-945.

10. Nowak RM, Emerman CL, Schaefer K, DiSantostefano RL, Vaickus L, Roach JM. Levalbuterol compared with racemic albuterol in the treatment of acute asthma: results of a pilot study. *Am J Emerg Med.* 2004;22:29-36.

11. Gawchik SM, Saccar CL, Noonan M, Reasner DS, DeGraw SS. The safety and efficacy of nebulized levalbuterol compared with racemic albuterol in the treatment of asthma in pediatric patients. *J Allergy Clin Immunol.* 1999;103:615-621.

12. Schreck D, Brotea C, Shah S. Comparison of racemic albuterol and levalbuterol in the treatment of acute asthma. *Ann Emerg Med.* 2001;38:S10. Abstract.

13. Carl JC, Myers TR, Kirshner HL, Kercsmar CM. Comparison of racemic albuterol and levalbuterol in treatment of acute asthma. *J Peds.* 2003;143:731-736.

14. Truitt T, Witko J, Halpern M. Levalbuterol compared to racemic albuterol: efficacy and outcomes in patients hospitalized with COPD or asthma. *Chest.* 2003;123:128-135.

15. Hendeles L, Hartzema A. Levalbuterol is not more cost-effective than albuterol for COPD (letter). *Chest.* 2003;124:1176-1178.

16. Sculpher MJ, Price M. Measuring costs and consequences in economic evaluation in asthma. *Resp Med.* 2003;97:508-520.

17. Eisenberg JM, Schulman KA, Glick H, Koffer H. Pharmacoeconomics: economic evaluation of pharmaceuticals. In: Strom BL, ed. *Pharmacoepidemiology.* 2nd ed. New York, NY: Wiley; 1994.

18. Sullivan S, Elixhauser A, Buist AS, Luce BR, Eisenberg J, Weiss KB. National Asthma Education and Prevention Program working group report on the cost effectiveness of asthma care. *Am J Respir Crit Care Med.* 1996;154(3 pt 2):S84-S95.