Albuterol Or Levalbuterol For The Treatment Of Asthma

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Citation

G Pesola, V D'Costa. *Albuterol Or Levalbuterol For The Treatment Of Asthma*. The Internet Journal of Asthma, Allergy and Immunology. 2003 Volume 3 Number 1.

Abstract

Albuterol is the most commonly used $_2$-agonist currently used in the treatment of asthma and COPD. Until recently, it was only available as a racemate, a 50:50 mixture of the dextro ((S)-albuterol) and levo ((R)-albuterol) rotatory forms. Previously, it was felt that the (S)-albuterol enantiomer was minimally active (distomer) relative to the (R)-albuterol enantiomer (eutomer). It is expensive to separate the racemic mixture of albuterol into its' individual enantiomers. If the racemate bronchodilates with less cost, the distomer was viewed as incidental isomeric ballast or filler. The general consensus has been that there was no need or incentive to increase the expense of production in synthesizing (R)-albuterol as an individual drug if the racemate could serve the same function at double the dose with no adverse effects. This view, however, has been subject to challenge and may not be correct.

The human 2 receptor has a greater than 90-fold affinity for (R)-albuterol relative to (S)-albuterol (1). This suggests that activation of $_2$ receptors occurs primarily from R-albuterol. This is consistent with pharmacodynamic studies (2,3). The distomer, aside from causing a small (possibly random or chiral inversion related) increase in potassium concentration had absolutely no systemic effects in 12 healthy volunteers given individual single oral doses of (R), (R,S), or (S)-albuterol (2). Inhaled doses of (R), (R,S), or (S)-albuterol in 15 healthy volunteers in a single day study gave no systemic effects with S-albuterol (3). These findings in humans are consistent with the concept that (S)-albuterol is a filler in racemic albuterol that is just going along for the ride.

REVIEW OF STUDIES

A number of studies have suggested that chronic dosing with (R,S)-albuterol for many months may result in an increase in bronchial hyperresponsiveness in some if not all asthmatics ($_{4,5,6}$). The mechanism underlying this effect is unknown but it appears to be a class effect of $_2$-agonists in general since it also occurs with terbutaline, fenoterol ($_7$) and the long acting $_2$-agonist salmeterol ($_8$). One of the postulated mechanisms for this effect for albuterol might be the adverse effect of the "inert" (S)-albuterol through non- $_2$-receptor mechanisms.

Animal studies have clearly demonstrated that bronchial hyperresponsiveness can occur with (S)-albuterol ($_{9,10}$). In addition, it appears that 10 days of treatment with R-albuterol in the guinea pig model does not cause bronchial hyperresponsiveness in contrast to (S)-albuterol and (R,S)-albuterol ($_{10}$). The (S)-albuterol induced bronchial hyperresponsiveness is not blocked by pretreatment with propranolol but is prevented by vagal nerve resection ($_9$). These studies suggest, in the animal model at least, that (S)-albuterol causes bronchial hyperresponsiveness by a non -adrenoceptor mechanism.

There are at least three human studies of acute dosing of (R), (R,S), or (S)- albuterol and the determination of bronchial hyperresponsiveness using methacholine ($_{11, 12, 13}$). The first suggested that inhalation of 100 ug of (R) or 200 ug of (R,S)- albuterol were bronchoprotective at 20 minutes but not 180 minutes ($_{11}$). At 180 minutes a 100 ug inhalation of (S)-albuterol increased bronchial hyperresponsiveness compared to placebo with no effect at 20 minutes. There were 10 mild volunteer asthmatics in each group. The other two studies looked at single inhalational dosing of (R), (R,S), and (S)- albuterol versus placebo and found no increased bronchial hyperresponsiveness at 180 minutes with (S)-albuterol ($_{12, 13}$). Both (R) and (R,S)-albuterol were bronchoprotective in the first hour or more as would be expected. Overall, these acute dosing studies in humans show no consistent convincing evidence that single inhalation doses of (S)- albuterol increase bronchial

hyperresponsiveness.

Tolerance to the nonbronchodilating effects of racemic β_2-agonists in asthmatics is well known ([14]). One chronic dosing study in humans compared the enantiomers of albuterol with racemic albuterol and placebo ([15]). Eleven mild to moderate asthmatics with an FEV_1 of at least 70% underwent a double blind 4 way crossover study receiving nebulized (R,S)-albuterol 2.5 mg, (R)-albuterol 1.25 mg, S-albuterol 1.25 mg or placebo three times a day for six days. Methacholine responsiveness did not change significantly in any group before or after treatment. The dose shift of methacholine changed significantly after six days in the (R,S) and (R)-albuterol groups implying less protection with single 200 ug doses of albuterol as is known for most β_2-agonists. In this one brief chronic dosing study in humans there was no evidence that S albuterol increased bronchial hyperresponsiveness.

Indirect evidence for toxicity of (S)-albuterol comes from a number of sources. It has been shown in bovine trachea that (S)-albuterol increases and (R)-albuterol decreases intracellular calcium ions, consistent with what would occur with bronchoconstriction or bronchodilation, respectively ([16]). This might imply that (S)-albuterol counteracts or minimizes the effects of R albuterol bronchodilation if the same findings occur in humans. This is further suggested when (R) or (S)-albuterol are exposed to isolated human bronchus ([17]). S-albuterol enhances and R-albuterol inhibits the contractile response of histamine and LTC_4 ([17]). These pharmacologic actions, if translated clinically, suggest that (S)-albuterol is a non β_2-agonist bronchoconstrictor that is actually inhibited or masked by the bronchodilating actions of its sister enantiomer, (R)-albuterol.

METABOLISM OF ALBUTEROL

Studies of metabolism in human tissues have revealed a 5-11 fold greater sulfoconjugation (and therefore deactivation) of the eutomer over the distomer in different human tissues ([18],[19]). Blood levels of the distomer after single doses of (R,S)- albuterol, given orally or inhaled, are much higher than the eutomer ([20],[21]). This probably translates into a predominance of the inactive (S)-albuterol product over time with repeated dosing of (R,S)-albuterol. The resulting blood levels of albuterol consist of the predominant inactive or potentially toxic (S)-albuterol and is the explanation why dose response curves from albuterol blood levels have never been successfully determined.

It should be remembered that any chiral drug is actually a mixture of two enantiomers, one of which is usually more active than the other. It is assumed that the less active enantiomer has no toxic properties and this may or may not be correct. In a sense, (R,S)-albuterol starts off as two drugs, one active and the other possibly toxic. The racemic mixture is a third drug, a combination of the two equal enantiomers. With time in the body, (R,S)-albuterol becomes predominantly (S)-albuterol secondary to stereoselective metabolism. It is unknown whether this transformation to predominantly (S)-albuterol over time might be the cause for a lot of the paradoxical bronchospasm seen with albuterol and other racemic β_2-agonist drugs present on the market currently. The alternative to this combination racemic drug is the use of the pure active enantiomer of albuterol, levalbuterol.

CLINICAL STUDIES COMPARING RACEMIC ALBUTEROL VERSUS LEVALBUTEROL

1. THE NELSON STUDY

The first major study comparing levalbuterol with racemic albuterol involved 362 asthmatics age 12 or older ([22]). Subjects were randomized to receive one of the following nebulized treatments three times daily for one month: levalbuterol 0.625 mg, levalbuterol 1.25 mg, 1.25 mg of racemic albuterol, 2.5 mg of racemic albuterol, or placebo. Serial pulmonary function testing with spirometry was done at baseline, 2 and 4 weeks. The sponsor of the study was Sepracor, who makes levalbuterol.

The mean peak change in FEV_1 was significantly greater than placebo at baseline for the first dose in all treatment groups. In addition, the mean peak change in FEV_1 at baseline (0.92 and 0.82L, respectively; p=0.03) but not at 4 weeks was significantly greater in the combined levalbuterol group compared to the combined racemic albuterol group. To determine the effect of chronic dosing on lung function, the mean predose FEV_1 at week 4 compared to baseline for all patients and for the subset of patients who did not receive inhaled corticosteroids was examined. Looking at all patients, there was a 0.1-liter improvement (about 6%) in predose FEV_1 in the subjects receiving levalbuterol and those on placebo and none in subjects on racemic albuterol. In the subset of patients not on inhaled corticosteroids, there was a 0.13 and 0.31 liter (7 and 15%) difference between predose FEV_1 in subjects receiving 0.625 mg and 1.25 mg of levalbuterol when compared with those receiving 1.25 and 2.5 mg of racemic albuterol, respectively. As the authors specifically note, the greatest improvement was in the 1.25

mg levalbuterol arm of the study. These latter results suggest, in particular, that chronic dosing with racemic albuterol may actually inhibit lung function since the 4 week pulmonary function values were slightly lower than baseline in the racemic albuterol group.

Side effects in this study ([22]) included an increase in heart rate after dosing which was significantly greater for racemic albuterol 2.5 mg compared to levalbuterol 0.625 mg at 4 weeks despite similar improvements in pulmonary function. The rescue albuterol treatment reduction was also significantly lower only in the levalbuterol 1.25 mg group.

Overall this study appears to show an improvement in lung function after dosing with levalbuterol 1.25 mg > levalbuterol 0.625 mg = racemic albuterol 2.5 mg > racemic albuterol 1.25 mg. In addition, rescue albuterol medication use was less with the levalbuterol 1.25 mg preparation and there is a suggestion of a reduction in lung function with chronic dosing which occurs with racemic albuterol (relative to placebo).

2. THE HANDLEY STUDY

A small double blind single dose dose-ranging study evaluated 20 asthmatics in a five-way crossover study looking at efficacy of three doses of levalbuterol (0.31, 0.63, and 1.25 mg), placebo, and racemic albuterol at 2.5 mg by nebulization ([23]). The primary outcome variables were: 1) the overall change in FEV_1 from predose to 6 hours post-dose, 2) the time to onset of bronchodilation defined as time from dosing until at least a 15% improvement in FEV_1 was observed, 3) the duration of effect, or the time the FEV_1 was maintained above baseline. Sepracor, maker of levalbuterol, supported the study.

All active treatment groups had an improvement in FEV_1 of 28-32% (greater than 15%) within 15 minutes of treatment as compared to placebo. The improvement in FEV_1 above 15% was maintained for at least 4 hours in the levalbuterol 0.63 and 1.25 mg groups and in the racemic albuterol group. The longest duration of effect for maintaining an FEV_1 above 15% of predose was with levalbuterol 1.25 mg (mean time 275 min), then levalbuterol 0.63 mg (mean time 237 min) and racemic albuterol 2.5 mg (mean time 221 minutes). Side effects were similar for all medications and reflected the amount of levalbuterol in a given preparation.

3. THE LOTVALL STUDY

A second dose ranging study involving 20 asthmatics in a randomized, double-blind, 4-way crossover study composed of 4 study days each separated by a minimum 3 day washout period was done and supported by Glaxo, a maker of racemic albuterol ([24]). On a given day the following doses were administered in a cumulative fashion at 25 minute intervals: 6.25, 12.5, 25, 50, 100, 200, 400, 800, and 1,600ug for R-or S-albuterol and 12.5, 25, 50, 100, 200, 400, 800, 1,600, and 3,200 ug for (R,S)-albuterol as well as placebo doses on one of the 4 days.

The results of the study clearly show a dose-related improvement in FEV_1 and side effects dependent on the amount of (R)-albuterol content only, whether or not (R)-albuterol or (R,S)-albuterol was used. There were no side effects noted with (S)-albuterol or placebo. The authors concluded that (S)-albuterol was an inert or inactive filler with no adverse side effects. In this single day dosing study, the results seemed to reflect the author's conclusions. It is hard to come up with alternative conclusions based on the data.

4. THE GAWCHIK STUDY

A pediatric study looked at racemic albuterol and levalbuterol in 28 asthmatic children aged 6 to 11 ([25]). The study was a randomized double-blind crossover study evaluating single doses in seven groups: 0.16, 0.31, 0.63, and 1.25 mg of levalbuterol, placebo, and 1.25 and 2.5 mg of racemic albuterol. Visits were scheduled 2 to 8 days apart with serial measurements of spirometry at baseline up to 6 hours post inhalation dose. Racemic albuterol was withheld for at least 8 hours prior to the study. The study was sponsored by Sepracor, maker of levalbuterol.

Definitive findings in the study were a greater improvement in lung function with 1.25 mg of levalbuterol compared to 2.5 mg of racemic albuterol and what appeared to be a crude dose response relationship between serum drug levels of levalbuterol and lung function, something that has never been present before with the use of albuterol. Heart rate effects were dependent on the dose of levalbuterol given.

5. THE MILGROM STUDY

A large pediatric study evaluated chronic dosing with levalbuterol and racemic albuterol in 338 pediatric asthmatics age 4 to 11 years ([26]). Eligible subjects were given a three times a day nebulization regimen for twenty-one days of one of 5 treatments: levalbuterol 0.31 or 0.63 mg, placebo, or racemic albuterol at 1.25 or 2.5 mg. The trial was randomized, double blind, and supported by Sepracor, maker of levalbuterol. The primary endpoint was FEV_1 peak

percent change on day 21 after treatment compared to baseline before treatment on day zero.

All active treatments improved significantly compared to placebo on day 21 in relation to the primary endpoint. Levalbuterol at doses of 0.31 and 0.63 mg appeared to be very similar in effect to racemic albuterol at 1.25 and 2.5 mg with similar or less side effects. Based on this study it was recommended that children with asthma in the age group 4-11 should start with a dose of levalbuterol of 0.31 mg when used for mild to moderate persistent asthma.

6. THE TRUITT STUDY

A very interesting retrospective chart review study took advantage of a hospital changeover policy in the use of albuterol ($_{27}$). The study, funded by Sepracor, looked at albuterol use during two 6-month periods July 1 to December 31, 1998 and July 1 to December 31, 1999. The primary clinical endpoint of the study was the total number of nebulizer treatments required of patients hospitalized with asthma or COPD during those two time periods. During the first time period, only racemic albuterol was used for nebulization at 2.5 mg every 4 hours as medically necessary. In second time period, the hospital had switched over to levalbuterol nebulizations of 1.25 mg every 8 hours as medically needed.

Levalbuterol treated patients required significantly less β_2-agonist and ipratropium bromide treatments in hospitalized patients compared to racemic albuterol ($_{27}$). This translated into a mean total cost of nebulizer therapy that was significantly greater in hospitalized patients with asthma and COPD in racemic albuterol treated patients compared to levalbuterol treated patients. After controlling for diagnosis, baseline FEV_1, and ipratropium use, levalbuterol was associated with a reduced length of hospital stay, total cost savings, and a decrease in the likelihood of hospital readmission. The decrease in hospital readmission in the next month was related to COPD and not asthma.

SUMMARY – CLINICAL STUDIES OF RACEMIC ALBUTEROL VERSUS LEVALBUTEROL

Overall, levalbuterol appears to improve pulmonary function to a slightly greater extent and last a little longer than racemic albuterol for the same dose of R-albuterol. The improvement in pulmonary function is similar for 2.5 mg of racemic albuterol and 0.625 mg of levalbuterol with less toxicity with the latter. Albuterol systemic toxicity seems to follow the absolute amount of R-albuterol present in a given preparation. In addition, there appears to be a greater overall cost savings with levalbuterol compared to racemic albuterol based on one retrospective study funded by Sepracor. The cost savings seems to be related to a reduction in length of stay in the hospital and a reduction in total nebulization therapy when levalbuterol is used relative to racemic albuterol. The etiologic reasons for these differences are unclear but might be related to the S-albuterol present in one preparation and not the other.

CONCLUSION

Albuterol structure and function was modeled after R-epinephrine to provide a more selective β_2-agonist action relative to R-epinephrine to treat bronchospastic lung disease. Unfortunately, (R,S)-albuterol and not (R)-albuterol was the result secondary to cost considerations and the general feeling that there would be no toxicity with the extra (S)-albuterol present in the racemic preparation. Although adverse side effects of (S)-albuterol have been difficult to prove directly in humans, they are easy to prove in the animal model, are suggestive in indirect in vitro studies in humans, and are a possibility in direct comparison studies in humans. This latter idea comes from the pharmacodynamic head to head comparison of both drugs, racemic albuterol and levalbuterol, in clinical studies that show differences in lung function and duration of activity for equivalent doses of (R)-albuterol. In addition, the use of (R)-albuterol instead of (R,S)-albuterol would make it easier to determine dose response relationships in humans. Chronic dosing of racemic albuterol will slowly increase residual (S)-albuterol concentrations due to differential human metabolism, making drug levels of albuterol nonsensical. Finally, based only on one study, but suggestive, it appears that levalbuterol may be more cost-effective than the use of racemic albuterol in hospitalized asthmatic and COPD patients treated with bronchodilators despite an almost 5-fold greater individual cost of levalbuterol. With all these considerations in mind, it makes much more sense and it may be safer to use the more pure drug levalbuterol for the treatment of all asthmatics.

FINAL NOTE

The only troubling aspect of this review is the competition inhere in a free-market system that might serve to undermine the outcomes of any study. Ideally, it would have been better to have had multiple studies free of sponsorship to eliminate a potential confounding variable when coming to conclusions. This needs to be remembered when contemplating the results of these studies.

References

1. Page CP, Morley J. Contrasting properties of albuterol stereoisomers. J Allergy Clin Immunol 1999;104:S31-41.
2. Fawcett JP, Boulton DW. Pharmacokinetics and pharmacodynamics of single oral doses of albuterol and its enantiomers in humans.
3. Gumbhir-Shah K, Kellerman DJ, DeGraw S, Koch P, Jusko WJ. Pharmacokinetic and pharmacodynamic characteristics and safety of inhaled albuterol enantiomers in healthy volunteers. J Clin Pharmacol 1998;38:1096-1106.
4. van Schayck CP, Graafsma SJ, Visch MB, et. al. Increased bronchial hyperresponsiveness after inhaling salbutamol during 1 year is not caused by subsensitization to salbutamol. J Allergy Clin Immunol 1990;86:793-800.
5. van Essen-Zandvliet EE, Hughes MD, et. al. Effects of 22 months of treatment with inhaled salbutamol and/or B2-agonists on lung function, airway responsiveness, and symptoms in children with asthma. Am Rev Respir Dis 1992;146:547-554.
6. Wahedna I, Wong CS, Wisniewski AFZ, et.al. Asthma control during and after cessation of regular beta2-agonist treatment. Am Rev Respir Dis 1993;148:707-712.
7. Taylor DR, Sears MR. Bronchodilators and bronchial hyperresponsiveness. Thorax 1994;49(2):190-191.
8. Cheung D, Timmers MC, Zwinderman AH, Bel EH, Dijkman JH, Sterk PJ. Long-term effects of a long-acting 2-adrenoceptor agonist, salmeterol, on airway hyperresponsiveness in patients with mild asthma. N Engl J Med 1992;327:1198-1203.
9. Mazzoni L, Naef R, Chapman ID, Morley J. Hyperresponsiveness of the airways to histamine following exposure of guinea pigs to racemic mixtures and distomers of beta2-selective sympathomimetics. Pulm Pharmacol 1994;7:367-376.
10. Keir S, Page C, Spina D. Bronchial hyperresponsiveness induced by chronic treatment with albuterol: role of sensory nerves. J Allergy Clin Immunol 2002;110:388-394.
11. Perrin-Fayolle M. Salbutamol in the treatment of asthma. Lancet 1995;346:1101.
12. Cockcroft DW, Swystun VA. Effect of single doses of S-salbutamol, R-salbutamol, racemic salbutamol, and placebo on the airway response to methacholine. Thorax 1997;52;845-848.
13. Ramsay CM, Cowan J, Flannery E, McLachlan C, Taylor DR. Bronchoprotective and bronchodilator effects of single doses of (S)-salbutamol, (R)-salbutamol and racemic salbutamol in patients with bronchial asthma. Eur J Clin Pharmacol 1999;55:353-359.
14. O'Connor BJ, Aikman SL, Barnes PJ. Tolerance to the nonbronchodilator effects of inhaled 2-agonists in asthma. N Engl J Med 1992;327:1204-1208.
15. Cockcroft DW, Davis BE, Swystun VA. Tolerance to the bronchoprotective effect of 2-agonists: comparison of the enantiomers of salbutamol with racemic salbutamol and placebo. J Allergy Clin Immunol 1999;103:1049-1053.
16. Mitra S, Ugur M, Ugur O, Goodman M, McCullough JR, Yamaguchi H. (S) albuterol increases intracellular free calcium by muscarinic receptor activation and a phospholipase C-dependent mechanism in airway smooth muscle cells. Mol Pharmacol 1998;53:347-354.
17. Templeton AGB, Chapman ID, Chilvers E, Morley J, Handley DA. Effects of (S)-albuterol on isolated human bronchus. Pulm Pharmacol 1998;11:1-6.
18. Walle UK, Pesola GR, Walle T. Stereoselective sulphate conjugation of salbutamol in humans: comparison of hepatic, intestinal, and platelet activity. Br J Clin Pharmacol 1993;35:413-418.
19. Eaton EA, Walle UK, Wilson HM, Aberg G, Walle T. Stereoselective sulphate conjugation of albuterol by human lung and bronchial epithelial cells. Br J Clin Pharmacol 1996;41:201-206.
20. Fawcett JP, Boulton DW. Pharmacokinetics and pharmacodynamics of single oral doses of albuterol and its enantiomers in humans. Clin Pharmacol Ther 1997;62:138-144.
21. Gumbhir-Shah K, Kellerman DJ, DeGraw S, Koch P, Jusko WJ. Pharmacokinetic and pharmacodynamic characteristics and safety of inhaled albuterol enantiomers in healthy volunteers. J Clin Pharmacol 1998;38:1096-1106.
22. Nelson HS, Bensch G, Pleskow WW, et. al. Improved bronchodilation with levalbuterol compared with racemic albuterol in patients with asthma. J Allergy Clin Immunol 1998;102:943-952.
23. Handley DA, Tinkelman D, Noonan M, Rollins TE, Snider ME, Caron J. Dose-response evaluation of levalbuterol versus racemic albuterol in patients with asthma. Journal of Asthma 2000;37:319-327.
24. Lotvall J, Palmqvist M, Arvidsson P, Maloney A, Ventresca GP, Ward J. The therapeutic ratio of R-albuterol is comparable with that of RS-albuterol in asthmatic patients. J Allergy Clin Immunol 2001;108:726-731.
25. Gawchik SM, Saccar CL, Noonan M, Reasner DS, DeGraw SS. The safety and efficacy of nebulized levalbuterol compared with racemic albuterol and placebo in the treatment of asthma in pediatric patients. J Allergy Clin Immunol 1999;103:615-621.
26. Milgrom H, Skoner DP, Bensch G, Kim KT, Claus R, Baumgartner RA, for the Levalbuterol Pediatric Study Group. J Allergy Clin Immunol 2001;108:938-945.
27. 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.

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