Safety of Levalbuterol Compared to Albuterol in Patients With a Tachyarrhythmia

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Abstract

Objective: To determine the safety of levalbuterol versus albuterol in patients with a tachyarrhythmia. **Data Sources:** A PubMed search was conducted using the MeSH search terms levalbuterol, albuterol, and tachyarrhythmia. Bibliographies of relevant articles were reviewed for additional citations. **Study Selection and Data Extraction:** Search results were limited to humans and randomized controlled trials. Those studies that excluded patients with predetermined tachyarrhythmias were excluded from this review. Trials that failed to compare levalbuterol and albuterol outcomes were excluded. **Data Synthesis:** Beta-2 receptor agonists are the mainstay of treatment in patients with respiratory disease, such as asthma or chronic obstructive pulmonary disease. Racemic albuterol has been linked to poor outcomes due to the fact that it contains both the S-isomer and the R-isomer. Levalbuterol, the “pure” R-isomer, has been thought to decrease cardiac side effects since it only contains the therapeutic component of the racemic mixture. Patients with tachyarrhythmias are at an increased probability to experience harmful, if not fatal, cardiac side effects from these drugs. Limitations of current studies include a lack of data in patient populations with baseline tachyarrhythmias. **Conclusions:** Tachyarrhythmias put a patient at increased risk of poor outcomes, including death. Evidence for using either racemic albuterol or levalbuterol for respiratory disease management in these patients is lacking and insufficient. Randomized controlled trials show that in intensive care unit patient populations there is no clear advantage to using levalbuterol over albuterol; however, this did not hold true in pediatric populations. No clinical trials exist that look at a direct comparison of these 2 agents in patients with underlying tachyarrhythmias. Further research into the most efficacious and safe β -2 receptor agonists in this specialized patient population should be conducted to help reduce potential harmful outcomes.

Keywords

levalbuterol, albuterol, tachyarrhythmia

Background

A common modality in the treatment of chronic obstructive pulmonary disease (COPD) and asthma includes the short-acting β -2 receptor agonists, which are the most effective bronchodilators available. Depending on where the β -2 receptors are located, different pharmacologic responses are seen when these receptors become activated. The most useful β -2 receptors in terms of asthma and COPD management are found in airway tissues. Once activated, these induce smooth muscle relaxation, increase ciliary beat, and inhibit mast cell degranulation.¹ Beta-2 receptors in the heart can cause positive chronotropic effects, which could be detrimental for patients who are also suffering from a tachyarrhythmia.

Tachyarrhythmias are disorders of heart rhythm that may present with a tachycardia, that is, a heart rate greater than 100 beats per minute. When the heart rate is too rapid, it may not effectively pump blood to the rest of your body, depriving

your organs and tissues of oxygen. This can cause these tachycardia symptoms, including dizziness, shortness of breath, heart palpitations, chest pain, and fainting. More important, tachyarrhythmias can increase the risk of death and other poor outcomes. It is important to recognize this risk, especially in the treatment of COPD or asthma exacerbations in patients who have a baseline tachyarrhythmia as they may be at an increased risk of these negative outcomes.

The conventional albuterol (sometimes known as salbutamol) is available as a racemic mixture composed of a 50:50 ratio of stereoisomers, S-albuterol and R-albuterol.²

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The paradoxical response in the form of worsening bronchospasm with use of racemic albuterol has been observed in some trials.^{3,4} Levalbuterol (*R*-albuterol) is the therapeutically active component of racemic albuterol and contributes most, if not all, clinical bronchodilator activity of the racemic mixture and could be more effective than albuterol in acute situations. Levalbuterol has a molecular structure similar to epinephrine, and it binds selectively to β -2 adrenergic receptors within the airways and promotes relaxation of airway smooth muscle.⁵ *S*-albuterol was considered an inert part of racemic albuterol, but recent reports have shown that *S*-albuterol results in mechanisms leading to bronchoconstriction.⁶ The levalbuterol, when administered as a single isomer, is supposed to be free from all of the potential detrimental effects of *S*-albuterol. A retrospective chart review that compared nebulized albuterol and levalbuterol for adverse events in patients with acute airflow obstruction showed that on day 3 of therapy, there was a statistically significant difference in mean change in heart rate between the 2 populations.⁷ However, this was not a clinically significant difference. Although drug manufacturers use this study to support utilizing levalbuterol over racemic albuterol in tachyarrhythmia patients, the study had major design flaws. This trial did not have a controlled dose and regimen since it was a retrospective chart review. The biggest flaw lies in the fact that the albuterol 2.5 mg doses and levalbuterol 0.63 mg doses were not equipotent. This study left a significant gap in data concerning the true benefit of levalbuterol over albuterol in tachyarrhythmia patients.

In 1997, Cockcroft and Swystun designed a study to compare 4 different mixtures of bronchodilators.⁸ In this double-blind, randomized, 4-way crossover study, 12 patients received *S*-salbutamol, *R*-salbutamol, racemic salbutamol, and placebo. These 12 patients had diagnosed asthma, but were studied during a period of time where they were well enough controlled to go without using a β -2 agonist in the 4 weeks prior to the study. While the primary outcome examined forced expiratory volume in 1 second (FEV_1) improvement and airway responsiveness to methacholine, it is of note that there was a statistically significant ($P < .0001$) difference between the 4 treatment groups with respect to a change in heart rate from baseline 20 minutes after administration. Baseline heart rates for the respective groups were as follows: racemic mixture (72.6), *R*-salbutamol (71.3), *S*-salbutamol (72.5), and placebo (73.7). At 20 minutes past administration, the heart rates for the groups were recorded as follows: racemic mixture (84.0), *R*-salbutamol (84.1), *S*-salbutamol (71.1), and placebo (74.4). Some limitations of this study include lack of generalizability due to this being from a single center in Canada; it was open-labeled and underpowered. With such a small population size and no clear history of the inclusion of patients with tachyarrhythmias, it will be difficult to

extrapolate these data to other situations; however, it does give a good direct comparison between the enantiomers and the racemic mixture.

In 2008, Tripp et al looked at the safety outcomes of levalbuterol HFA metered dose inhaler (MDI) and racemic albuterol HFA MDI in asthmatic patients in a randomized, modified-blind, active-controlled, multicenter, 2-way crossover study.⁹ The 49 participating subjects were randomized to 16 cumulative doses of levalbuterol (45 μ g per dose) or racemic albuterol (90 μ g per dose) administered over a 2-hour period. After having a 7-day washout period, the subjects were then crossed over to the other treatment. There were 4 scheduled clinic visits. Patients were not allowed to take outside β -2 receptor agonists (outside of the designated rescue medication), nonprescription asthma medication, ipratropium bromide, inhaled corticosteroids, systemic corticosteroids, or both. The rescue medication, pirbuterol, was withheld 7 hours prior to clinic visit. At the first visit, all baseline values were recorded; notably, heart rate was recorded 15 minutes after each cumulative dose, and every 30 minutes for 8 hours after the final dose. At visits 2 and 3, 16 cumulative doses of levalbuterol or racemic albuterol were administered in the following regimen: 1 actuation at 0 and 30 minutes, 2 actuations at 60 minutes, 4 actuations at 90 minutes, and 8 actuations at 120 minutes. Mean $\pm$ standard deviation (SD) baseline heart rate was similar between the 2 groups (levalbuterol: 73.6 ± 12.3 beats per minute; racemic albuterol: 71.0 ± 8.8 beats per minute). There was a greater increase in mean heart rate observed for racemic albuterol at each dose level. No statistical analysis was performed on the heart rates. When looking at these data, one must consider the dosing given for these 2 agents. While it is helpful for examining potency, these are not typical doses for either levalbuterol or racemic albuterol; this makes it hard to compare for regular rescue inhaler/maintenance use. Responses that are observed after noncumulative dosing could be vastly different from the cumulative dosing that this study looked at. This trial also does not mention any baseline tachyarrhythmias as well as if any surfaced postdosing, which limits the external validity to our study population. Other limitations include the allowance of rescue β -2 agonists, lack of a power analysis, and a small sample size. Other concomitant medications that the patients were taking were not described, and thus cannot rule out the patients taking other medications that could have affected heart rate.

The 2 previously mentioned studies looked at overall healthy adults; they both support the use of levalbuterol over albuterol on the basis of cardiac adverse effects (ie, increased heart rate); however, it leaves a significant gap in terms of application to those patients with baseline tachyarrhythmias. The purpose of this drug information request was to examine the literature for safety of using levalbuterol or albuterol in patients with tachyarrhythmias.

Literature Search

A PubMed search was conducted using the MeSH search terms levalbuterol, albuterol, and tachyarrhythmia. The search was limited to articles written in English on randomized control trials that looked at patients whose heart rate could be monitored both pre- and post-bronchodilator administration. Studies that excluded patients with underlying tachyarrhythmias were not included in this review. The randomized clinical trials must also have compared some sort of outcome using levalbuterol and albuterol as part of their study design. Bibliographies of relevant articles were reviewed for additional citations. The reviewed articles are discussed based on their observed populations, including intensive care unit patients and pediatrics.

Intensive Care Unit Patients

In 2011, Khorfan et al conducted a randomized, single-blind, crossover, prospective study in 70 critically ill patients who were treated with nebulized bronchodilators.¹⁰ The investigators did exclude patients with a baseline heart rate greater than 110 beats per minute; however, this trial was included in this review because some patients had heart rates between 101 and 109 beats per minute, although they were not specifically identified. Patients were assigned to either group A or group B. Group A received nebulized albuterol 2.5 mg alternated with levalbuterol 0.63 mg every 4 to 6 hours. Group B received nebulized levalbuterol 1.25 mg alternated with 2.5 mg of albuterol every 4 to 6 hours. Each patient was also given nebulized ipratropium bromide 500 μ g with each treatment. The primary outcome was variable heart rate measured in beats per minute. The change in heart rate was quantified as the difference between pretreatment and posttreatment measures. Forty-six patients were randomized to group A with an average baseline heart rate of 87.6 beats per minute, and 24 patients were randomized to group B with an average heart rate of 87.2 beats per minute. The investigators looked at prechange to postchange heart rates for each drug regimen. In group A, a mean $\pm$ SD change in heart rate after albuterol 2.5 mg ($n = 303$) was 0.89 ± 4.5 beats per minute compared with 0.85 ± 5.3 beats per minute after levalbuterol 0.63 mg ($n = 301$; $P = .89$). In group B, the heart rate actually decreased by 0.16 ± 5.1 beats per minute after albuterol 2.5 mg ($n = 114$) compared with an increase of 1.4 ± 5.4 beats per minute after levalbuterol 1.25 mg ($n = 118$; $P = .03$). Five arrhythmia events occurred during the total course of 836 treatments. In group A, one of the episodes happened after a patient used albuterol, while another had premature ventricular contractions after levalbuterol 0.63 mg. In group B, 2 patients experienced premature ventricular contractions after both levalbuterol and albuterol. One patient from group B experienced ventricular bigeminy after levalbuterol 1.25 mg. This study showed that the use of albuterol and ipratropium

does not cause significant tachycardia or other tachyarrhythmias; it also fails to show a clear benefit for using levalbuterol over albuterol on the basis of potential detrimental side effects for the racemic mixture. This study was unique in that it included patients who were at a high risk for tachyarrhythmias; however, because this study did not use separate treatment groups, it is difficult to separate the effects of levalbuterol from albuterol. This study only mentioned overall average heart rates rather than individual measurements. Other limitations include a lack of generalizability since it only includes critically ill adults at a single center, as well as being a single-blind study.

Lam and Chen conducted a prospective, randomized, crossover study conducted in a medical intensive care unit and surgical intensive care unit examining patients who needed respiratory therapy every 4 hours to maximize respiratory function.¹¹ The investigators excluded patients taking β -adrenergic-receptor antagonists as well as those who were hemodynamically unstable. The design of the study used a crossover model. Four hours after the most recent bronchodilator treatment, each patient was given at least 2 consecutive doses of albuterol or levalbuterol. Their heart rate was monitored and recorded from a continuous electrocardiogram just before the first dose of each study drug, at the end of the second dose delivery, and at 5, 10, 15, 30, 60, 90, 120, 180, and 240 minutes after their respective treatments. The mean maximum heart rate increase for each drug was compared to the baseline heart rate before treatment. Twenty patients were randomized, and 10 of these patients had tachycardia at baseline (tachycardia defined as greater than 90 beats per minute). The results of this trial showed that in patients with a baseline tachycardia, the mean largest heart rate increase was 1.4 beats per minute for the albuterol group and 2.0 beats per minute for the levalbuterol group ($P > .05$). In patients without baseline tachycardia, the mean largest heart rate increase was 4.4 beats per minute with albuterol ($P = .04$) and 3.6 beats per minute with levalbuterol ($P = .03$). In patients with baseline tachycardia, the highest mean heart rate occurred 15 minutes after administration of albuterol and 5 minutes after administration of levalbuterol. The investigators did not identify the types of tachyarrhythmias that were included in the study. It is also difficult to only attribute the rise in heart rate to the administration of the study drugs. Other limitations include small sample size at a single center, nonblinded design, as well as a lack of information about concomitant medications being taken by the study population. However, this small subset population with tachyarrhythmias was included in the study, which is extremely beneficial in setting the stage for future studies.

Pediatrics

In 2008, Punj et al conducted a randomized double-blind clinical study looking at 60 children who presented to the emergency room for an acute asthma exacerbation.¹² Children who were already prescribed and taking preventative therapy, such

as long-acting β -agonists or steroids, were excluded. Thirty were randomized to levosalbutamol 0.63 mg per dose (which is the Indian equivalent of levalbuterol) and 30 were randomized to salbutamol 2.5 mg (which is the Indian equivalent of albuterol) per dose. To judge the cardiac effect of the drug, one of the parameters the investigators monitored was heart rate per minute. Pretreatment baseline heart rates were 109 ± 18.2 beats per minute for the levosalbutamol group and 108.53 ± 17.96 beats per minute in the salbutamol group ($P > .05$). Posttreatment observations of heart rate for the levosalbutamol group showed a slight decrease to 108.43 ± 13.25 beats per minute, and a significant increase to 123.07 ± 15.04 beats per minute in the salbutamol group ($P < .05$). This study showed no increase in heart rate or tachycardia for the levosalbutamol group, while showing a significant increase when looking at racemic salbutamol. The conclusions are limited to a small population size and failed to monitor for cardiac parameters outside of increased or decreased heart rates. Electrocardiograms were not used to assess patients for other tachyarrhythmias. Additional limitations include lack of generalizability due to being conducted at a single center, as well as incomplete blinding by the investigators.

Ralston et al designed a prospective, double-blinded, randomized controlled study to compare outcomes associated with levalbuterol and racemic albuterol combined with ipratropium in acute pediatric asthma.¹³ One of their secondary outcomes looked at percent change in heart rate. Patients were randomized to either a combination of racemic albuterol plus ipratropium or to levalbuterol. Each patient was allowed a maximum of 6 nebulizer treatments. Initial heart rates were 103 in the levalbuterol group (SD = 2.4) and 100 in the racemic albuterol/ipratropium group (SD = 2.5). The safety outcome looking at heart rate was divided into the increase from baseline to maximum heart rate and baseline heart rate to the patient's final heart rate. For the levalbuterol group, the increase of patients' heart rate from the initial to final showed a mean change of 10 beats per minute, while the mean change for the racemic albuterol group was 26 beats per minute ($P < .001$). The increase in heart rate from the initial baseline to the maximum rate in the levalbuterol group was 16 beats per minute and 29 beats per minute for the racemic albuterol group ($P = .002$). Also of interest, the investigators discussed new symptoms that arose in the 2 groups, including tremor, nervousness, nausea or vomiting, palpitations, headache, and any symptoms. None of these new symptoms were statistically significant between the 2 groups, although they were numerically higher in the racemic albuterol group. The safety outcomes were secondary outcomes, and thus not the major focus of this trial. Limitations include a lack of generalizability because it was conducted at a single center.

Wilkinson et al assessed the efficacy of racemic albuterol versus levalbuterol for the treatment of acute asthma exacerbations in children aged 6 to 17.¹⁴ The primary

endpoint was improvement in FEV₁ between the 2 groups, with one of the secondary endpoints being percent change in heart rate. This was a prospective, randomized, double-blind, placebo controlled trial. Subjects were randomized in blocks of 10 to either 7.5 mg of racemic albuterol (2.5 mg per dose) or 3.75 mg of levalbuterol in normal saline given over the course of an hour. Patients were also treated with 2 mg/kg of oral prednisolone or prednisone as well as 2 unit doses of ipratropium bromide (1000 μ g). The investigators measured the adverse effects from the 2 treatment groups. Neither group had a baseline heart rate recorded, so it is difficult to accurately interpret and extrapolate these results to patients with a tachyarrhythmia. The percent change in heart rate for the albuterol group receiving the first nebulizer was 7.56% and 12.1% for the levalbuterol group ($P = .215$). The percent change in heart rate after the second nebulizer treatment was 13.2% for the albuterol group and 13.0% for the levalbuterol group ($P = .612$). This trial was underpowered for detecting a meaningful difference in heart rates, and the lack of baseline values makes application of the results difficult.

Carl et al compared racemic albuterol and levalbuterol for the treatment of acute asthma at an urban tertiary children's hospital.¹⁵ In this randomized, double-blind, controlled trial, children aged 1 to 18 years of age were assigned to either nebulized albuterol 2.5 mg or 1.25 mg levalbuterol every 20 minutes for a maximum of 6 doses. Primary outcome was hospitalization rate, with a secondary endpoint of adverse events, including mean heart rate. There were fewer numbers of admission rates in the levalbuterol group ($n = 101$) than in the albuterol group ($n = 122$; $P = .02$). There was no reported adverse events seen in either group, and no difference in mean heart rates (130.1 ± 23.3 beats per minute for levalbuterol; 129.7 ± 25.5 beats per min for albuterol; $P = .94$). This study was not powered to find a difference in heart rates; also, no patient of tachyarrhythmia was mentioned since baseline heart rates were not included.

Discussion

Many trials have been conducted looking at patient responses to different β -2 receptor agonists, which are considered the drug of choice in terms of rescue bronchodilation. Racemic albuterol, or salbutamol in some countries, is the most commonly used β -2 receptor agonist due to its relatively predictable response and overall inexpensiveness in comparison to some of the other drugs in this class on the market, specifically levalbuterol.

Few studies have looked at the relationship between albuterol and levalbuterol and their safety when used in tachyarrhythmia patients. The chart review conducted by Scott and Frazee did not have equipotent dosing, but showed a potential benefit in levalbuterol that needed to be investigated further.⁷ The literature on the morbidity and mortality

in these patients using a β -2 receptor agonist is lacking. The only data that exist are found mainly in efficacy and safety randomized control trials as secondary outcomes. However, most of these trials do not include, or fail to mention, any baseline tachyarrhythmia patients in their study protocol. In theory, levalbuterol, which is the “pure” *R*-isomer of racemic albuterol, should be safer and more tolerated in this specific patient population because it lacks the *S*-isomer albuterol that has been associated with worsening outcomes and increased chronotropic side effects. This has not been proven in clinical trials, and thus only extrapolated data, like what were shown in this review, are available for interpretation.

Although there are no direct randomized controlled trials looking at the use of levalbuterol or albuterol in tachyarrhythmia patients, the trials included in this review can help prescribers and clinicians to understand potential cardiac implications. In an otherwise healthy adult population, both trials showed increasing heart rates when using racemic albuterol over levalbuterol; however, these populations also did not include tachyarrhythmia patients in their population and so the external validity is compromised. The literature related to intensive care patients shows no potential benefit in using levalbuterol over albuterol in terms of increased heart rate or increased worsening outcomes due to tachyarrhythmias. In pediatric patients, there was a lack of significant increase in the heart rate for patients using levalbuterol, although no tachyarrhythmias were mentioned at baseline. The findings of these trials suggest pediatric patients may benefit from levalbuterol when deciding between albuterol, as racemic albuterol trended to cause increased heart rates and cardiac side effects.

Summary

Tachyarrhythmias put a patient at increased risk of poor outcomes, including death. Evidence for using either racemic albuterol or levalbuterol for respiratory disease management in these patients is lacking and insufficient. Randomized controlled trials show that in intensive care unit patient populations there is no clear advantage to using levalbuterol over albuterol; however, this did not hold true in pediatric populations. No clinical trials exist that look at a direct comparison of these 2 agents in patients with underlying tachyarrhythmias. Further research into the most efficacious and safe β -2 receptor agonists in this specialized patient population should be conducted to help reduce potential harmful outcomes.

Declaration of Conflicting Interests

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