

## CLINICAL INVESTIGATION

**Comparison of Levalbuterol and Racemic Albuterol Based on Cardiac Adverse Effects in Children**

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**OBJECTIVE** To compare the cardiac effects of levalbuterol with those of racemic albuterol based on changes in heart rate (HR) in pediatric patients.

**METHODS** The medical records of hospitalized children ages 1 month to 12 years, who received either levalbuterol or racemic albuterol via nebulizer for 3 consecutive doses between January 2006 and December 2008 were reviewed. The documented HR was collected prior to and after each administered dose of bronchodilator. The primary outcome was the largest percentage of change in HR between groups. Secondary outcomes of comparisons of the number of patients who had more than a 10% change in HR and incidence of tachycardia were included.

**RESULTS** A total of 50 patients, 25 in each group, was included in the study. All patients in the racemic albuterol group received 2.5 mg per dose, while most of the patients in the levalbuterol group received 0.63 mg per dose (19 patients, 76%). Only 6 levalbuterol patients received a dose of 1.25 mg. Nineteen of 25 patients (76%) in the levalbuterol group were tachycardic prior to the first recorded dose compared to 15 patients (60%) in the racemic albuterol group ( $p = 0.36$ ). The median of the largest percentage of change in HR was 4.1% (interquartile range [IQR], 1.8–8.7) in the levalbuterol group compared to 5% (IQR, 1.9–7.8) in the racemic albuterol group ( $p = 0.763$ ). Four patients in the levalbuterol group experienced an HR increase of more than 10% compared to 5 patients in the racemic albuterol group ( $p = 1.0$ ).

**CONCLUSION** Levalbuterol and racemic albuterol bronchodilator therapies produced similar effects on HR. No clinically significant differences were detected in HR changes between the two treatment groups, despite administration of a larger equipotent albuterol dose in the racemic albuterol group than in the levalbuterol group.

**INDEX TERMS** adverse drug effects, albuterol, beta agonists, cardiac, heart rate, levalbuterol, pediatric, tachycardia

**ABBREVIATIONS** ED, emergency department; FEV<sub>1</sub>, forced expiratory volume in 1 second; HR, heart rate; IQR, interquartile range; MPIS, modified pulmonary index score; SD, standard deviation

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**BACKGROUND**

Racemic albuterol and levalbuterol are bronchodilators that activate the  $\beta_2$ -receptors located in the bronchioles and are used to treat asthma exacerbations.

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These agents differ in their composition. Racemic albuterol is a 50:50 mixture of both R- and S-enantiomers, while levalbuterol consists only of the R-enantiomer of albuterol.<sup>1</sup> Based on the chemical mixture, the equipotent dose of levalbuterol is presumed to be one-half that of the racemic albuterol dose, but the exact distribution and disbursement of levalbuterol to the bronchioles is unknown. In addition, the R-enantiomer stimulates the  $\beta_2$ -receptor with 100-times more affinity than the S-enantiomer.<sup>1</sup> Although the S-enantiomer may

not possess bronchodilating effects, it may be associated with detrimental effects such as bronchospasm and inflammation.<sup>1,2</sup> In addition, the S-enantiomer of albuterol is metabolized more slowly than the R-enantiomer, leading to higher plasma concentrations, and the half-life is longer.<sup>3</sup>

Aside from *in vitro* evidence of unfavorable effects associated with the S-enantiomer of albuterol, *in vivo* evidence of differences in efficacy and safety are contradictory. Pediatric studies have concluded that there is no improvement in forced expiratory volume in 1 second (FEV<sub>1</sub>) with levalbuterol compared to racemic albuterol.<sup>4-8</sup> Clinical evaluation of reduced hospitalization rates when levalbuterol is substituted for racemic albuterol in the emergency department (ED) for management of acute exacerbation is inconsistent; one study showed a reduction in hospitalization rate,<sup>9</sup> while another study found no difference.<sup>7</sup>

Safety studies have also evaluated the differences in effects on heart rate (HR) due to the presumed effect of the S-enantiomer. One study of 20 adult patients specifically evaluated this endpoint and found no differences in the maximum increase in HR between the S- and R-enantiomer.<sup>10</sup> Newhouse and colleagues<sup>11</sup> evaluated the implication of cardiotoxicity associated with  $\beta$ -agonists (i.e., fenoterol and albuterol) in adults. They concluded there was no increased risk of dysarrhythmia and life-threatening events, but prolongation of the QTc interval was observed with fenoterol. To our knowledge, the evaluation of changes in HR in the pediatric population receiving levalbuterol and racemic albuterol has not been the primary focus of any study. Our objective was to compare the cardiac safety (i.e., changes in HR) of levalbuterol with that of racemic albuterol in pediatric patients.

## METHODS

### Study Design

This was a retrospective chart review of children who were admitted to a tertiary care children's hospital located within an academic medical center. All required institutional review boards approved the study. Patients were included if they were admitted to the general pediatric unit between January 2006 and December 2008, were between 1 month and 12 years of age, and received either racemic albuterol or levalbuterol via nebulizer, administered as 3 consecutive treatments. Consecutive treatments were defined as a 1- to 6-hour interval between nebulizations. Patients who received ipratropium concomitantly were also included. Patients were excluded if their HR was not documented in the medical record, if they had an underlying chronic cardiac condition (i.e., congen-

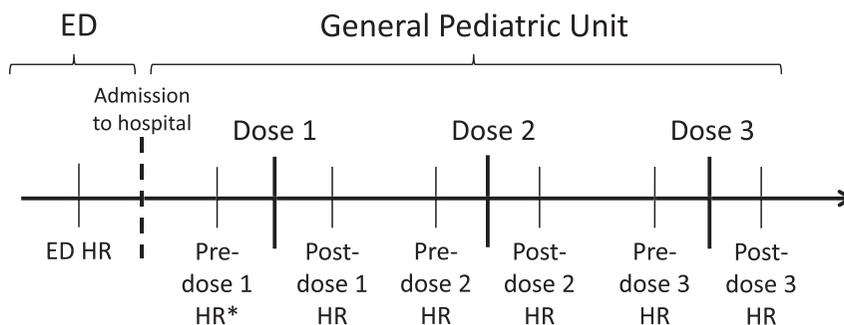
ital heart disease, arrhythmia, Wolff-Parkinson-White syndrome), were intubated, were receiving concurrent administration of medications affecting the HR (i.e., beta blockers, vasopressors, or racemic epinephrine), or were receiving continuous administration of bronchodilator therapy.

Patients receiving levalbuterol were screened for inclusion and selected for the study first. Those patients given racemic albuterol were then screened and matched 1:1 with patients to whom levalbuterol was administered. Patients were matched for age, date of discharge, and modified pulmonary index score (MPIS).<sup>12</sup> The MPIS is a validated indicator of severity of illness in children with asthma. This test evaluates 6 different categories including oxygen saturation on room air, accessory muscle use, inspiratory-to-expiratory flow ratio, degree of wheezing, and HR and respiratory rate values adjusted for the patient's age. A score of 0 to 3 is assigned for each of these 6 categories, resulting in a score ranging from 0 to 18, indicating lowest to highest severity of asthma-related illness, respectively.

Baseline demographics collected were age, gender, weight, and home medications. At the time of presentation to the ED, the patient's oxygen saturation, respiratory rate, and characteristics of wheeze, accessory muscle use, and use of supplemental oxygen were collected to determine the MPIS and severity of respiratory distress. Information collected from the ED included medications administered, presence of fever, reason for hospital visit, and documented HR evaluated for the presence of tachycardia. Tachycardia was defined throughout the study as a HR greater than the 98th percentile for age.<sup>13</sup>

Additional information collected after admission to the general pediatric unit included presence of fever, hemoglobin (to assess for anemia, defined as 2 standard deviations [SD] less than the mean hemoglobin for age),<sup>14</sup> and dose and time of levalbuterol and racemic albuterol administrations for a total of 3 bronchodilator treatments. The patient's documented HR was collected prior to and after each of the 3 bronchodilator treatments (total of 6 HR values collected per patient). The percentage of change in HR associated with each of the 3 doses per patient was calculated, and the largest change was identified. Baseline tachycardia was defined as the HR that was documented just prior to the first dose of bronchodilator therapy administered after admission to the general pediatric unit (Figure 1).

The primary outcome was defined as the largest percentage of change in HR for each treatment group. There were three secondary outcomes. The first secondary outcome compared the largest



**Figure 1.** Study Design

percentage of change in HR between the two treatment groups after stratification for the presence of baseline tachycardia. The next secondary outcome involved a comparison of the number of patients in each treatment group who had more than a 10% increase in HR following any of the 3 doses. The final secondary outcome compared the incidence of postbronchodilator tachycardia associated with each individual bronchodilator dose without prebronchodilator tachycardia between the two treatment groups.

#### Statistical Methods and Data Analysis

Descriptive statistics were used when appropriate. Comparisons of baseline demographic variables were achieved using two-sided Student *t* and chi-square tests for continuous and nominal data, respectively. The endpoints were analyzed using the Mann-Whitney *U* test for continuous data and chi-square or Fischer's exact test for nominal data. A sample size of 17 patients per treatment group was required to detect a 15% difference between the groups in the largest percentage of HR change, assuming 80% power and SD of  $\pm 15\%$ . Alpha was set at 0.05 for statistical significance.

## RESULTS

Of the 63 patients who received levalbuterol during the study period, 25 patients met the inclusion criteria. All reasons for study exclusion are cited in Figure 2; however, the most common reasons were missing information ( $n = 21$ ) and receiving less than 3 doses ( $n = 9$ ). A total of 112 patients who received racemic albuterol during the specified time period were matched with the 25 patients in the levalbuterol group.

Patient baseline demographics are reported in Table 1. There were no statistically significant differences for age, gender, or MPIS between the levalbuterol and racemic albuterol groups. Although levalbuterol was the rescue medication

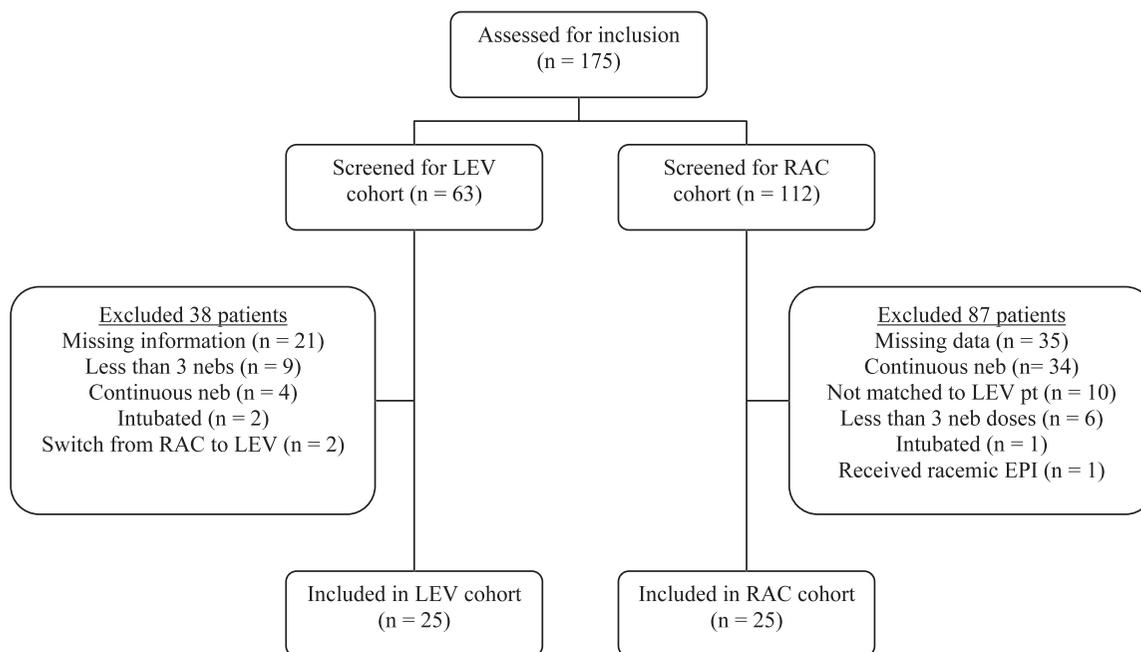
significantly more often used at home by the patients in the levalbuterol group, the use of racemic albuterol in the ED was not statistically different from the use of levalbuterol (Table 1).

Most of the patients received bronchodilator therapy for asthma exacerbation and/or upper respiratory infection. There were also no statistical differences in the incidences of tachycardia in the ED between the two groups. A total of 75 bronchodilator doses per group were observed in this cohort, while in the pediatric unit, all patients in the racemic albuterol group received 2.5 mg per dose. Most of the patients in the levalbuterol group received 0.63 mg per dose (19 patients, 76%). Only 6 levalbuterol patients received a dose of 1.25 mg. No difference was detected in mean time between the first and second dose for either group, but the mean time between the second and third dose was significantly longer for those receiving levalbuterol than for those in the racemic albuterol group (3.7 hours compared to 2.4 hours, respectively;  $p = 0.016$ ).

Almost 70% of all patients had tachycardia before the first  $\beta_2$ -agonist dose was given; however, the incidence did not differ between the two groups (Table 1). No significant difference was detected in median largest percentage of change in HR between patients who subsequently received levalbuterol (4.1; interquartile range [IQR], 1.8–8.6) and racemic albuterol (5.0; IQR, 1.9–7.8) ( $p =$  not significant [NS]) (Table 2).

Four and five patients in the levalbuterol and racemic albuterol groups, respectively, had an increase in HR greater than 10% from pre- to postbronchodilator therapy. When patients were stratified for either the presence or absence of baseline tachycardia, there was no statistically significant difference in the largest percentage of change in HR between the two treatment groups (Figure 3).

Of the 75 total bronchodilator doses per group observed in this cohort, the number of doses with a nontachycardic HR prebronchodilator therapy was



**Figure 2.** Identification of Study Cohort

EPI, epinephrine; LEV, levalbuterol; NA, Not applicable; neb, nebulization; RAC, racemic albuterol

24 in the levalbuterol group and 25 in the racemic albuterol group. The incidence of postbronchodilator therapy tachycardia associated with each non-tachycardic prebronchodilator dose was 7 of 24 (30.4%) and 5 of 25 (20%) in the levalbuterol and racemic albuterol groups, respectively ( $p = \text{NS}$ ).

## DISCUSSION

The role of levalbuterol in the management of pediatric patients with asthma remains controversial. One of the proposed benefits of this agent is its presumed lack of effect on HR. Therefore, we sought to compare the differences between the intermittent administration of nebulized levalbuterol and racemic albuterol based on HR changes in children. We found no statistically significant difference in the mean largest change in HR (i.e., >10% increase in HR) or in clinically significant alterations between the two groups. The magnitude of the difference in HR was modest, but it may prove clinically significant in patients with a history of arrhythmias, structural heart disease, or cardiac conditions that could worsen with an episode of tachycardia. Likewise, after patient stratification based on the presence or absence of tachycardia at baseline, there was still no significant difference in the largest percentage of change in HR between the two treatment groups. In examining the full cohort,

we found 12 patients (48%) in the levalbuterol group and 14 patients (56%) in the racemic albuterol group who were tachycardic both pre- and postdose for all 3 doses of bronchodilator therapy ( $p = \text{NS}$ ).

A literature search did not reveal previous studies that compared levalbuterol with racemic albuterol equipotent doses based on HR changes in the pediatric population, but studies were identified that evaluated the difference in HR changes as a secondary outcome. Nonequipotent comparisons of HR changes have been made. In a randomized, double-blind study, Migrom et al<sup>5</sup> compared 3-times-per-day treatment with nebulized levalbuterol (0.31 or 0.63 mg), racemic albuterol (1.25 or 2.5 mg), and placebo based on FEV<sub>1</sub>, HR, and QTc interval differences. No statistically significant differences were detected in HR and QTc intervals between treatment groups except when the levalbuterol 0.31-mg dose was compared to the racemic albuterol 2.5-mg dose. An equipotent comparison was not analyzed for HR changes between the levalbuterol 0.63-dose and racemic albuterol 1.25-mg dose groups. The prospective, double-blinded, randomized controlled study of pediatric asthmatics by Ralston et al<sup>22</sup> compared levalbuterol, 1.25 mg, to the combination of racemic albuterol, 5 mg, and ipratropium bromide, 0.25 mg, both nebulized, with regard to ED length of stay data, percentage of

**Table 1.** Baseline Demographics and Characteristics of the Study Population (n=25)

Characteristic	LEV	RAC	p value
Demographics			
Mean $\pm$ SD age (yr)	4.3 $\pm$ 3.5	4.4 $\pm$ 3.6	NS
% of female patients	56	40	NS
Median (range) weight percentile (IQR)	50 (25–75)	25 (10–90)	NS
Home therapies			
Use of controller medications prior to admission	15 (60%)	12 (48%)	NS
Mean $\pm$ SD number of controller medications	1.5 $\pm$ 0.6	1.2 $\pm$ 0.6	NS
Use of levalbuterol as home rescue medication	12 (48%)	1 (4%)	0.001
Emergency Department			
Asthma exacerbation as reason for visit	10 (40%)	17 (68%)	NS
Upper respiratory infection as reason for visit	12 (48%)	7 (28%)	NS
Dehydration as admitting complaint	0	1	NS
Oxygen supplementation	7 (28%)	9 (36%)	NS
Median (range) MPIS (IQR)	5 (4–7)	6 (4–6)	NS
Received RAC in the ED	15 (60%)	22 (88%)	NS
Received LEV in the ED	4 (16%)	3 (12%)	NS
Received ipratropium in the ED	11 (44%)	13 (52%)	NS
Tachycardia in the ED	0	5 (20)	NS
Fever in the ED	7 (28%)	8 (32%)	NS
Pediatric unit			
Fever in the pediatric unit	3%	4%	NS
Incidence of baseline tachycardia*	19 (76%)	15 (60%)	NS
Mean $\pm$ SD dose (mg/dose)	0.78 $\pm$ 0.27	2.5	NA
Mean $\pm$ SD time between 1st and 2nd dose (hr)	2.8 $\pm$ 0.9	2.6 $\pm$ 1.2	NS
Mean $\pm$ SD time between 2nd and 3rd dose (hr)	3.7 $\pm$ 2.5	2.4 $\pm$ 0.9	0.016
Emergency Department or Pediatric unit			
Received systemic corticosteroids	18 (72%)	20 (80%)	NS
Anemia	2 (15%)†	3 (23%)‡	NS

ED, emergency department; IQR, interquartile range, 25th to 75th percentile; LEV, levalbuterol; MPIS, modified pulmonary index score; NA, not applicable; NS, not significant; RAC, racemic albuterol; SD, standard deviation.

\* Baseline tachycardia as a heart rate >98th percentile for age and defined using the heart rate that was documented prior to the first dose of bronchodilator therapy administered after admission to the general pediatric unit.

† n = 15.

‡ n = 13.

**Table 2.** Effects of Levalbuterol and Racemic Albuterol on Change in Heart Rate (n=25)

Endpoint	LEV	RAC	p value
Median (range) of largest percentage of change in HR (IQR)	4.1 (1.8–8.7)	5.0 (1.9–7.8)	NS
Patients with >10% increase in HR*	4 (16%)	5 (20%)	NS

HR, heart rate; IQR, interquartile range; LEV, levalbuterol; NS, not significant; RAC, racemic albuterol.

\* A 10% change in HR was selected as a clinically relevant inpatient change in heart rate.

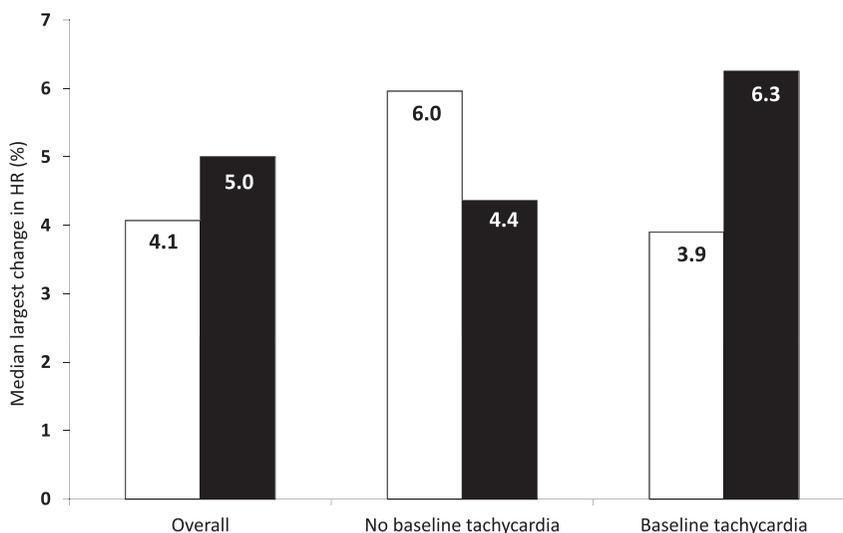
change in peak expired flow rate, and percentage of change in HR. The median percentage of increase in HR for racemic albuterol with ipratropium (26%) exceeded that of levalbuterol (9%) ( $p < 0.001$ ). That study demonstrated a dose-response relationship between the dose of levalbuterol and beta-adrenergic-mediated increase in HR; 1.25 mg was associated with less tachycardia than the higher S-enantiomer dose of 2.5 mg in the group receiving a combination of racemic albuterol with ipratropium.

In our study, the lack of a presumed equipotent dose administration of levalbuterol and racemic albuterol reflects common practice (initial dose of levalbuterol is typically 0.63 mg, while racemic albuterol initial dose is 2.5 mg, containing 1.25 mg S-enantiomer). Because most of the patients in the levalbuterol group received a lower than equipotent dose of racemic albuterol, based on exposure to the S-enantiomer, the outcome of increase in HR would be expected to be less in the levalbuterol group than the HR change in the “larger dose” racemic

albuterol group. Even with the larger dose of the S-enantiomer of albuterol, the racemic albuterol group was not associated with a significant increase in HR compared to the levalbuterol group.

In pediatric patients, case reports have described albuterol-induced supraventricular tachycardia after nebulized therapy.<sup>15–20</sup> Supraventricular tachycardia is the most common childhood arrhythmia, defined as an HR greater than 200 beats per minute (bpm), narrow QRS complex, regular R-R interval, and absent or abnormal P wave.<sup>21</sup> Electrocardiogram findings were not reviewed in our study, but no patient experienced an HR greater than 200 bpm.

After consideration of the efficacy and safety profiles of the products, cost comparisons between the products are warranted. The product costs are considerably different (levalbuterol by Sepracor, \$4.68 per unit dose of 0.63 mg or 1.25 mg; racemic albuterol by Nephron, \$0.80 per unit dose of 2.5 mg),<sup>23</sup> and the overall impact of these differences

**Figure 3.** The Largest Percentage of Heart Rate Change Stratified by the Presence of Baseline Tachycardia\*

HR, heart rate

□ = levalbuterol ■ = Racemic albuterol

\* Baseline tachycardia was determined using the HR just prior to the first dose of bronchodilator therapy administered after admission to the general pediatric unit and was defined as a heart rate >98th percentile for age.

may be substantial to an institution when the potential volume of their use is taken into account.

Several limitations to our study should be considered when interpreting the results. The study relied on data documentation in the patient's medical record. Additionally, the retrospective, observational design does not allow cause and effect conclusions. Due to standard practice in our institution, an equipotent comparison of levalbuterol and racemic albuterol was not accomplished, but the comparison of the lower levalbuterol dose with the higher racemic albuterol dose failed to demonstrate a statistically or clinically significant difference. The use of albuterol in the ED prior to admission to the pediatric unit could potentially confound the results. However, the incidence of racemic albuterol administration in the ED prior to admission was high, no statistically significant difference between groups was detected in utilization, as well as difference in incidence of tachycardia in the ED between the groups was not statistically significant. In addition, our limited sample size most likely led to suboptimal power for some of the secondary endpoints.

## CONCLUSIONS

In summary, no significant difference was detected between levalbuterol and racemic albuterol in HR change, even though twice the equipotent dose of racemic albuterol was used as part of our institution's standard of practice. Although, there was no significant difference in heart rates between the groups, the modest difference in HR observed may warrant additional study in pediatric populations with cardiac conditions.

**DISCLOSURE** The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

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