International Journal for Pharmaceutical Research Scholars (IJPRS)

V-4, I-4, 2015 ISSN No: 2277 - 7873

RESEARCH ARTICLE

Clinical Impact of Levalbuterol versus Racemic Albuterol on Cardiovascular Vital Signs in Patients with Asthma and Chronic Obstructive Pulmonary Disease (COPD)

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Manuscript No: IJPRS/V4/I4/00195, Received On: 08/11/2015, Accepted On: 16/11/2015

ABSTRACT

More pharmaceutical companies are utilizing the stereochemistry of racemic mixtures as a new method of drug discovery, which make up about 25% of agents on the market. Levalbuterol, the R-enantiomer of albuterol, is now marketed for treatment of asthma in the United States with the claim of a lower incidence of cardiac side effects. This study aims to examine the impact of each agent on cardiovascular vital signs.

KEYWORDS

Levalbuterol, racemic albuterol, tachycardia, R-albuterol

INTRODUCTION

A new approach in drug development and design throughout the pharmaceutical industry capitalizes on a common topic in most college medicinal chemistry courses – pharmacotherapeutic activity related to stereochemistry within racemic mixtures, a characteristic of up to 25% of drugs on the market today. Individual enantiomers may demonstrate different levels of activity, pharmacological effect, and may be metabolized via alternate metabolic pathways. It is because of these differences in metabolism, pharmacologic activity, and potency that scientists focus on fundamental chemical properties to develop agents that are clinically shown to be equally efficacious to their racemic counterparts. One such example of this is seen when comparing racemic albuterol to its R-enantiomer, levalbuterol.

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Levalbuterol, marketed as Xopenex® in the United States, is available both as a metered-dose inhaler and a nebulizer solution in multiple strengths. It is currently approved by the FDA for the treatment of asthma-related symptoms, but has been used as an off-label treatment of chronic obstructive pulmonary disease. Levalbuterol has been shown to have similar outcomes when compared to racemic albuterol in controlling asthmatic symptoms with a lower incidence of side effects in clinical trials.[1,2]

It is theorized that by eliminating the S-albuterol enantiomer contained in albuterol that the incidence of tachycardia and other non-desirable side effects will decrease.[3] S-albuterol has a longer half-life than levalbuterol and may cause bronchial hyperactivity, leading to contraction of the smooth muscles of the respiratory tract. Animal studies and pharmacokinetic studies done *in vitro* have further demonstrated that S-albuterol does not contribute to the therapeutic activity of albuterol, which may lead to the decrease in respiratory function previously discussed. While there is no quantitative impact

on pulmonary function, literature from the 1990s-2000s showed that there may be an increased incidence of "airway hyperactivity, paradoxical bronchospasm, decreased bronchoprotection, and even increased mortality."[4]

The objective of this study was to evaluate the incidence of adverse effects that impact the cardiovascular system, specifically an increase of systolic blood pressure or incidence of tachycardia to justify automatic, therapeutic substitution of levalbuterol to racemic albuterol for all nebulized orders. The authors of this study have no financial or other potential conflicts of interest. No funding was required or obtained to carry out this study.

MATERIAL AND METHODS

Patients receiving levalbuterol or racemic albuterol were evaluated for the effects of each medication on the cardiovascular system through the use of hospital database analysis.

This was a two arm study looking at patients from December 2013 to July 2014 admitted with a diagnosis related to pulmonary disease or exacerbation. Patients were stratified based on what agent was used for relief of symptoms during their length of stay. All nebulized doses of levalbuterol and racemic albuterol were included; metered-dose inhalers were excluded.

The data collected was retrospectively examined, collected via electronic chart review, and analyzed to determine clinical significance of side effect profiles and outcomes of the agents.

Primary outcomes include the incidence of tachycardia and average elevation in systolic blood pressure after patients have received a dose of either drug as an inpatient or in the emergency department prior to admission as recorded in the patient's electronic medical record. Secondary outcomes include the need for adjunct therapy, average dose required for relief of symptoms (e.g. strength/frequency), number of nebulization doses required during hospital stay, length of stay, and inpatient mortality. Tachycardia was defined as any heart rate more than 100 beats/minute within 3 hours after administration of a nebulization or the first heart rate measured within 6 hours of administration. Rise in systolic blood pressure was defined as an increase of 10 mmHg observed within 3 hours after administration of a nebulization; if no value was available in the first 3 hours, then the first value within 6 hours after dose administration was recorded. Need for adjunctive therapy constituted the addition of any pharmacologic agents to the patient's medication list required to manage therapy in addition to albuterol or levalbuterol, with the exception of nebulized ipratropium. Indication for treatment was ascertained from the patient's past medical history as documented in their admission history and physical. All other secondary endpoints, excluding mortality, were obtained from the patient's medication use summary in the hospital's electronic medical records.

Patients were included in the study if they were over 18 years of age, were administered at least one dose of levalbuterol or racemic albuterol for relief of symptoms, must have been admitted to a telemetry floor, and had an ICD9 code of 493.0 (extrinsic asthma), 493.1 (intrinsic asthma), 493.2 (chronic obstructive asthma), 493.8 (other forms of asthma), 493.9 (asthma unspecified), or 496.0 (chronic obstructive pulmonary disease, other)[5]. Levalbuterol does not hold an FDA-approved indication for chronic obstructive pulmonary disease, but was included in this analysis as it is often used off-label for treatment. Patients were excluded if they had admission diagnoses not fulfilling one of the pre-specified ICD9 codes, a history of implantable cardioverter-defibrillator (ICD), pacemaker, paroxysmal supraventricular tachycardia, or any other diagnosed arrhythmia except atrial fibrillation, hypersensitivity and/or documented allergy to albuterol, use of phenylephrine, epinephrine, norepinephrine, vasopressin, dobutamine, dopamine, milrinone, midodrine, or digoxin during hospital stay, use of SABA agents via metered-dose inhaler while inpatient, were pregnant, or hospitalized for less than 24 hours Data was collected using the hospital's electronic medical records to scan for patients with ICD9 codes whose diagnoses satisfy inclusion criteria. All patient information was properly de-

identified and followed all privacy laws to protect patient anonymity. Data collected included age, gender, race, medication used for treatment while inpatient – name, dose, strength, frequency, indication for therapy, patient heart rate, patient blood pressure, total length of stay, survivability on discharge, and cost of therapy.

Statistical Analysis

The variables of age, length of stay, average elevation of heart rate, average elevation of systolic blood pressure were analyzed using the student's t-test. All categorical data was analyzed with χ^2 or Fisher's exact tests (gender, race, dose of medication used, mortality, outpatient medications, and indication for therapy). All tests used a 95% confidence interval with an α of 0.05.

RESULTS AND DISCUSSION

The study had an eligible number of 1860 patients at the hospital campus, of which 594 were excluded for not being admitted to an inpatient bed with continuous telemetry monitoring. The study investigators were able to screen 529 patient charts, of which only 83 patients (levalbuterol n = 30; racemic albuterol n = 53) were included in the study as seen in figure 1.

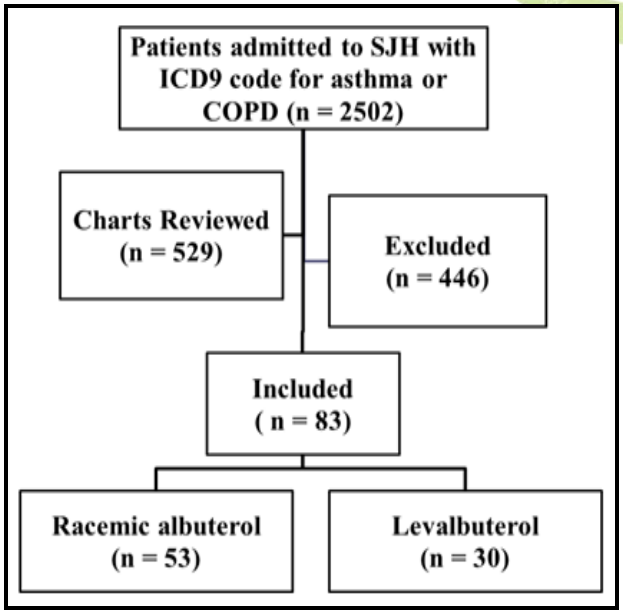

Figure 1: Study design

The most common reasons for exclusion included not receiving a dose of either study drug, use of vasopressors or other contraindicated medications, or use of an HFA inhaler method of delivery. Baseline characteristics for included patients can be found in table 1.

Table 1: Baseline characteristics

Characteristic	Racemic albuterol (n = 53)	Levalbuterol (n = 30)	p-value
Age – yrs. (SD)	65.6 (± 12.3)	63.5 (± 16.9)	0.563
Male gender – no. (%)	24 (45.3)	11 (36.7)	0.549
Caucasian – no. (%)	48 (90.6)	25 (83.3)	0.534
Asthma history – no. (%)	10 (18.9)	10 (33.3)	0.338
COPD history – no. (%)	47 (81.1)	20 (66.7)	0.031
Beta-blocker use – no. (%)	14 (26.4)	24 (80.0)	0.300
Anticholinergic use – no. (%)	48 (90.6)	11 (36.7)	< 0.001
Baseline average heart rate – bpm (SD)	80.5 (± 17.7)	91.3 (± 17.3)	0.002
Baseline average SBP – mmHg (SD)	127.6 (± 11.3)	137.9 (± 11.3)	0.066

The primary outcome of tachycardia occurred in 12 patients receiving levalbuterol (40%) and ten patients (18.9%) receiving racemic albuterol (p = 0.066). The mean change in heart rate for racemic albuterol was 2.21 beats per minutes versus 1.57 beats per minute in the levalbuterol arm (p = 0.787). The incidence of a clinically relevant increase in systolic blood pressure of more than 10 mmHg occurred in 12 patients receiving racemic albuterol (22.6%) compared to ten patients in the levalbuterol arm (33.3%). Results are available in table 2.

Table 2: Primary outcomes

Characteristic	**Racemic albuterol (n = 53)**	**Levalbuterol (n = 30)**	**p-value**
Incidence of tachycardia – No (%)	10 (18.9)	12 (40)	0.066
Mean change in heart rate – bpm (SD)	2.21 (± 9.76)	1.57 (± 10.64)	0.787
Incidence of clinically-relevant increase in SBP – No (%)	12 (22.6)	10 (33.3)	0.423
Mean change in SBP – mmHg (SD)	0.96 (± 22.16)	1.67 (± 19.75)	0.882

A subanalysis was conducted excluding patients who had received beta-blocker therapy while hospitalized. The primary outcome of tachycardia occurred in eight patients of 39 patients in the racemic albuterol arm (21.1%) compared to nine of the 18 patients in the levalbuterol arm (50%), although it failed to reach statistical significance (p = 0.051). The incidence of a clinically relevant increase in systolic blood pressure occurred in 11 racemic albuterol patients and 5 levalbuterol patients (p = 0.973). Results are listed in table 3.

Table 3: Sub-analysis of patients on receiving beta-blocker therapy

Characteristic	**Racemic albuterol (n = 53)**	**Levalbuterol (n = 30)**	**p-value**
Incidence of tachycardia – No (%)	8 (21.1)	9 (50)	0.051
Mean change in heart rate – bpm (SD)	1.31 (± 10.14)	3.72 (± 9.29)	0.395
Incidence of clinically-relevant increase in SBP – No (%)	11 (28.2)	5 (27.8)	0.973
Mean change in SBP – mmHg (SD)	5 (± 21.6)	0.83 (± 23.7)	0.514

Secondary outcomes (table 4) for the average number of nebulizations needed per hospitalization, mean length of stay, and patient mortality all were not statistically significant. The need for adjunct therapy was required in 21 patients receiving racemic albuterol (39.6%) and 24 patients receiving levalbuterol (80%) (p = 0.0009). This did not include the addition of nebulized ipratropium in patients as all but five albuterol patients received a combination of albuterol and ipratropium, and is likely related to the lower rate of COPD in the levalbuterol arm. Inhaled corticosteroids, combination long-acting beta$_2$-agonists with corticosteroids (e.g. fluticasone/salmeterol), and long-acting anticholinergic agents (e.g. tiotropium) were the most common agents added to patient regimens. Most notable of the secondary endpoints was the average cost of treatment being significantly higher in those patients being treated with

levalbuterol ($3.37 vs. $101.11) for a course of treatment during hospitalization (p = < 0.0001). This figure was generated based on the average number of nebulizations required for each medication per hospitalization stay and the average wholesale price available at the time of data collection.

Table 4: Secondary outcomes

Characteristic	**Racemic albuterol (n = 53)**	**Levalbuterol (n = 30)**	**p-value**
Need for adjunct therapy – n (%)	21 (39.6)	24 (80)	0.0009
Average number of nebulizations used during admission – doses (SD)	17.5 (± 25.7)	15.2 (± 21.9)	0.664
Mean length of stay – days (SD)	6.3 (± 6.23)	7.0 (± 5.26)	0.587
Inpatient mortality – n (%)	0 (0)	1 (3.3)	0.361
Average cost of treatment ($)*	3.37	101.11	< 0.0001

The results of this study showed that the use of racemic albuterol compared to levalbuterol for the treatment of asthma and chronic obstructive pulmonary disease had little clinical advantage over one another. The incidence of tachycardia and elevation in systolic blood pressure was found to be neither clinically nor statistically significant in either case, even when beta-blocker therapy was excluded; this is a first since currently available literature does not provide insight to impact on systolic blood pressure despite package labeling that warns against an increase for levalbuterol. A search of recent literature shows studies that focus primarily on pediatric patients.[6,7]. Results in these studies showed that there was no clinically significant impact on heart rate, similar to the results of our study. Bio et al, however, only had six patients receive a dose of 1.25 mg of levalbuterol, which was the most common dose received by patients in our study.[7] In studies examining patients in an intensive care environment, it was shown that either agent showed no significant impact on heart rate, regardless of baseline tachycardia and had similar incidences of tachyarrhythmias, the most common of which being premature ventricular contractions.[8,9] A study by Scott et al. looked at administration in emergency room patients and found that the only significant impact on heart rate was 2.7 bpm higher in patients after receiving albuterol, but was also shown to lack any clinical significance when compared to low-dose levalbuterol.[9] Moreover, larger studies, including one by Kelly et al that enrolled 192 patients, showed that the increase in heart rate with either agent was marginal. This study was most similar to our study design where the majority of patients received racemic albuterol (n = 142) compared to levalbuterol (n = 40) or both agents (n = 10).[3]

This study reinforces that the formulary substitution at our study facility provided both an economic benefit and a therapeutically equivalent solution. With a roughly equivalent requirement of nebulizations per admission, the economic decision of substitution is quite evident since the average course of albuterol in this study cost roughly 30 times less than a course of levalbuterol, albeit that both are available generically.

The study did, however, have some limitations. First, the study was not powered to detect a significant difference between either arm; therefore, the chance of a type II error occurring still exists. This may explain the discrepancy between larger clinical trials and our study when examining the incidence of tachycardia. A larger

patient population would be required to decrease the chance of this occurring. Second, the measurements of the vital signs were done without respect to time of dose administration. Instead, they were collected as scheduled and collected up to 6 hours after administration of a dose if they did not meet the primary criteria of 3 hours after the dose was received. Third, the study did not collect all of the vital sign measurements within the specified time windows for an average value; only the maximum value was collected during the timeframe, which could have been the cause of other medications.

CONCLUSION

Levalbuterol offers little clinical benefit of decreasing impact on cardiovascular vital signs compared to albuterol. The authors concluded that the use of racemic albuterol in place of levalbuterol was a sound decision by the Pharmacy and Therapeutics Committee of our study facility based upon the results, which are also reflective of what current literature is available.

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