INTRODUCTION

Levalbuterol (Xopenex, Sepracor) is the R-isomer of the beta-agonist albuterol. Although racemic albuterol is supplied as a 50:50 mixture of both the R- and S-isomers, Xopenex contains only the R-isomer, the primary isomer responsible for the bronchodilator effects of racemic albuterol.1,2

The theoretical superiority in bronchodilation of levalbuterol over albuterol has not been well substantiated in hospitalized patients, yet its use has increased significantly at our 318-bed suburban community hospital over the past three years. An informal survey of prescribers at our institution, primarily private physicians, suggested that its use increased under the assumption that levalbuterol would be better tolerated in patients with tachycardia. Some in vitro studies have suggested that the inactive S-isomer might have detrimental effects, including hyperresponsiveness with continued use,1 possible increased eosinophil activation,1 paradoxical bronchospasm,2 and even increased mortality.4 These claims are based largely on preclinical data, but with no randomized controlled trials to support them, the clinical importance of these findings is unknown.

In 2005, levalbuterol, along with guidelines for its use, was added to our hospital’s formulary. The hospital’s P&T committee-approved guidelines in 2005 can be summarized as follows:

1. Levalbuterol will be dispensed if one of the following criteria is met:
   • The patient was taking levalbuterol prior to admission.
   • The respiratory therapist determines that albuterol is causing adverse effects (e.g., palpitations or agitation).
   • The patient has significant tachycardia (defined as a baseline heart rate greater than 120 beats/minute or a rise of greater than 40 beats/minute over the baseline rate with treatment).
   • The patient is younger than 18 years of age.
   • Nebulizer treatment is being administered in an outpatient area, such as the emergency department (ED).

2. Levalbuterol will be automatically dispensed for all levalbuterol orders that do not meet these criteria.

The committee developed these guidelines to reflect its stance that levalbuterol should be considered a second-line therapy to albuterol and that it should be reserved for patients who experience intolerable side effects from albuterol. The guidelines did not impose restrictions on dose or frequency of levalbuterol use in patients who met these criteria; however, the pharmacists were asked to send a pharmacist-to-physician communication sheet to the chart for all orders that exceeded the FDA’s approved frequency of three doses per day. As a result of the increase in usage and the subsequent increase in expenditures, an audit of levalbuterol use was conducted.

STUDY OBJECTIVES

Our primary objective was to determine whether levalbuterol use was in compliance with P&T committee-approved guidelines. Secondary objectives were as follows:

- to describe the change in heart rate associated with both levalbuterol and albuterol nebulization treatments
- to compare the number of treatments of levalbuterol and albuterol use per day
- to determine whether the use of levalbuterol was in compliance with the dosage guidelines in the package insert
- to describe other adverse events associated with levalbuterol and albuterol nebulization treatments

METHODS

After obtaining approval from the institutional review board, we performed a retrospective chart review. We identified patients for inclusion via a computerized report generated for all patients who had received levalbuterol in January 2008; any inpatient who received at least one levalbuterol treatment between January 6, 2008, and January 19, 2008, was included. After the chart review was completed, the data were analyzed in a Microsoft Excel spreadsheet.

RESULTS

Forty-six patients (47 admissions) had received a prescription for levalbuterol during this two-week time frame (one patient had been admitted twice and received levalbuterol during both admissions). The records of four of these patients revealed inadequate documentation and were excluded. We analyzed a total of 43 admissions: 64 orders were for scheduled nebulizer treatments (29 for levalbuterol and 35 for albuterol).

The average age of the sample population was 71.7 years (standard deviation [SD] = 13.6; range, 30–94 years). There were 15 women and 28 men. The average length of stay was 5.5 days (SD = 4.5; range, 1–23 days). Most of the patients stud-
ied were being treated for chronic obstructive pulmonary disease (COPD) (n = 28); only one patient had a diagnosis of asthma. The remaining 14 patients lacked a documented history of either COPD or asthma, and an indication for nebulizer treatment could not be determined.

A total of 1,066 breathing treatments (430 with albuterol and 636 with levalbuterol) were administered to the patients in this sample population throughout their entire admission. Twenty-seven patients (63%) received at least one dose of both albuterol and levalbuterol during their hospital stay. Patients received an average of 4.5 treatments per day (SD = 0.9) while they were being treated with albuterol and 4.1 treatments per day (SD = 1.0) while they were being treated with levalbuterol. Most of the time (84%), the order for levalbuterol was initiated in a critical-care unit (CCU): 21 orders in the ED, 13 in telemetry, and two in the intensive-care unit (ICU).

Of the 29 orders written for scheduled levalbuterol, only three (10%) were appropriately written to be given every eight hours or three times daily. The remaining 14 scheduled orders (48%) were for four times daily or every six hours, and the rest (n = 12, 41%) were for every four hours. In addition, 14 scheduled orders (48%) were accompanied by as-needed doses, which would increase the daily ordered dose beyond that indicated. Albuterol orders were usually written to be given every four hours (n = 26, 74%), and 51% of all albuterol scheduled orders were accompanied by doses given as needed, most frequently every two hours (n = 14, 40%) (Table 1).

Of the 43 patients reviewed, 15 (35%) met the P&T committee–approved criteria for levalbuterol use. Of those patients meeting the criteria, nine were able to do so because levalbuterol was a home medication and six patients met the criteria because of a pre-treatment heart rate of 120 beats/minute or more. None of the patients experienced adverse effects from either albuterol or levalbuterol, according to the respiratory-care notes.

Pre-treatment and post-treatment heart rates were documented 77.2% of the time for albuterol (332 of 430 treatments) and 79.1% of the time for levalbuterol (503 of 636 treatments). The mean (±SD) pre-treatment heart rates were 87.6 ± 11.1 beats/minute for albuterol and 87.9 ± 14.7 beats/minute for levalbuterol. Of those treatments with documented pre-treatment and post-treatment heart rates, 48.8% of albuterol treatments and 48.1% of levalbuterol treatments resulted in no change or in a lower heart rate. Only one treatment (with levalbuterol) resulted in an increase of greater than 20 beats/minute from the pre-treatment heart rate. The change in heart rate associated with albuterol and levalbuterol treatments is outlined in Figure 1.

**DISCUSSION**

Most of the levalbuterol usage at our institution did not comply with the P&T committee-approved guidelines. This may reflect the lack of access by the staff pharmacists to necessary patient information (e.g., heart rate, a list of home med-

<table>
<thead>
<tr>
<th>Medication</th>
<th>Every 4 Hours</th>
<th>Every 6 Hours q.i.d.</th>
<th>Every 8 Hours t.i.d.</th>
<th>Other</th>
<th>Precription Includes a p.r.n. Order</th>
<th>Average No. of Treatments Given per Day</th>
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<tbody>
<tr>
<td>Levalbuterol (n = 29)*</td>
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<td>14</td>
<td>3</td>
<td>0</td>
<td>14</td>
<td>4.1</td>
</tr>
<tr>
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<td>26</td>
<td>6</td>
<td>1</td>
<td>2</td>
<td>18</td>
<td>4.5</td>
</tr>
</tbody>
</table>

p.r.n. = as needed; q.i.d. = four times daily; t.i.d. = three times daily.

* Based on the total number of written orders.

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**Table 1 Trends in Levalbuterol (Xopenex) and Albuterol Usage**

**Figure 1 Change in heart rate (HR) after breathing therapies with albuterol and levalbuterol (Xopenex). The graph shows the percentage of total therapies (n = 1,066) categorized by pre-treatment to post-treatment changes in HR. Nebulizations without pre-dose and post-dose HRs documented are excluded from the figure (i.e., 22.8% of albuterol therapies and 20.9% of levalbuterol therapies). bpm = beats/minute. For the last color key, there are zero data points (not represented).**
Drug Utilization Evaluation: Levalbuterol (Xopenex)

ications) at the point of order verification. Without the ability to leave the pharmacy and to review the patients’ charts for the guideline criteria when the order was received, the pharmacists were compelled to verify all prescriptions for levalbuterol that included “do not substitute” in order not to delay treatment. In addition, the misconception on the part of prescribers that the side-effect profile for levalbuterol was superior to that of racemic albuterol drove the high volume of orders.

Our data demonstrated no clinically significant differences in the change in heart rate between levalbuterol and albuterol under typical usage conditions at our institution. To our knowledge, only one clinical study has been designed to compare the heart rate increase induced by nebulized levalbuterol and albuterol in a prospective fashion. The randomized, crossover study by Lam and Chen compared changes in heart rate with nebulized albuterol 2.5 mg and levalbuterol 1.25 mg in 20 ICU patients, including 10 patients with baseline tachycardia, at 10 time points beginning immediately after the dose was given and extending up to four hours after each treatment.5

In patients with baseline tachycardia, the mean largest heart rate increase was 1.4 beats/minute (1.3%) with albuterol and two beats/minute (2.1%) with levalbuterol; neither of these changes was statistically significant. Similarly, in patients without baseline tachycardia, the mean largest increase in heart rate was 4.4 beats/minute with albuterol (6.7%; P = 0.04) and 3.6 beats/minute with levalbuterol (5%; P = 0.03). Although the increase in heart rate for patients without baseline tachycardia reached statistical significance, one could argue that these changes of less than five beats/minute are not clinically significant.

Larger studies, although not designed specifically to address changes in heart rate, have produced similar results. A randomized, double-blind, parallel-group study by Nelson et al. compared the efficacy and safety of albuterol or levalbuterol with placebo, used regularly in 328 adults with asthma.6 After four weeks of treatment three times daily, the authors compared ventricular heart rates 15 minutes after treatment with baseline rates. They found an increased heart rate for all treatment groups as follows:

- 2.3 beats/minute with levalbuterol 0.63 mg
- 6.7 beats/minute with levalbuterol 1.25 mg
- 2.5 beats/minute with albuterol 1.25 mg
- 5.7 beats/minute with albuterol 2.5 mg

Other published studies that mention changes in heart rate and other adverse events have shown similar results.7-10

We also wanted to ensure that we were not restricting a therapeutically superior product by limiting the use of levalbuterol. A review of the literature revealed that many levalbuterol trials, although they included an albuterol treatment arm, established efficacy only when placebo was the comparator. Few comparative efficacy studies of hospitalized patients with COPD or asthma have been published.

Donohue et al. compared the number of nebulizations, symptom and pulmonary function outcomes, and costs in a multicenter study of 479 hospitalized patients with COPD or asthma. The patients were randomly assigned to receive either levalbuterol or albuterol.11 Choosing a total number of nebulizations during hospitalization as the primary efficacy endpoint, the authors noted that patients receiving levalbuterol needed significantly fewer median total and scheduled nebulizations than those in the albuterol group.

This finding is somewhat misleading, because the treatment protocol allowed for levalbuterol 1.25 mg every six to eight hours but albuterol 2.5 mg could be given according to the individual hospital’s protocol every one to four hours. No patients in either treatment group required rescue medications; therefore, the difference in number of treatments is likely to be a result of the less frequent dosing protocol and the longer half-life of levalbuterol rather than a difference in comparative efficacy.

Other efficacy outcomes, including a change in forced expiratory volume in one second (FEV1) from baseline to hospital discharge, symptom assessment scores, and patients’ general well-being scores, improved significantly from baseline measures but did not differ significantly between groups. Although the authors identified a statistically significant difference between treatment groups for beta-mediated adverse effects scores, this was an open-label study and scores were based on patients’ reported symptoms rather than on objective data such as heart rate.

A retrospective chart review by Truitt et al. compared clinical efficacy, patient outcomes, and medical costs in hospitalized patients treated with levalbuterol or albuterol.12 The review included 234 patients admitted with a diagnosis code for COPD or asthma. Patients receiving levalbuterol during their hospitalization were less likely to be readmitted within 30 days (5.7%) compared with patients being treated with albuterol (16.4%) (P = 0.01). The mean total cost of nebulizer therapy was also higher for albuterol; however, the average wholesale price (AWP) was used for reference pricing, and this cost differs greatly from acquisition costs for most hospitals. Other findings, such as a shorter length of stay and lower overall hospital costs in the levalbuterol group, did not reach statistical significance.

To date, the Donohue and Truitt studies appear to be the only ones published that have addressed the comparative efficacy of levalbuterol and albuterol in hospitalized adults.11,12 Neither study assessed spirometry values in detail, which are important indicators of efficacy for bronchodilators.

In another study by Donohue et al., spirometry values were evaluated in outpatients with COPD. In this multicenter, randomized, double-blind controlled trial, 209 patients with COPD received levalbuterol 0.63 mg or 1.25 mg, albuterol 2.5 mg, or placebo three times daily for six weeks.13 The primary endpoint was the average FEV1 area-under-the-curve (AUC) concentration (0 to 8 hours) over weeks 0, 2, and 6. All active treatments demonstrated an improvement in the FEV1 AUC concentration compared with placebo (P < 0.05), although the improvement was not statistically significant when levalbuterol was compared with albuterol.

The use of rescue medications, compared with their use at baseline (in doses per day), changed over time; fewer rescue treatments were needed by the patients receiving levalbuterol 1.25 mg than by those receiving albuterol (P = 0.02), suggesting improved clinical control of COPD. Again, one would expect that the albuterol patients would require more rescue
treatments than the levalbuterol group, because of albuterol’s shorter half-life, when both agents are scheduled to be given three times daily, regardless of comparative efficacy.

A study by Datta et al. in 30 patients with stable COPD also revealed no significant difference in post-treatment FEV₁ between levalbuterol and albuterol.14 Although the authors noted significant improvements in FEV₁ compared with placebo for all treatment groups, there were no significant differences between bronchodilator groups at any time period. The authors also observed no significant differences between groups in oxygen saturation, hand tremor, or heart rate.

In the Nelson trial described earlier, which had evaluated changes in heart rate in asthma patients receiving levalbuterol or albuterol, efficacy was also assessed.6 Nelson found that the change in peak FEV₁ response to the first dose in the combined levalbuterol group (both 0.63-mg and 1.25-mg doses) was significantly greater than in the combined albuterol group (both 1.25-mg and 2.5-mg doses) (0.92 vs. 0.82 L, respectively; P = 0.03). After four weeks of therapy three times daily, the results were similar but not statistically significant (0.84 and 0.74 L, respectively).

We recognize that additional non-medication costs might have been incurred if the use of albuterol resulted in more admissions from the ED. In a multicenter, randomized, double-blind trial by Nowak et al., 627 adults with asthma received oral prednisone 40 mg and either levalbuterol 1.25 mg or albuterol 2.5 mg every 20 minutes for one hour, then every 40 minutes for up to three supplementary doses.15 Additional therapies, as needed, could be started after three hours. This study identified a significant improvement in FEV₁, after the first dose of levalbuterol, compared with albuterol (P = 0.021), but the difference was not significant with cumulative doses after that. The median time to discharge and overall hospitalization rates were similar for both groups.

We shared the results of our evaluation and literature review with several physician groups, including the specialties of pulmonology, emergency medicine, critical care, family practice, cardiology, and neonatology. After gaining their support, we presented the evaluation to our P&T committee and recommended that levalbuterol be moved to nonformulary status and that all prescriptions for levalbuterol be automatically interchanged to albuterol. The recommendation was accepted. Eliminating levalbuterol use at our 318-bed hospital resulted in an estimated savings of nearly $5,000 in the first month after the 18% price increase that went into effect that month was taken into account. When these savings are annualized and combined with those of our sister hospital, a 500-bed tertiary care center, we expect to accrue a savings of more than $100,000 per year.

CONCLUSION

Restricting the use of levalbuterol was not successful at our institution. Removing levalbuterol from the formulary was clinically justified and has resulted in significant savings in medication expenditures. It is anticipated that with a nonformulary status for levalbuterol, we will continue to enjoy reduced expenditures for nebulized bronchodilators without incurring additional costs stemming from any lack of therapeutic benefit by using albuterol.

REFERENCES