Levalbuterol Is Not More Cost-Effective Than Albuterol for COPD

To the Editor:

In a recent issue of CHEST, Truitt et al (January 2003)\(^1\) claimed that their retrospective chart review demonstrated that “levalbuterol afforded clinical and pharmaco-economic advantages over racemic albuterol” in the treatment of hospitalized patients with COPD and asthma. The primary end point of the study was the total number of nebulizer treatments required. However, the target care path that was in operation during the historical cohort required albuterol to be administered every 4 h (six treatments per day), while in the current cohort levalbuterol was administered every 8 h (three treatments per day). Thus, the statistically significant difference in the primary end point was a result of differences in the care plans. There were no statistically significant differences in the number of extra treatments required by either cohort. Surprisingly, the reviewers missed this fatal flaw in the study design.

The combination of more treatments, by design, and an artificially higher cost basis for albuterol resulted in a spurious statistical difference for the total cost of nebulizer therapy. They used the “average wholesale price” (AWP), but no hospital pharmacy ever pays the AWP. For many hospitals, the acquisition cost of racemic albuterol is around $0.32 per 2.5-mg dose compared to $1.82 per 1.25 mg for an equivalent dose of levalbuterol (ie, a 5.7-fold difference). In contrast, the AWP for the two products are $1.21 and $2.08, respectively (a 1.7-fold difference).\(^2\)

No conclusions can be drawn about clinical advantages since the treatments were not administered in a double-blind randomized manner. Moreover, in patients with COPD (about 80% of the patients), FEV\(_1\) did not significantly increase from hospital admission to hospital discharge in either cohort. In such patients, it is possible that dosing every 8 h with albuterol would be as effective as dosing every 4 h since these patients show little response to bronchodilators. Also, we are incredulous about the statement that levalbuterol “appeared to have a more prolonged therapeutic effect.” The basis for this statement was a difference in the hospital readmission rate, but since this was a retrospective chart review, other factors such as differences in hospital discharge medication (data not presented) may have affected this end point.

Last, “not significant” was designated as p > 0.1 when the convention is p > 0.05. As a consequence, the authors inferred that important pharmaco-economic end points were different when they were not statistically different. For example, the authors state that those treated with levalbuterol “had shorter lengths of hospital stay” and “decreased costs for hospitalization,” but the p values for these end points for patients with COPD were 0.07 and 0.11, respectively.

We conclude that the differences between albuterol and levalbuterol in this study were a result of differences in the number of treatments required by the care plan, invalid cost calculations, and the emphasizing of numerical differences that were not statistically significant by conventional criteria.

Reference

1 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

References

1 Truitt T, Witko J, Halpern M. Levalbuterol compared to racemic albuterol; efficacy and outcomes in patients hospitalized with COPD and asthma. Chest 2003; 123:128–135

To the Editor:

We welcome the opportunity to respond to the letters to the editor in CHEST regarding our recent article (January 2003).\(^1\)

We agree with Dr. Crater that in retrospective studies, care must be taken to ensure that treatment groups are fully comparable. This is why we compared treatment with racemic albuterol and levalbuterol among patients with the same diagnosis codes, who had been treated at the same hospital, by the same pulmonologists, and during the same months of two sequential years. Furthermore, as indicated in the footnote to Table 1 of our article, there were no significant differences in age, gender distribution, racial distribution, percentage of patients hospitalized in the past year, steroid use, or hospital admission and discharge FEV\(_1\) and FVC levels between the levalbuterol and racemic albuterol groups. We also acknowledged and addressed the limitations of the study in the “Discussion” section of our article, including the limitations associated with a retrospective study performed at a single institution.

Dr. Crater expressed concern that one of the references cited in the manuscript (Reference 6) is a letter that was published in Lancet. However, research letters published in Lancet undergo peer review prior to publication. Furthermore, multiple other references cited in this article (References 7 to 14) present evidence from in vitro and animal studies of the detrimental effects of (S)-albuterol.

It is also correct that individuals with asthma comprised a greater proportion of those who received racemic albuterol compared with those who received levalbuterol (28% vs 17.9%, respectively). However, separate analyses were performed comparing patients with asthma to those with COPD in the two study populations. Length of hospitalization was 1 day less among patients with COPD and 1.2 days less among patients with asthma when treated with levalbuterol, although these differences were not significant (p = 0.097 and p = 0.07, respectively). The reduction in the need for nebulizer treatments among patients treated with levalbuterol vs those treated with racemic albuterol was greater for patients with asthma than for patients with COPD. Furthermore, as presented in Table 4, multivariate regressions controlling for diagnosis (ie, asthma vs COPD) indicated statistically significant impacts of levalbuterol treatment.
compared with racemic albuterol treatment on the length of hospitalization and the total costs. Finally, while the percent predicted FEV₁ on hospital admission among patients with asthma was lower during the racemic albuterol treatment period compared with the levalbuterol treatment period (44.6% vs 48.6%, respectively), this difference was not statistically significant, as noted in the footnote of Table 2. Thus, the differences between the racemic albuterol and levalbuterol treatments presented in our study were not due to differences in the relative proportion of patients with asthma to those with COPD in each group.

We also reported that patients in the levalbuterol group had a reduction in the 30-day hospital readmission rate. As this was a finding present in the data, we thought that it would be inappropriate not to report it. However, we were careful not to attribute this finding to the in-hospital use of levalbuterol. While levalbuterol treatment may have been partially responsible for the reduction in 30-day hospital readmissions, we indicated that multiple post-hospital discharge factors that were not included in the medical charts, and therefore could not be evaluated, also might have affected hospital readmission.

Dr. Crater’s letter questioned the effectiveness of doing every 8 h with racemic albuterol. While this is certainly a reasonable question, it is not the question our study addressed. We note that the Food and Drug Administration-approved prescribing information states that the usual starting dose of levalbuterol for patients ≥12 years of age is 0.63 mg administered three times per day (ie, every 6 or 8 h). Patients with more severe disease or those who do not respond adequately may benefit from a dosage of 1.25 mg tid. Although the label for racemic albuterol states that it should be administered three or four times a day by nebulization, in our clinical experience hospitalized patients require more frequent use (ie, every 3 to 4 h). In a pilot study that we conducted prior to our retrospective review,2 we found that despite treatment with racemic albuterol, 2.5 mg every 4 h, 25% of patients had breakthrough symptoms that required as-needed therapy. Thus, our results clearly indicated the advantages of treatment with levalbuterol compared with racemic albuterol for hospitalized patients with asthma and COPD.1,2

With respect to Dr. Crater’s concern on the introduction of levalbuterol therapy in a “real-world” context, patients were not asked whether they would accept this change of therapy. The use of levalbuterol every 8 h was instituted as the standard practice for the treatment of patients with asthma and COPD at Halifax Regional Hospital. By July 1, 1999, this regimen was the standard practice and was used on a routine basis. Thus, there was no patient discussion regarding a switch from therapy every 4 h to every 8 h, which could potentially bias their responses.

The comment of Drs. Hendeles and Hartzena that the statistically significant difference in the total number of nebulizer treatments was due to differences in care plans misses the point of our study. We clearly stated in our article that the purpose of our study was to evaluate the impact of levalbuterol therapy on clinical effectiveness, patient outcomes, and direct medical costs. We wanted to confirm that levalbuterol could be used in clinical practice and was used on a routine basis. Thus, there was no patient discussion regarding a switch from therapy every 4 h to every 8 h, which could potentially bias their responses.

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Autopsy Data in the Trial by Barritt And Jordan

To the Editor:

I read with interest the special report by Dalen (November 2002), who discussed the mortality of untreated pulmonary thromboembolism (PE). The only prospective randomized trial of anticoagulants vs placebo that showed benefit in acute PE was performed at the Bristol Royal Infirmary in 1957 and published shortly thereafter. Dalen quotes mortality of untreated PE as 38%.

In the study by Barritt and Jordan, 5 of 19 untreated patients died, which equates to 26% mortality, and it is unsure where the 38% quoted comes from. In addition, last year, an audit of the autopsy records of the participants enrolled in this landmark trial was conducted in order to ascertain the findings at death, as the original report was incomplete and has therefore been criticized. The findings are shown in Table 1. The audit, conducted within the Department of Pathology at the Bristol Royal Infirmary, illustrate two observations about the participants enrolled in the trial by Barritt and Jordan and who died with untreated PE: (1) coincidental morbidity and infection was likely to be contributory to their demise; and (2) a large amount of residual thrombus or clot burden was found both in the lung and in other venous sites with potential to embolize to the lung.

These observations should be kept in mind when deciding the cost/benefit ratio of anticoagulation in those patients identified to have small (subsegmental or less) PE with no source of potential thromboemboli and no continuing risk factors for venous thromboembolism. This difficult clinical question needs to be addressed especially in the light of rapidly improving imaging technology such as multidetector spiral CT angiography with which smaller PEs are detected.

Stephen Iles, BSc
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Table 1—Autopsy Findings of the Five Patients Who Died With PE Randomized to No Anticoagulation

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age, yr/sex</th>
<th>Underlying Diagnosis</th>
<th>Anatomic Site of Pulmonary Emboli</th>
<th>Source of Thromboemboli</th>
<th>Coincidental Infection Noted</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54/female</td>
<td>Extensive breast carcinoma</td>
<td>Left main branch</td>
<td>Right femoral DVT</td>
<td>Mixed organism empyema, bronchopneumonia and abscess</td>
</tr>
<tr>
<td>2</td>
<td>56/male</td>
<td>Post operation for intestinal obstruction (adhesions)</td>
<td>Main trunk</td>
<td>Left femoral DVT, hepatic vein thrombosis Bilarteral popliteal DVT</td>
<td>Biliary tree sepsis</td>
</tr>
<tr>
<td>3</td>
<td>78/female</td>
<td>Post fractured ankle</td>
<td>Main trunk</td>
<td>Bilarteral femoral DVT, right ventricular mural thrombus</td>
<td>Bronchopneumonia, fungal lung abscess Staphylococcus aureus lung abscess</td>
</tr>
<tr>
<td>4</td>
<td>57/male</td>
<td>Myocardial infarction</td>
<td>Left lobar</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>41/male</td>
<td>Nephrotic syndrome secondary to primary amyloidosis</td>
<td>Both main branches</td>
<td>Left calf DVT, renal vein thrombosis</td>
<td>None</td>
</tr>
</tbody>
</table>

*From the study by Barritt and Jordan. DVT = deep vein thrombosis.