A Randomized Controlled Trial To Assess the Optimal Dose and Effect of Nebulized Albuterol in Acute Exacerbations of COPD*

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Study objectives: Despite the widespread use of short-acting, inhaled β₂-agonists in acute exacerbations of COPD (AECOPDs), little is known about their optimal dose. The aims of this study are to compare the bronchodilator response to incremental doses of inhaled albuterol during and after recovery from an AECOPD, and to compare the effects of regular nebulized albuterol, 2.5 mg and 5 mg, on the speed of recovery.

Methods: Eighty-six patients admitted with an AECOPD were recruited. Each patient was administered incremental doses of inhaled albuterol on hospital admission and following recovery. Dose-response curves were constructed based on FEV₁ and peak expiratory flow rate (PEFR) recorded after each incremental dose. Patients were then randomized in a double-blind fashion to receive 2.5 mg or 5 mg of nebulized albuterol q4h until recovery. Twice-daily PEFR, the number of extra doses of bronchodilators, and side effects reported were recorded.

Results: Maximal bronchodilation (Emax) FEV₁ (maximal bronchodilatory response to albuterol) increased from 0.64 ± 0.27 L/min during the exacerbation to 0.94 ± 0.35 L/min during recovery (p < 0.001). The Emax PEFR increased from 147.53 ± 62.46 L/min to 222.94 ± 73.82 L/min after recovery (p < 0.001). There was no significant difference in rate of recovery of PEFR (p = 0.684), duration of hospital stay (p = 0.084), or side effects (p = 0.506) between the groups receiving 2.5 mg or 5 mg of nebulized albuterol.

Conclusions: There was significant improvement in Emax to inhaled albuterol as the COPD exacerbation resolved. There was no significant difference in outcomes including length of hospital stay or recovery of lung function between patients treated with regular 2.5 mg vs 5 mg of nebulized albuterol during an AECOPD.

Key words: acute exacerbation; albuterol; β₂-agonists; COPD; dose response

Abbreviations: AECOPD = acute exacerbation of COPD; BTS = British Thoracic Society; Emax = maximal bronchodilation; MDI = metered-dose inhaler; PEFR = peak expiratory flow rate

COPD secondary to cigarette smoking is a major cause for morbidity and mortality. Acute exacerbations of COPD (AECOPDs) occur regularly during the course of the disease (median rates, 2.4 to 3 episodes per year) and are associated with progressive loss of lung function, dyspnea, and reduced quality of life.1–3 While the airflow obstruction in COPD is largely irreversible, a systematic review4 of 13 randomized, placebo-controlled, crossover studies involving 296 patients with stable COPD found that regular use of an inhaled β₂-agonist increased postbronchodilator FEV₁ by 140 mL/s and peak expiratory flow rate (PEFR) by 39 L/min, and significantly reduced daily breathlessness score compared to placebo. β₂-agonists also reduce breathlessness by reducing dynamic pulmonary hyperinflation.5 In asthmatics, the bronchodilatory effects of β-agonists are dose related, with incremental doses producing increasing bronchodilation.6 To date, no trials have sufficiently evaluated the dose-response relationship to short acting β-agonists in AECOPD.

A commonly used dose of nebulized albuterol in AECOPD is 5 mg every 4 to 6 h. There is little evidence to support that this is the optimal dose for
bronchodilation in AECOPD. A questionnaire study done in the United Kingdom among physicians with an interest in respiratory disease showed a fivefold difference in the dose of nebulized albuterol they commonly prescribed (range, 2.5 to 12.5 mg) per 24 h. Previous COPD guidelines of the British Thoracic Society (BTS) recommend 2.5 to 5 mg of nebulized albuterol q4h for moderate-to-severe exacerbations. The more recent National Institute for Clinical Excellence/BTS evidence-based guidelines could not recommend a specific dose in AECOPD. In stable COPD, earlier studies have shown that 87% of maximal bronchodilation is achieved with an inhaled dose of 2 mg of terbutaline and 97% with a dose of 4 mg. In a larger group of stable COPD patients receiving albuterol, 87% of patients achieved 90% of their maximal bronchodilation (Emax) with doses of inhaled albuterol ≤ 1.2 mg.11 Whether such dose-response effects are applicable in AECOPD is unknown. Studies in asthmatics have also shown that the bronchodilatory effect of ipratropium and terbutaline changes during the course of recovery from an exacerbation of asthma, with ipratropium becoming more effective as the patient recovers. Whether a similar response occurs to inhaled albuterol in AECOPD is again undetermined. The aims of this study are as follows: (1) to determine whether bronchodilatory responses to inhaled short-acting β-agonists improve as the patient recovers from the AECOPD, and (2) to determine whether using doses of inhaled albuterol at doses > 2.5 mg q4h is likely to improve inpatient outcome in terms of length of hospital stay and recovery of airflow obstruction or have more significant side effects.

Materials and Methods

Patients

This was a multicenter study done in the respiratory departments of four teaching hospitals in Yorkshire, England. Eighty-six patients admitted with an exacerbation of previously known COPD based on BTS criteria were recruited into the study. All patients had a FEV1 < 80% of the predicted value with < 15% and/or 200-mL reversibility to inhaled bronchodilators. AECOPDs among patients admitted to hospital were diagnosed if two of the three factors were present, namely increased dyspnea, increased sputum volume, and change in color of sputum, again according to BTS criteria. All patients were > 45 years of age, and were current or ex-smokers with at least a 20-pack-year smoking history. Patients with uncompensated respiratory failure (arterial pH < 7.35 and PCO2 > 6.0 kilopascals), lobar pneumonia, pneumothorax, lobar or hing collapse, bronchiectasis, cardiac failure, bronchial carcinoma, or suspected pulmonary embolism were excluded from the study. Asthmatics and nonsmokers were also excluded. Patients with severe exacerbations of COPD requiring IV aminophylline therapy or noninvasive positive pressure ventilation were excluded to avoid possible bias arising from other bronchodilatory therapies received.

Study Design

The study protocol was approved by the local ethics committee. Suitable patients with AECOPD were recruited into the study within 24 h of hospital admission. Written informed consent was obtained from each patient at the beginning of the study. Dose responses to incremental doses of albuterol were determined at least four hours after receiving their last bronchodilator. Bedside baseline spirometry was recorded in an upright position using a computerized portable spirometer (Micro GP: Micro Medical Ltd; Rochester, Kent, UK). The best FEV1 after three reproducible measurements was used in the analysis. The best of three peak flow recordings using a mini-Wright peak flowmeter (Clement Clarke, Essex, UK) were similarly recorded. Incremental doses of albuterol (cumulative doses of 0 µg, 200 µg, 400 µg, 800 µg, 1,600 µg, and 3,200 µg) were then administered sequentially every 20 min from a metered-dose inhaler (MDI) through a large-volume spacer device by the investigator. FEV1 and peak flows were recorded 15 min after each dose. A 5-min interval was allowed between attempting respiratory measurement and the next dose of the albuterol (Fig 1). The total dose administered in this way remained within the therapeutic range recommended for the treatment of AECOPD. Once the patient had recovered sufficiently to be discharged from the hospital, all the above measurements were repeated. Dose-response curves were constructed for each dose within 24 h of hospital admission and just prior to discharge after stabilization of the AECOPD.

After the first measurement, patients were randomized to receive either 2.5 mg or 5 mg of nebulized albuterol in a double-blind fashion until recovery from the exacerbation. This was administered every 4 h from a jet nebulizer (Porta-Neb; Medic-Aid Limited; Sussex, UK) mixed with 2.5 mL of preservative-free, normal saline solution over a period of 10 min. All nebulizers were administered in air with a flow rate of 6 L/min. All patients received 30 mg/d po of prednisolone for at least 7 days. Other treatments such as antibiotics were administered based on clinical need as judged by the treating clinician. There was no significant difference between groups as regards other treatments received such as antibiotics, oral theophyllines, nebulized anticholinergic bronchodilators, and inhaled, long-acting β-agonists.

Extra doses of 2.5 mg of nebulized albuterol were administered if indicated for relief of dyspnea. Patients subsequently commenced on IV aminophylline and receiving invasive and noninvasive ventilatory support were withdrawn from the study. Patients requiring a second antibiotic for a hospital-acquired chest infection were also withdrawn.

PEFR measurements were recorded twice daily 30 min after nebulized bronchodilatation using a mini-Wright peak flowmeter during the hospital stay. Rate of recovery of peak flows (< 20% diurnal variation), duration of hospital stay in days until medically fit for discharge, and additional doses of bronchodilators requested were recorded for each patient. Side effects of drugs were recorded by patients and medical and nursing staff throughout the study. The number of withdrawals and reasons were recorded.

Statistics

Dose-response curves for FEV1 and PEFRs were constructed within 24 h of hospital admission and within 24 h prior to discharge after the treating clinician believed that the AECOPD had been stabilized sufficiently to allow hospital discharge. Emax
and the difference between baseline FEV₁ or PEFR and maximal FEV₁ or PEFR were calculated at the onset and after recovery from the exacerbation. Power calculations estimated that 60 patients would be required to demonstrate a 10% difference in FEV₁ or PEFR at the beginning and after completion of treatment of AECOPD at a two-sided significance level of 5% with a β-error of 20%. To avoid the complicating effects of baseline changes on the detection of tolerance, we used polynomial regression to calculate Emax for each dose-response curve. Emax for FEV₁ and PEFR measurements during the dose-response curves to albuterol was chosen as the primary outcome variable to compare the effect of the two albuterol treatment doses and the response to albuterol during and after the AECOPD. Analysis of FEV₁ and PEFR data for each treatment dose was performed using a Student paired t test. Changes in mean Emax FEV₁ and PEFR achieved with each cumulative albuterol dose were compared by multifactorial analysis of variance to establish any significant effect between treatments. Power calculations suggested that 40 patients would be required in each albuterol treatment group to detect a 20% difference in length of hospital stay and length of time to peak flow recovery with a β-error of 20%. Length of hospital stay and length of time to peak flow recovery between albuterol (2.5 mg vs 5 mg) groups were compared using a χ² test. Side effects experienced by the two groups were compared using the Wilcoxon test; p values < 0.05 were considered statistically significant.

RESULTS

Among the 86 COPD patients admitted with acute exacerbation, there was slight female predominance (47 female and 39 male patients). The mean age of the patients was 69.26 ± 9.25 years (± SD) [range, 47 to 90 years], and the mean FEV₁ was 0.816 ± 0.41 L/min (range, 0.30 to 2.14 L/min; 18 to 70% of predicted). Table 1 shows the characteristics of patients included in the study.

The study did not show any significant difference in terms of outcome between patient groups receiv-

### Table 1—Patient Characteristics and Comparison Between Groups of Patients With AECOPD Receiving Either Nebulized Albuterol, 2.5 mg or 5 mg q4h

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Albuterol 2.5 mg</th>
<th>Albuterol 5 mg</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>40</td>
<td>46</td>
<td>NS</td>
</tr>
<tr>
<td>Male/female gender</td>
<td>21/19</td>
<td>18/28</td>
<td>NS</td>
</tr>
<tr>
<td>Mean age, yr</td>
<td>68</td>
<td>58</td>
<td>NS</td>
</tr>
<tr>
<td>Withdrawals</td>
<td>2</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>Side effects</td>
<td>1</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>Death (renal failure)</td>
<td>1</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Side effects</td>
<td>10</td>
<td>11</td>
<td>NS</td>
</tr>
<tr>
<td>Mean length of stay, d</td>
<td>6</td>
<td>9</td>
<td>NS</td>
</tr>
<tr>
<td>Time to PEFR recovery, d</td>
<td>4</td>
<td>3.32</td>
<td>NS</td>
</tr>
<tr>
<td>Extra doses of albuterol at 2.5 mg/d (mean)</td>
<td>0.055</td>
<td>0.078</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Data are presented as No. NS = not significant.*
ing 2.5 mg or 5 mg of albuterol during an AECOPD. A confounding effect of added nebulized inhaled ipratropium bromide was believed to be unlikely, as the numbers who received the drug were similar in each of the albuterol dose subgroups, and a Cochrane review\textsuperscript{14} of the subject has not demonstrated an additive effect of ipratropium to inhaled, short-acting \(\beta\)-agonists in AECOPD. The time taken to attain peak flow recovery was 4 days in the 2.5-mg group and 3.32 days in the 5-mg group (\(p = 0.684\)). There was no significant difference in the length of hospital stay prior to the patient being medically fit for discharge (6 days vs 9 days, \(p = 0.084\)). Tremor was more common in the 5-mg group, but overall the difference in reported side effects were not statistically significant (\(p = 0.506\)).

The incremental dose-response measurements demonstrate significant improvement in the dose response to inhaled albuterol, measured as FEV\textsubscript{1} and peak flow after recovery from the exacerbation (\(p < 0.01\) for both FEV\textsubscript{1} and PEFR) [Table 2]. Fifty percent of Emax during AECOPD in this study was achieved with a cumulative dose of 400 \(\mu\)g of inhaled albuterol and 90\% of Emax with a cumulative dose of 3,200 \(\mu\)g. Figure 2 shows the improvement in FEV\textsubscript{1} response in the whole COPD study population during and after the AECOPD. A significant improvement in bronchodilator response to albuterol between the onset and end of the AECOPD measured using FEV\textsubscript{1} (Emax FEV\textsubscript{1}, 0.64 \pm 0.27 to 0.94 \pm 0.38 L, \(p < 0.001\)) and PEFR (Emax PEFR, 147.53 \pm 62.46 to 222.94 \pm 73.8 L/min, \(p < 0.001\)) was demonstrated.

Figures 3, 4 show the mean FEV\textsubscript{1} response during and after the exacerbation in the two subgroups of patients who had been randomized to either 2.5 mg or 5 mg of albuterol q4h throughout the hospital admission. They clearly demonstrate significant improvement in the dose response measured as FEV\textsubscript{1} after the recovery from the AECOPD independent of the dose of albuterol they had been randomized to receive during hospital admission. Using analysis of variance for repeated measures, it was possible to compare the dose response during and after AECOPD for FEV\textsubscript{1} and PEFR for both albuterol doses. For both FEV\textsubscript{1} and PEFR, there were significant improvements as recovery from AECOPD occurred with \(p\) values < 0.001.

**Discussion**

This study demonstrates that there is no significant difference in clinical outcome in patients treated every 4 h with either 2.5 mg or 5 mg of nebulized albuterol throughout an AECOPD. These results complement earlier reports of patients with stable COPD in which near-Emax occurred with smaller doses of nebulized terbutaline than those conventionally used over 12 weeks without development of drug tolerance.\textsuperscript{10} Fifty percent of Emax during AECOPD in this study was achieved with a cumulative dose of 400 \(\mu\)g of inhaled albuterol, and 90\% of Emax was achieved with a cumulative dose of 3,200 \(\mu\)g. This complements previous studies in which Emax was achieved in stable COPD in the

Table 2—PEFR and FEV\textsubscript{1} Response (\(n = 86\)) to Incremental Doses of Inhaled Albuterol Within 24 h of Hospital Admission With an AECOPD and at the End of AECOPD Prior to Hospital Discharge*

<table>
<thead>
<tr>
<th>Cumulative Dose Albuterol, (\mu)g</th>
<th>PEFR During AECOPD, L/min</th>
<th>PEFR End AECOPD, L/min</th>
<th>FEV\textsubscript{1} During AECOPD, L</th>
<th>FEV\textsubscript{1} End AECOPD, L</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>159 \pm 6.75</td>
<td>192 \pm 8.38</td>
<td>0.6757 \pm 0.03</td>
<td>0.7922 \pm 0.04</td>
</tr>
<tr>
<td>200</td>
<td>165 \pm 6.96</td>
<td>197 \pm 8.38</td>
<td>0.7060 \pm 0.03</td>
<td>0.8381 \pm 0.04</td>
</tr>
<tr>
<td>400</td>
<td>169 \pm 7.31</td>
<td>202 \pm 8.39</td>
<td>0.7297 \pm 0.03</td>
<td>0.8681 \pm 0.04</td>
</tr>
<tr>
<td>800</td>
<td>171 \pm 7.38</td>
<td>207 \pm 8.38</td>
<td>0.7491 \pm 0.03</td>
<td>0.8823 \pm 0.04</td>
</tr>
<tr>
<td>1,600</td>
<td>174 \pm 7.13</td>
<td>209 \pm 8.39</td>
<td>0.7494 \pm 0.03</td>
<td>0.8949 \pm 0.04</td>
</tr>
<tr>
<td>3,200</td>
<td>177 \pm 6.86</td>
<td>215 \pm 8.46</td>
<td>0.7547 \pm 0.03</td>
<td>0.9016 \pm 0.04</td>
</tr>
</tbody>
</table>

*Data are presented as mean \(\pm\) SEM.
majority at doses of albuterol < 0.6 mg \(^6\) and at a dose of 0.8 mg in a smaller cohort of AECOPD patients.\(^{15}\) The AECOPD dose-response data also add confidence to our conclusions about outcome and may help deflect criticism that the power of the study may not have been adequate to demonstrate small differences.

Using the smaller dose of 2.5 mg of albuterol may have cost implications, as the exacerbations of COPD are a significant economic burden to health services. The cost of one dose of 2.5 mg of nebulized albuterol in the hospital is 12.45 pence, and that of a 5-mg nebulizer is 24.90 pence. In the patients we studied, the 2.5-mg group received 1,626 doses of nebulized albuterol, which costs £4,048 or £101.20/patient/AECOPD, and the 5-mg group received 1,740 doses costing £8,665 or £188.37/patient/AECOPD. However, only mild-to-moderate exacerbations were included in this study. Patients with severe AECOPD were excluded, as they are more likely to receive other confounding treatments such as noninvasive ventilation and IV aminophylline.

There was no statistically significant difference in the occurrence of side effects such as tremor, palpitations, and tachycardia between the two groups. It was noted that tremor was more common in the 5-mg group, but the difference did not reach statistical significance. This is in contrast to an earlier study\(^6\) showing a significant dose-related response in pulse rate, tremor, and palpitations. The same study,\(^6\) which measured plasma albuterol levels, found that 3 mg of nebulized albuterol produced satisfactory bronchodilation and fewer side effects and suggested this was related to systemic absorption. The current study shows that use of 5 mg of nebulized albuterol as opposed to 2.5 mg in AECOPD did not produce any clinically significant improvements in outcome such as length of stay in hospital, time taken to recovery, extra doses of bronchodilators required, deaths, or withdrawal from the study. Therefore, this study supports the regular use of 2.5 mg of nebulized albuterol in moderate, nonacidotic AECOPD.

The kinetics of \(\beta\)-receptor sensitivity in COPD remains to be fully elucidated. As desensitization results from agonist occupancy, it has been suggested that receptor sensitivity may be attenuated at higher doses of short-acting \(\beta\)-agonists or by longer-acting, partial \(\beta\)-agonists. The difference in receptor sensitivity may be explained by an agonist-influenced alteration in the spatial arrangement of the receptor, which in turn modifies the characteristic of the \(\beta\)-adrenoreceptor.\(^{16,17}\) In this study, the dose-response curves to albuterol show a parallel left shift associated with clinical improvement during and at the end of the AECOPD, independent of the dose of regular nebulized albuterol used throughout hospital admission. The implication of this observation is that there has been no dose-related change in the receptor sensitivity to albuterol while the patients recover. Such a change would have been expected to produce a change in slope of the response. Rather, it implicates some other factor such as access of the drug to the \(\beta_2\)-receptors. This may be as a result of bronchoconstriction, mucosal edema, sputum retention or, more likely, because of hyperinflation and gas trapping.\(^{18–21}\) These factors would be expected to subside as the exacerbation resolves. It does emphasize the importance of making decisions about the need for chronic nebulizer use when the patient is in...
stable state rather than in exacerbation. The use of corticosteroids in AECOPD is supported in that they reduce mucosal edema through their antiinflammatory effect and may thereby enhance drug delivery into the distal airways.

Similar results were seen in a study on the effect of recovery on the responses to nebulized ipratropium in acute asthma. There is some evidence that cumulative administration of β-agonists in asthmatics produces a greater airways response than noncumulative administration as sequential doses of drugs penetrate further into the lungs. Studies in asthma with radiolabeled markers have shown that reduced airway caliber may alter peripheral lung deposition of inhaled drugs and therefore affect bronchodilator response. Lipworth and Clark evaluated the effect of airway caliber on lung deposition and bioavailability of inhaled albuterol in normal subjects, and patients with mild and severe exacerbations of asthma, and found significant alteration in early lung deposition profile of albuterol in severe asthmatics. They demonstrated attenuated β2-adrenoreceptor airway response measured as forced expiratory flow, mid-expiratory phase and systemic parameters such as tremor in severe asthmatics compared to mild asthmatics and normal subjects, implying less systemic absorption from obstructed small airways. The clinical significance of the observation is that it tends to support the use of higher doses of inhaled β2-agonists during an exacerbation of asthma than used in stable disease. Whether this observation is applicable to AECOPD is not known; however, this supposition is not supported by the current study in mild-to-moderate exacerbations.

In conclusion, the results of this study support the use of smaller regular doses of nebulized albuterol during acute non-acidotic moderate exacerbations of COPD. A dose of 2.5 mg of albuterol is as effective as 5 mg in terms of clinical outcome and is significantly cheaper. The bronchodilator dose-response effects of inhaled albuterol at the time of hospital admission with AECOPD are clearly of a lower magnitude than those recorded after recovery. However, the dose-response curves suggest that the improvement in dose-response to albuterol as these patients recover is not due to a change in β-adrenergic receptor sensitivity, but rather it is likely due to effects such as an improved access of the drug to smaller airways as the inflammatory component of the AECOPD resolves.

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