Comparison of Domiciliary Nebulized Salbutamol and Salbutamol From a Metered-dose Inhaler in Stable Chronic Airflow Limitation*

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Nineteen patients (12 men) mean age, 63.4 years (range, 32 to 78), with stable chronic airflow limitation, mean FEV₁, 0.55 L (range, 0.3 to 1.05 L), completed an eight-week, double-blind, double cross-over study comparing nebulized salbutamol and salbutamol from a metered-dose inhaler (MDI). Salbutamol from both delivery systems produced bronchodilation. The doses of salbutamol inhaled via the nebulizer and MDI producing maximal bronchodilatation were established by cumulative dose-response curves. The contents of the nebulizer and MDI were inhaled four times a day, one system containing salbutamol and the other a placebo. Cross-over of salbutamol from one system to the other occurred every two weeks. There was no significant difference between the two delivery methods in daily peak expiratory flow rate (PEFR), severity of symptoms, or extra bronchodilator usage. Two weekly laboratory assessments of spirometry, PEFR, and exercise tolerance also showed no significant differences. Careful assessment is recommended before the provision of domiciliary nebulizers.

Inhaled bronchodilators are frequently prescribed for patients with chronic airflow limitation (CAL) despite minimal or, on occasions, no reversibility of airway obstruction being demonstrated. These drugs are generally taken in the form of a metered dose inhaler (MDI) by the outpatient, although administration via a nebulizer is common in the hospital. During a stay in hospital, patients with CAL often attribute their feeling of improved well-being to this change in the method of bronchodilator delivery. This perceived clinical benefit has resulted in patients’ requests to continue with nebulization at home.1

**Patients and Methods**

Patients were referred from outpatient Chest Clinics at a time when their clinical condition was stable. All patients were currently using inhaled β₂-agonists. The study was approved by the Hospital Ethical Committee, and patients gave their written consent.

Two assessments were carried out on each patient prior to the study. On both occasions, all bronchodilator therapy was withheld after midnight. The method used was the same on both days. On the first morning the cumulative dose of salbutamol from the nebulizer required to produce greatest bronchodilatation was established. After 30 minutes, rest forced expiratory volume in the first second (FEV₁) and relaxed vital capacity (VC) were measured using a spirometer (Vitalograph). Resting pulse rate and peak expiratory flow rate (PEFR) (Wright peak flow meter) were also recorded. Salbutamol, 2.5 mg (0.5 ml) diluted to 4 ml with 0.9 percent saline solution, was administered via an Inspiron Mini-Neb nebulizer driven by an air compressor at a flow rate of 7 L/min. All patients used a facemask and were instructed to breathe tidally. Nebulization was continued to the end of visible aerosol production (13 to 14 minutes). PEFR, FEV₁, VC, and pulse rate were recorded at 15 and 30 minutes following inhalation and then at 10-minute intervals until no further increase in FEV₁, VC, or PEFR occurred. At this point, a further 2.5 mg of salbutamol was given by the same method, and PEFR, FEV₁, VC, and pulse rate recorded as before. If an increase in PEFR, FEV₁, or VC occurred, another 2.5 mg was given, and the process repeated until further drug doses produced no increase in PEFR or spirometric values. Response to salbutamol MDI using increments of 200 μg (2 puffs) was assessed by the same method on the second morning. Patients were instructed to activate the MDI at the start of a slow, steady inhalation, to breath-hold for ten seconds, and to pause for one minute between successive doses. Patients unable to use an inhaler satisfactorily were excluded. The dose of salbutamol from the nebulizer and MDI producing the greatest bronchodilatation in each patient were used in the subsequent study.

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Manuscript received June 27; revision accepted November 3.
Table 1—Results of Peak Expiratory Flow Rate, Spirometry, Total Lung Capacity in 23 Patients*

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Mean</th>
<th>SEM</th>
<th>Mean % Pred</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁, L</td>
<td>0.55</td>
<td>0.04</td>
<td>(22.9)</td>
</tr>
<tr>
<td>VC, L</td>
<td>1.86</td>
<td>0.09</td>
<td>(53.4)</td>
</tr>
<tr>
<td>PEFR, L/min</td>
<td>114</td>
<td>8.2</td>
<td>(25.1)</td>
</tr>
<tr>
<td>TLC, L</td>
<td>7.1</td>
<td>0.31</td>
<td>(122.1)</td>
</tr>
<tr>
<td>RV, L</td>
<td>4.8</td>
<td>0.26</td>
<td>(231)</td>
</tr>
<tr>
<td>Dsb, mmol/Kp/min</td>
<td>13.1</td>
<td>1.33</td>
<td>(54)</td>
</tr>
</tbody>
</table>

*Values expressed as mean ± SEM; figures in brackets show mean % predicted normal. Three patients were unable to perform TLC measurement because of claustrophobia.

Three timed walks were carried out in a level, enclosed corridor by the method of McGavin et al., and the farthest distance covered was taken as the baseline measure. One walk was performed at the end of each assessment morning, and the third 30 minutes after nebulized salbutamol in the dose established by the cumulative technique.

Patients showing an increase in pulmonary function following salbutamol from both delivery systems were enrolled in an eight-week, double-blind, double cross-over study. Fifteen patients were taking a fixed dose of prednisolone (range, 5 to 20 mg), and the remainder had been shown to be unresponsive to corticosteroids. All patients were disabled as a result of their respiratory condition, and four patients were housebound.

Each patient was supplied with an Inspiron air compressor and Inspirion Mini-Nebs. Patients were instructed to use the nebulizer and MDI four times a day, taking the nebulizer first. They were randomly allocated to one of two treatment regimens, so that they inhaled either salbutamol nebulizer and placebo MDI or saline nebulizer and salbutamol MDI for the first two weeks, with cross-over of salbutamol between the delivery systems occurring at the end of weeks 2, 4, and 6. Patients recorded PEFR (Wright mini peak flow meter) the highest of three attempts, before and 30 minutes after treatment four times a day, a symptom score for day and night time cough and breathlessness on a 0-3 scale, and extrasymptomatic bronchodilator usage. In addition, daytime breathlessness was recorded on a 100-mm horizontal visual analog scale (VAS), and instruction in the use of the VAS was given during the assessment mornings. This was completed by the patient and spouse (where appropriate) without conferring, with scales from separate days placed in individual sealed envelopes. Throughout the study, concurrent medication remained constant. Laboratory assessment was carried out at the end of each two-week period. The timing of this was kept constant for the individual and took place four hours after the last treatment. All unused study medication was returned, and this treatment was used in the laboratory assessment. PEFR, FEV₁, and VC were recorded before and 15 minutes after treatment (nebulizer and MDI). Thirty minutes after inhalation, one walking test was performed.

Analysis of Results

Analysis of data was carried out using nonparametric statistical tests, Wilcoxon signed pairs for paired data, and Mann-Whitney U test for unpaired data. Spearman’s rank correlation was used for correlation of PEFR and breathlessness (VAS) and for patient and spouse recordings of breathlessness (VAS).

Results

The details of the 23 patients enrolled in the study are shown in Table 1. Nineteen patients completed the study. Reasons for withdrawal were: tremor from nebulized salbutamol; clinical exacerbation during the first period of nebulized salbutamol; severe back pain due to osteoporosis, and noncompliance with the study. The results of the cumulative dose-response studies to inhaled salbutamol in the 19 patients are shown in Table 2. PEFR was significantly higher postnebulizer (p<0.05), but there was no significant difference in FEV₁ or VC.

Daily PEFR

Table 3 shows the PEFR in 19 patients. For the group, the increase in PEFR on nebulized salbutamol was not significant. However, four patients had significantly higher PEFR on active nebulizer.

Symptomatic Bronchodilator Use

Six patients required no extra bronchodilator for symptomatic relief during the study. In the remaining 13 patients the mean numbers of puffs per day used on the nebulizer and MDI were 2.4 and 2.7, respectively. This difference was not significant.

Subjective Results

All patients verbally reported an improvement in their symptoms during the study period and attributed this to the nebulizer, but analysis of the visual analog and symptom scores for breathlessness showed no significant difference between the nebulizer and MDI. The symptom score for cough was similarly uninfluenced by either treatment method. PEFR was not correlated with visual analog score for breathlessness. Five spouses completed a VAS recording severity of the patients’ breathlessness; in two, patient and spouse readings were significantly correlated (p<0.01).

Table 2—Reversibility to Inhaled Salbutamol in 19 Patients (Mean ± SEM)

<table>
<thead>
<tr>
<th></th>
<th>Nebulizer</th>
<th>MDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smallest dose</td>
<td>2.5mg (9 patients)</td>
<td>200μg (10 patients)</td>
</tr>
<tr>
<td>of salbutamol</td>
<td>5mg (10 patients)</td>
<td>400μg (7 patients)</td>
</tr>
<tr>
<td>producing maximal bronchodilatation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEFR, L/min</td>
<td>38 (5)</td>
<td>32 (5) (p&lt;0.05)</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>0.23 (0.04)</td>
<td>0.18 (0.03) NS</td>
</tr>
<tr>
<td>VC, L</td>
<td>0.63 (0.09)</td>
<td>0.60 (0.07) NS</td>
</tr>
</tbody>
</table>

Table 3—Daily PEFR (L/min) in 19 Patients (Mean ± SEM)

<table>
<thead>
<tr>
<th></th>
<th>Nebulizer</th>
<th>MDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>1</td>
<td>194±18.8</td>
<td>234±18.6</td>
</tr>
<tr>
<td>2</td>
<td>216±18.9</td>
<td>245±19.9</td>
</tr>
<tr>
<td>3</td>
<td>216±19</td>
<td>239±18.8</td>
</tr>
<tr>
<td>4</td>
<td>215±18.7</td>
<td>238±19.8</td>
</tr>
</tbody>
</table>
Two-weekly FEV₁ and Relaxed VC

Mean pretreatment and posttreatment FEV₁ and VC were higher on active nebulizer, but this difference was not significant (Fig 1). Statistical analysis was not possible on the results of individual patients because of the small number of readings made.

Walking Distance

There was a significant increase in walking distance between the first and second practice walks (p<0.005) but no significant difference between the second and third. During the study, 16 patients reported an increase in exercise tolerance, and the four patients previously housebound were able to walk outdoors. Walking distance was significantly improved at two weeks (range, 25 to +137 m) (p<0.005) and remained above baseline at eight weeks (p<0.03). No significant deterioration in walking distance occurred at assessment one month after completion of the study. There was no significant difference between the nebulizer and MDI as measured by the walking test.

Discussion

Previous studies of patients with chronic bronchitis and emphysema and severe chronic asthma report benefit from domiciliary nebulization. Our study, however, is the first to compare salbutamol by nebulizer and MDI in a double-blind, cross-over design. The nebulizer and MDI have been compared in an open study with no placebo in 24 patients with severe chronic asthma, with the finding of considerable improvement in symptoms from the nebulizer reflected in higher PEFR in some patients. In agreement with these studies a subjective improvement was reported by our patients, which they attributed to the use of a nebulizer at home. This improvement occurred after two weeks of the study irrespective of the mode of salbutamol administration. It is possible that an increase in the dose of β₂-agonist in some patients and overall improved compliance with therapy may have produced this. However, the design of this study (ie, no total placebo run-in period) does not allow elimination of a placebo response to the nebulizer. Several of the patients studied had previously requested nebulizer therapy at home. The benefit from home nebulization reported by the patients was reflected in the number of patients wishing to continue treatment on completion of the study. Only one thought that the MDI was quicker and more convenient.

A walking test was incorporated in the assessment, since improved exercise tolerance in the absence of obvious bronchodilatation is not infrequently reported by patients with severe CAL receiving nebulized drugs. In this study the walking test was not helpful in identifying patients benefiting from nebulizer therapy. It may be that patients recruited to the study believed they were receiving preferential treatment and that
this contributed to the significant increase in walking
distance after two weeks. Perhaps very little further
improvement could have been achieved. Patient moni-
toring of PEFR provided the only objective daily
measure of response, and in some patients two-weekly
spirometry did not appear to correlate with this.
Although it is not known which of the two measure-
ments was more accurate, the addition of regular
spirometry may be helpful.

A cumulative dose response technique was used to
establish the doses of salbutamol required from the
nebulizer and MDI for a plateau of response, and it is
possible that this method may have produced greater
response than single-dose administrations in some
patients.9 The minimum starting dose of nebulized
salbutamol was 2.5 mg, and in retrospect doses similar
to the initial 200-μg MDI inhalation should probably
have been used. However, despite this discrepancy,
the doses of salbutamol inhaled from the nebulizer and
MDI in the study closely resemble those generally
prescribed for the domiciliary treatment of patients
with CAL.

The 19 patients completing the study composed a
heterogeneous group of patients with severe CAL. The
total number was too small to allow subdivision of the
group on the basis of clinical history or degree of
reversibility. This study failed to demonstrate overall
benefit from domiciliary nebulization in the group of
patients. However, since individual variation in re-
spose occurred, it remains necessary to carefully
assess each patient, ideally using a double-blind tech-
nique. For the minority of patients who are unable to
master the required expertise for use of an inhaler,
cheaper alternatives to the nebulizer in the form of the
Rotahaler and spacer devices are available.

ACKNOWLEDGMENTS: The authors wish to thank Allen and
Hanbury’s Ltd, for generous financial support and for supplying the
air compressors, nebulizers, and salbutamol. Our thanks are also
due to Kerry Jones for typing the manuscript.

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