Delivery of Albuterol and Ipratropium Bromide from Two Nebulizer Systems in Chronic Stable Asthma* Efficacy and Pulmonary Deposition

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Bronchodilator responses to both nebulized albuterol (salbutamol) and ipratropium bromide and aerosol delivery to the tracheobronchial tree have been assessed in eight patients with chronic stable asthma (mean baseline FEV$_1$ 50 percent; reversibility >20 percent). Two commercially available nebulizer systems were used, namely, a Turret nebulizer operated at a compressed gas flow rate of 12 L/min (droplet MMD, 3.3μ) and an Inspiron nebulizer driven at 6 L/min (MMD, 7.7μ). Albuterol was given as doses of 250μg, 500μg, 1000μg (cumulative dose, 2 mg) and ipratropium bromide as doses of 30μg, 50μg, 100μg, and 200μg (cumulative dose, 400μg) at intervals of 35 minutes. For albuterol, bronchodilatation was significantly (p<0.05) greater at all dosage levels with the Turret. For ipratropium, bronchodilatation was similar for both nebulizers. Measurements of aerosol deposition using $^{99m}$Tc-labelled pentetic acid (diethylenetriamine pentaacetic acid; DTPA) showed that 9.1±1.1 percent and 2.7±0.2 percent of the dose reached the lungs during nebulization to dryness for Turret and Inspiron, respectively (p<0.01); distribution within the lungs was similar for the two aerosols. Selection of nebulizer apparatus can influence delivery of aerosol and subsequent bronchodilator response to albuterol in patients with chronic stable asthma but is less important for aerosol delivery of ipratropium bromide in these patients.

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Nebulizers are used in inhalation therapy for delivery of relatively large doses of bronchodilator drugs, for patients who cannot use an MDI correctly, and for delivery of other drugs that cannot conveniently be given by MDI. The efficacy of nebulizer therapy is likely to depend partly upon the amount of aerosol drug able to reach the lungs or upon the distribution of aerosol within the airways. Aerosol deposition is dependent upon the size of the droplets, which varies according to the nebulizer and the driving flow rate. Droplets smaller than 5μ in diameter are ideal for penetration to the small conducting airways, since such droplets may avoid deposition by impaction in the oropharynx and in the larger, more central airways of the lung. By contrast, droplets in the range of 5μ to 10μ deposit chiefly in the central airways, as well as in the oropharynx. Recent studies suggest that adrenergic receptors are present in high concentrations in the small conducting airways and that cholinergic receptors are present predominantly in the larger airways; it would seem therapeutically advantageous to target both of these classes of drugs to their principal site of action. In this study, we have assessed both aerosol deposition and the bronchodilator efficacies of albuterol and ipratropium bromide delivered from two commercially available nebulizers as aerosols with MMDs less than 5μ and more than 5μ, in order to ascertain the importance of aerosol size when administering β-adrenergic agonists and anticholinergic agents. Both drugs have been administered in a dose-response fashion in order to avoid possible saturation of receptors with the first dose of bronchodilator, which might mask any therapeutic advantage to be gained by altering the size of the aerosol.

Materials and Methods

Patients

Eight patients with chronic stable asthma, whose FEV$_1$ increased by at least 20 percent following 200μg of albuterol from an MDI, were investigated. All were receiving β-adrenergic agonists regularly by MDI, and these were withdrawn 12 hours prior to each study. Of the subjects, five were men, and three were women, and their mean age was 49 years (range, 25 to 64 years), with a mean
baseline FEV₁ of 50 percent (range, 23 to 105 percent) of the value predicted for age, height, and sex. Before commencing the investigation, each patient gave informed consent in writing; the studies were approved by the hospital's ethical practices committee.

**Design of Study**

Subjects were studied on six randomized occasions with an interval of at least 48 hours between study days. Two studies involved the inhalation of albuterol delivered in a dose-response fashion from two different nebulizers, two further studies involved aerosol ipratropium bromide, again delivered in a dose-response fashion, while the remaining two studies involved the assessment of aerosol deposition from each nebulizer using radiolabelled droplets. The nebulizer systems were chosen to give widely differing droplet size distributions and were as follows: (1) a Turret nebulizer (Medic-Aid, Ltd) fitted with a mouthpiece driven at a compressed gas flow rate of 12 L/min, yielding an aerosol with an MMD of 3.3 µ and in which 70 percent of the aerosol mass was contained in droplets smaller than 5 µ in diameter (Malvern Instruments 2600 HSD Analyzer); and (2) an Inspiron nebulizer (Bard International, Ltd) fitted with a mouthpiece driven at 6 L/min; the droplet MMD was 7.7 µ and only 25 percent of the aerosol mass was contained in droplets smaller than 5 µ in diameter.

Both aerosols were heterodisperse with geometric SDs of 1.75 and 1.90, respectively. Patients inhaled by relaxed tidal breathing with the nebulizer run to "dryness." Two milliliters of solution was initially placed in each nebulizer, with albuterol or ipratropium bromide diluted with physiologic saline solution where appropriate. This volume was chosen in order to minimize times for nebulization, although larger volumes may be nebulized more efficiently. The quantity of fluid released was determined by weighing each nebulizer before and after nebulization.

**Bronchodilator Response**

On arrival at the laboratory, patients rested for 15 minutes; measurements were then made of FEV₁ and FVC by spirometer (Vitalograph), PEFR by Wright peak flowmeter, and Vmax50% and Vmax25% by a spirometer (Ohio) coupled to an X-Y plotter. Each reading was taken as the best of three attempts; Vmax50% and Vmax25% were measured from the flow-volume curve which gave the highest baseline FVC on each day; Pulse rate was also recorded. On the days of albuterol, patients then received 250 µg of albuterol, followed by further doses of 250 µg, 500 µg and 1,000 µg (cumulative dose, 2,000 µg) at 35-minute intervals in order to construct dose-response curves. On the days of ipratropium, patients received doses of 70 µg, 140 µg, 100 µg, and 200 µg (cumulative dose, 400 µg) at 35-minute intervals. Measurements of pulmonary function and pulse rate were repeated 30 minutes after each dose.

**Radioaerosol Studies**

Indices of pulmonary function (FEV₁, FVC, PEFR, Vmax50% and Vmax25%) were measured, and subjects subsequently received 2 ml of pentetic acid (diethylenetriamine pentaacetic acid; DTPA) labeled with 37 MBq (1 mCi) of ⁸⁵³⁷Kr from either the Turret or Inspiron nebulizer. The Turret nebulizer incorporated its own one-way valve system for venting exhaled aerosol to a filter, but the exhalation port of the Inspiron was connected to an Ambu Valve and thence to a filter. Immediately following inhalation, a posteroanterior view of the lungs and stomach was obtained using a gamma camera with a large field of view (General Electric 400T) connected on-line to a computer (Noderecrst V77 600). A lateral view of the oropharynx was also obtained. The percentage of the dose in the lungs was determined by comparing the counts in a computer-generated "region of interest" drawn around the lungs with those from a known amount of activity placed in a perspex lung "phantom." Counts being corrected for tissue attenuation during their passage to the detector. Oropharyngeal deposition was determined from the sum of activities detected in mouth, pharynx, esophagus, and stomach. Regional delivery of radioaerosol was determined by dividing the pulmonary fields into central, intermediate, and peripheral zones (Fig 1), with the 20 percent contour of an "⁸¹Kr ventilation scan being used to define the edges of the lungs as previously described.

**Statistical Analysis**

Changes in data on pulmonary function and aerosol deposition for the two aerosols were compared by the Wilcoxon rank-sum test for paired data. The Spearman rank correlation test was used to look for relationships between aerosol deposition parameters and the percentage of predicted baseline pulmonary function indices.

**RESULTS**

**Baseline Pulmonary Function, Nebulizer Output, and Nebulization Time**

There were no differences between the study days in pulmonary function indices before aerosol inhalation (Table 1). The volumes of fluid released were similar for each of the two nebulizers (1.2 ± 0.2 ml [mean ± SEM] for Turret and 1.3 ± 0.2 ml for Inspiron). The time for nebulization to dryness was

**Table 1**

<table>
<thead>
<tr>
<th>Data</th>
<th>FEV₁, L</th>
<th>PEFR, L/min</th>
<th>Vmax25%, L/sec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albuterol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turret</td>
<td>1.24 ± 0.15</td>
<td>224 ± 22</td>
<td>0.27 ± 0.03</td>
</tr>
<tr>
<td>Inspiron</td>
<td>1.28 ± 0.20</td>
<td>238 ± 37</td>
<td>0.33 ± 0.06</td>
</tr>
<tr>
<td>Ipratropium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turret</td>
<td>1.31 ± 0.21</td>
<td>240 ± 21</td>
<td>0.30 ± 0.05</td>
</tr>
<tr>
<td>Inspiron</td>
<td>1.28 ± 0.18</td>
<td>228 ± 24</td>
<td>0.31 ± 0.04</td>
</tr>
<tr>
<td>Radioaerosol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turret</td>
<td>1.24 ± 0.13</td>
<td>224 ± 29</td>
<td>0.28 ± 0.04</td>
</tr>
<tr>
<td>Inspiron</td>
<td>1.27 ± 0.15</td>
<td>228 ± 28</td>
<td>0.27 ± 0.05</td>
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</tbody>
</table>

*Table data are means ± SEM.*

**Figure 1. Patterns of deposition for aerosols released from Turret nebulizer (flow rate, 12 L/min) and from Inspiron nebulizer (flow rate, 6 L/min) in one asthmatic patient. Pulmonary delivery was enhanced with Turret. Inset shows division of left (L) and right (R) lungs into peripheral (P), intermediate (I), and central (C) zones.**

**CHEST / 96 / 1 / JULY, 1989**
5.6 ± 0.3 minutes for the Turret but 8.4 ± 0.2 minutes for the Inspiron, owing to the lower compressed gas flow rate through this nebulizer.

**Albuterol Bronchodilator Response**

There were significant (p<0.05) differences present between the two aerosols for each of the pulmonary function parameters for at least one point on the dose-response curve, with bronchodilatation being greater for the Turret nebulizer system. Figures 2 and 3 show the increases in FEV₁ and Vmax25%; similar findings were obtained for PEFR, FVC, and Vmax50%. The data were examined to determine whether successive doses of bronchodilator produced incremental improvements in pulmonary function. The third dose of 500 µg of albuterol (cumulative dose, 1 mg) produced significant (p<0.05) rises for the Turret in FVC and in Vmax50% and for the Inspiron in FEV₁, PEFR, and Vmax50% the final dose of 1 mg (cumulative dose, 2 mg) produced no further change in any pulmonary function index for either aerosol. Changes in pulse rate were small and not significant; pulse rate rose from 72.6 ± 4.8 to 78.1 ± 4.8 beats per minute with the Turret and from 70.3 ± 5.5 to 76.5 ± 4.8 beats per minute with the Inspiron.

**Ipratropium Bromide Bronchodilator Response**

In contrast to the studies with albuterol, there were no significant differences in the dose-response curves between the two ipratropium bromide aerosols for any of the pulmonary function parameters (Fig 4 and 5). The data were tested to look for incremental improvements in pulmonary function with successive doses of bronchodilator. For the Turret the second dose of 50 µg (cumulative dose, 100 µg) produced significant improvements in Vmax25% and Vmax50% (p<0.05), although the final two doses did not significantly improve any pulmonary function test. For the Inspiron, the third dose of 100 µg (cumulative dose, 200 µg) produced significant increases in Vmax50% (p<0.05) and PEFR (p<0.05). Pulse rate increased from 71.4 ± 6.2 to 75.8 ± 4.8 beats per minute with the Turret and from 72.6 ± 4.6 to 77.8 ± 5.8 beats per minute with the Inspiron; these changes were not significant.

**Radioaerosol Studies**

Scans comparing patterns of deposition from the two nebulizers are shown in Figure 1. The total amounts of aerosol reaching the lungs for the group of

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**FIGURE 2.** Percent improvement in FEV₁ following inhalation of albuterol (salbutamol) as aerosols with MMD of 3.3 µm and 7.7 µm.

**FIGURE 3.** Percent improvement in Vmax25% following inhalation of albuterol (salbutamol) as aerosols with MMD of 3.3 µm and 7.7 µm.

**FIGURE 4.** Percent improvement in FEV₁ following inhalation of ipratropium bromide as aerosols with MMD of 3.3 µm and 7.7 µm.

**FIGURE 5.** Percent improvement in Vmax25% following inhalation of ipratropium bromide as aerosols with MMD of 3.3 µm and 7.7 µm.
Table 2—Deposition of Nebulized Aerosols Inhaled by Eight Patients with Obstructive Disease of the Airways*

<table>
<thead>
<tr>
<th>Nebulizer</th>
<th>Data</th>
<th>Turret (12 L/min)</th>
<th>Inspiron (6 L/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent of dose in:</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Whole lung</td>
<td>9.1 ± 1.1 (76)</td>
<td>2.7 ± 0.2† (44%)</td>
<td></td>
</tr>
<tr>
<td>Central zone</td>
<td>3.4 ± 0.5 (28)</td>
<td>1.1 ± 0.1† (18%)</td>
<td></td>
</tr>
<tr>
<td>Intermediate zone</td>
<td>2.0 ± 0.2 (17)</td>
<td>0.6 ± 0.1† (10%)</td>
<td></td>
</tr>
<tr>
<td>Peripheral zone</td>
<td>3.7 ± 0.6 (31)</td>
<td>1.0 ± 0.1 (16%)</td>
<td></td>
</tr>
<tr>
<td>Oropharyngeal deposition, percent of dose</td>
<td>2.9 ± 0.5 (24)</td>
<td>3.5 ± 0.4 (56%)</td>
<td></td>
</tr>
<tr>
<td>Peripheral/central zone ratio</td>
<td>1.13 ± 0.17</td>
<td>0.98 ± 0.10</td>
<td></td>
</tr>
</tbody>
</table>

*Table data are means ± SEM; numbers within parentheses are percentages of total deposition in body (ie, lungs plus oropharynx).
†p = 0.01 for comparison between two aerosols.
‡p<0.01 for comparison between two aerosols.

patients are shown in Table 2; whole-lung deposition rose from 2.7 ± 0.2 (mean + SEM) percent of the dose for the Inspiron nebulizer to 9.1 ± 1.1 percent of the dose for the Turret (p = 0.01). Aerosol deposition in each of the central, intermediate, and peripheral zones (Table 2) was significantly (p = 0.01) higher for the Turret than for the Inspiron. There was a trend towards a higher ratio of peripheral zone activity to central zone activity for the Turret, but this was not statistically significant. A smaller percentage of the dose was deposited in the oropharynx for the Turret, but again this difference was not significant. When results were expressed as percentages of total deposition in the body (ie, lungs plus oropharynx), deposition in the lungs was significantly higher (p<0.01) and deposition in the oropharynx significantly lower (p<0.01) for the Turret nebulizer (Table 2).

For the Turret nebulizer, there were positive correlations between peripheral zone deposition and the percentage of predicted baseline Vmax25% (rs = 0.792; p<0.05) and between the peripheral/central zone ratio and the percentage of predicted baseline PEFR (rs = 0.827; p<0.05). For the Inspiron nebulizer, peripheral zone deposition was positively correlated with the percentage of predicted values of baseline FEV1 (rs = 0.833; p = 0.02) and Vmax25% (rs = 0.899; p<0.01).

**DISCUSSION**

For albuterol, a significantly better effect was found using the Turret nebulizer. Since the mode of inhalation (relaxed tidal breathing) was the same on each day, it is probable that the observed differences in bronchodilator effect were related to the difference in the quantities of aerosol delivered to the lungs. Radiotracer studies using the same nebulizer systems showed that over three times more aerosol reached the lungs for the Turret nebulizer compared to the Inspiron. This results partly from improved delivery to the body (12.0 percent of the dose deposited in lungs plus oropharynx from the Turret, compared to 6.2 percent of the dose from Inspiron) and partly from selective delivery of the smaller aerosol droplets within the lungs (76 percent of deposited aerosol was in the lungs for the Turret, but only 44 percent for the Inspiron). The finding of enhanced delivery with a small droplet aerosol confirms earlier work from this laboratory.16

By contrast, the studies with ipratropium bromide showed no difference in bronchodilatation between the two aerosols. A possible explanation for this negative finding is that the first dose of ipratropium was too large, but we consider this unlikely, since subsequent doses from both nebulizers produced further bronchodilation. Less aerosol reached the lungs with the Inspiron, but with this nebulizer, there was a trend towards a pattern of more central deposition within the lungs. It is possible, therefore, that enhanced delivery to cholinergic receptors in large central airways with the Inspiron compensated for reduced delivery to the lungs as a whole, resulting in both nebulizers being equally effective in terms of bronchodilator response to ipratropium bromide.

Several previous studies have compared the efficacies of β-adrenergic agonist aerosols of differing droplet sizes, although there have been no previous analogous studies with ipratropium bromide. Studies by Hadfield et al17 and by Douglas et al18 both failed to find any difference in bronchodilator response to albuterol delivered at different compressed gas flow rates (and hence with different droplet sizes); however, both of these studies used single doses of 1 mg or greater, which might have produced a maximal effect even with an inefficient nebulizer system, and furthermore, measurements were restricted to tests of the function of the large airways. Clay et al,19 using a single dose of 2.5 mg of terbutaline sulfate, demonstrated greater improvement in the function of the small airways (Vmax50% and Vmax25%) when using an aerosol with an MMD of less than 2μm. The efficacies of β-adrenergic agonists of differing droplet sizes administered in a dose-response fashion were compared by Douglas et al,20 but response was not enhanced for the smaller droplet size. These authors used various dilutions of rimiterol and chose to nebulize for a fixed period, and this difference in the design of the study may be a factor accounting for the discrepancy between their study and ours. Two other studies showed similar dose-response curves for β-adrenergic agonists administered as two different droplet sizes,21,22 but drug concentrations had been adjusted to give an equivalent pulmonary dose with each droplet size.

CHEST / 96 / 1 / JULY, 1989 9
Only a small percentage of the aerosol dose reached the lungs from the nebulizers used in this study, in agreement with the findings of previous studies.12,13,23-25 Although several of the scans showed qualitative differences in distribution within the lungs for the two aerosols, there was no significant difference for the group as a whole. For monodisperse aerosols inhaled by normal subjects, penetration of aerosol to the pulmonary periphery increases with decreasing droplet size,1,2 but our results suggest that this effect may be less marked for heterodisperse therapeutic aerosols inhaled by patients with obstruction of the airways. Our results are in agreement with those of Mitchell et al,26 who found similar regional distributions within the lungs for nebulized aerosols with MMDs of 1.4μ and 5.5μ inhaled by patients with chronic severe asthma. It is possible that the division of the lungs into only three zones in our studies was too simple to detect changes in distribution, although we were able to demonstrate enhanced penetration of both 3.3μ and 7.7μ aerosols to the pulmonary periphery in patients with relatively mild obstruction of the airways. It is interesting to note that in the case of pressurized MDIs, similar distribution patterns within the lungs were noted in normal subjects and in patients with chronic bronchitis.26

Many clinicians probably regard all nebulizers as essentially equivalent, but our data demonstrate that this is not the case. Choice of both nebulizer and compressed gas flow rate (and hence choice of compressor) are potentially important because many nebulizer systems release droplets which are too large for a significant quantity of drug to enter the lungs.27 In the case of β-adrenergic agonists, this aspect is often masked by the very large doses that are conventionally prescribed, so that even relatively inefficient nebulizers may be efficacious. When doses of albuterol of 2 mg or less are being nebulized, we would recommend the use of a nebulizer with a droplet MMD of less than 5μ. For anticholinergic agents, the choice of nebulizer seems less important, although it would be useful to undertake further dose-response studies with different nebulizer systems using doses even smaller than those in the present investigations.

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