Effect of nebulised aerosol size on lung deposition in patients with mild asthma

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ABSTRACT A radioaerosol technique has been used to investigate whether the size distribution of aerosols released from a jet nebuliser affects the amount of aerosol delivered to the lungs. Six subjects with mild asthma (FEV\textsubscript{1} 81% of predicted) were studied on three occasions. On each visit they received one of three aerosols tagged with technetium-99m in 0-9% saline. The aerosols were generated by either (A) a Turret nebuliser operated at 81 min\textsuperscript{-1} (mass median diameter (MMD) 1-8 μm); (B) an Upmist nebuliser operated at 61 min\textsuperscript{-1} (MMD 4-6 μm); or (C) an Inspiron Mini-neb operated at 41 min\textsuperscript{-1} (MMD 10-3 μm). The aerosols were given in a randomised single blind manner and inhaled under identical conditions of inspiratory volume and frequency. The mean (SD) percentage of aerosols A, B, C released from the nebulisers during inhalation that was recovered in an expiratory filter was 23 (6), 25 (4), and 24 (4) respectively. Of the aerosols released from the nebuliser and deposited in the body, the percentage deposited in the lung was 79 (3) for aerosol A, 59 (4) for aerosol B, and 44 (5) for aerosol C. The remaining aerosol was deposited in the oropharynx and swallowed. It is concluded that small nebulised aerosols (MMD < 2 μm) deliver a larger dose to the lungs and should be used to maximise lung deposition.

Jet nebulisers are frequently used to deliver solutions of aqueous drugs to the lungs in aerosol form. A wide variety of nebulisers is available, with little uniformity in their usage. It has been shown that the size distribution of aerosols released varies considerably between nebulisers, and that the flow rate of compressed gas used to drive the nebuliser directly affects the size of the aerosol, a reduction in aerosol size occurring with increased flow rate.\textsuperscript{1}

The size distribution of an aerosol is known to be a primary determinant of the amount that reaches the lungs during inhalation. Pulmonary deposition increases with decreasing particle size down to 0-5 μm below which an aerosol has a high airborne stability and tends to be exhaled without being deposited.\textsuperscript{2} It is generally accepted that lung deposition is greater with particles in the size range 2-5 μm,\textsuperscript{3} particularly in obstructive lung disease, where the airways are narrowed and an aerosol will penetrate less deeply.\textsuperscript{4}

Rees et al\textsuperscript{5} found that for β agonist aerosols delivered by metered dose inhaler an aerosol with particles smaller than 5 μm achieved better bronchodilatation than one containing larger particles. In the case of nebulised aerosols, however, the results are more contentious. A nebulised terbutaline aerosol with a mass median diameter (MMD) of 2 μm achieved better bronchodilatation of small airways than the same amount of a 5 or 10 μm aerosol inhaled under identical conditions of inspiratory volume and frequency.\textsuperscript{5} Hadfield et al,\textsuperscript{7} however, and Douglas et al\textsuperscript{8} were unable to show any therapeutic advantage when they used nebulisers under varying operating conditions that affect aerosol size. But in neither of these studies were the aerosols inhaled under controlled conditions of inspiratory flow rate or volume, both of which are known to affect aerosol deposition\textsuperscript{3}; and both studies were limited to measurement of large airways function.

To try to resolve these discrepancies and elucidate the effect of nebulised aerosol size on the amount of aerosol reaching the lungs, we have used a radioaerosol technique to measure the proportion of three different sized aerosols deposited in the lungs or exhaled, under identical conditions of inspiratory volume and frequency.

Methods

PATIENTS
Six men with mild asthma participated in the study. Their mean age was 40-5 (SEM 5) years, their mean
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FEV1, 81.3% (2%) of the value predicted for their age, sex, and height, and the mean coefficient of variation of their FEV1 between studies 4-95%. All subjects were life long non-smokers or ex-smokers and all were regular users of inhaled β agonist aerosols only. These were withdrawn 12 hours before each study. We obtained the permission of the local ethical committee for the investigation and informed written consent from each subject.

**Radioaerosol**

Technetium-99m (99mTcO4-) in 0.9% saline (0.32 mol/l NaCl) was used as the radioaerosol. This solution has been used previously and has been shown not to affect the droplet size of aerosol from the nebuliser. Because of its small molecular weight, however, the solution is cleared rapidly from the lung by diffusion. For this reason the radioaerosol was inhaled with the subjects seated in front of a gamma camera so that the entire imaging procedure could be completed within seven minutes of their starting the inhalation. This is within the half time of the solution in the lung. The radiation dose to the subjects resulting from inhalation of 500μCi of 99mTcO4- in this form was estimated to be 6.1 mrad to the lungs and 0.24 mrad to the whole body.

**Nebulisers**

Three different makes of nebuliser operated under three different flow rates of compressed air were used to generate the three radioaerosols. Nebuliser selection was made on the basis of previous work and the nebulisers used were those used in a recent study to compare bronchodilator efficacy of nebulised terbutaline aerosols. Each nebuliser was characterised for its aerosol output and size distribution before use by a Malvern laser particle sizer by a technique previously described. Aerosol A was generated by a Turret nebuliser operated at 81 min⁻¹. The resulting aerosol was found to have a MMD of 1.8 μm with 80% of the aerosol mass contained in droplets smaller than 5 μm. Aerosol B was generated by an Upmist nebuliser operated at 61 min⁻¹, and this gave an aerosol with an MMD of 4.6 μm with 50% of the aerosol mass contained in particles smaller than 5 μm. Aerosol C was generated by an Inspiron Mini-nebuliser driven at 41 min⁻¹; this gave an aerosol with an MMD of 10.3 μm and with 20% of the aerosol mass in particles smaller than 5 μm.

**Study Design**

The three aerosols were given in a randomised, single blind manner, with a minimum interval of three days between studies. Each study started at the same time of day.

On arrival subjects had their baseline lung function measurements recorded. FEV1 and forced vital capacity (FVC) were measured by Vitalograph; peak expiratory flow (PEF) by Wright peak flow meter; and maximum flow at 50% and 25% of vital capacity (Vmax50 and Vmax25) by an Ohio dry spirometer linked to a Gould XY Plotter. The subjects were then seated with their backs against a large field of view gamma camera linked to a Nodecrescent computer. An image of regional ventilation was obtained with krypton-81m (81mKr) in the posterior view to delineate the lung outlines for subsequent analysis of the radioaerosol scans. After the 81mKr image had been obtained the subjects inhaled the radioaerosol, remaining seated in the same position (fig 1). Their nostrils were occluded by a noseclip and they inhaled the aerosol directly from the nebuliser through a mouthpiece. The nebuliser and an expiratory filter were housed in a lead lined box. The subjects regulated their breathing by means of an audible electronic device that signalled 14 breaths a minute, inspiration lasting one third of the cycle. Inspired air was inhaled through a Voldyne Volumetric Exerciser, which enabled the subjects to regulate their inspired volume to 700 ml. Exhaled air passed through a one way valve and into an expiratory filter to trap any exhaled radioaerosol. The radioaerosol was released from the nebuliser during inspiration only by the use of a triggering device on the air line to the nebuliser.

The radioaerosol inhalation took place over 120 seconds. Immediately afterwards the nebuliser and
Clay, Clarke

Pulmonary function indices (means with standard errors in parentheses) on the three study days in six subjects

<table>
<thead>
<tr>
<th>Aerosol A</th>
<th>Aerosol B</th>
<th>Aerosol C</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁ (l)</td>
<td>3.14 (0.20)</td>
<td>3.26 (0.23)</td>
</tr>
<tr>
<td>FVC (l)</td>
<td>5.19 (0.30)</td>
<td>5.18 (0.33)</td>
</tr>
<tr>
<td>PEF (l min⁻¹)</td>
<td>438 (23)</td>
<td>448 (18)</td>
</tr>
<tr>
<td>Vmax₅₀ (l s⁻¹)</td>
<td>1.89 (0.28)</td>
<td>2.04 (0.25)</td>
</tr>
<tr>
<td>Vmax₃₅ (l s⁻¹)</td>
<td>0.70 (0.17)</td>
<td>0.69 (0.13)</td>
</tr>
</tbody>
</table>

FVC, forced vital capacity; PEF, peak expiratory flow; Vmax₅₀, Vmax₃₅, maximum flow at 50% and 25% of vital capacity.

Equipment were removed from the proximity of the gamma camera and an image of the regional deposition of the aerosol within the lungs was obtained over 120 seconds. The gamma camera was then raised and another image of oropharyngeal deposition obtained over 120 seconds. The entire imaging procedure was completed within seven minutes from the start of inhalation.

**Analysis**

The amount of radioaerosol released from the nebulisers during the inhalation procedure was measured by weighing the nebuliser before and after inhalation. The amount of exhaled radioaerosol was measured by counting the activity in the expiratory filter with a scintillation counter. The expired radioaerosol was then deducted from the amount of radioaerosol released from the nebuliser during inhalation, enabling the proportion of exhaled radioaerosol to be estimated. The images of radioaerosol deposition were stored in the computer and subsequently analysed by identifying "regions of interest" that included the lungs, stomach, oesophagus, trachea, and oropharynx.

Non-parametric statistical tests were applied, the Friedman analysis of variance to identify differences between the three treatments and the Wilcoxon rank sum test for paired data to identify differences between individual treatments. A p value of \( \leq 0.05 \) was taken to indicate statistical significance.

**Results**

The pulmonary function indices recorded on the three study days for the six patients are shown in table 1. There was no statistical difference between baseline pulmonary function on the three occasions.

The percentage of the radioaerosol released from the nebulisers but retained in the expiratory filter was 23 (6) for aerosol A, 25 (4) for aerosol B, and 24 (4) for aerosol C; the differences were not significant (\( p > 0.05 \)).

Figure 2 shows the distribution of the three radioaerosols in one subject. There is a considerable reduction in pulmonary aerosol deposition with increased aerosol MMD (aerosol A > aerosol B > aerosol C) and an associated increase in oropharyngeal deposition. Aerosol deposited in the oropharynx was subsequently swallowed and can be seen in the stomach.

The difference in pulmonary deposition between the three radioaerosols was significant (\( p < 0.05 \)).

![Regional distribution of deposited radioaerosols in one subject, showing the percentage of deposited aerosol in the oropharynx (OP), gastrointestinal tract (GIT), and lungs.](http://thorax.bmj.com/)

![Figure 2](http://thorax.bmj.com/)
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With aerosol A (MMD 1-8 μm) the percentage of the dose deposited in the lungs was 79 (3), with aerosol B (MMD 4-6 μm) 59 (4) and with aerosol C (MMD 10-3 μm) 44 (3). Deposition of aerosol A was greater than that of aerosol B and aerosol C (p < 0.05) and more of aerosol B than of aerosol C was deposited (p < 0.05) (fig 3).

Discussion

These results show that the size distribution of the radioaerosols used in this study were associated directly with the amount of aerosol deposited in the lung. Almost twice as much aerosol A (MMD 1-8 μm) was deposited in the lung as aerosol C (MMD 10-3 μm).

Because the mode of inhalation was standardised, we may reasonably assume that the differences we observed in deposition are primarily attributable to the aerosol MMD. The size of an aerosol from any nebuliser is influenced by the flow rate of compressed air used to drive the device, and nebuliser C was deliberately run at a flow rate below that recommended for therapeutic use. Had it been driven at a higher flow rate, the aerosol MMD would have been reduced and lung dose would have increased accordingly.

Particles smaller than 0.5 μm have a high airborne stability and tend to be exhaled without being deposited. The proportion of aerosol as small as this, however, was much less than the 25% that was exhaled with all three aerosols. There was no difference in the proportion of the radioaerosols exhaled and trapped in the expiratory filter with the three nebulisers. This fraction probably represents aerosol inhaled at the tail end of inspiration, when there would be insufficient penetration into the airways and residence time for deposition to occur. This appears to override any effect of particle size. Although nebuliser treatment therapy is intended for tidal breathing, a breathhold interval between inhalation and exhalation has been shown to enhance total lung deposition, although this may be impractical for severely dyspnoeic patients.

In this study the aerosol with the larger particle size showed greatest deposition in the oropharynx as expected. For many drugs the inhaled route provides a greater degree of bronchodilatation or less bronchoconstriction in response to non-specific or antigen challenge than does the same dose of drug given by the oral route. This is due to greater access of drug to the airways and to the fact that some drugs are inactivated when given by the oral route.

Several studies have shown that the response to increasing doses of an inhaled bronchodilator can attain a plateau where further doses will not increase the response. This may explain why Hadfield et al., using 1-0 mg salbutamol and Douglas et al., using 1-0 and 5-0 mg salbutamol, failed to show any beneficial effect when aerosol size was reduced. Douglas et al. found that the flow rate of compressed air used to drive a nebuliser did not affect the dose-response relationships of inhaled rimeterol. Their study, however, was limited to investigation of FEV, and did not measure changes in small airways function, which have been shown to be directly affected by aerosol MMD.

The magnitude of dose normally prescribed with jet nebulisers compensates for the small dose that is accessible to the airways. It may well be that if the size distribution of nebulised aerosols is optimised smaller doses than those currently used would achieve an equal bronchodilator effect. This would be cheaper than current practice and would mean that patients were not given unnecessarily large amounts of drug. The penetration of drug particles into the lung in patients with airways obstruction would be increased—an important aspect in the treatment of acute asthma. This may also be important in the case of drugs such as antibiotics, which are increasingly being advocated in aerosol form in the management of cystic fibrosis. If aerosol size is optimised care with dosage would be important since more drug is likely to pass via the alveoli into the circulation, thereby giving rise to systemic side effects.

Stainforth et al. and Williams et al. have found that there is considerable variation in hospital practice with nebuliser usage. Our results show that such variation can result in wide differences in lung deposition of nebulised drugs. To maximise lung deposition of aerosol it is necessary to optimise nebulised aerosol size.
References


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