

# Optimal particle size for $\beta_2$ agonist and anticholinergic aerosols in patients with severe airflow obstruction

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## Abstract

**Background** – The optimal particle size of a  $\beta_2$  agonist or anticholinergic aerosol in patients with severe airflow obstruction is unknown.

**Methods** – Seven stable patients with a mean forced expiratory volume in one second (FEV<sub>1</sub>) of 37.9% of the predicted value inhaled three types of monodisperse salbutamol and ipratropium bromide aerosols with particle sizes of 1.5  $\mu\text{m}$ , 2.8  $\mu\text{m}$ , and 5  $\mu\text{m}$ , respectively, and a placebo aerosol. The volunteers inhaled 20  $\mu\text{g}$  salbutamol and 8  $\mu\text{g}$  ipratropium bromide, after which lung function changes were determined and analysed with repeated measurements analysis of variance (ANOVA).

**Results** – Greater improvements in FEV<sub>1</sub>, specific airway conductance (sGaw) and maximum expiratory flow at 75%/50% of the forced vital capacity (MEF<sub>75/50</sub>) were induced by the 2.8  $\mu\text{m}$  aerosol than by the other particle sizes.

**Conclusions** – In patients with severe airflow obstruction the particle size of choice for a  $\beta_2$  agonist or anticholinergic aerosol should be approximately 3  $\mu\text{m}$ .

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Keywords: aerosols, particle size, bronchodilators.

In two previous publications we have reported on the optimal particle size of  $\beta_2$  agonist and anticholinergic aerosols.<sup>1,2</sup> We have shown that, in asthmatic patients with a forced expiratory volume in one second (FEV<sub>1</sub>) > 70% of predicted, salbutamol and ipratropium bromide aerosols consisting of particles with a median mass aerodynamic diameter (MMAD) of < 2.8  $\mu\text{m}$  elicited significantly higher degrees of lung function changes than a 5  $\mu\text{m}$  aerosol. These findings were explained by taking into account the filter characteristics of the airways. Airways filter particles out of the inhaled air; 5  $\mu\text{m}$  particles deposit rapidly in the extrathoracic/upper airways while smaller particles escape rapid deposition and reach the dilatable parts of the airways better than the 5  $\mu\text{m}$  particles, resulting in higher local doses assuming equal doses are administered.<sup>3</sup>

The narrower the airways, the higher the tendency to deposit, and particle deposition patterns shift to the central airways.<sup>3</sup> Heyder *et al* showed that 3.5  $\mu\text{m}$  particles deposit preferentially in the alveoli of normal subjects, while in our previous study smaller particles caused

the greatest bronchodilatation.<sup>4</sup> To reach the smaller airways in such cases it may be necessary for the particle size of the inhaled aerosol to be decreased. In patients with severe airflow obstruction, aerosols with a smaller particle size may be more suitable. We therefore carried out experiments to determine the most suitable particle size for bronchodilator aerosols in patients with severe airflow obstruction.

## Methods

### PATIENTS

Eight patients (six men) started the trial but one dropped out for personal reasons. The mean (SD) age of the remaining seven was 55 (4) years, and the mean forced expiratory volume in one second (FEV<sub>1</sub>) was 37.9 (7.3)% of the predicted value. In all patients a more than 15% increase in baseline FEV<sub>1</sub> after inhalation of 200  $\mu\text{g}$  salbutamol had been measured just before the trial. None of the patients was smokers. All used inhaled corticosteroids and none used disodium cromoglycate or oral anti-asthma medications. Their regular medication other than corticosteroids was discontinued 6–8 hours before the start of the trial, and long acting  $\beta_2$  agonists were stopped 15 hours before the trial. All patients gave their written consent before entry into the study which was approved by the hospital ethics committee.

### AEROSOL GENERATION

Monodisperse aerosols (geometric SD < 1.2) were produced by a spinning top generator<sup>5</sup> consisting of a small disk rotating at 12 000 rpm. Liquid is fed to the centre of the disk and the high centrifugal force causes identical sized droplets to leave the rim. These droplets are dried by hot air and led to a small tank from which the patients inhale. The diameter of the resulting dry particles is governed by the concentration of the drug and the viscosity of the solution. Salbutamol and ipratropium bromide solutions (50% water/50% ethanol) of different concentrations were used to yield aerosols with an MMAD of 1.5  $\mu\text{m}$ , 2.8  $\mu\text{m}$ , and 5  $\mu\text{m}$ , respectively. Each time a patient was due to start the aerosol inhalation the mass of salbutamol or ipratropium bromide per litre of air and the particle diameter of the dry aerosol particles in the tank were measured by an Aerodynamic Particle Sizer 33 (TSI, St Paul, Minnesota, USA). This is a “time of flight” particle sizer and gives both the particle size distribution and the mass contained in the aerosol in  $\mu\text{g}$  per litre of air. To calculate the volume of air to be inhaled we divided the dose

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to be administered by the mass of salbutamol or ipratropium bromide per litre of air. If sufficient aerosol containing air had been inhaled, the aerosol inhalation was discontinued by switching over to non-aerosol containing air.

#### PROCEDURE

Each patient was studied at the lung function laboratory with intervals of one week between visits. The baseline FEV<sub>1</sub> during the sessions was not allowed to vary by more than 10%. At each session the baseline lung function and lung function 30 minutes after administration of the aerosol were measured. Based on previous experience, the doses used were 20 µg salbutamol and 8 µg ipratropium bromide (dosage expressed as µg delivered to the mouth). The inhalation manoeuvre consisted of inhalation of a slow vital capacity with a flow of 40–60 l/min, followed by a breath holding period of 10 seconds and a slow exhalation. The aerosol was administered during the entire inhalation manoeuvre. The inhalation flow and volume were measured by a hot wire anemometer placed close to the mouth of the patient. The amount of aerosol deposited in the anemometer was negligible. Before the aerosol inhalation the patients were taught the inhalation technique and they had the opportunity to correct the inhalation flow by watching an indicator connected to the anemometer.

Administration of the aerosols was performed in a randomised single blind manner. On the first day a placebo aerosol was administered in order to facilitate early detection of any adverse reactions of the patient to equipment or solvents. In addition, the placebo measurement served to determine the spontaneous variability in airway obstruction during the measurement period.

#### LUNG FUNCTION ASSESSMENT

The lung function was assessed 30 minutes after inhalation of the aerosol by an assistant who was not aware of the type of aerosol administered. The specific airway conductance (sGaw) was measured with a body plethysmograph, the FEV<sub>1</sub>, forced vital capacity (FVC), and vital capacity (VC) by means of spirometric tests, and the peak flow (PEF) and maximum expiratory flow at 75/50/25% of the forced vital capacity (MEF<sub>75/50/25</sub>) were derived from maximal expiratory flow-volume curves.

#### DATA ANALYSIS

The change in lung function was expressed as a percentage of the predicted value.<sup>6</sup> Significant

*Table 1* Mean improvement in lung function (% predicted) after inhalation of aerosols with different particle sizes or placebo

Lung function parameter	Particle size of aerosol			
	Placebo	1.5 µm	2.8 µm	5 µm
sGaw	-2.88*	-14.46	-21.93	-12.86
FEV <sub>1</sub>	0.08*	3.57*	8.87	3.84*
MEF <sub>75</sub>	-0.43*	1.44*	4.85	1.95
MEF <sub>50</sub>	-0.30*	0.58*	4.23	1.17*

\* indicates significant difference compared with the 2.8 µm aerosol.

sGaw = specific airways conductance; FEV<sub>1</sub> = forced expiratory volume in one second; MEF<sub>75</sub>, MEF<sub>50</sub> = maximum expiratory flow at 75% and 50% of forced vital capacity.

*Table 2* Mean (SD) improvement in lung function (as % predicted) after inhalation of a 2.8 µm salbutamol or ipratropium bromide aerosol

Lung function parameter	20 µg salbutamol	8 µg ipratropium bromide
sGaw	-22.4 (17.3)%	-21.4 (16.9)%
FEV <sub>1</sub>	8.5 (7)%	9.3 (4.1)%
MEF <sub>75</sub>	3.4 (4.6)%	6.3 (4.1)%
MEF <sub>50</sub>	3.4 (4.8)%	5 (3.2)%

sGaw = specific airways conductance; FEV<sub>1</sub> = forced expiratory volume in one second; MEF<sub>75</sub>, MEF<sub>50</sub> = maximum expiratory flow at 75% and 50% of forced vital capacity.

differences due to particle size of the aerosol, type of drug, and interaction between drug and aerosol size were determined using repeated measurements analysis of variance (ANOVA).<sup>7</sup> A significant interaction, in this case, means that the difference between salbutamol and ipratropium bromide is not constant and depends on the particle size of the aerosol administered. When a statistically significant change was observed, the within group mean sum of squares was used to calculate the least significant difference. In all calculations a p value of < 0.05 was considered to be significant.

#### Results

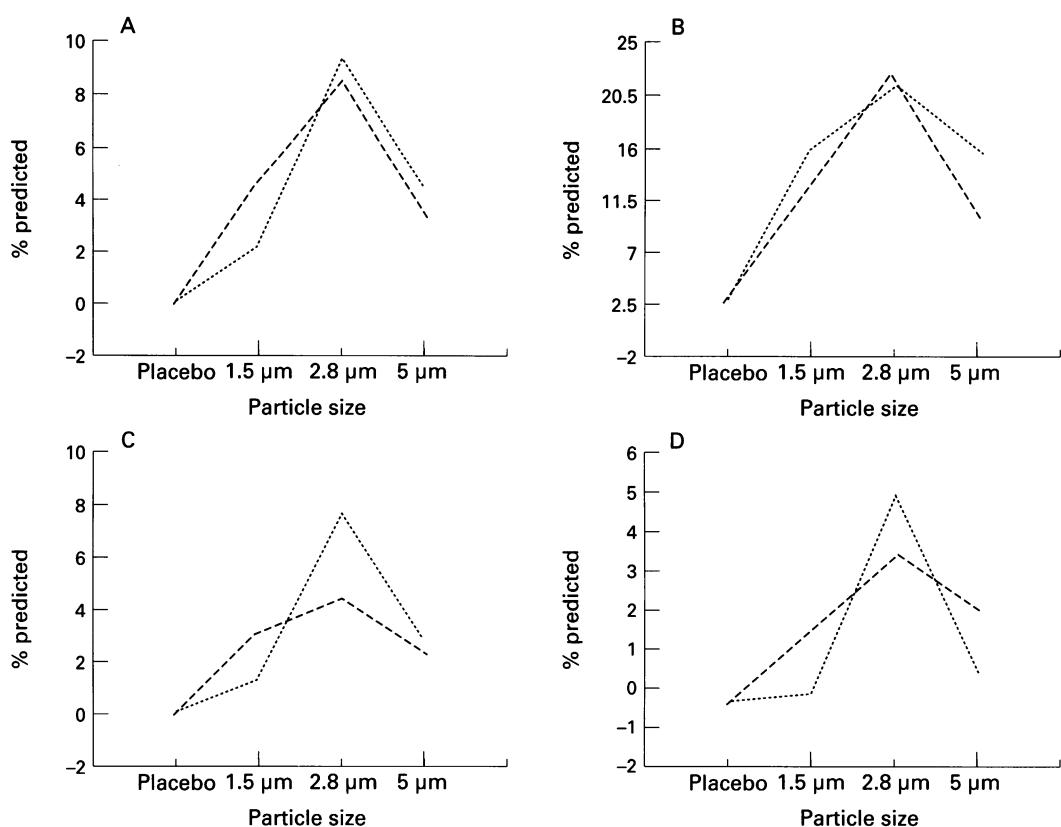
All patients completed the study without noticeable side effects. No significant change was measured in any of the lung function parameters during the inhalation of placebo, nor were any significant differences seen between the bronchodilator responses of salbutamol and ipratropium bromide. Comparing identical particle sizes, there were no significant differences between salbutamol and ipratropium bromide.

Significant differences were found in FEV<sub>1</sub> ( $p < 0.001$ ), MEF<sub>75</sub> ( $p = 0.02$ ), MEF<sub>50</sub> ( $p < 0.001$ ), and sGaw ( $p = 0.01$ ) with different particle sizes (fig 1, table 1). In table 2 the improvements in various lung function parameters after administration of 20 µg salbutamol and 8 µg ipratropium bromide, respectively, as 2.8 µm aerosols are given.

#### Discussion

In patients with severe airflow obstruction the particle size of choice for an aerosol is approximately 3 µm, both for ipratropium bromide and salbutamol. These results are comparable to our earlier findings with salbutamol and ipratropium bromide in patients with mild asthma in whom the greatest bronchodilatation was elicited by aerosols with an MMAD of < 2.8 µm.<sup>1,2</sup>

We believe that these findings are explained by the filtering characteristics of the extrathoracic/upper airways. Large particles are filtered out quickly in the central airways due to a high impaction probability. Only small particles will escape deposition in the extrathoracic/upper airway.<sup>3</sup> The dose of inhaled drugs in the lungs or lower airways therefore depends on the filter characteristics of the extrathoracic/upper airways. Due to the fact that particles of < 2.8 µm MMAD pass



**Figure 1** Improvement in (A) forced expiratory volume in one second (FEV<sub>1</sub>), (B) specific airways conductance (sGaw), and maximum expiratory flow at (C) 75% and (D) 50% of forced vital capacity (MEF<sub>75/50</sub>) following administration of placebo or salbutamol (---) and ipratropium bromide (.....) aerosols of increasing particle sizes, expressed as percentage change of the predicted value.

through the extrathoracic/upper airways better than the larger 5  $\mu\text{m}$  particles, the actual dose in the airways is higher.

The observation that a 2.8  $\mu\text{m}$  aerosol induced greater bronchodilatation than the 5  $\mu\text{m}$  aerosol, both in patients with mild and severe airway obstruction, suggests that the degree of airflow obstruction in the lower airways is not the most important factor determining response. The most likely explanation for the difference is the filtering characteristics of the non-constrictive extrathoracic/upper airways.

In contrast to the earlier studies, we found that the 1.5  $\mu\text{m}$  aerosol induced significantly less bronchodilatation than the 2.8  $\mu\text{m}$  aerosol, probably because of differences in the deposition patterns. Smaller particles will always pass the central airways better than larger particles, so even in severely constricted patients a more peripheral deposition pattern of 1.5  $\mu\text{m}$  particles can be expected. Changes in lung function parameters are composed of changes in both central and peripheral airways. It is conceivable that in severely constricted patients the peripheral airways are less able to dilate, so deposition of bronchodilators in the peripheral airways results in less total dilatation. The smaller improvement in the peripheral lung function parameters strengthen this hypothesis. We have not visualised the deposition patterns of our aerosols in the airways, so we cannot prove this explanation. The alternative explanation would be that small particles deposit less well and are exhaled to a higher degree causing low pulmonary deposition. However, due to the severe

constriction, one would expect a higher deposition probability leading to fewer particles being exhaled and higher doses.<sup>8</sup>

As in our previous experiments we used low dosages and obtained significant bronchodilation. We based the choice of administering only 20  $\mu\text{g}$  salbutamol and 8  $\mu\text{g}$  ipratropium bromide on the assumption that the lung deposition of monodisperse aerosols is very high compared with polydisperse aerosols delivered by a metered dose inhaler. Many studies have shown that 10–20% of the actuated dose reaches the airways and is effective.<sup>9</sup> 10% of a standard 200  $\mu\text{g}$  salbutamol dose is 20  $\mu\text{g}$ , as is 8  $\mu\text{g}$  of a standard ipratropium bromide dose delivered through a metered dose inhaler. We do not know the relative efficacy of our formulations compared with metered dose inhalers because this study was not set up as a direct comparison. The prestudy check of the patients, however, included measurement of the reversibility after 200  $\mu\text{g}$  salbutamol via a metered dose inhaler and it was found that the mean (SD) improvement in FEV<sub>1</sub> was 7.6 (2.7)% compared with 8.5 (7)% after 20  $\mu\text{g}$  salbutamol as a 2.8  $\mu\text{m}$  aerosol. We therefore feel that it is possible to induce clinically significant bronchodilatation using low dosages of correctly formulated bronchodilators.

We conclude that, in patients with severe airflow obstruction, the most suitable particle size of a  $\beta_2$  agonist and anticholinergic aerosols is approximately 3  $\mu\text{m}$ . Significant bronchodilation is obtainable with 10% of standard dosages using metered dose inhalers.

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