The optimal particle size for beta-adrenergic aerosols in mild asthmatics*

Introduction

The treatment of asthma and chronic obstructive pulmonary diseases (COPD) has improved considerably with the introduction of drugs by inhalation. As compared to oral administration, dosages could be decreased substantially and the incidence of side effects was diminished considerably. Unfortunately, the currently available inhalation preparations show one major disadvantage: only a small quantity of the administered mass reaches the airways\(^1\). Part of the problems is caused by the fact that only highly polydisperse aerosols are available. Such aerosols contain large particles, which are not effective, because they deposit extrathoracical.

The site of deposition of the particles in the airways depends strongly on the way of inhalation and the size of the particles. Targeting of deposition can be achieved by adjusting the inhalation manoeuvre and the particle size. A way to improve the efficacy therefore is to determine the optimal particle size, since adequately targeted \(\beta_2\)-mimetic agents will induce the strongest decrease in airway obstruction\(^2\). The deposition patterns of aerosols in the lung will be influenced, however, by the degree of constriction of the airways, so one is forced to stratify patients. Only few studies have focused on the relationship between particle size of a \(\beta_2\)-mimetic aerosol and its efficacy\(^3\ 4\ 5\ 6\ 7\). However, it is impossible to conclude from these studies, the optimal particle size, since the results of the various studies are contradictory.

To determine the optimal particle size we compared the effects of salbutamol aerosols with variable diameters on the degree of lung function improvement in a group of asthmatic patients with mildly impaired lung function. To do so we use monodisperse aerosols because polydisperse aerosols contain overlapping particle size distributions, which will obscure differences between larger and smaller particles.

**Materials and methods**

**Patients**

Eight mild asthmatic patients participated in the trial (3 women and 5 men). The average age (sd) was 40 (10) years, the mean $\text{FEV}_1$ (sd) was 72.3 (6.8) percent of the predicted value. In all patients a bronchodilator response of >15% after inhalation of 200 µg salbutamol had been measured just before the trial. None of the patients were smokers. All patients used corticosteroids by inhalation, cromoglycate or long-acting $\beta_2$-mimetic agents were not used. Oral anti-asthma medication was not allowed. Except the corticosteroids, their regular medication was discontinued 6-8 hours before the start of the trial. All patients gave their written consent before the entry of the trial, which was approved by the hospital ethics committee.

**Aerosol generation**

Monodisperse aerosols (geometric SD <1.2) were produced by a spinning top generator. A spinning top generator consists of a small disk, rotating at 12000 rpm. Liquid is fed to the centre of the disk and the high centrifugal force causes droplets to leave the rim of the disk. These droplets are all of the same size. These droplets are dried by hot air and led to a small tank, from which the patients inhaled. The concentration of the drug in the solution and the viscosity of it governs the diameter of the resulting dry particles. Salbutamol solutions (50% water/50% ethanol) of 0.1%, 1% and 10% were used to yield aerosols with a mass median aerodynamic diameter (MMAD) of 1.5 µm, 2.8 µm, and 5 µm, respectively. Each time a patient was due to start aerosol inhalation, the mass of salbutamol 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, Min). For each dose the volume of air inhaled was calculated by dividing the dose by the mass of salbutamol per litre of air. If sufficient aerosol-containing air had been inhaled, switching over to non-aerosol containing air discontinued the aerosol inhalation.

**Procedure**

Each patient was studied at the lung function laboratory with intervals of one week. The baseline $\text{FEV}_1$ during each session was not allowed to vary more than 10%. Each
session consisted of 4 cycles, which consisted of measurement of the lung function 15 and 30 minutes after administration of the aerosol. A next cycle started within 5 minutes after the previous one. First, 5 µg salbutamol was administered, followed by 5 µg, 10 µg and 20 µg during the second, third and fourth cycle, respectively, resulting in cumulative doses of 5 µg, 10 µg, 20 µg and 40 µg salbutamol. (All dosages are expressed as µg delivered to the mouth). The inhalation manoeuvre consisted of inhalation of the slow vital capacity with a flow of 40-60 L/min, followed by a breath-holding period of 10 seconds and a slow exhalation. A hot wire anemometer placed close to the mouth of the patient measured the inhalation flow and volume. The amount of aerosol deposited in the anemometer was negligible. Before the aerosol inhalation the patients were taught to inhale and they had the opportunity to correct the inhalation flow by watching an indicator connected to the anemometer. Administration of the aerosols was done 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 measuring period.

Lung function assessment

The lung function was assessed 15 and 30 minutes after inhalation of the aerosol. The lung function assistant was not informed about the type of aerosol administered. The $R_{tot}$ was measured with a body plethysmograph, the $FEV_1$, FVC, and VC by means of spirometry, and the PEF and $MEF_{75/50/25}$ were derived from maximal expiratory flow-volume curves.

Statistics

The change in lung function was expressed as a percentage of the predicted value. Four dose-response curves were generated, one for each type of aerosol. These dose-response curves were analysed for effects related to the type of aerosol (aerosol-size effect), effects of increasing dosages (dose effect), and interaction between size and dosage using repeated measurements anova. Any differences between the measurements at t = +15 and t = +30 minutes were evaluated with the paired T-test.
The mean lung function improvement over all four dosages will be higher for the most potent aerosol as compared to the less potent aerosols. In order to find out whether a less potent aerosol deviates significantly from the most potent aerosol, it was calculated how large the deviation between these means should be before it was fair to speak of significance. In this respect the method of Schuirmann was applied, this method is comparable to the LSD-test\textsuperscript{10}. In all calculations an $\alpha$-value of 0.05 was considered to be significant.

**Results**

All 8 patients completed the four sessions. None of the values of the lung function parameters, measured 30 minutes after administration of the aerosol differed significantly from those measured 15 minutes after administration. Therefore, only an evaluation is given of the measurements conducted 15 minutes after aerosol administration.

In Fig. 1 the dose-response curve for the FEV\textsubscript{1} and peak flow are represented. In any of the parameters no change was measured during the inhalation of placebo. The evaluation of the dose effects demonstrated that for all lung function parameters statistically significant differences existed between dosages, with the higher dosages causing a stronger bronchodilation ($p<0.05$). The interaction between the dose and the effects of the three types of salbutamol aerosols was non-significant for all lung function parameters ($p>0.1$), which indicates that the dose-response curves run parallel.

In evaluating the aerosol-size effect, the analysis of variance demonstrated significant differences with reference to placebo for the FEV\textsubscript{1} ($p<0.01$), the PEF ($p<0.01$), de FVC ($p<0.01$), the MEF\textsubscript{75} ($p<0.01$), the MEF\textsubscript{50} ($p<0.01$) and the MEF\textsubscript{25} ($p<0.01$). This implies that all the dose-response curves of the salbutamol aerosols are located higher than the placebo curves. For the $R_{tot}$ ($p=0.116$) and the VC ($p=0.068$) no significant differences due to the different aerosol-sizes were demonstrable. The reason for this is to be found in the strong spontaneous variability of the $R_{tot}$ and/or the minor improvement of the VC.
Fig. 1 Dose-response curves for the FEV₁ and peak flow
A significant difference with reference to 2.8 µm aerosol will occur for the FEV\textsubscript{1} if the deviation between the means exceeds 2.9%, for the PEF this deviation should be at least 5.9%, for the MEF\textsubscript{75,50,25} at least 5.4%, 4.3% and 4.9%, respectively, and, finally, for the FVC at least 9.4%. In the case of the FEV\textsubscript{1} and the MEF\textsubscript{75,50,25} a statistically significant difference occurred between the 5 µm aerosol and the 2.8 µm aerosol. For the PEF a significant difference was found between the 1.5 µm and the 2.8 µm aerosol. For the FVC the differences were too small to be significant.

Table 2 lists the mean improvements as %predicted with 95% confidence intervals after administration of 40 µg salbutamol for all lung function parameters. Despite the low dosage a significant improvement of the lung function can be observed. The improvement in the VC was not significant.

None of the patients reported any adverse effects as a result of the experiment.

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<table>
<thead>
<tr>
<th>Lung function parameter</th>
<th>Particle size of the aerosol (µm)</th>
<th>Significant different aerosols</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.5</td>
<td>2.8</td>
</tr>
<tr>
<td>FEV\textsubscript{1}</td>
<td>12.8(4.3)</td>
<td>14.6(6.5)</td>
</tr>
<tr>
<td>FVC</td>
<td>8.9(5.6)</td>
<td>9.6(9.3)</td>
</tr>
<tr>
<td>MEF\textsubscript{25}</td>
<td>12.1(6.6)</td>
<td>14.9(9.5)</td>
</tr>
<tr>
<td>MEF\textsubscript{50}</td>
<td>15.2(6.7)</td>
<td>18.5(9.4)</td>
</tr>
<tr>
<td>MEF\textsubscript{75}</td>
<td>17(4.4)</td>
<td>21.4(9)</td>
</tr>
<tr>
<td>PEF</td>
<td>9(7.1)</td>
<td>15(7)</td>
</tr>
<tr>
<td>Rtot</td>
<td>-27.6(93)</td>
<td>-84.3(92)</td>
</tr>
<tr>
<td>VC</td>
<td>7(7.8)</td>
<td>8.1(9.4)</td>
</tr>
</tbody>
</table>

**Table 1 Mean (sd) improvement in lung function (%predicted) over all four dosages per type of aerosol (NS= non significant)**
### Table 2 Mean improvement in lung function (% predicted) following 40 µg salbutamol administered as a 2.8 µm aerosol

<table>
<thead>
<tr>
<th>Lung function parameter</th>
<th>Improvement (% predicted)</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEF\textsubscript{75}</td>
<td>28.8</td>
<td>06.4 37.6</td>
</tr>
<tr>
<td>R\textsubscript{tot}</td>
<td>-102.2</td>
<td>-29.0 -175.0</td>
</tr>
<tr>
<td>PEF</td>
<td>19.8</td>
<td>12.4 27.1</td>
</tr>
<tr>
<td>VC</td>
<td>9.3</td>
<td>-0.11 18.7</td>
</tr>
</tbody>
</table>

**Discussion**

The increase in FEV\textsubscript{1} and the MEF\textsubscript{75/50/25} after the 5 µm aerosol differed significantly from the 2.8 µm aerosol, while there were no significant differences between the 1.5 µm and the 2.8 µm aerosol. The increase in the PEF was highest after the 2.8 µm aerosol, not being significantly different from the 5 µm aerosol. No size-effect was present in case of the VC, FVC and the R\textsubscript{tot}. We were able to show these differences in a relatively small group of volunteers. This is due to a low intrasubject variability and the use of repeated measurement anova, which eliminates the interindividual variability. Patel et al. also showed comparable differences in a small group of volunteers\textsuperscript{3}.

The lung has the capacity to intercept a large portion of the inhaled particles rapidly and effectively by several mechanisms that cause particles to deposit on the mucous membrane. Two important processes in this context are impaction and sedimentation\textsuperscript{11}. Impaction means that particles are not able to follow changes in the direction of the air stream and deposit. This mechanism is of particular relevance for large or heavy particles. Sedimentation is a time-dependent process related to the velocity with which particles fall down under the influence of gravitation. The speed of fall becomes constant at the moment the resistance of the air is equal to gravitation. These two mechanisms cause large particles to deposit in the upper airways, whereas smaller particles escape from impaction and penetrate the airways more deeply. So a deposition pattern in the airways is evident. Targeting the deposition towards a segment of the airways can be achieved by selecting the right particle-size of the aerosol or by adjustment of the breathing-technique\textsuperscript{2}. 

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\textsuperscript{1} Patel et al. (1993).

\textsuperscript{2} Patel et al. (1994).

\textsuperscript{3} Patel et al. (1995).
It is possible that in the efficacy of β2-mimetic agents a significant role is played by the fact that the β2-receptors are not uniformly distributed in the airways. In a number of publications an increase in the number of receptors is reported in association with distances further into the periphery of the lung. Assuming that a greater effect is obtained when the concentration at the receptor is higher, there is a ratio for matching the deposition pattern of β2-mimetics to the beta-adrenoceptor distribution.

In the present study we have based ourselves on the assumption that a more peripheral deposition was desirable. One way to achieve this is by a slow and deep inhalation of the aerosols. In addition, the particles were reduced in size. Reduction in size, however, cannot be continued without impunity. "Too small" particles are known to have a terminal velocity that is so small that they hardly deposit. This implies that there is an ideal particle size: not too large and not too small. The optimal particle size will depend on a number of factors, i.e. the preferred deposition pattern, the condition of the airways - in this context their diameter - and the inhalation technique.

We decided on an upper limit of 5 µm, because various studies have demonstrated that particles with a MMAD above 5 µm only reach the airways to a limited extent. The lower limit of 1.5 µm was chosen on technical grounds (since both the spinning top generator and the aerodynamic particle sizer are characterised by a functional lower limit of 0.5 - 1 µm), and it has been documented that particles with a MMAD below 0.5 µm hardly deposit in the airways.

In asthmatics Clay found that a 1.8 µm terbutaline aerosol induces a stronger MEF50/25 improvement than a 4.6 µm or a 10.3 µm aerosol, whereas Patel found that a 2.5 µm isoproterenol aerosol is more potent than a 5 µm aerosol. Johnson observed a significant difference between a 3.3 µm and a 7.7 µm salbutamol aerosol, as did Ruffin between a 1.5 µm and a 3.2 µm isoproterenol aerosol; the outcome of both studies was in favour of the smaller aerosol. However, from all these data it is not feasible to derive an optimal aerosol diameter. Moreover, the matter is complicated by the negative findings of Hultquist and Mitchell: neither of these investigators found any differences in potency between 1.5 µm and 4.8 µm aerosols and 1.4 µm and 5.5 µm aerosols, respectively.

The results of our study demonstrate that in asthma patients with a mild airway obstruction an aerosol with a MMAD of around 2.8 µm is to be preferred. The results
of our study confirm the conclusion drawn by Patel that a 2.5 µm aerosol is more potent than a 5 µm aerosol, but add to it that smaller aerosols are of no benefit. At the same time an explanation is found for the negative findings of Hultquist and Mitchell\textsuperscript{4}. Both investigators have selected aerosol diameters that lead to minor differences in potency. The discrepancy between these and other investigators thus is merely an apparent one, to be attributed to the choice of particle sizes. The results obtained by Clay are not easy to explain. However, this study the aerosols were administered by means of various nebulisers\textsuperscript{7}. It is possible that these nebulisers have released divergent dosages, which might be interpreted as differences in potency.

The results of our study can be explained as follows: particles of 5 µm will be deposited extrathoracical to a greater extent than the smaller particles, which are able to penetrate the airways deeply. (In case of the 1.5 µm aerosol the smallest amount can be expected extrathoracic). So small particles are to be preferred for a deep penetration. However these particles deposit in minute quantities, so a deep penetration is at the expense of a lower mass deposited\textsuperscript{14}. As for the PEF, it is striking that the 5 µm particles perform better than the 1.5 µm particles: the bulk of the 1.5 µm particles pass the central and the extrathoracic compartment. Here we see a contrast with the more peripherally oriented lung function parameters: the 5 µm aerosol is inferior to the two others. The 5 µm aerosol reaches the peripheral compartment to a lower degree. The lower potency of the 1.5 µm aerosol can be ascribed to its limited tendency to deposit. The fact that in all cases 2.8 µm particles induce a better effect than 5 µm particles can be attributed to the difference in extrathoracic deposition\textsuperscript{17}. We did not measure the deposition patterns of these aerosols within the lung. So we are not sure whether the differences in potency are to be ascribed to a better matching between the β\textsubscript{2}-receptor distribution and the deposition. One can state however that the results of this investigation are in line with theoretical predictions of deposition patterns\textsuperscript{17}. The deposition of particles is never confined to a small segment of the airways: one always encounters wide patterns. The calculations of Gerrity show that in many segments of the airways comparable number of particles will deposit, while the changes in the patterns due to differences in particle-size are not overwhelming\textsuperscript{18}. In asthmatics the same conclusions were drawn\textsuperscript{19}. We therefore feel that the high extrathoracic deposition of large particles and a low one for smaller particles
combined with an inherent low deposition for very small particles offers a good explanation for our results. Without taking the receptor distribution into account. In agreement with Patel and Mitchell we conclude that it is possible to induce adequate bronchodilation with very small dosages. In Table 2 we have included the improvement of lung function after 40 µg salbutamol. This dosage is only one fifth of frequently used MDI-dosages and one tenth of the dosages usually administered by dry-powder inhalation (DPI). These low dosages lead to such a distinct bronchodilation because they are monodisperse, contrary to the aerosols administered by metered dose or dry-powder inhalers. In the usual polydisperse aerosols only a minor fraction (depending on the formulation) of the mass will consist of particles <2.8 µm. We conclude that in mild asthmatics the mean particle diameter of a β2-mimetic aerosol should be around 2.8 µm for optimal improvement of the lung function. The dosage of salbutamol can be reduced for such aerosols.


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