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The optimal particle size for parasympathicolytic aerosols in mild asthmatics

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Abstract

Background: the optimal particle size of a parasympathicolytic aerosol is unknown. Methods: eight stable asthmatics with a mean FEV_1 of 72% of the predicted value inhaled three types of monodisperse ipratropium bromide aerosols, with particle sizes of 1.5, 2.8 and 5 μm, respectively, and a placebo aerosol. The volunteers inhaled 8 μg ipratropium bromide, after which lung function improvement was determined. The changes in lung function were analysed with repeated measurements ANOVA. Results: according to the changes in FEV_1 and $MEF_{50/25}$ the 1.5/2.8 μm aerosol induced significantly better bronchodilatation than the 5 μm aerosol. No particle size effect was noticeable with regard to changes in R_{tot}, VC, FVC and PEF. Conclusions: in mild asthmatics the particle size of choice for a parasympathicolytic aerosol should be ≤ 2.8 μm.

Keywords: Aerosol; Particle size; Ipratropium bromide; Lung function testing; Spinning top generator

1. Introduction

In a previous publication we reported on the optimal particle size of a β_2-mimetic aerosol (Zanen et al., 1994). We found that a salbutamol aerosol consisting of particles with an MMAD of 1.5/2.8 μm elicited a higher degree of lung function improvement than a 5 μm aerosol. These results were explained by adopting the hypothesis that the degree of penetration of particles into the airways is an important factor. Particles need to pass the extrathoracic/upper airways to reach the lower airways. In the extrathoracic/upper airways large particles are filtered out of the inhaled air to a greater extent than smaller ones. Therefore, the deposited amount of particles in the lower airways is lower in the case of large particles. In mild asthmatics it appeared that this dose reduction is large enough to cause less intense bronchodilatation.

It is not certain whether this outcome is transferable to other types of bronchodilators, such as ipratropium bromide. The distribution of the receptors may play a role. The β_2-adrenoreceptors are located mainly in the periphery of the airways, the muscarinic receptors being preferentially encountered in the central airways (Barnes et al., 1982, 1983). One can conceive that for a salbutamol particle it is harder to reach the re-

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ceptor than for an ipratropium bromide particle, therefore it must be smaller. On the other hand, such small particles will pass the upper airways better than large ones, missing the muscarinic receptor. Our hypothesis is that the optimal particle size of an ipratropium bromide aerosol will be larger than of a salbutamol aerosol. Due to the resulting centrally orientated deposition pattern, the match to the receptor distribution is better. To reject or accept this hypothesis we determined the relationship between the particle size of an ipratropium bromide aerosol and the lung function improvement in asthmatic patients with a mild reduction of the FEV_1.

2. Materials and methods

2.1. Patients

Eight mild asthmatic patients participated in the trial (five women and three men) (five of them also took part in the previous trial). The average age (SD) was 39.6 (14.4) years, and the mean FEV_1 (SD) was 72 (14.3) percent of the predicted value. In all patients a bronchodilator response of $\geq 15\%$ after inhalation of 200 μg salbutamol had been measured just before the trial. None of the patients were smokers. All but one used corticosteroids by inhalation; cromoglycate or long-acting β_2-mimetic agents were not used. Oral anti-asthma medication was not allowed. Except for the corticosteroids, their regular medication was discontinued 6–8 h 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.

2.2. Aerosol generation

Monodisperse aerosols (geometric SD < 1.2) were produced by a spinning top generator (Cheah and Davies, 1984). 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. The 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 in the solution and its viscosity. Ipratropium bromide 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, 2.8 and 5 μm, respectively. Each time a patient was due to start the aerosol inhalation, the mass of ipratropium bromide per l 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, MN). For each dose the volume of air inhaled was calculated by dividing the dose by the mass of ipratropium bromide per l of air. If sufficient aerosol-containing air had been inhaled, the aerosol inhalation was discontinued by switching over to non-aerosol containing air.

2.3. Procedure

Each patient was studied at the lung function laboratory with intervals of 1 week. The baseline FEV_1 during each session was not allowed to vary more than 10%. Each session consisted of measurement of the lung function 30 min after administration of the aerosol. From the previous study we learned that, when using monodisperse aerosols of these size ranges, small dosages of drug (5–10% of an MDI dosage) are needed; we therefore decided to administer only 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 s and a slow exhalation. 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 aerosol inhalation the patients were taught to inhale and had the opportunity to correct the inhalation flow by watching an indicator connected to the anemometer. Administration of the aerosols was carried out in a randomized single-blind manner. On the first day a placebo aerosol was administered in order to facilitate early de-

tection 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.

2.4. Lung function assessment

The lung function was assessed 30 min 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 $MEF_{50/25}$ were derived from maximal expiratory flow-volume curves.

2.5. Statistics

The change in lung function was expressed as a percentage of the predicted value. These changes were analyzed for effects related to the type of aerosol (aerosol-size effect) using repeated measurements ANOVA (Girden, 1992). In order to discover 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, which method is comparable to the LSD test (Schuirmann, 1987). In all calculations an α value of 0.05 was considered to be significant.

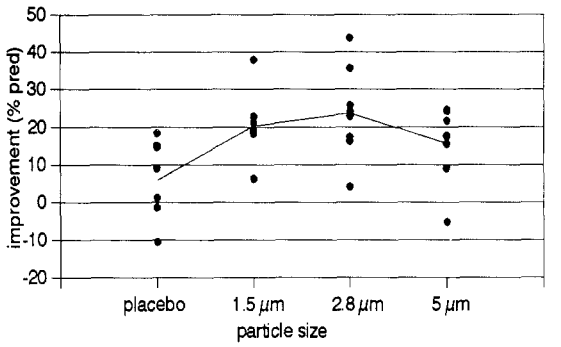

Fig. 1. Scatterplot showing individual FEV_1 improvements (% pred). On the *X*-axis the type of aerosol is depicted and on the *Y*-axis the improvement. The solid line connects the average improvements.

3. Results

All eight patients completed the four sessions. In Table 1 the change in all lung function parameters is represented. No significant change was measured in any of the parameters during the inhalation of placebo.

In evaluating the aerosol-size effect, the analysis of variance demonstrated significant differences with reference to placebo for the FEV_1 ($p < 0.01$), PEF ($p = 0.001$), FVC ($p = 0.034$), MEF_{50} ($p < 0.001$) and MEF_{25} ($p = 0.001$). For

Table 1
Mean (SD) improvement in lung function (% predicted) after inhalation of ipratropium bromide aerosols with different particle sizes

Lung function parameter	Particle size of the aerosol			Significant different aerosols
	1.5 μm	2.8 μm	5 μm	
VC	13.6(13)	11.5(12.5)	7.7(7.8)	NS
R_{tot}	−74.4(73.2)	−114.8(97.1)	−104.5(135.9)	NS
FVC	12.4(12.4)	13 (12.5)	9.4(10.8)	NS
FEV_1	20.3(8.7)	23.7(12.1)	15.6(9.8)	1.5/2.8 vs 5
MEF_{25}	23.7(15)	19.3(14.7)	15.3(12.7)	1.5/2.8 vs 5
MEF_{50}	24.7(10.7)	24.7(12.1)	17.7(10.3)	1.5/2.8 vs 5
PEF	21 (7.2)	22 (13.2)	16.6(12.4)	NS

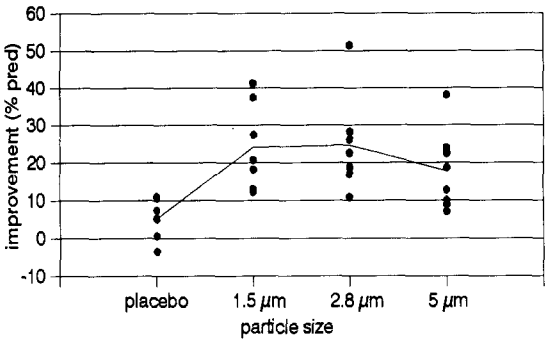

Fig. 2. Scatterplot showing the individual MEF_{50} improvement (% pred). *X*-, *Y*-axis and solid line as in Fig. 1.

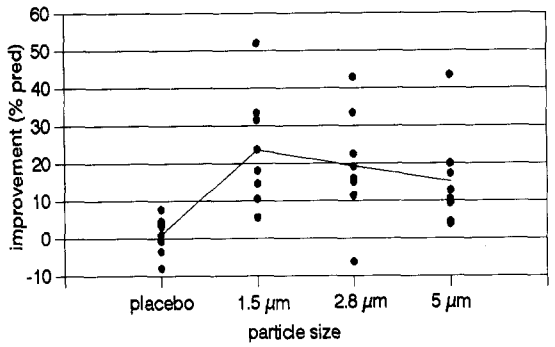

Fig. 3. Scatterplot showing the individual MEF_{25} improvement (% pred). *X*-, *Y*-axis and solid line as in Fig. 1.

the R_{tot} ($p = 0.202$) and VC ($p = 0.052$) no significant differences were demonstrable.

A significant difference with reference to the best aerosol will occur for the FEV_1 if the deviation between the means exceeds 5.7%; for the PEF this deviation should be at least 7.5%, for the $MEF_{50/25}$ at least 6.3 and 8.2%, respectively, and, finally, for the FVC at least 5.5%. In the case of the FEV_1 and $MEF_{50,25}$, a statistically significant difference occurred between the 5 μm aerosol and the 1.5/2.8 μm aerosol. For all other parameters the differences were too small to be significant. None of the patients reported any adverse effect as a result of the experiment.

4. Discussion

The increase in FEV_1 and $MEF_{50/25}$ after the 5 μm aerosol was significantly less than after the 1.5/2.8 μm aerosol. No differences due to changing aerosol sizes were detectable in the case of the other lung function parameters. These findings strongly resemble our earlier findings with salbutamol: in those experiments the optimal particle size was also ≤ 2.8 μm (Zanen et al., 1994). In contrast to the previous study no aerosol-size effect was noticeable in the case of the PEF. Our initial hypothesis pointed in another direction. To achieve an optimal match between the deposition pattern and muscarinic receptor distribution a central deposition pattern seemed logical. Centrally orientated patterns will occur after inhaling large particles. Contrary to our thoughts the results of this study indicate that the optimal particle size (= deposition patterns) for β_2-mimetics and parasympathicolytic drugs are similar. Hence, the distribution of the receptors, as reported in the literature, does not seem to play an important role. The explanation we offer for these results is of a physical nature. In our previous publication we suggested that the way particles penetrate into the lower airways, combined with a local effect, explains all findings. All particles, but especially large ones, are filtered out quickly in the central airways due to a high impaction probability. Only small particles will escape from extrathoracical/central deposition (Lippmann et al., 1980). The dose in the lungs or lower airways therefore heavily depends on the filter characteristics of the extrathoracic/upper airways. The 'lung-dose' will be greater in the case of small particles. This is reflected by the increased bronchodilatation after administration of the 1.5/2.8 μm aerosols.

In contrast to the earlier study we could not find a better PEF improvement after the 5 μm compared to the 1.5 μm aerosol. If the theory is correct, one would expect that the smallest particles would pass the central airways and only a small amount would deposit. As a result, the improvement of the PEF, which is strongly influenced by the condition of the central airways, should be lower. This not the case (although the statistical power to detect differences was comparable to the previous experiment). Svartengren et al. (1991) showed that in some patients the cut-off point of the oropharynx, due to local anatomical structures, is very low. Two of the volunteers (not

present in the earlier study) showed rather low lung function changes after inhaling the 5 μm aerosol, thereby reducing the mean improvement of all lung function parameters and obscuring the differences between the effects of the 5 and 1.5 μm aerosols of the PEF, as found before. These volunteers must 'suffer' from a low oropharyngeal cut-off point. This explanation underlines the importance of choosing an aerosol with a small particle size and low geometric standard deviation (GSD).

Our results are in in accordance with those of Padfield et al. (1983) but not with those of Johnson et al. (1989). Padfield et al. showed that an aerosol with 35% of the particles ≤ 6.4 μm elicited better bronchodilatation than an aerosol with only 10% ≤ 6.4 μm. Johnson et al. could not detect any differences between aerosols with a median mass diameters (MMD) of 3.3 and 7.7 μm. The authors reported a lower whole lung (and local airway) dose after administration of the largest aerosol with much of the coarse aerosol deposited extrathoracically. The explanation for this negative finding was that the percentual higher central deposition of the 7.7 μm aerosol compensated for the lower total and local dose. In other words, a low central dose is to be preferred over a high peripheral one. We do not believe that this is a plausible explanation. It suggests that the dose-response curve for centrally deposited ipratropium bromide is steeper. However, the reported dose-response curves of the MEF_{25} are much steeper than those of the FEV_1. This fact is not consistent with the explanation given.

Ipratropium bromide and salbutamol (or other β_2-mimetics) are frequently combined in metered dose inhalers or nebulisers. It is believed that the combination induces larger and/or longer bronchodilatations than the single components. By definition, both drugs will be administrated in the same droplet or dry particle, thus showing the same particle size distribution. If ipratropium bromide needed a coarse aerosol to be most active and salbutamol a fine one, the combination would be rendered less effective than the two drugs delivered independently. Our finding that both drugs exhibit the same optimal particle size makes such a combination a rational one.

We conclude that in mild asthmatics the mean particle diameter of a parasympathicolytic aerosol should be 2.8 μm for optimal improvement of the lung function. As for β_2-mimetic aerosols the dosage compared to conventional polydisperse aerosols can be reduced for such aerosols.

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References

Barnes, P.J., Basbaum, C.B. and Nadel, J.A., Autoradiographic localization of autonomic receptors in airway smooth muscle. *Am. Rev. Respir. Dis.*, 127 (1983) 758–762.

Barnes, P.J., Basbaum, C.B., Nadel, J.A. and Roberts, J.M., Localization of β-receptors in mammalian lung by light microscopic auto-radiography. *Nature*, 299 (1982) 444–447.

Cheah, P.K.P. and Davies, C.N., The spinning top aerosol generator-improving the performance. *J. Aerosol. Sci.*, 15 (1984) 741–751.

Girden, E.R., *ANOVA: Repeated Measures*, Sage, Newbury Park, 1992.

Johnson, M.A., Newman, S.P., Bloom, R., Talee, N. and Clarke, S.W., Delivery of albuterol and ipratropium bromide from two nebulizer systems in chronic stable asthma. *Chest*, 96 (1989) 6–10.

Lippmann, M., Yeates, D.B. and Albert, R.E., Deposition, retention and clearance of inhaled particles. *Br. J. Ind. Med.*, 37 (1980) 337–362.

Padfield J.M., Winterborn I.K., Pover G.M. and Tattersfield A., Correlation between inertial impactor performance and clinical performance of a bronchodilator aerosol. *J. Pharm. Pharmacol.*, 35 (1983) 10p.

Schuirmann, D.J., A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. *J. Pharmacokinet. Biopharm.*, 15 (1987) 657–680.

Svartengren, M., Anderson, M., Bylin, G., Philipson, K. and Camner, P., Mouth and throat deposition of 3.6 μm radiolabelled particles in asthmatics. *J. Aerosol. Med.*, 4 (1991) 313–321.

Zanen, P., Go T.L. and Lammers J.-W.J., The optimal particle size for β-adrenergic aerosols in mild asthmatics. *Int. J. Pharm.*, 107 (1994) 211–217.