

The Influence of a Nose-Clip on Inhalation Therapy in Asthmatic Children

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ABSTRACT

In our study we investigated if wearing a nose-clip during inhalation therapy in asthmatic children changes breathing patterns and hence, influences aerosol delivery. Aerosol delivery was measured in 30 asthmatic children (age range 4–7 years) inhaling in random order with and without a nose-clip from both a pressurized metered-dose inhaler (pMDI) through a holding chamber and a nebulizer. Breathing patterns were measured using a pneumotachograph inserted between the delivery device and the patient. Aerosol delivery to the patient was measured on a filter inserted in the inspiratory limb of the system. Inspiratory volume and inspiratory flow were significantly higher when inhaling with a nose-clip from both a pMDI ($p = 0.004$; $p = 0.025$) and a nebulizer ($p = 0.003$; $p = 0.038$). Aerosol deposition on the inspiratory filter while inhaling from a nebulizer was significantly higher when wearing a nose-clip ($p < 0.0005$), but not while inhaling from a pMDI with holding chamber ($p = 0.32$). Aerosol delivery from a nebulizer is increased when inhaling with a nose-clip. This may have major implications on nebulized aerosol therapy. (*Pediatr Asthma Allergy Immunol* 2003;16[3]:129–135.)

INTRODUCTION

DESPITE AEROSOL THERAPY being the choice of treatment for asthmatic children, surprisingly little is known about its technical and practical aspects.^{1–4} The main practical aspect a physician is facing when dealing with a child is its lack of cooperation and compliance. Therefore, the cooperation needed to use a certain device should be minimal. Passive cooperation with an inhalation device, such as acceptance of a face mask, should be expected from a young child. In older children, non-compliance can be a major problem. Passive and certain active cooperation, such as the use of a mouthpiece, specific inhalation maneuvers and handling of inhalation devices should generally be expected from an older child.

In addition, several technical aspects are important for the inhalation route of drug administration. The deposition level and deposition pattern of inhaled particles depends on three different variables (ventilatory parameters, respiratory tract morphologies and characteristics of the delivery device and of the aerosol) and can be expressed as a function of these. In addition, the various deposition mechanisms that are inertial impaction, sedimentation and diffusion are a function of these three variables. The interaction of all these vari-

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ables may lead to a very specific deposition pattern in children, as children have very characteristic breathing patterns and a very unique airway morphology. Children have generally low tidal volumes, low inspiratory flows and high breathing rates.⁵

The aim of the inhalation therapy is to deposit the drug at its site of action in the airways, in order to achieve a high, local and clinically relevant effect while avoiding serious systemic side effects. To achieve this goal, it is therefore important to know the influence of various parameters and hence, to optimize the delivery of aerosolized drugs to the airways of asthmatic children.

The benefit of a nose-clip on improved inhalation therapy in asthmatic children is often discussed among health care professionals. However, its effect has never been studied before. We performed a pilot study in adults inhaling with and without a nose-clip from a nebulizer.⁶ Wearing a nose-clip led to an increase of 113% in drug delivery from the nebulizer. Based on these findings and in view of the lack of appropriate and published studies in the literature, we aimed to study the effect of wearing a nose-clip in asthmatic children inhaling through a mouthpiece from both a pressurized metered-dose inhaler (pMDI) with a holding chamber and a nebulizer.

MATERIALS AND METHODS

We recruited 30 asthmatic children, aged 4–7 years (nine children aged 4 years, five children aged 5 years, eight children aged 6 years and eight children aged 7 years, respectively) from our outpatient clinic. All children were trained in and used to inhalation therapy with both a nebulizer and a pMDI with holding chamber. They were under regular treatment with inhaled bronchodilators and steroids. Written informed consent was obtained from all parents, and the study was approved by the local ethics committee.

The systems assessed were the Pari-LC-star[®] nebulizer using the Pari-Turbo[®] compressor (Pari GmbH, Starnberg, Germany) and the Nebuchamber[®] holding chamber (AstraZeneca, Lund, Sweden). After an initial instruction and demonstration, the children inhaled salbutamol in random order, once while wearing a nose-clip and once without, from the nebulizer or the holding chamber, with a 5-min interval between the use of the different devices. Hence, the children served as their own control in this cross-over study in which each child required four separate tests. Drug was collected by a filter (Curity, anesthesia filter, viral/bacterial retentive, Kendall, USA) with a dead space of 45 mL. The filter was inserted between the face and the inhalation system. Breathing patterns were measured with a pneumotachograph (Brasco; Pari GmbH, Starnberg, Germany) inserted in the mouthpiece and analyzed with a breathing monitor (Brasco; Pari GmbH, Starnberg, Germany; Fig. 1).

The nebulizer was filled with 2 mL containing 1 mL NaCL 0.9% and 1 mL salbutamol (1mg/mL, Ventolin[®], Glaxo, Switzerland). The children inhaled for 3 min from the nebulizer. When the holding chamber was used, four single actuations from a salbutamol pMDI (100 μ g/actuation, Ventolin[®]) were delivered.

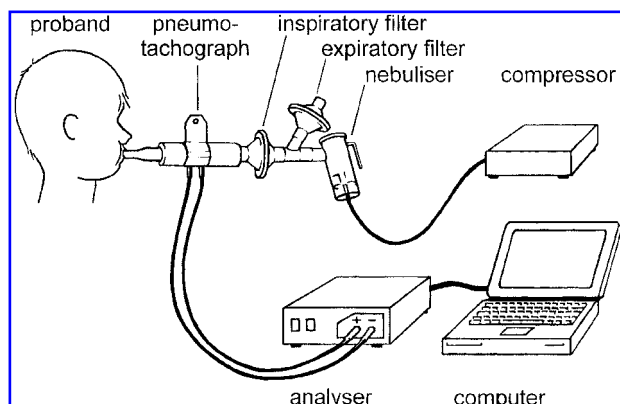


FIG. 1. Study set-up with the pneumotachograph, and an expiratory and inspiratory filter inserted in the inspiratory and expiratory limb of the inhalation system (nebulizer).

ered into the holding chamber. After each actuation, the children had to take one deep, slow breath. Passive deposition of salbutamol on the filter independent from the inhalation by the children was determined. This was done by running the nebulizer for 5 min with the standard 2-mL fill and attached filter, or by actuating the pMDI in the standard way into the holding chamber with attached filter.

After each test, the nebulizer, the holding chambers, the actuators, and the filters were washed with 45 mL of methanol (HPLC grade), and then 5 mL of NaOH were added. Subsequently the samples were analyzed for their salbutamol content. The amount of salbutamol was measured using an ultraviolet spectrophotometric method (wavelength = 246 nm) and was expressed as a percentage of the total nebulized or actuated dose. To determine the amount of the total nebulized dose, the amount of salbutamol left in the nebulizer was subtracted from the initial amount of 5 mg. The total amount of actuated dose from the holding chamber was determined from the total recovery of salbutamol from the spacer, the actuator, and the filter. The deposition of salbutamol on the inspiratory filter was expressed as a percentage of the total actuated or nebulized dose.

Statistical analysis was carried out using ANOVA (statview 512+, Albacus Concepts, CA) with a significance level of 95% (i.e., $p < 0.05$). Normally distributed data were given as mean (standard deviation [SD]); otherwise, median and range were given. For repeatedly determined variables in the same individual, either repeated t -test in case of two determinations, or in case of more determinations, repeated measurements ANOVA with contrast vector analysis was performed. To address the question whether children's age group may influence any parameter, all variables were plotted in function of the children's age group. One-way ANOVA was used to analyze differences between groups.

RESULTS

The mean (range) passive deposition of salbutamol on the filter independent of inhalation by the children, expressed as a percentage of the total nebulized dose, was 0.8% and ranged from 0.5% to 1.0%. There was no passive deposition on the filter for the holding chamber. The deposition of salbutamol on the filter was expressed as a percentage of the total actuated or nebulized dose.

The mean (SD) percentage filter deposition of salbutamol delivered from a pMDI through a holding chamber using a nose-clip was 47.7% (4.7%). The percentage filter deposition of salbutamol delivered from a pMDI through a holding chamber without a nose-clip was 47.1% (3.6%). There was no significant difference between filter deposition of salbutamol delivered from a pMDI through a holding chamber with or without a nose-clip ($p = 0.31$). However, there was a significant difference in breathing patterns. The inspiratory volume (V_{insp}) was 441 (206) mL when wearing a nose-clip and was significantly higher than 393 (207) mL without a nose-clip ($p = 0.004$). In addition, inspiratory flow (V'_{insp}) was 511 (138) mL·sec⁻¹ when wearing a nose-clip and was significantly higher than 461 (172) mL·sec⁻¹ without a nose-clip ($p = 0.025$). The percentage filter deposition of salbutamol delivered from a nebulizer using a nose-clip was 13.7% (2.8%). The percentage filter deposition of salbutamol delivered from a nebulizer without a nose-clip was 10.8% (2.7%). There was a significant difference between filter deposition of salbutamol delivered from a nebulizer with or without a nose-clip ($p < 0.0005$). This difference in filter deposition from a nebulizer with or without a nose-clip was found in all age groups (age 4, $p = 0.009$; age 5, $p = 0.027$; age 6, $p = 0.01$; age 7, $p = 0.01$).

In addition, there was a significant difference in breathing patterns. The V_{insp} was 402 (110) mL when wearing a nose-clip and was significantly higher than 351 (133) mL without a nose-clip ($p = 0.003$). In addition, V'_{insp} was 570 (130) mL·sec⁻¹ when wearing a nose-clip and was significantly higher than 516 (177) mL·sec⁻¹ without a nose-clip ($p = 0.003$).

The V_{insp} as well as the V'_{insp} were significantly higher when inhaling from the pMDI with holding chamber without nose-clip compared to inhalation from the nebulizer ($p = 0.03$; $p = 0.02$). However, when inhaling with a nose-clip, there were no significant differences in both V_{insp} as well as V'_{insp} ($p = 0.07$; $p = 0.07$).

In order to address the question whether children's age group may influence any of the measured parameters, all parameters were plotted against the children's age group. The filter deposition percentages were the only parameters dependent of age group when using pressure nebulizer without, and especially with nose clip ($p = 0.003$ or $p < 0.0005$, respectively; Fig. 2). Neither with, nor without nose-clip was such an age dependency found when a pMDI with holding chamber was used ($p = 0.80$ or $p = 0.29$, respectively; Fig. 2).

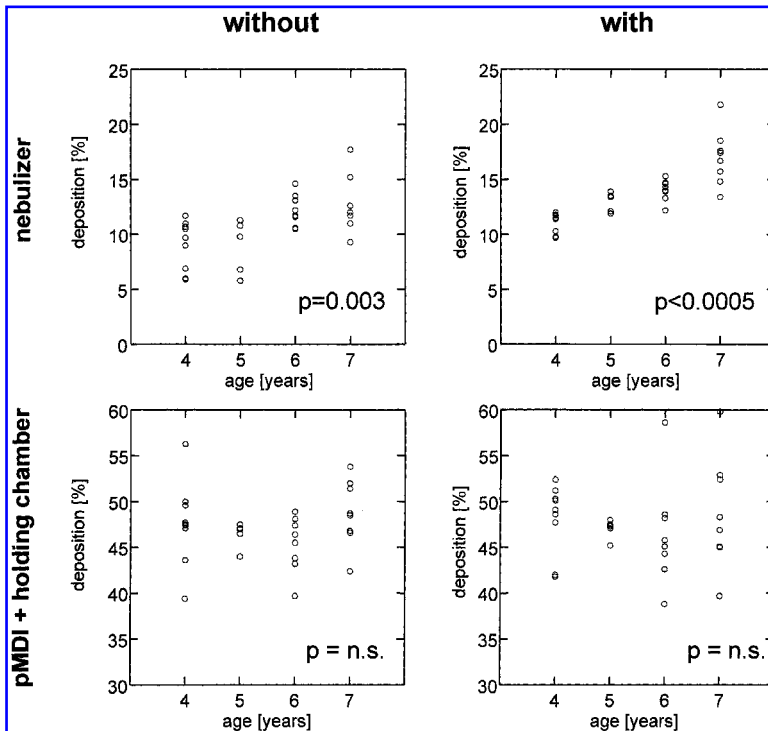


FIG. 2. The filter deposition percentages were the only parameters dependent on age group when using the pressure nebulizer without and, especially, with a nose-clip. Neither with nor without the nose-clip was such an age dependency found when the pMDI with holding chamber was used.

DISCUSSION

We showed that breathing patterns in asthmatic children inhaling with or without a nose-clip are significantly different. In addition, we have shown that these changes in breathing patterns lead to a significant difference in drug deposition on a filter when inhaling from a nebulizer. However, no difference in drug deposition on a filter was found when inhaling from a pMDI through a holding chamber.

It has previously been shown that lung deposition is much lower in children compared to adults when inhaling from both pMDI/holding chamber and nebulizer.^{7,8} These differences in lung deposition have been attributed to age specific breathing patterns. Children have relatively low inspiratory and expiratory flows and low tidal volumes. They do often not cooperate with inhalation therapy and cry during the procedure. Crying leads to changes in breathing patterns and to decreased lung deposition.⁹ The interaction of age specific breathing patterns and unique characteristics of inhalation devices may limit their use. For example, the use of dry powder inhalers, which requires a high inspiratory flow, is limited for the use in older children.¹⁰ Low inspiratory flow and low tidal volumes are especially a problem when inhaling through a spacer carrying electrostatic charges, as the residence time of aerosol is low.¹¹ Plastic spacers carry random electrostatic charges. The net effect of these charges is attraction of aerosol particles onto plastic surface. This will significantly reduce the drug available for inhalation from plastic spacers; the electrostatic activity of plastic spacers reduces the initial dose available for inhalation and reduces the aerosol half-life of aerosol in the spacer, thus reducing the time available for inhalation. On the other hand, metal spacers are non-electrostatic spacers made of a conducting material and do not carry any electrostatic charges. The clearance of aerosol from spacers greatly depends on the breathing pattern during inhalation.¹² A cone-shaped spacer may be cleared more efficiently by a maximal deep and fast inhalation, whereas a tube shaped spacer may be cleared more efficiently by several shallow and slow inhalations.¹² The resistance of the valves of holding chambers differs and aerosol delivery

is increased by removing the valves.^{13,14} Whereas aerosol delivery from a pMDI through an electrostatic holding chamber is greatly influenced by breathing patterns, it has been shown that *in vitro* aerosol delivery from a pMDI through a non-electrostatic holding chamber is not significantly influenced by breathing patterns.¹⁵ This previous *in vitro* finding may explain the finding of the present study that aerosol delivery when inhaling from a pMDI through a non-electrostatic holding chamber does not vary when inhaling with or without a nose-clip despite changes in breathing patterns. Another explanation could be that given the measured inspiratory volumes of all thirty children with and without nose-clips versus the volume of the holding chamber (165 mL), the aerosol in the holding chamber may have been already fully inhaled with each single breath.

Inspired nebulized aerosols from a conventional nebulizer are diluted more for large than for small subjects, because of air entrainment which occurs when inspiratory flow exceeds nebulizer flow.¹⁶ Based on this finding, breath enhanced nebulizers were invented.¹⁷ Aerosol delivery from breath enhanced nebulizers increases with increased inspiratory flow. This finding explains the finding in the present study that changes in breathing patterns when inhaling with a nose-clip improves nebulized aerosol delivery.

Instrumental deadspace and resistance are known to alter breathing patterns and pulmonary mechanics and to increase work of breathing.¹⁸ There may have been a consistent influence of breathing patterns by the inserted filter, which added further deadspace to the delivery system in our study set-up. In addition, differences in V_{insp} and V'_{insp} between pMDI/holding chamber and nebulizer may be explained by differences in deadspace and resistance between the two inhalation devices.

Aerosol research in general has previously focused on measurements of total aerosol delivery and hence, total lung deposition.¹⁹ However, increased lung deposition may not be the important factor determining clinical effectiveness of inhaled therapy. The distribution of the aerosol within the airways may be far more important and hence, even a small dose applied may be clinically efficient, when reaching the right localization within the airways. Using new pMDIs with smaller particle size than old pMDIs increases the total lung deposition by fivefold, whereas the clinical outcome measurements are only increased by twofold.^{20,21} Many factors can influence the distribution of the aerosol delivered to the lungs. The main factors include particle size, particle velocity from delivery device and tidal breathing flows and volumes. Particle size is of particular importance and can influence whether the aerosol is deposited in the throat and upper airway, the central airways, the peripheral airways or the alveolar spaces. In general, particles $>5 \mu\text{m}$ are deposited centrally, those between 2 and $5 \mu\text{m}$ result in peripheral airway deposition, while particles $<2 \mu\text{m}$ accumulate in the alveoli.²² Recent studies in adults with inhaled bronchodilators have demonstrated that there are optimal particle sizes at which the clinical effect is greatest.^{22,23} These results have illustrated the importance of targeting specific inhaled drugs at the individual respiratory diseases, rather than adopting a blanket approach to aerosol therapies. Zanen et al. have demonstrated in adult asthmatic patients that the improvement in lung function was greatest after inhalation of salbutamol particles with a diameter of $2.8 \mu\text{m}$ compared to particles of $<2 \mu\text{m}$.^{23,24} As the distribution of β_2 -receptors is throughout the airways within smooth muscle, then the delivery of a β_2 -mimetic to the alveoli will merely serve to increase systemic absorption of the drug and hence side effects. In contrast the use of small diameter particles ($<2 \mu\text{m}$) would maximize delivery to the alveolar spaces and hence be ideal for control of disease originating in the pulmonary tissues.²⁵ Increased drug delivery due to increased V_{insp} and V'_{insp} shown in our study by a filter inserted between the inhalation device and the patient represents drug inhaled and deposited in the oropharynx and both the central and peripheral airways. At higher V'_{insp} contribution from impaction would be greater. Thus, it is likely that oropharyngeal deposition and deposition in the central airways would be higher and potentially aerosol delivery to the peripheral airways lower when inhaling with a nose-clip.

In summary, wearing a nose-clip when inhaling from a pMDI through a non-electrostatic holding chamber does not improve aerosol delivery. In contrast, wearing a nose-clip when inhaling from a nebulizer with breath enhancement increases aerosol delivery. This finding may have an impact on nebulized aerosol therapy.

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