

Aerosol delivery to young children by pMDI-spacer: Is facemask design important?

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This study aimed at identifying in a daily-life setting the influence of facemask design on drug delivery via a spacer to young children. In a 4-week randomized crossover study, 24 children (7–23-months old) with recurrent wheeze tested the AstraZeneca®, Galemed®, and Hans Rudolph® facemask combined with the NebuChamber® at home. Each mask was tested twice daily for seven consecutive days. Filters positioned between the NebuChamber and facemask trapped the budesonide aerosol (200 µg, Pulmicort®). Parents were asked to score the child's degree of cooperation during administration on diary cards. The administration procedure was evaluated through video recordings. Mean filter dose (standard deviation (s.d.)), expressed as % of nominal dose, was 39% (14), 47% (12), and 42% (11) for the AstraZeneca, the Galemed and the Hans Rudolph mask, respectively. Irrespective of the degree of cooperation, the Galemed mask gave significantly higher mean filter doses than the other masks (level of significance) ($p < 0.045$). Median (range) within-subject dose variability, expressed, as coefficient of variation (CV), was 37% (19–255), 32% (9–114), and 30% (9–115) for the AstraZeneca mask, the Galemed mask and the Hans Rudolph mask, respectively, not significant. Dose variability increased with decreasing cooperation for all three masks ($p = 0.007$). Drug delivery to young children with recurrent wheeze by means of the NebuChamber can be enhanced using the Galemed facemask. Dose variability seems to be independent of facemask design but mainly depends on cooperation.

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In infants and pre-school children inhalation therapy with β_2 -agonist and corticosteroids can be effective in the treatment of recurrent wheeze (1–6). The pressurized metered dose inhaler (pMDI)-spacer-facemask combination can be an efficient system to deliver aerosolized drug to young children. Efficiency, however, can be influenced by device-related factors – static charge, spacer volume, facemask design, and pMDI properties – and patient-related factors – breathing pattern, cooperation and administration technique (2, 4, 5, 7–11).

Previous studies suggest that facemask design is important for the efficiency of drug delivery (11, 12). In a daily-life study we observed that obtaining and maintaining a good seal between the mask and the face is especially difficult in

uncooperative young children (11). We found that dose delivery relates to the degree of cooperation for the NebuChamber® (AstraZeneca, Sweden) fitted with a face-shaped mask, but not for the detergent coated Babyhaler® (GlaxoWellcome, UK) with a round facemask. In this study, however, we did not systematically evaluate the relationship between facemask design and the efficiency of aerosol delivery. Therefore, we performed a daily-life study examining how facemask design affects the efficiency of aerosol delivery to young children by means of a spacer (NebuChamber). Furthermore, possible factors influencing filter dose and dose variability – like cooperation, inhalation technique, age, and symptoms – were studied.

Materials and methods

Study population

Twenty-four children aged 7–23 months, treated for recurrent wheeze with inhalation therapy twice daily, were recruited from the outpatient clinics of the Erasmus MC-Sophia (Rotterdam, The Netherlands), the Reinier de Graaf Gasthuis (Delft, The Netherlands) and the Albert Schweitzer Ziekenhuis (Dordrecht, The Netherlands). None of the subjects suffered from other disorders that could affect cooperation or lung function. Written informed consent was obtained from all parents. The Ethics Review Committee of Erasmus MC approved the study.

Study design

In a 4-week randomized crossover study, we visited the children at home five times. Parents were asked to follow standardized instructions, which have been described previously (11), on the use of inhalation therapy. In addition, they were asked to administer the study medication before the child's regular inhalation treatment, which was continued using their own medication and device. In a 1-week run-in period, the children practiced with three different masks (see Materials) in combination with the NebuChamber. In the following three study weeks, the children tested in randomized order each mask-NebuChamber combination twice daily for one week. Each week the children received a clean NebuChamber and facemask. To assess drug delivery, the parents were asked to place a new filter between the NebuChamber and the mask before each administration. For each child a maximum of 42 filters could thus be obtained.

After every administration procedure parents were asked to fill out a diary card, evaluating cooperation and symptoms during the study period (11). Cooperation during administration was assigned a score ranging from 0 (good cooperation) to 3 (fighting). The symptoms cough, wheeze and shortness of breath were each assigned a score ranging from 0 (no symptoms) to 4 (severe symptoms). The total symptom score, with a maximum of 12, was defined as the sum of the scores for cough, wheeze and shortness of breath. At the end of each study week, we recorded the administration procedure on video. Three observers scored in random order all video recordings, using a video checklist as described previously (11).

Materials

A pMDI (Pulmicort® 200 µg, AstraZeneca, Sweden) delivered budesonide aerosol through the metal NebuChamber® (250 ml, AstraZeneca, Sweden) in combination with three different masks: the original facemask of the NebuChamber, hereafter called the AstraZeneca mask, the Galemed® (Galemed Corporation, Taiwan) facemask and the Hans Rudolph® (Hans Rudolph Inc., USA) facemask (Fig. 1). The face-shaped AstraZeneca mask has a thin and rather stiff rim. The round Galemed mask has a thick and flexible rim. The face-shaped Hans Rudolph mask has a thick rim and a flap to stabilize the mask on the chin. A plastic adapter was used to fit the Hans Rudolph mask onto the NebuChamber.

Each child received a new budesonide pMDI, primed by shaking and firing 10 waste puffs. A filter (Marquest®, MQ303, USA) inserted between the spacer and the facemask trapped the aerosol discharged by the spacer. The filter holders fitted tightly to the mouthpiece of the Nebuchamber. The filter holder of a Marquest filter added 38 ml of dead space. The pressure drop over the filter is 230 Pa at 60 l/min (13).

Filter analysis

All filters were analyzed in a blinded fashion at the laboratory of the Erasmus MC, Department of Hospital Pharmacy (Rotterdam, The Netherlands). The filters were washed with ethanol containing an internal standard (fluocinolone acetate). Budesonide amounts were measured by high performance liquid chromatography (HPLC), using an ethanol-water (43:57) mobile phase and a Supelcosil LC-18 column (5 µm particles, 5 × 0.46 cm (inner diameter)). Budesonide was detected by UV-spectrophotometry at a wavelength of 254 nm. The coefficient of variation (CV) of the method was < 3%.

Statistical analysis

SPSS for Windows Version 9.0 and SAS were used for statistical analyses. Filter dose, calculated as the amount of budesonide deposited on the filter, was expressed as a percentage of the nominal dose. The filter dose variability was expressed as the within-subject CV. Study week sessions that yielded less than three filters, either in the morning sessions or in the evening sessions, were excluded from analysis.

The mean ($\pm$ s.d.) filter doses of the 14 samples collected each week was calculated for each child.

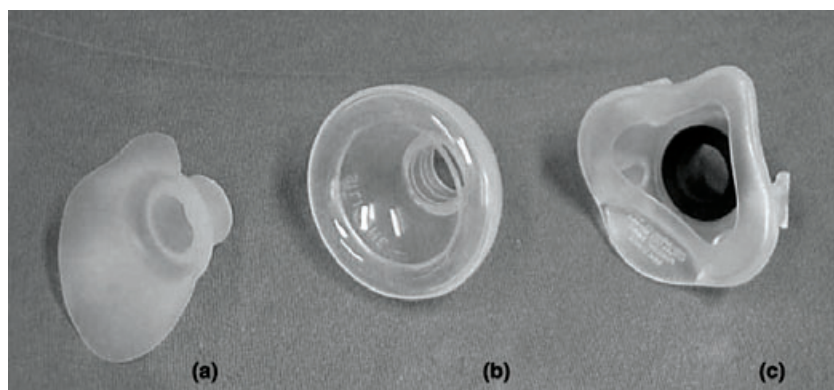


Fig. 1. (a) The AstraZeneca mask; (b) the Galemed mask; (c) the Hans Rudolph mask.

t-Tests were carried out to compare mean filter doses for each mask, after ensuring that the results were normally distributed. Wilcoxon's signed rank test was used to compare the CVs for the three masks. Relationships between filter dose and age, filter dose and cooperation score, filter dose variability and age, and filter dose variability and cooperation score were assessed using Spearman's correlation coefficient (*r*) and Repeated Measurements ANOVA (analysis of variance) (SAS PROC MIXED). Mean total symptom scores and mean cooperation scores obtained from the weekly diary cards were compared using the Friedman test. A $p \leq 0.05$ (two-sided) was considered to indicate significant differences.

Items on the video checklist relating to the child's cooperation, i.e., 'Child breathes for at least 15 s through the facemask from the start of the administration' and 'Child breathes quietly through the facemask from the start of the administration', were correlated with the filter dose obtained while the video recording took place, using SAS PROC MIXED.

Results

Twenty-five children were enrolled into the study. One dropped out after the run-in period because of non-compliant parents. Twenty-four children (18 boys) completed the study. Median (range) age was 15 (7–23) months. Inhalation devices used before study entry were: Nebu-Chamber (n = 6), Babyhaler (n = 9), Aero-Chamber® (Trudell Medicals, London, Ontario, Canada) (n = 8), and nebulizer (n = 1). A total of 285, 289 and 295 filters were collected for the AstraZeneca facemask, the Galemed facemask and the Hans Rudolph facemask, respectively. Only 5 (3.5%) of the total number of 144 week-sessions were excluded from analysis because less than three morning or evening filters were collected.

Filter dose

Mean filter dose (s.d.) was 39% (14), 47% (12), and 42% (11) for the AstraZeneca mask, the Galemed mask and the Hans Rudolph mask, respectively. Mean filter dose of the Galemed mask was significantly higher than that of the AstraZeneca mask ($p = 0.003$) and the Hans Rudolph mask ($p = 0.045$). The AstraZeneca mask and the Hans Rudolph mask did not significantly differ in mean filter dose. Simultaneous evaluation of masks and cooperation scores showed significant differences between the AstraZeneca mask and the Galemed mask and between the Galemed mask and the Hans Rudolph mask for both good/moderate cooperation (scores 0 and 1) and poor cooperation (scores 2 and 3) (Fig. 2). For good/moderate cooperation, mean filter dose (s.d.) was 43% (12), 49% (11), and 44% (9) for the AstraZeneca mask, the Galemed mask and the Hans Rudolph mask, respectively. For poor cooperation, mean filter dose (s.d.) was 32% (17), 45% (14), and 38% (13) for the AstraZeneca mask, the Galemed mask and the Hans Rudolph mask, respectively. Children showing good/moderate cooperation had on average a 4.5% higher filter dose ($p = 0.03$) than children showing poor cooperation. However, the differences between the masks were not significantly different for the good/moderately cooperative children compared to the poorly cooperative children. Furthermore, the difference between good/moderate and poor cooperation for the AstraZeneca mask was not significantly different from the difference in cooperation score for the Galemed and Hans Rudolph mask. Filter dose did not correlate with age for any of the three masks.

Filter dose variability

Median (range) filter dose variability was 37% (19–255), 32% (9–114), and 30% (9–115) for the

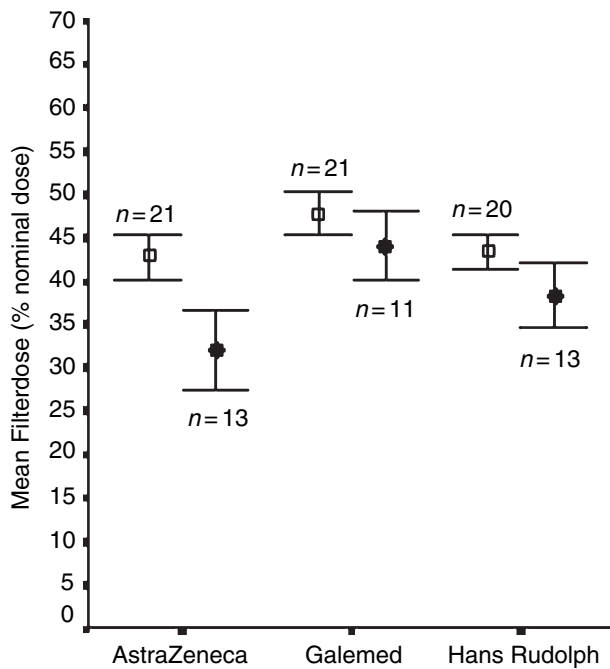


Fig. 2. Mean filter doses expressed as percentage of the nominal dose ($\pm$ s.e.m. (standard error of the mean)) for children with good/moderate cooperation (□) and with poor cooperation (●) for the AstraZeneca, the Galemed, and the Hans Rudolph masks.

AstraZeneca mask, the Galemed mask and the Hans Rudolph mask, respectively (ns). The AstraZeneca mask and the Galemed mask showed a significant positive correlation between the filter dose variability and the cooperation score ($p < 0.02$). The slopes of the regression curves of filter dose variability vs. the cooperation score were not significantly different (Fig. 3). The slope of pooled data from the three masks showed a significant positive relation ($p = 0.007$). An increase of 1 point on the cooperation scale (worse cooperation) led to a 32% increase in filter dose variability. Filter dose variability showed a negative correlation with age only for the Hans Rudolph mask ($r = -0.5$, $p = 0.01$).

Symptom and cooperation scores

Median (range) symptom scores for the AstraZeneca mask, the Galemed mask and the Hans Rudolph mask were 0.2 (0–9), 0.5 (0–8), and 1.3 (0–10), respectively (ns).

Median cooperation score was 1.1, 0.9, and 1.1 for the AstraZeneca mask, the Galemed mask and the Hans Rudolph mask, respectively (ns). Poor cooperation (score 2 or 3) during the administration procedure was assigned in 28%, 33%, and 36% of all scores for the AstraZeneca mask, the Galemed mask and the Hans Rudolph mask, respectively.

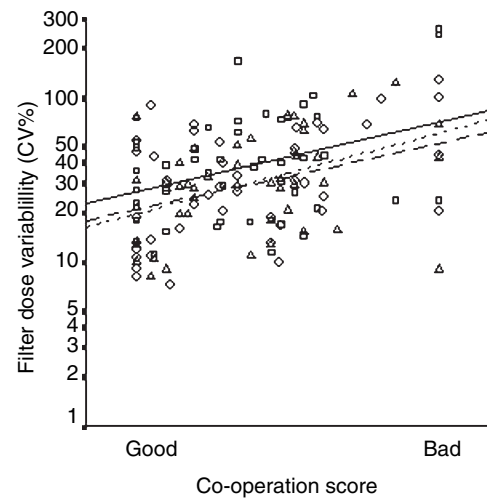


Fig. 3. Scatter plot of the filter dose variability (CV%) on a logarithmic scale vs. cooperation score for the AstraZeneca, the Galemed, and the Hans Rudolph masks. —, □ AstraZeneca mask; ····, × Galemed mask; ---, Δ Hans Rudolph mask.

Video recordings

Children breathing at least 15 s through the facemask from the start of administration had significantly higher filter doses ($p < 0.03$). Filter doses of children breathing quietly during administration did not differ from that of children crying during administration.

Discussion

This daily-life study was carried out to examine the influence of facemask design on the efficiency of aerosol delivery by means of the NebuChamber to young children with recurrent wheeze. We found that the round facemask (Galemed) gave a significantly higher filter dose than the pre-shaped facemasks (AstraZeneca and Hans Rudolph).

Few studies have suggested that facemask design affects the efficiency of aerosol delivery (11, 12). However, the systematic evaluation of the relationship between facemask design and efficiency of aerosol delivery in daily life has only been attempted by Amirav et al. (14). They found filter doses (as % of the nominal dose) of 28.1% and 21.6% for a round facemask and the AstraZeneca facemask, respectively (14). Although, the magnitude of difference between the round facemask and the AstraZeneca mask in this study is similar to ours, it is striking that mean filter doses in Amirav's study are less than half of the filter doses found in our study and previous filter studies (7, 11, 15, 16). The filter dose for the round mask in Amirav's study was

even lower than the lowest filter dose in our study. Differences in the mean filter doses between Amirav's study and our study can be explained by the differences in study design. In Amirav's study the observational period started immediately after instruction. In contrast, in our study subjects practised 1 wk with the spacer, masks and the filter method before they were randomized, such that learning effects were reduced. In addition, in Amirav's study subjects inhaled two puffs once daily, whereas our study subjects inhaled one puff twice daily. As a result we collected not only twice as many filters for each subject, but most likely fewer mistakes per administration procedure were made because of the single-puff-dosing (4, 8, 17).

As suggested previously by other authors, our study supports the view that patient-related factors are important for the efficiency of aerosol delivery (7, 11, 18, 19). Moreover, in children younger than 2 yr patient-factors, such as cooperation, are probably more important than facemask design. Young children often fight the administration procedure, such that it is difficult to obtain and maintain a complete facemask seal (7, 11, 20). Since our *in vitro* work showed that even a small leak dramatically reduces filter dose, the significantly lower filter doses in uncooperative children can be explained by the incomplete seal (21). The uncooperative children had significantly lower filter doses for all masks, and the differences in filter doses between the masks did not relate to cooperation. Hence, we may conclude that, independent of the facemask design, it is difficult to obtain a tight seal when the child is uncooperative. We also found that the dose variability increased significantly when a child did not cooperate. However, we did not find significant differences between the filter dose variability of the different masks, while we expected that the filter dose variability would be highest for the mask with the lowest filter dose. Furthermore, we did not find a difference in cooperation score between the masks. It is, therefore, unlikely that facemask design influences cooperation. Clearly, many young children do not like to have any mask pressed on their face.

In this study, the filter dose represents the total amount of aerosol delivered to the patient. It does not provide information on lung deposition or clinical efficacy. Lung dose depends on various patient-related factors, such as airway anatomy and breathing pattern. In the video analysis we showed that mean *filter dose* of children breathing quietly during administration was not significantly different from that of children crying during administration. Although the mean filter

dose was similar, *lung dose* in crying children will be very low, since most of the drug delivered to the patient will be deposited in the oropharynx (9). In cooperative children, however, it is likely that a higher percentage of the drug delivered to the patient will be deposited in the lung.

In conclusion, the efficiency of aerosol delivery can be improved using a round facemask. However, whether this improvement in delivery efficiency is clinically relevant can only be determined by clinical efficacy studies (22). Since such a high percentage of young children are fighting the aerosol administration and these children do not easily accept any mask on their face, we should focus more on the improvement in acceptability of aerosol therapy in young children.

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