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TECHNICAL NOTE

A metal aerosol holding chamber devised for young children with asthma

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A metal aerosol holding chamber devised for young children with asthma. H. Bisgaard. ©ERS Journals Ltd 1995.

ABSTRACT: The low tidal volume and flow in preschool children may reduce the efficiency of aerosol delivery from a pressurized metered-dose inhaler (pMDI) through a traditional holding chamber.

A prototype small-volume steel holding chamber with two one-way valves was devised to prolong aerosol availability in the chamber and to ensure unidirectional airflow. Dead space between the valves was minimized to less than 2 ml. The dose-delivery and rate of passive disappearance of a budesonide pMDI aerosol were compared between this prototype and the large-volume, single-valved plastic Nebuhaler®, in 164 asthmatic children less than 8 yrs of age.

***In vitro,* the half life of aerosol disappearance in the steel prototype and the plastic Nebuhaler® was >30 s and 9 s, respectively. *In vivo,* the prototype delivered an age-independent mean dose of 38% of the nominal dose, and the Nebuhaler® delivered an age-dependent mean dose, ranging from 42% of the nominal dose in children ≥4 yrs to 19% of the nominal dose in infants.**

We conclude that the use of plastic for holding chambers may influence dose-delivery, and single-valve control may cause age-dependent dose-delivery. Reproducible age-independent drug-delivery may be achieved by pMDI aerosol inhaled through a small-volume metal holding chamber with separate inlet and outlet valves and minimized dead space. This holding chamber would improve the possibilities of aerosol therapy for young children.

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The treatment of young children (aged 7 yrs and under) and infants with aerosols generated from pressurized metered dose inhalers (pMDIs) and then inhaled from holding chamber devices has recently been advocated in controlled studies of inhaled β_2-agonists [1–4] and inhaled steroids [5–7]. The holding chambers which are currently available for young children are often home-made, and include modified saline containers [1], coffee cups [3], and devices adapted from those designed for adult use [5]. The treatment of young children with aerosols from pMDIs, however, puts special demands on the holding chamber because of the low tidal volume and tidal flow of these children [8]. There are two major problems: firstly, the passive disappearance of the aerosol from the holding chamber during the time the young child needs to inhale the appropriate volume; and, secondly, the control of breathing from the holding chamber through a valve system operating at low flow rates.

A prototype holding chamber was, therefore, devised to improve the time available for inhalation of the aerosol, and to ensure unidirectional inhalation from the holding chamber and exhalation to the exterior [8]. The time available for inhalation was prolonged by using steel, which is a nonelectrostatic material, to construct a small volume holding chamber; unidirectional flow from the holding chamber was achieved by separate inlet and outlet valves, with a minimal dead space of less than 2 ml between the valves. We set out to study the effect of this metal holding chamber on the passive disappearance of the aerosol *in vitro,* and an overall evaluation of the prototype was made *in vivo* by comparing the dose it delivered to young children suspected of suffering from asthma with that delivered from a traditional large-volume, plastic holding chamber with single-valve control (the Nebuhaler®).

Materials, Patients and Methods

Materials

Budesonide pMDI at a 200 µg·dose^{-1} was used as a tracer in the studies.

A prototype holding chamber was devised, which had a volume of 220 ml and was forged in steel. The holding chamber was spherical in shape with the inlet aiming at the centre. Two one-way valves ensured unidirectional flow from the holding chamber during inha lation, and to the exterior of the chamber during exhalation. The inlet valve was a flap valve opening from the centre. The inlet valve opened from the holding chamber to the face-mask and closed spontaneously at

zero pressure difference, and the outlet valve opened from the face-mask to the exterior and also closed spontaneously at zero pressure difference.

The commercially available large-volume (750 ml) polycarbonate holding chamber, the Nebuhaler® (Astra Draco, Sweden), is equipped with a valve which controls inhalation from the holding chamber, but has an unguarded side hole, which is intended for exhalation. The holding chamber used in the *in vivo* study was primed with benzalkonium chloride, which abolish the adherence of budesonide to the inside of the holding chamber.

The kinetics of passive aerosol disappearance was studied by mechanically suctioning the aerosol, at a flow rate of 28 L·min^{-1}, through filters at 2, 5, 10, 20 and 30 s after the time of its actuation from the pMDI into the holding chambers. The half life ($T_{1/2}$) of the aerosol was estimated from the time taken for airborne droplets within the holding chambers to disappear, and was interpolated in the semilogarithmic relationship of time *versus* the dose of aerosol. These measurements were repeated in two specimens of each holding chamber, with five doses in each.

The droplet sizes of the aerosol produced in the two holding chamber devices were analysed by an impactor; the aerosol was carried through an Anderson sampler at a flow rate of 28 L·min^{-1}. The amount of drug contained in droplets with an aerodynamic diameter less than 4.7 µm, termed small droplets, was then expressed as a percentage of the total aerosol dose.

Patients

All of the children enrolled in the study suffered from recurrent wheezing, which had been verified by a medical doctor on more than two occasions, and which could be alleviated through inhalation of β_2-agonists. On the day of the study, they did not exhibit any clinical symptoms of upper airway infection or lower airway obstruction.

Methods

The children and their parents were carefully instructed in the inhalation technique, and the child inhaled one dose of budesonide aerosol pMDI from each holding chamber system. The Nebuhaler® was held in a horizontal position for optimal valve function, as recommended by the manufacturer. The pMDI was shaken immediately prior to activation and was fired into the holding chamber after ensuring a close fit of the face-mask. The child inhaled from the holding chamber for 60 s. Passive co-operation of the child was encouraged, in an attempt to test them during a quiet respiratory pattern.

The aerosol was inhaled from the holding chambers through a Respirgard-II MQ-303 filter (Marquest Medical Products), shown in figure 1. This filter offered low resistance to airflow and retained almost all of the budesonide. The latter was demonstrated in pilot studies in which less than 0.1% of the initial dose could be collected on a second filter placed behind the first filter. The pressure drop over the filter is 230 Pa at 60 L·min^{-1} (data on file). The filter holder added a dead space of

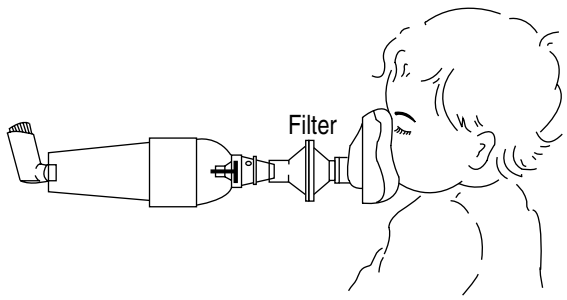

Fig. 1. – Filter which was interposed between the spacer inlet valve and the face-mask. The dose of aerosol collected on the filter was an estimate of the dose available for inhalation.

46 ml. The filter and filter holder were washed with ethanol to dissolve any retained drug, and the amount of budesonide recovered was determined by liquid chromatography using an internal standard (Astra Draco, Sweden). The coefficient of variation of the assay was 3%. The total amount of drug released to the child was estimated from the combined doses on the filter and filter holder.

Children younger than 4 yrs of age used a tight-fitting face-mask (Astra Meditec, Sweden) in order to avoid the inhalation bypassing the holding chamber through the nose or around the mouthpiece. Children aged 4–8 yrs inhaled directly from the mouthpiece of the filter.

Assessments

The minute volume and breathing frequency was measured by a Magtrak II respiratory monitor for 1 min whilst the child was wearing the face-mask. Inlet and outlet valves separated the expiration from the inspiration which passed through the respiratory monitor. Accordingly, only a dead space of 8 ml between the valves were added to the inspiratory line of the children. These measurements were made independently from the aerosol inhalation studies, but during the same clinic visits.

Lung function assessments were conducted with a Vitalograph Compact (Vitalograph Ltd, Buckingham, UK) whenever the child was willing to exert the necessary effort.

Statistical evaluation

The central tendency was represented by the age-group mean value and the scatter by the standard deviation (SD). The coefficient of variation (CoV) was calculated to illustrate the variation between children in the same age-group. Age-group mean values were compared by t-test, and the age-dependent changes by analysis of variance. The significance level was defined as p=0.05.

Study design

The study was performed in the summer of 1991 and designed as a single centre, single-blind, cross-over study. All patient handling was performed by the same person. The study was open to the patient and to the investigator

with regard to the devices and filters, but was blind to the analysing laboratory. The randomization code was not broken until all of the data had been analysed and a clean file had been declared by the study monitor, who also verified source data and drug accountability.

The study was performed in accordance with the Declaration of Helsinki and was accepted by the local Ethics Committee (KA91082). All parents gave their informed consent.

Results

A total of 164 children, aged between 6 months and 7 yrs, completed the study. There were 62 girls and 102 boys. Their minute volumes, breathing frequencies and tidal volumes are given in table 1. Another two children could not comply with the conditions.

The average $T_{1/2}$ of the dose of budesonide aerosol in the prototype small-volume steel holding chamber was longer than 30 s, compared with 9 s in a new large-volume plastic holding chamber (Nebuhaler®). The $T_{1/2}$ of the large-volume chamber, which had been primed with benzalkonium chloride, was comparable to that of the steel holding chamber.

The amount of budesonide contained in small droplets, the small particle fraction, was similar in the Nebuhaler® (60%) and the prototype device (69%).

The dose delivered to the mouth by the prototype metal holding chamber is depicted in figure 2, and it can be seen that no age-dependent change in the inhaled dose was found (p=0.84) in this device. A mean total dose of 38% of the nominal dose was obtainedby the whole group of children. The dose obtained from the Nebuhaler® (fig. 3) was significantly dependent on the age of the child (p<0.0001): children younger than 12 months received a mean dose of 19% of the nominal dose, while children ≥4 yrs received 42%. The doses delivered from the two devices in each age-group differed in the age-groups of 6 months to 1 year, 1–2 yrs, and 2–3 yrs. In each of these three age-groups, the doses obtained from the Nebuhaler® were significantly reduced compared to those from the prototype metal holding chamber (p<0.01 in each case). The relationships between age and the dose delivered from the two devices did not change if age was substituted with the height of the child.

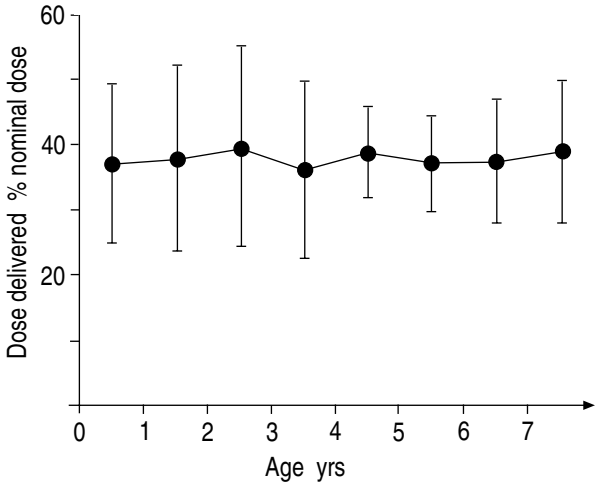

Fig. 2. – Dose of budesonide delivered to the mouth (% nominal dose) of children from a budesonide pressurized metered dose inhaler *via* a small volume (220 ml) holding chamber of steel with separate inlet and outlet valves. Data are presented as mean±SD.

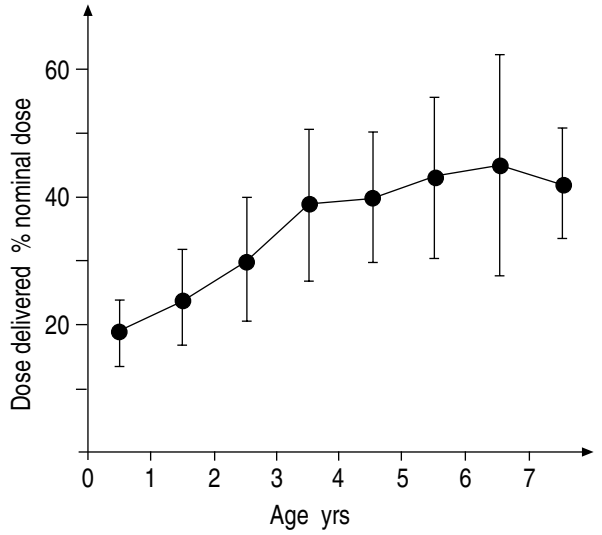

Fig. 3 – Dose of budesonide delivered to the mouth (% nominal dose) of children from a pressurized metered dose inhaler, *via* a large volume (750 ml) holding chamber of polycarbonate with one one-way valve (Nebuhaler®). The polycarbonate had been primed with benzalkonium chloride to minimize adsorption of aerosol to the polycarbonate holding chamber. Data are presented as mean±SD.

Table 1. – Biometric data of the study group of 164 young chldren

	Age-group yrs							
	0.5–1	1–2	2–3	3–4	4–5	5–6	6–7	7–8
Patients n*	12	25	20	15	26	26	23	17
Weight kg*	10.1±1.5	11.6±1.3	13.3±1.4	16.3±1.9	18.4±1.9	19.6±2.5	22.2±3.2	24.5±3.7
FEV_1 L*	-	-	-	-	-	1.0±0.2	1.2±0.3	1.5±0.2
V'_E L·min^{-1}*	4.8±1.1	4.6±1.6	4.3±1.7	4.4±1.6	6.3±2.5	5.9±2.6	6.8±2.4	6.7±3.1
f_R breaths·min^{-1}*	25±6	27±8	26±6	22±4	26±8	21±7	23±6	21±5
V_T L*	0.19±0.04	0.18±0.08	0.17±0.07	0.20±0.07	0.25±0.08	0.28±0.13	0.30±0.10	0.33±0.11
V_T ml·kg^{-1}	19	15	12	12	13	14	13	13

*: values are mean±SD. FEV_1: forced expiratory volume in one second; V'_E: minute ventilation; f_R: respiratory frequency; V_T: tidal volume.

Table 2. – Coefficient of variation (CoV) of dose delivered from two different holding chambers in different age-groups

	Age-group yrs							
	0.5–1	1–2	2–3	3–4	4–5	5-6	6–7	7–8
CoV%								
Nebuhaler®	29	32	32	30	25	25	34	17
Prototype	33	37	39	37	18	20	25	28

The variation in the dose delivered was similar in the two devices, as demonstrated by the CoV in each age-group (table 2). It is notable that the CoV seemed to improve in children ≥4 yrs, which also coincides with the group of children who used mouthpieces instead of face-masks.

Discussion

The prototype holding chamber described in the present study was cast in steel. This material does not carry an electrostatic charge and, therefore, does not attract aerosol droplets. Aerosol droplets generated from pMDIs are often electrically charged [9, 10] and, consequently, may be attracted electrostatically to the plastic surfaces of holding chambers. An antistatic lining of a plastic holding chamber was recently found to increase its output of sodium cromoglycate aerosol [10]. Similarly, in the present study, the $T_{1/2}$ of budesonide aerosol in the metal holding chamber (greater than 30 s) was longer than its $T_{1/2}$ in an unused plastic holding chamber (9 s). The difference between the holding chamber materials did not affect the size distribution of droplets.

Adherence of the aerosol to the chamber wall can be reduced by priming the plastic holding chamber. Repetitive use of pMDI with the holding chambers will have a priming effect (data on file), although this is difficult to predict and is liable to be changed with time and by cleaning procedures. Accordingly, it is important to consider from which material the holding chamber is manufactured, and, with respect to this, metal seems to be reliable in preventing the adsorption of aerosol droplets.

The volume of the metal prototype chamber was 220 ml, which was chosen to balance the limitation of the expected small tidal volumes of young children with the increased loss of aerosol in small holding chambers. A smaller holding chamber will contain a higher concentration of aerosol and will require less time to empty, but the total dose contained in airborne droplets is reduced as a result of impaction, adsorption, sedimentation and coagulation of the aerosol. *In vitro* studies of cromoglycate pMDI aerosol substantiated that young children would receive more drug in respirable droplets from small-volume holding chambers [11]. However, the tidal volumes observed in the children in the present study were considerably higher than those applied in *in vitro* models [11]. The standard literature references normally applied report tidal volumes of 7–9 ml·kg^{-1}, which remain unchanged after the neonatal period [12]. In this study, however, tidal volumes of 12–14 ml·kg^{-1} were measured in children aged 2–7 yrs, and even higher tidal volumes of 15–19 ml·kg^{-1} were found in children younger than 2 yrs. The respiratory monitor added no dead space since it was added to the inspiratory line, which was separated from the expiratory line by a valve of 8 ml dead space. It could be speculated that carbon dioxide accumulates in the face-mask used in children younger than 4 yrs and stimulates this apparent hyperventilation, although this is not consistent with an unchanged tidal volume in children of 2–3 yrs who used a face-mask and those of 4 yrs and older who used a mouthpiece. Nevertheless, given a minute volume above 4.3 L·min^{-1}, a holding chamber volume of 750 ml may be of minor influence on the dose-delivery *in vivo* even in young children.

The valve system of the prototype should allow the inspiratory flow to pass exclusively from the holding chamber to the child, and the expiratory flow to the exterior. The Nebuhaler® typifies the traditional holding chamber designed for use in adults and older children, and it is equipped with a single valve to the holding chamber and unguarded side holes to the exterior. During shallow breathing, the pressure changes generated may be insufficient to open and close the valve, and expiration may pass partly through the holding chamber, thus expelling some of the aerosol. Furthermore, during inspiration, the inhaled aerosol may be entrained by air inhaled through the unguarded side hole. In the present study, the Nebuhaler® holding chamber was held in its recommended horizontal position, which ensured optimal functioning of the valve. The plastic had been primed prior to use to eliminate the electrostatic property of the holding chamber as a confounding factor. The dose-delivery from the Nebuhaler® exhibited a profound and significant age-dependence: children ≥4 yrs obtained a dose of 42% of the nominal dose, which decreased to 19% in children younger than 12 months. This appears to be explained from the unreliable valve control of this holding chamber. In the prototype, inlet and outlet valves ensured unidirectional breathing from the holding chamber to the child and expiration to the outside. The dead space was minimized to less than 2 ml. Accordingly, the dose of 38% was delivered, irrespective of the age of the child.

The scatter of the dose-delivery was disappointing in both devices. In children younger than 4 yrs, who all used face-masks, the CoV ranged 29–37%. This scatter seemed to be reduced in older children, who used a mouthpiece. A close fit between the face-mask and the child's face was assured in each case, and could hardly explain the increased scatter in the younger children.

The delivery of pMDI aerosol from the devices available is poorly documented. Most of the applications have been studied by the demonstration of a clinical response to inhalations of a β_2-agonist. However, the β_2-agonist was administered in doses considerably above the minimal effective dose. The response is, therefore, not critically dependent on reproducible and effective drug delivery. However, the delivery of inhaled steroids requires a predictable and reproducible dose regardless of the age and co-operation of the child, and an optimal drug delivery with a major fraction of the aerosol in small droplets [8]. Better methods are, therefore, required to

evaluate these delivery devices. In the present study, the dose of budesonide deposited on a filter interposed between the holding chamber and the face-mask was regarded as the total dose available for inhalation by young children from these holding chamber systems. This is not a measure of the dose actually reaching the lungs, which would be influenced by several other factors, including the droplet profile, flow rate and airway diameter, as well as nasal *versus* mouth breathing. The dose deposited on the filter is, however, a measure of the total dose delivered to the child as an aerosol, though this may be an underestimate as a result of the influence of the dead space of the filter holder. This artefact could itself introduce an apparent age-dependent dose-delivery, since the dead space constitutes an increasing fraction of the tidal volume with decreasing age. However, no such relationship was observed from the prototype, which delivered a dose that was independent of age. The large minute volume, even in young children, is probably the reason for the lack of influence of the dead space of the filter.

In conclusion, the use of plastic for holding chambers may affect dose-delivery inadvertently, and the use of a single valve system in the control of the holding chamber may cause age-dependent dose-delivery. Reproducible drug delivery which is independent of the age of the child, however, may be obtained from an aerosol actuated from a pMDI and inhaled through the prototype device. This is a metal holding chamber of 220 ml, which is equipped with a face-mask fitted with inlet and outlet valves and minimized dead space. Such a holding chamber would improve the prospects of aerosol therapy for young children.

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References

1. Mallol J, Barrueto L, Girardi G, Toro O. Bronchodilator effect of fenoterol and ipratropium bromide in infants with acute wheezing: use of MDI with a spacer device. *Pediatr Pulmonol* 1987; 3: 352–356.
2. Conner WT, Dolovich BM, Frame RA, Newhouse MT. Reliable salbutamol administration in 6 to 36 month old children by means of a metered-dose inhaler and Aerochamber with mask. *Pediatr Pulmonol* 1989; 6: 263–267.
3. Yuksel B, Greenough A, Maconochie I. Effective bronchodilator treatment by a simple device for wheezy premature infants. *Arch Dis Child* 1990; 65: 782–785.
4. Kraemer R, Frey U, Sommer CW, Russi E. Short-term effect of albuterol, delivered *via* a new auxiliary device in wheezy infants. *Am Rev Respir Dis* 1991; 144: 347–351.
5. Bisgaard H, Munck SL, Nielsen JP, Petersen W, Ohlsen SV. Inhaled budesonide for treatment of recurrent wheezing in early childhood. *Lancet* 1990; 336: 649–651.
6. Noble V, Ruggins R, Everard ML, Milner AD. Inhaled budesonide for chronic wheezing under 18 months of age. *Arch Dis Child* 1992; 67: 285–288.
7. Connett GJ, Warde C, Wooler E, Lenney W. Use of budesonide in severe asthmatics aged 1–3 years. *Arch Dis Child* 1993; 69: 351–355.
8. Bisgaard H. Aerosol treatment of young children. *Eur Respir Rev* 1994; 4: 15–20.
9. Fry FA. Charge distribution on polystyrene aerosols and deposition in the human nose. *Aerosol Sci* 1970; 1: 135–146.
10. O'Callaghan C, Lynch J, Cant M, Robertson C. Improvement in sodium cromoglycate delivery from a spacer device by use of an antistatic lining, immediate inhalation and avoiding multiple actuations of drug. *Thorax* 1993; 48: 603–606.
11. Everard MI, Clark AR, Milner AD. Drug delivery from holding chamber with attached face-mask. *Arch Dis Child* 1992; 67: 580–585.
12. Polgar G, Weng TR. The functional development of the respiratory system: from the period of gestation to adulthood. *Am Rev Respir Dis* 1979; 120: 625–629.