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International Journal of Pharmaceutics 168 (1998) 147–152

international journal of pharmaceutics

Inertial sizing of aerosol inhaled during pediatric tidal breathing from an MDI with attached holding chamber

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Received 27 June 1997; received in revised form 27 January 1998; accepted 28 January 1998

Abstract

A procedure that allows cascade impaction to be used to measure the particle size distribution of the aerosol inhaled from a holding chamber with a square wave tidal breathing pattern is described. A constant flow rate of 28.3 l/min occurs through an Anderson impactor while tidal breathing occurs through the holding chamber by using a two-way valve system and a piston connected to a computer controlled stepper motor. Replicas of infant (7 months old) and child (4 years old) faces are used to allow collection of the aerosol at the entrance to simulated nostrils during tidal breathing at flow rates and tidal volumes near predicted values for these ages. Ventolin® and Beclovent® MDIs with the Space-Chamber® holding chamber (with infant or pediatric mask) are tested. Although significantly less drug ($P < 0.01$) is inhaled with the infant face replica than the child face replica or the adult-mouthpiece study of Finlay et al. (1997), these differences are largely due to differences in amounts inhaled in large particles, since no significant difference is found in the amount inhaled in particles < 2.1 μm for salbutamol or < 3.3 μm for beclomethasone between the infant, child or adult-mouthpiece results. These results indicate that caution may be needed when evaluating holding chambers using in vitro data on total mass inhaled, since differences can be caused by differences in large particles that do not contribute significantly to lung deposition.

Keywords: Spacer; Salbutamol; Beclomethasone; Infant; Child

1. Introduction

Metered dose inhalers (MDIs) are a convenient and well-used means of delivering therapeutic compounds to the lung for the treatment of respiratory disease. However, because of the need to coordinate inhalation with triggering of an MDI, holding chambers with masks are often attached to the MDI when used in a pediatric setting with patients approximately 4 years old and younger. In this way, children that are unable to consis-

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0378-5173/98/$19.00
PII S0378-5173(98)00059-3

tently perform a controlled, single-breath maneuver upon actuation of the device can instead perform tidal breathing through the device.

Because of the large number of different holding-chamber/MDI combinations and differences in the performance of each combination with different formulations (Ahrens et al., 1995; Barry and O'Callaghan, 1996), in vitro assessment of such devices is often done to help narrow the field for clinical efficacy studies. However, the aerosol inhaled from a holding chamber during pediatric tidal breathing can be expected to be different from the aerosol inhaled from the same holding chamber with a typical adult single breath. Such differences arise because of differing amounts of gravitational and electrostatic deposition in the chamber due to differing residence times, as well as differing amounts of impaction on valves due to different flow rates through the device. Thus, although many in vitro studies have been done to characterize the aerosol emitted by various holding chambers at constant flow rates typical of adults, such studies cannot be used to infer the characteristics of these devices during pediatric tidal breathing. For these reasons, holding chambers intended for pediatric use have been evaluated in vitro by various authors (Everard et al., 1992; Bisgaard, 1995; Bisgaard et al., 1995) by connecting a filter to the device and determining the amount of drug inhaled from various different holding chambers with different MDI formulations during pediatric tidal breathing. However, such studies do not provide any information on particle sizes that may occur from the device. This is unfortunate, since particle size is a major determinant of lung deposition of an inhaled aerosol.

Two difficulties have prevented this desired particle sizing from being done: (1) flow rates associated with young pediatric patients are much lower than the flow rates of commonly used inertial sizing methods, such as impingers or impactors, precluding previous authors from using these devices to measure particle size at pediatric inhalation flow rates, and (2) such sizing methods require a constant flow rate and cannot be used directly with a cyclic breathing pattern. Recently, Wildhaber et al. (1996) have partially addressed the first of these difficulties by measuring particle sizes from a number of holding chambers at a reduced flow rate through a multistage liquid impinger. However, the low flow rate through their impinger prevented them from obtaining data on differences in particle sizes in the respirable range, allowing only differences in amounts collected in all particles $< 9.6\ \mu$m to be obtained. In the present work a procedure is described that overcomes the two above mentioned difficulties, and is applied to measure particle sizes using an Anderson cascade impactor and a new holding chamber, the Space-Chamber® (Medical Developments, Melbourne, Australia). The Space-Chamber has a volume of 250 ml and is constructed of polycarbonate. Data is obtained for salbutamol and beclomethasone MDIs with attached Space-Chambers and two different simulated pediatric breathing patterns.

2. Materials and methods

The apparatus shown in Fig. 1 was used to allow a square wave tidal breathing pattern to occur through a holding chamber while the inhaled aerosol was collected at a constant flow rate of 28.3 l/min into an Anderson Mark II cascade impactor (Graseby Anderson, Smyrna, GA). Dur-

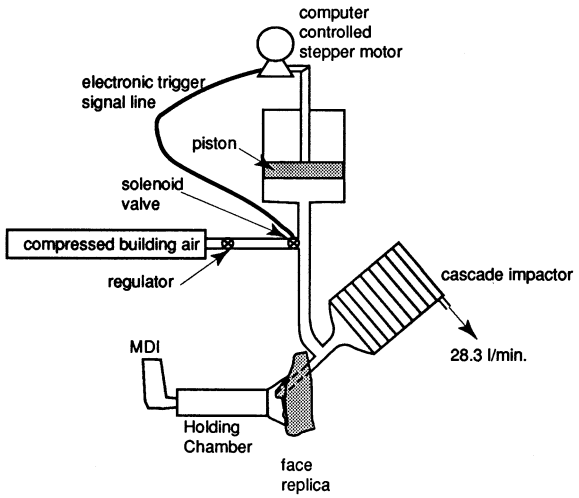

Fig. 1. Schematic drawing of apparatus used to supply square wave tidal breathing to holding chamber while a constant flow rate of 28.3 l/min flows to the cascade impactor.

ing simulated inhalation at a flow rate of Q l/min, the two-way solenoid valve (Asco Electric, Brantford, Ont.) remained open with the adjustable regulator on the building air supplying 56.6 l/min, the piston drawing $28.3 + Q$ l/min, and the cascade impactor drawing 28.3 l/min, resulting in inhalation through the holding chamber at Q l/min. During exhalation at the same flow rate Q, the solenoid valve remained closed, the impactor drew 28.3 l/min and the piston pushed $28.3 + Q$ l/min into the three-way tee, resulting in exhalation through the holding chamber at Q l/min. No inspiratory or expiratory pauses were used. The two-way solenoid valve was triggered electronically by a signal from the stepper motor controller when the piston switched direction. The flow rates in the impactor and through the holding chamber during tidal breathing simulation were measured using a calibrated in-house venturi flow meter to determine whether fluid transients caused time-dependent deviations from the desired flow rates. Inhaled volume during each cycle was found to deviate by less than 5 ml from its desired value at all times during the breathing cycles used here, indicating transient flows were negligible.

In order to provide an appropriate connection volume between the mask on the holding chamber and the cascade impactor, face replicas approximating the faces of children aged 7 months (hereafter to referred to as the infant face replica) and aged 4 years (hereafter referred to as the child face replica) were sculpted using quick dry clay and live subjects as models. The replicas were enameled and varnished to allow washing and collection of residues from them. A cylindrical plastic plug (drawn schematically as dashed lines in Fig. 1) containing two small, cylindrical metal tube inserts running the length of the plug was placed behind the face replica where the nasal cavity would be. The cylindrical metal inserts extended through the face replica, having their entrance located such that they mimicked the diameters and location of the entrance to the nostrils. The cylindrical plastic plug containing the metal tube inserts was inserted inside copper tubing and joined via a copper tube T-connection to the impactor and wall air/breathing machine flows. Total connection volume between the 'nostril' entrance of the cylindrical metal tube inserts and the entrance to the cascade impactor airstream was less than 3 ml, which is neglibible compared to the connection volume inside the face mask between the face and holding chamber.

A tidal volume of $V_t = 75$ ml, and equal inhalation/exhalation flow rates of $Q = 4.8$ l/min were used with the infant face replica, while $V_t = 230$ ml and $Q = 11.1$ l/min were used with the child face replica. These values are near predicted values for the ages of children on which the face replicas were based (Taussig et al., 1977; ATS/ERS, 1993).

All flow rates were turned on prior to attaching the Space-Chamber holding chambers to the face replica. The Space-Chamber face masks (Pari, Mississauga, Ont.) were attached to the face replicas with modelling compound to ensure a tight seal. Infant face masks (part no. 44B7222) were used with the infant face replica, while pediatric face masks (part no. 44B7223) were used with the child face replica. After attaching the MDI and Space-Chamber holding chamber to the face mask, the MDI was then actuated into the holding chamber while tidal breathing was occurring, in order to simulate patient use. The holding chamber was removed from its face mask after five complete breaths and connected through a filter (# 303, Marquest, Englewood, CO) to a separate vacuum pump to remove all remaining suspended aerosol from it. We will refer to this filter as the waste filter. This procedure was repeated at 30-s intervals ten times with salbutamol (100 μg per actuation, Ventolin®, Glaxo-Wellcome) and 15 times with beclomethasone (50 μg per actuation, Beclovent®, Glaxo Wellcome). The entire procedure was repeated with each of three different Space-Chamber holding chambers with the two different sized face masks and face replicas.

When not being used for testing, the MDIs were stored horizontally on their side. Immediately prior to testing, five shots were fired to waste from the MDI well away from the test apparatus. The MDI was shaken between all shots fired. Prior to use, all holding chambers were washed first with dish soap and water, then with distilled water and finally with methanol, to ensure no

Table 1
Amounts of drug collected in different locations, normalized to one actuation, with standard deviation in brackets are shown for the various delivery combinations for salbutamol (100 μm/actuation) and beclomethasone (50 μg/actuation)

Delivery specifics	Total collected	Impactor	Fine particle		
			<4.7 μm	<3.3 μm	<2.1 μm
Salbutamol: 7 months old	99.7 (2.0)	23.9 (2.3)	23.9 (2.3)	22.5 (2.1)	15.3 (0.7)
Salbutamol: 4 year old	98.8 (2.5)	34.6 (2.6)	32.8 (3.1)	30.0 (2.2)	18.4 (1.5)
Salbutamol: Finlay et al. (1997)	99.88 (0.82)	46.9 (1.0)	46.87 (0.97)	40.37 (0.89)	16.81 (1.19)
Beclomethasone: 7 months old	50.5 (1.1)	11.6 (1.2)	10.3 (0.3)	8.3 (0.2)	5.7 (0.4)
Beclomethasone: 4 year old	50.3 (0.3)	18.2 (1.4)	15.3 (1.2)	12.1 (1.3)	8.8 (1.3)
Beclomethasone: Finlay et al. (1997)	50.09 (0.31)	18.7 (1.4)	15.74 (1.29)	10.88 (1.62)	6.69 (1.32)

Data obtained by Finlay et al. (1997) for adult-mouthpiece Space-Chambers tested at a constant flow rate of 28.3 l/min is included for reference.

contaminants were present in the spectrophotometric analysis. Following washing, the chambers were allowed to air dry.

The amount of drug depositing on the face replicas, in the metal tubes connecting the nostril entrance to the impactor flow entrance, on the waste filter used to remove aerosol from the holding chamber between shots, and on the different stages of the impactor was assayed using UV spectrophotometery (model 8452A, Hewlett-Packard, Mississauga, Ont.). Drug was washed from the different locations using 0.01 N NaOH for salbutamol, and methanol for beclomethasone. UV analysis was performed at 238 nm for beclomethasone and 244 nm for salbutamol.

All tests were done at room temperature under ambient conditions of $50 \pm 10\%$ RH, as measured with a hygrometer (Fisher, Ont.).

Statistical analysis of the results was done using ANOVA (using SYSTAT, SYSTAT, Evanston, IL), with Tukey HSD multiple means comparisons used to determine which delivery methods differed significantly. Differences were deemed significant at a P-value of 0.01, unless otherwise stated.

3. Results

Amounts of drug collected in various locations are shown in Table 1. Amounts collected on the face replicas, the waste filter and in the tubing connecting the 'nostrils' to the impactor airstream were negligible (<1 μg on average) and are not shown in Table 1. Also included in Table 1 for reference are the amounts collected by Finlay et al. (1997) with five Space-Chambers (adult-mouthpiece model) connected to an Anderson impactor at a flow rate of 28.3 l/min for 8 s with the same drug formulations used here. Mitchell and Nagel (1997) report values for drug inhaled onto filters from Space-Chambers during simulated pediatric tidal breathing that are much smaller than those given here. This difference is probably due to the use of a newer valve design in the Space-Chambers used in the present study.

Differences between total amounts collected using either of the face replicas or by Finlay et al. (1997) (using Space-Chambers with adult-mouthpieces, or using MDIs alone) are not statistically significant for either salbutamol or beclomethasone.

The amounts of salbutamol collected on the impactor and in particles with aerodynamic diameter <4.7 or <3.3 μm differ significantly between the two face replicas as well as between either face replica and the adult-mouthpiece data of Finlay et al. (1997). Differences between amounts collected in particles with aerodynamic diameter <2.1 μm between the three salbutamol delivery methods shown in Table 1 are not statistically significant.

For beclomethasone, statistically significant differences occur in the amount collected on the

impactor and in particles < 4.7 μm between the infant face replica and either the child face replica or the adult-mouthpiece data of Finlay et al. (1997). No other differences in Table 1 reach statistical significance for beclomethasone.

Fig. 2 shows the cumulative size distributions for salbutamol, obtained from amounts collected on the impactor stages with the two face replicas. Also shown for reference is the size distribution data obtained by Finlay et al. (1997) using adult-mouthpiece Space-Chambers. The mass median aerodynamic diameter (MMAD) for the infant face replica (1.8 μm) is significantly smaller than for the child face replica (2.0 μm), and both of these are significantly smaller than the adult-mouthpiece data of Finlay et al. (1997) (2.4 μm). For each stage of the impactor, significant differences occur in either cumulative % mass or % mass collected among the three delivery methods shown in Fig. 3.

Fig. 3 shows cumulative mass distributions for beclomethasone. Significant differences ($P < 0.05$) in MMAD occur only between the infant face replica (2.1 μm) and the adult-mouthpiece data of Finlay et al. (1997) (2.9 μm). The child face replica gives an MMAD of 2.2 μm, which does not differ statistically from either the infant face replica or Finlay et al. (1997). For each stage of the impactor, significant differences occur in either cumulative % mass or % mass collected among the three delivery methods shown in Fig. 3.

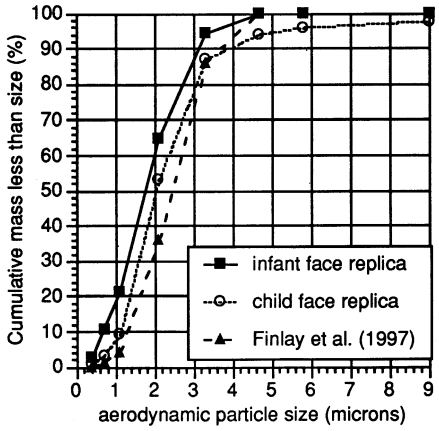

Fig. 2. Particle size distribution as determined by cascade impaction for salbutamol with the two face replicas (each data point is the average of three measurements). Data from Finlay et al. (1997) using adult-mouthpiece Space-Chambers at 28.3 l/min is included for reference.

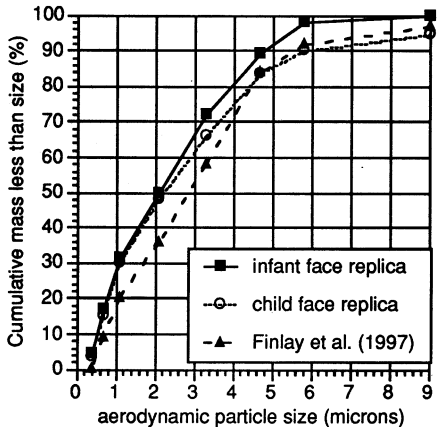

Fig. 3. Particle size distribution as determined by cascade impaction for beclomethasone with the two face replicas (each data point is the average of three measurements). Data from Finlay et al. (1997) using adult-mouthpiece Space-Chambers at 28.3 l/min is included for reference.

4. Discussion

Our results indicate that significantly less salbutamol was inhaled with the infant face replica (24% of label claim) than the child face replica (33% of label claim), and that both face replicas inhaled significantly less than in the adult-mouthpiece study of Finlay et al. (1997) (47% of label claim). These results can be explained by differences in deposition of aerosol in the holding chamber due to differences in residence time of the aerosol in the holding chamber prior to inhalation (caused by the different tidal volumes and flow rates).

Similar differences in total inhaled drug are observed with beclomethasone, with the infant face replica giving significantly less drug (23% of label claim). However, in contrast with salbutamol, the child face replica inhaled essentially the same amount of drug as in the adult-mouthpiece study of Finlay et al. (1997) (36 vs. 37% of label claim). This difference from salbutamol may be

explained by the larger particle size of the beclomethasone aerosol, so that impaction on valves in the holding chamber may limit the amount of beclomethasone inhaled at the much higher flow rate of Finlay et al. (28.3 l/min).

For both beclomethasone and salbutamol it is interesting to note that the differences in inhaled drug between the infant, child and adult-mouthpiece cases in Table 1 are caused by differences in the amount inhaled in larger particle sizes, since we find no signifance to the difference in amounts inhaled in particles < 3.3 μm for beclomethasone or < 2.1 μm for salbutamol. The size distributions in Figs. 2 and 3 confirm this conclusion, showing that the inhaled aerosol increases in size in progression from the infant face replica to the child face replica to the adult-mouthpiece data of Finlay et al. These results are expected, since increasing residence times will cause gravitational and electrostatic deposition to preferentially increase for larger particle sizes. However, these results also indicate that caution may be needed when making inferences on holding chamber performance from data on amounts of drug inhaled onto filters, since differences in inhaled drug can be largely caused by differences in amounts inhaled in larger particle sizes that may not contribute significantly to lung deposition.

The relatively small amounts of drug collected on the waste filter (used to evacuate the aerosol from the holding chamber between consecutive tests) indicates that taking more than the five breaths used here would not likely result in significantly larger amounts of inhaled drug.

The small amounts of drug collected on the face replicas indicates that impaction of aerosol on the face replicas or the nostril entrances is unimportant. This agrees with data in the industrial hygiene literature (Vincent, 1995) on the inhalability of aerosols near the size seen here. This indicates that less accurate representation of the facial features may be adequate in performing experiments like those done here. However, the connection volume between the surface of the face and the holding chamber mask, as well as the distance between the exit of the holding chamber and the 'nostrils' or mouth, should be as close to that expected in vivo, otherwise differences in the rebreathing of this connection volume may cause differences between in vitro and in vivo results.

Acknowledgements

The laboratory help of H. Orszanska, T. Gear and B. Hennig and the financial support of the Allergy and Asthma Teaching Unit, Vancouver, B.C., the Alberta Lung Association, and the Canadian Cystic Fibrosis Foundation (summer studentship) is gratefully acknowledged.

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