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Extra-Fine Particles Improve Lung Delivery of Inhaled Steroids in Infants*

A Study in an Upper Airway Model

Hettie M. Janssens, MD, PhD; Johan C. de Jongste, MD, PhD; Wim C. J. Hop, MD, PhD; and Harm A. W. M. Tiddens, MD, PhD

Background: **The particles of a new hydrofluoroalkane-134a (HFA)-beclomethasone dipropionate (BDP) metered-dose inhaler (Qvar; 3M Pharmaceuticals; St. Paul, MN) are considerably smaller than those of chlorofluorocarbon (CFC)-BDP. This may improve lung deposition in infants who inhale nasally and have irregular breathing patterns and small airways.**
Aim: **To compare the dose delivered to the lungs of HFA-BDP and CFC-BDP at different breathing patterns using an upper airway model of an infant.**
Methods: **An anatomically correct upper airway model of a 9-month-old child with an open nasal airway was connected to an impactor and breathing simulator. HFA-BDP, 100 μg, and CFC-BDP, 100 μg, were delivered to the model through a detergent-coated, small-volume spacer. The total dose leaving the model (lung dose), its particle size distribution, and median mass aerodynamic diameter (MMAD) were assessed during simulated tidal breathing with tidal volumes (VTs) of 50 mL, 100 mL, and 200 mL, and 30 breaths/min. Dose was expressed as percentage of nominal dose.**
Results: **Lung doses for HFA-BDP were 25.4%, 26.5%, and 30.7% compared with 6.8%, 4.8%, and 2.1% for CFC-BDP at VTs of 50 mL, 100 mL, and 200 mL, respectively. The dose of particles < 2.1 μm to the lung for HFA-BDP was 23 to 28% compared with 0.6 to 0.8% for CFC-BDP. The lung dose of CFC-BDP mainly consisted of particles between 2.1 μm and 4.7 μm. MMAD for HFA-BDP was 1.2 μm, and 2.6 to 3.3 μm for CFC-BDP depending on VT. The lung dose for CFC-BDP decreased significantly with increasing VT. HFA-BDP lung dose did not alter significantly with VT.**
Conclusions: **In this infant model study, the use of HFA-BDP with a high dose of particles < 2.1 μm improves the dose delivered to the lungs substantially. Furthermore, the large proportion of extra-fine particles in HFA-BDP results in lung doses less dependent on breathing pattern compared with CFC-BDP.** ***(CHEST 2003; 123:2083–2088)***

Key words: aerosol deposition; airway model; beclomethasone; hydrofluoroalkane; infants; metered-dose inhalers

Abbreviations: BDP = beclomethasone dipropionate; CFC = chlorofluorocarbon; EFPD = extra-fine particle dose; FPD = fine particle dose; HFA = hydrofluoroalkane-134a; MMAD = median mass aerodynamic diameter; pMDI = pressurized metered-dose inhaler; SAINT = Sophia Anatomical Infant Nose-Throat; VT = tidal volume

Inhaled steroids have been shown to reduce symptoms in infants with wheezing.[1] A convenient way to administer inhaled steroids to the lungs of infants is by a pressurized metered-dose inhaler (pMDI) combined with spacer and attached face mask[2]; however,[1] only a small proportion of the administered dose is deposited in the lungs of young children,[3,4] and the inhaled dose is highly variable.[5] The replacement of chlorofluorocarbons (CFCs) by ozone-friendly propellants, such as hydrofluoroalkane-134a (HFA), has been an opportunity to revise the delivery properties of pMDIs.[6] The new HFA-beclomethasone dipropionate (BDP) [Qvar; 3M

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Pharmaceuticals; St. Paul, MN] has a large proportion of small particles compared with conventional formulations. This has been shown to result in a higher and a more peripheral lung deposition in adults.[7] There are reasons to believe that these small particles may also be beneficial for treatment of infants. Firstly, infants inhale aerosols mainly nasally.[8] Small particles are more likely to bypass the nose and to be deposited in the lungs compared with larger particles.[9] Secondly, infants may not cooperate during the administration procedure, leading to crying or irregular and fast breathing while inhaling the aerosol. Crying and high inspiratory flow rates have been shown to result in decreased lung deposition,[4,10] with only small particles reaching the lungs.[11] Thirdly, the narrow airways of infants are characterized by high-velocity and turbulent airflow causing increased deposition of particles in the proximal airways.[12,13] Small particles are more likely to reach the peripheral airways.[14] Dose delivered to the lungs of the new HFA-BDP has not yet been studied in infants. Lung deposition studies in infants using radiolabeled aerosols are difficult to perform and subject to ethical discussion.[15] To facilitate aerosol research in relation to young children, we recently developed an anatomically correct model of the upper airways of an infant.[16] The dose passing through this model, which includes the face, nasal cavity, and larynx the subglottic region, was shown to compare well with available *in vivo* lung deposition data.[4,11,17,18] We hypothesized that HFA-BDP would deliver a substantially higher dose to the lungs with less dependence on breathing pattern or inspiratory flow rate, compared with CFC-BDP.

Materials and Methods

Upper Airway Model

A model of the upper airways of an infant was used for the aerosol deposition measurements. This model, the Sophia Anatomical Infant Nose-Throat (SAINT) model, was extensively described elsewhere.[16] In short, the SAINT model is a CT scan-derived, stereolithographically made, anatomically correct model of the upper airways of a 9-month-old infant. The model includes the face, nasal cavity, and pharynx to the subglottic region. The nasal airway is open for air passage; the oral airway is closed. To mimic sticky mucosa and to eliminate any electrostatic charge present on the inner surface of the model, the inner surface of the model is coated with a thin layer of glycerol/Brij-35 (polyoxyethylene 23 laurylether) mixture by pipetting 4 mL into the model and allowing the excess fluid to drip out.

pMDI/Spacer

Two pMDIs containing BDP were tested. HFA-BDP (Qvar) was compared with CFC-BDP (Becotide; GlaxoWellcome; Uxbridge, UK). Before testing, the pMDIs were primed by shaking and firing 10 waste puffs. The pMDIs were used in combination with a small-volume plastic spacer (Aerochamber; Trudell Medical; London, Canada). The spacer was used with the infant facemask as provided by the manufacturer. Electrostatic charge can develop on the inner surface of a plastic spacer, which decreases drug delivery by retaining the drug in the spacer.[19] To reduce the electrostatic charge of the spacer, it was coated with household detergent. Several hours before use, the spacer was washed in diluted detergent and subsequently left to drip dry. Detergent coating has been shown to reduce electrostatic charge on the inner surface of the spacer.[20,21]

Experimental Set-up

The SAINT model was connected to a breathing simulator (Pari Sinus Breathing Simulator; Pari GmbH; Starnberg, Germany) and an Andersen 8-stage cascade impactor (Graseby Andersen; Smyrna, GA) by means of a three-way glass connection (Fig 1). A constant flow of 28.3 L/min through the impactor was balanced with an inflow of 28.3 L/min through the glass connection, resulting in zero flow through the model. When the breathing simulator was switched on, there was simulated tidal breathing through the model and a constant flow through the impactor. This set-up has been previously described and validated.[22,23] Lung dose was defined as the total dose leaving the SAINT model, expressed as a percentage of nominal dose. Fine particle dose (FPD) was defined as the mass of the lung dose in particles < 4.7 μm (impactor stage 3 to 8) expressed as a percentage of nominal dose. Extra-fine particle dose (EFPD) was defined as the mass of the lung dose in particles < 2.1 μm (impactor stage 5 to 8) expressed as a percentage of nominal dose. Particle size of lung dose was expressed as median mass aerodynamic diameter (MMAD).

Breathing Simulation

Aerosol delivery was tested at various tidal volumes (VTs) using sinusoidal tidal breathing patterns with the following settings for the breathing simulator: respiratory duty cycle (inspiratory time/total respiratory cycle time) of 0.42, and VTs of 50 mL, 100 mL, and 200 mL with fixed respiratory rate of 30 breaths/min. A respiratory duty cycle of 0.42, VT of 100 mL, and respiratory rate of 30 breaths/min are in accordance with reference values appropriate for the age of the subject used to construct the model.[24] Measurements for each VT were done three times in a randomized order.

Study Procedure

The SAINT model was attached to the clean impactor, and the breathing simulator was started. The pMDI/spacer with facemask was shaken and placed on the face of the model, ensuring an airtight fit using therapeutic putty (Carters; Westbury, UK). Within 5 s of being shaken, one puff of HFA-BDP or CFC-BDP was actuated into the spacer just before the start of an inspiration. Aerosol was drawn from the spacer during 30 s of simulated tidal breathing. Ten separate puffs were actuated for each impactor measurement to get detectable amounts of drug on the impactor plates. The experiments were performed in ambient conditions with 30 to 40% humidity.

Drug Analysis

Drug on the impactor plates and glass connection was dissolved in ethanol containing an internal standard (fluocinolone acetonide). BDP was quantified using a validated high-perfor-

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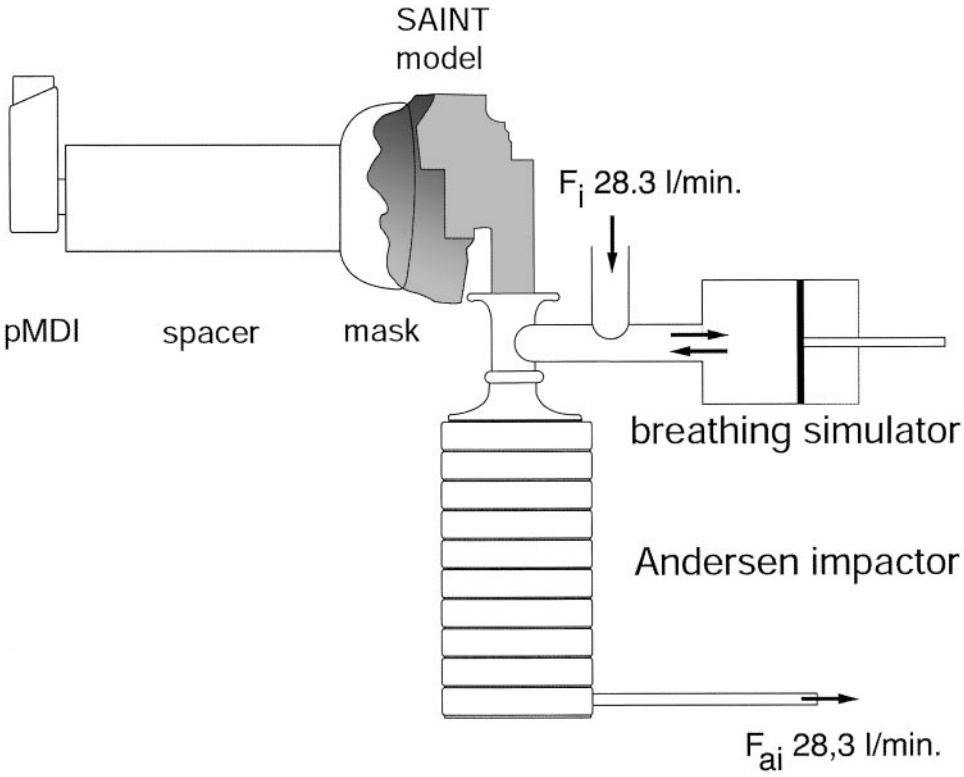

FIGURE 1. Experimental set-up used to measure lung dose and particle size from pMDI/spacer during simulated tidal breathing. The breathing simulator supplied tidal breathing through the SAINT model and pMDI/spacer with a constant flow of 28.3 L/min through the impactor (Fai), balanced by an inflow (Fi) of 28.3 L/min. A three-way glass connection attached all the parts together.

mance liquid chromatography method, comprising an ethanol: water (43:57) mobile phase and a Supelcosil LC-18 column (5 μm particles; 5 × 0.46-cm inner diameter). The coefficient of variation of the method was < 3%.

Statistical Analysis

The amount of BDP found is expressed as a percentage of nominal dose. Results shown are means (± SEM). Comparisons between dose delivery from HFA-BDP and CFC-BDP were tested using an independent-sample *t* test for each VT. The following variables were tested: lung dose, FPD, EFPD, and MMAD. The correlations between VT and these variables were investigated using Pearson correlation coefficients. Analysis of covariance was used to show differences between the relationships of HFA-BDP and CFC-BDP deposition variables with VT. Statistical significance was set at $p \leq 0.05$.

RESULTS

Results for lung dose are shown in Figure 2A. Lung doses for HFA-BDP were 25.4% (2.0), 26.5% (3.6), and 30.7% (0.5) compared with 6.8% (1.1), 4.8% (0.7), and 2.1% (0.1) for CFC-BDP at VTs of 50 mL, 100 mL, and 200 mL, respectively. The differences between HFA-BDP and CFC-BDP were highly significant ($p < 0.001$) for all VTs. Furthermore, the lung dose of HFA-BDP did not significantly depend on VT, whereas lung dose of CFC-BDP showed a significant decrease with increasing VT.

Results for FPD (particles < 4.7 μm) are shown in Figure 2B. FPDs for HFA-BDP lung dose were 24.1% (1.9), 24.5% (2.7), and 28.7% (0.5) compared with 5.8% (1.0), 4.4% (0.6), and 1.9% (0.1) for CFC-BDP at VTs of 50 mL, 100 mL, and 200 mL, respectively. The differences between HFA-BDP and CFC-BDP were highly significant for all VTs ($p < 0.001$). Furthermore, FPD of HFA-BDP did not significantly depend on VT, whereas FPD of CFC-BDP showed a significant decrease with increasing VT.

Results for EFPD (particles < 2.1 μm) are shown in Figure 2C. EFPDs for HFA-BDP lung dose were 23.6% (1.9), 23.5% (3.1), and 28.3% (0.5) compared with 0.8% (0.2), 0.6% (0.3), and 0.6% (0.1) of CFC-BDP at VTs of 50 mL, 100 mL, and 200 mL, respectively. The differences between HFA-BDP and CFC-BDP were highly significant ($p < 0.001$). EFPD of HFA-BDP and of CFC-BDP showed no significant correlation with VT.

Results for MMAD of lung dose are shown in

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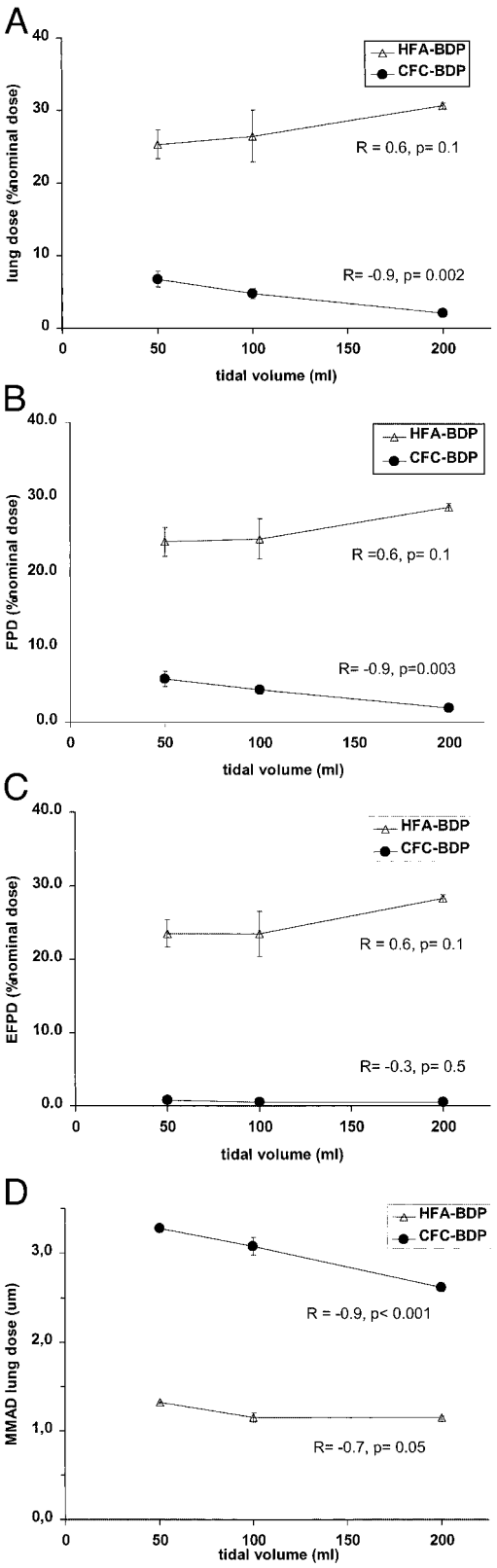

FIGURE 2. Comparison of aerosol deposition measurements in SAINT model with HFA-BDP and CFC-BDP in relation to VT. Results are mean (SEM) of three measurements. *A*, Lung dose; *B*, FPD (< 4.7 μm); *C*, EFPD (< 2.1 μm); *D*, MMAD. $p < 0.001$ for differences between HFA-BDP and CFC-BDP at all VTs.

Figure 2D. MMADs of HFA-BDP were 1.3 μm (0.03), 1.1 μm (0.1), and 1.1 μm (0.05) compared with 3.3 μm (0.01), 3.1 μm (0.05), and 2.6 μm (0.02) of CFC-BDP at VTs of 50 mL, 100 mL, and 200 mL, respectively. The differences between HFA-BDP and CFC-BDP were highly significant ($p < 0.001$). MMAD of CFC-BDP showed a significant decline with increasing VT, whereas this decline was small and borderline significant for the HFA-BDP.

Calculations of the separate regression lines for both HFA-BDP and CFC-BDP showed that the slopes were significantly different ($p \leq 0.008$), for lung dose, FPD, and MMAD, but not for EFPD. This means that the relationships with VT significantly differed between HFA-BDP and CFC-BDP except for EFPD.

DISCUSSION

We studied the relation between lung dose and particle size for HFA-BDP and CFC-BDP delivered by pMDIs with a spacer device at different VTs in an anatomically correct upper airway model of an infant. The lung dose of HFA-BDP was 3.5-fold to almost 15-fold higher compared with CFC-BDP for different VTs. Furthermore, the lung dose of HFA-BDP was independent of VT, whereas the lung dose of CFC-BDP showed a significant decrease with increasing VT. The lung dose of HFA-BDP consisted mainly of particles < 2.1 μm, whereas the lung dose of CFC-BDP consisted mainly of particles between 4.7 μm and 2.1 μm.

Our study is in agreement with previous lung deposition studies using radiolabeled aerosols in adults, where lung deposition was up to 10-fold higher with HFA-BDP pMDI compared with CFC-BDP, when used without a spacer.[7] The lung dose found using the SAINT model of approximately 30% for HFA-BDP is in line with a study[25] measuring lung deposition of radiolabeled HFA-BDP in children. Lung deposition of 41%, 45%, and 54% of metered dose was found for children 5 to 7 years old, 8 to 10 years old, and 11 to 14 years old, respectively, when inhaling HFA-BDP via an Autohaler (3M Pharmaceuticals).[25] That we found a lower dose can be explained first by the fact that we used a spacer, and second by the younger age of the child used for the model compared with the age of the children in the deposition study. The older children inhaled with a single breath via the mouth, whereas the model inhaled through the nose during tidal breathing, which is the usual situation for a 9-month-old child. Infants preferably breathe through the nose, whether the mouth is open or not, as shown in a radiolabeling study by Chua et al.[8] Inhalation

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through the nose reduces the amount of drug delivered to the lungs.[8] In addition, with tidal breathing some of the aerosol is lost with exhalation, as there is no breath-holding. Furthermore, the expression of lung deposition as a percentage of metered dose (or ex-valve dose) is likely to result in a slightly higher value than when expressed as a percentage of nominal dose (or label claim). Studies testing radiolabeled CFC-salbutamol pMDI (Ventolin; GlaxoWellcome; Research Triangle Park, NC) used with an Aerochamber found lung depositions of 0.67% for preterm infants[3] and 1.97% for children < 5 years of age.[4] These deposition data are comparable with, respectively, the EFPD and FPD found with the CFC-BPD. Our results suggest that the HFA-BDP, due to smaller particles, will give a considerable higher lung dose in infants than CFC formulations with the same spacer.

Although the lung doses found with our model reasonably correspond with *in vivo* data, the data should still be considered as *in vitro* data. The aerosols were administered in optimal conditions, with idealized breathing patterns. Additionally, differences in upper airway geometry between children are likely to result in different lung deposition for a given pMDI/spacer combination. Therefore, the data found with the model should be considered as estimations of the *in vivo* situation. The relative differences are more informative than the absolute values.

Lung dose of HFA-BDP was not dependent on VT, whereas lung dose of CFC-BDP decreased rapidly with increasing VT. With increasing VT, peak inspiratory flow rate increases. It has been shown in adults that fast inhalation leads to lower lung deposition compared with slow inhalation.[26] Flow will have a turbulent pattern with high inspiratory flow rate in the narrow upper airways. As a result, coarse particles are more likely to deposit in the upper airways by inertial impaction, and thus lung dose will be lower. This appears not to be the case for the EFPD of CFC-BDP and HFA-BDP, which is largely independent of breathing pattern. Since 90% of the lung dose of HFA-BDP consists of particles < 2.1 μm, the lung dose is less dependent on breathing pattern compared with CFC-BDP. Only 13% of the lung dose of CFC-BDP has particles < 2.1 μm.

The lung dose in our model indicates the dose delivered beyond the subglottic level. It does not give information on the distribution of drug in the lower airways; however, particle size gives an indication on where the aerosol may deposit, as it has been shown in several theoretical and clinical aerosol deposition models that small particles deposit more peripherally in the airways than larger particles.[27] A lung deposition study[7] in adults showed that the distribution of HFA-BDP was more peripheral in the lungs compared with CFC-BDP. The relation between particle size and deposition pattern is not known for infants. It is likely that the high EFPD of the HFA-BDP will improve peripheral deposition in infants.

The clinical consequences of the improved aerosol characteristics might be considerable. A high lung dose which is independent of breathing pattern may be an advantage for children who are not cooperative during the administration of aerosol. It has been shown that crying reduces lung deposition from a pMDI/spacer to almost zero.[10] Almost 50% of young children are not cooperative during the administration procedure.[5] These children might benefit from HFA-BDP for control of asthma symptoms. With the increased lung dose in infants and potential for improved lung distribution, it is expected that the daily dose of HFA-BDP needed to control asthma symptoms will be substantially reduced compared with CFC-BDP. In adults with asthma, it was shown that the dose of HFA-BDP could be reduced 2.6 times to obtain the same improvement in lung function as with CFC-BDP.[28] Clinical efficacy studies are needed to assess the lowest effective dose of HFA-BDP in infants.

In conclusion, aerosol deposition tests using the SAINT model and simulated breathing show that HFA-BDP with a spacer gives substantially higher lung doses than CFC-BDP with a spacer. Furthermore, the large proportion of EFPDs in HFA-BDP results in lung doses less dependent on breathing pattern compared with CFC-BDP. Further research is needed to show that HFA-BDP improves treatment efficacy in infants.

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