The Delivery of Chlorofluorocarbon-Propelled Versus Hydrofluoroalkane-Propelled Beclomethasone Dipropionate Aerosol to the Mechanically Ventilated Patient: A Laboratory Study

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We describe a laboratory investigation comparing the delivery of chlorofluorocarbon (CFC)- and hydrofluoroalkane (HFA)-formulated beclomethasone dipropionate (BDP) by metered-dose inhaler and holding chamber (AeroChamber HC MV) in a simulation of a mechanically ventilated adult patient. METHODS: We equipped each HC MV ($n = 5$) with an 8.0 mm diameter endotracheal tube (ETT), locating the HC MV in the inspiratory limb of a breathing circuit linked to a mechanical ventilator set to simulate tidal breathing at tidal volume = 830 mL, respiratory rate = 15 breaths/min, inspiratory-expiratory ratio of 1:2.1, peak inspiratory pressure = 20 cm H_2O. Temperature and humidity settings were 35±1°C and 100% relative humidity (close to body conditions). We compared delivery of 5-actuations of CFC- and HFA-BDP (both 50 μg/actuation), measuring total emitted mass captured by a filter at the distal end of the ETT. In a separate study, we inserted the distal end of the ETT within the entry cone of a cascade impactor so that the aerosol particle size distribution could be determined with the circuit at similar environmental conditions as described previously. We made benchmark measurements with circuit temperature and humidity at room ambient conditions (21±1°C and 54±5% RH respectively). RESULTS: Total emitted mass (5 measurements/device) was significantly greater for HFA-BDP (14.1±1.1 μg/actuation) compared with CFC-BDP (2.4±0.8 μg/actuation) (paired *t* test, $p < 0.001$). More HFA-BDP (2.7 ± 0.2 μg/actuation) was lost from the delivery system during exhalation (0.9 ± 0.4 μg/actuation for CFC-BDP) ($p < 0.001$). The mass median aerodynamic diameter (MMAD) increased from 1.2 μm (room ambient) to 2.8 μm (higher temperature and humidity conditions) for HFA-BDP. In contrast, MMAD for CFC-BDP remained close to 4.6 μm under either condition, but particles finer than about 4.0 μm increased in size when the circuit was saturated. CONCLUSIONS: Total emitted mass for HFA-BDP was increased by a factor of 5.8 compared with CFC-BDP, due largely to the finer particle size distribution of the HFA-based solution formulation. Additional water vapor required to operate the breathing circuit at close to body conditions resulted in fine particle growth with both formulations. *Key words: mechanical ventilation, aerosol, beclomethasone dipropionate, chlorofluorocarbon, hydrofluoroalkane.* [Respir Care 2003;48(11):1025–1032. © 2003 Daedalus Enterprises]

Introduction

As part of the drive to eliminate chlorofluorocarbon (CFC) propellant, in accord with the Montréal protocol of 1987, the reformulation of beclomethasone dipropionate (BDP) with hydrofluoroalkane (HFA) 134a propellant enabled the manufacturer to develop a metered-dose inhaler (MDI) formulation that generates an aerosol with substantially finer particles.[1] In subsequent studies, HFA-BDP has

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been shown to be associated with better airway targeting to the finer airways and alveoli.[2–3] The HFA-propelled BDP formulation has a mass median aerodynamic diameter (excluding the ballistic component) of approximately 1.1 μm, compared with 3.5–4.0 μm with CFC-propelled BDP formulations, determined in the laboratory under room ambient conditions.[1]

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Aerodynamic diameter is a parameter defined as the diameter of a hypothetical spherical particle of density 1.00 g cm^{-3} that settles in air at the same falling velocity as the physical particle.[4] This is a more useful concept than physical (microscopy-measured) diameter to describe aerosol motion during respiration.[5] The enhanced penetration to the lungs has been shown to result in equivalent clinical outcomes in response to the delivery of less medication with HFA-BDP.[6–8] For instance, Busse et al[6] reported that 2.6 times as much CFC-BDP would be needed to achieve the same improvement in forced expiratory volume in the first second (FEV_1) as HFA-BDP with asthmatics suffering deterioration in symptom control after discontinuation of inhaled corticosteroids. Gross et al[7] observed a 2:1 dose relationship between CFC-BDP and HFA-BDP to achieve similar control for patients with moderate asthma, based on morning peak expiratory flow. However, comparative studies of these 2 BDP formulations have so far been focused on delivery to nonintubated patients, in whom aerosol delivery to the lower respiratory tract is modified by oropharyngeal deposition of particles larger than about 4–6 μm.[9]

Limited clinical investigations have so far been undertaken with inhaled corticosteroids in intubated patients. However, Nava and Compagnoni recently concluded that a brief trial of fluticasone propionate might induce a bronchodilatory response in adults in stable condition with severe COPD and chronic hypercapnic respiratory failure.[10] Several authors have discussed the use of this class of therapeutic agents to treat mechanically ventilated infants with chronic lung disease. In one instance, reduced need for mechanical ventilation was demonstrated after treatment with 600 μg budesonide twice daily.[11]. However, in another study the authors concluded that inhaled BDP conferred no advantage compared with intravenous dexamethasone, although they noted that the group receiving 800 μg BDP/day trended towards a more rapid decrease in ventilator and oxygen requirements than a cohort receiving only 400 μg BDP/day.[12]

If inhaled corticosteroid therapy is to be effective across the various patient classes, it is self-evident that there is a need to optimize delivery, and the availability of the finer aerosol produced by HFA-BDP may go some way to achieving this goal. However, circuit humidification to saturation conditions at body temperature, which is necessary to prevent hypothermia, inspissation of secretions, destruction of the airway epithelium, and atelectasis,[13] may reduce aerosol penetration to the lower respiratory tract.[14]

The purpose of the present laboratory-based investigation was 2-fold: the first part was intended to compare the delivery of HFA-BDP and CFC-BDP via holding chamber equipped with endotracheal tube (ETT) to a model of a tidally breathing adult patient; the second part examined the effect of circuit humidification on the aerosol particle size distributions of the 2 formulations. Our data are intended to provide guidance for the design of future clinical investigations.

Methods

In the breathing simulator part of the study, we inserted a holding chamber (AeroChamber HC MV [holding chamber for mechanical ventilation]; Monaghan Medical, Plattsburgh, New York) into the inspiratory limb of an adult ventilator circuit (Hudson-RCI, Temecula, California), with the distal end adjacent to the circuit Y-piece (Fig. 1). We operated the ventilator circuit (ConchaTherm III dual heated-wire servo control heater; Hudson RCI, Temecula, California) so that the air at the Y-piece was maintained at 35 $\pm$ 1° C and 100% relative humidity. We verified these conditions independently by a temperature probe placed within the circuit as well as by the observation of condensation on the walls of the circuit. We attached an adult ETT (Magill 8.0-mm internal diameter; Euromedical Industries, Kedah, Malaysia) directly to the Y-piece with a disposable bacterial/viral filter holder (Respirgard model 303; Marquest Medical Products, Englewood, Colorado) without straightening the curvature that would be present in clinical use. The filter holder was therefore positioned at the distal end of the ETT, which would normally be located in the vicinity of the carina. The filter holder held an electret filter in a self-contained housing. The other end of the filter holder was attached to a test lung (model 1600; Michigan Instruments, Grand Rapids, Michigan). We operated the breathing simulator using an adult ventilator (Adult Star; Infrasonics, San Diego, California) set up in Assist/Control mode without an inspiratory hold (continuous mandatory ventilation), which delivered a tidal volume of 830 mL, inspiratory-expiratory ratio of 1:2.1, respiratory frequency of 15 breaths/min (1.3 s/inhalation), peak inspiratory flow of 53–54 L/min, peak inspiratory pressure of 20 cm H_2O, and zero positive end-expiratory pressure. Peak inspiratory flow was reached rapidly after onset of inhalation, followed by a more gradual decrease to zero flow just before exhalation, rather than following a sinusoidal pattern, as would have been the case if a piston-in-tube breathing simulator had been used. We adjusted

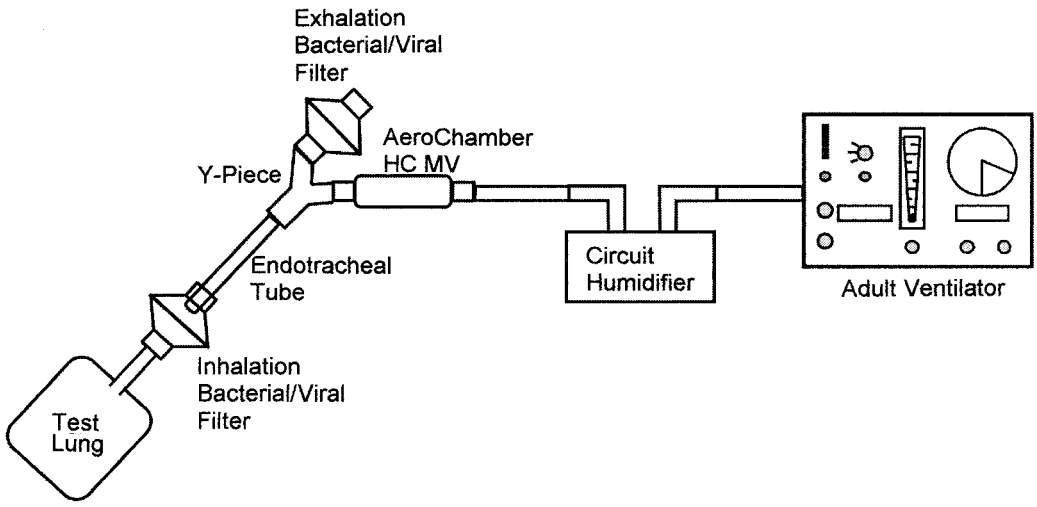

Fig. 1. Experiment set-up. The AeroChamber HC MV is upstream in the ventilator circuit and adjacent to the Y-piece.

the compliance of the test lung so that complete deflation occurred at the end of each exhalation. The choice of tidal volume was based on advice that values > 500 mL are associated with improved aerosol delivery, based on lung modeling studies.[15] However, it is recognized that lower values closer to 500 mL are normal in current clinical practice to minimize the risk of volutrauma.

We inserted a canister of HFA-BDP (Qvar-50, 3M Pharmaceuticals, Canada) into the receptacle of the AeroChamber HC MV and delivered 5 actuations (50 μg/actuation) at 20-second intervals (5 breathing cycles), actuating at the onset of an inhalation. Between each actuation the canister was removed from the receptacle, shaken gently for 5 seconds, and then carefully reinserted into the receptacle of the HC MV just before the next actuation. We undertook the shaking of each MDI canister as part of a protocol that applies for all types of formulation. Qvar, being a solution of BDP in ethanol and HFA 134a propellant, does not require shaking of the canister to deliver a consistent mass of active pharmaceutical ingredient per actuation. After the actuations we removed the filter from the circuit and measured the collected BDP by washing the filter with 100% methanol and assaying the resulting solution by HPLC [high-performance liquid chromatography] UV-spectrophotometry (Star HPLC System; Varian Associates, Walnut Creek, California). We conducted the procedure (MDI actuations followed by HPLC spectrophotometry assay) a total of 5 times with each of 5 AeroChamber HC MV devices. We subsequently made a similar series of measurements with CFC-BDP (Vanceril-50; Schering-Plough, Kenilworth, New Jersey) with the same AeroChamber HC MV devices. In each instance, total emitted mass was calculated by dividing the total mass of BDP recovered from each filter by the number of actuations of the MDI.

In supplementary tests (1 measurement with each AeroChamber HC MV with each formulation) we also installed a filter (Respirgard model 303; Marquest Medical Products, Englewood, Colorado) on the exhalation limb of the ventilator circuit, adjacent to the Y-piece. This filter captured any aerosol that remained in the ETT and Y-piece following each MDI actuation We refer to this material as 'exhaled' mass, since it was collected during only the exhalation portion of the breathing cycle. Assay for collected BDP and calculation of the mass collected by the exhalation filter followed the procedure already described for the measurements of BDP captured on the filter at the distal end of the ETT.

We configured the HC MV in a parallel experiment to determine changes in the particle size distribution of HFA- and CFC-BDP aerosols brought about by circuit humidification. In the humidification experiments we placed the AeroChamber HC MV (Figure 2) in the same part of the ventilator circuit, but with the distal end of the ETT positioned on axis with the inlet of an 8-stage Andersen cascade impactor (Mark-II; Thermo Andersen, Smyrna, Georgia). The impactor received a flow of 28.3 L/min ± 5%. We did not use an induction port, because the purpose was to simulate delivery to the carinal region rather than oral inhalation. The curvature that occurs when the ETT is placed through the upper airway was maintained, but the ETT was orientated in the vertical plane in order that the impactor could also be operated vertically.

In the measurements to establish benchmark aerosol particle size distribution, we obtained the air supply from the surrounding atmosphere at room ambient conditions (21° C and 54% relative humidity, equivalent to a water vapor content of 13.1 mg/L). This supply entered the inspiratory limb of the ventilator circuit via the connector that would normally be fitted to the air/oxy-

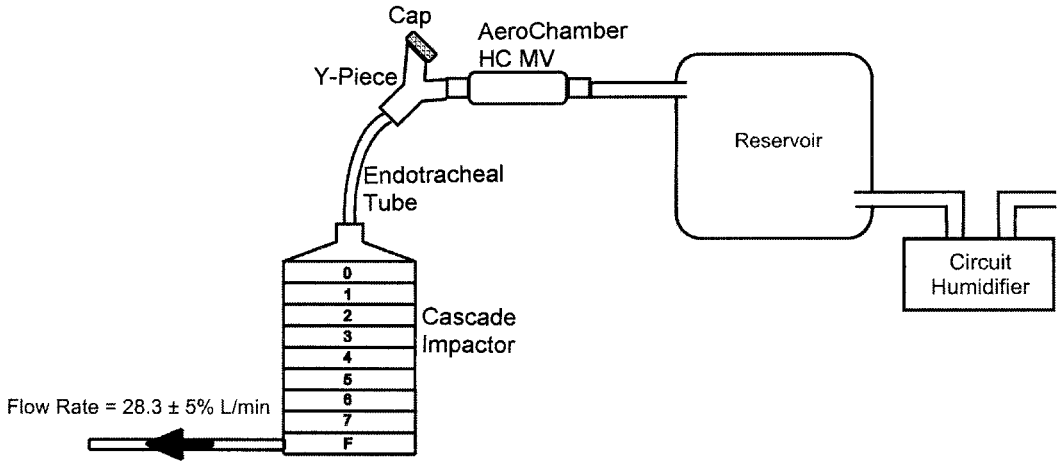

Fig. 2. Experiment configuration for cascade impactor measurements. The distal end of the endotracheal tube is on axis to the entry cone of the cascade impactor. An induction port was not used because the objective was to simulate aerosol delivery via endotracheal tube (ie, directly to the carinal region) rather than via oral inhalation.

gen supply port of the ventilator. We plugged the exhalation limb at the Y-piece so that all the air passed via the inspiratory limb only. In the measurements intended to measure size distribution data under conditions equivalent to those in the simulated breathing studies, we prehumidified this air supply using a heated-wire humidification system (ConchaTherm; Hudson RCI, Temecula, California) we attached a 33-L spherical reservoir, to which the entry connector of the inspiratory limb was attached. The inspiratory limb was also heated so that the air entering the AeroChamber HC MV and passing to the ETT was maintained at 35 ± 1° C and 100% relative humidity, equivalent to a water vapor content of 40.0 mg/L.

We delivered 5 actuations of HFA-BDP through each of the 5 AeroChamber HC MV devices, following the same protocol described for the simulated breathing experiments (measurement/device). The BDP collected on each impactor stage was assayed as described above. We undertook the same procedure with CFC-BDP.

We used the paired *t* test (SigmaStat; SPSS, Chicago, Illinois) to compare total mass emitted at the distal end of the ETT with each condition. Differences were considered statistically significant when $p < 0.05$.

Results

The measurements of the total mass emitted at the distal end of the ETT during the simulated breathing are summarized in Figure 3. The total emitted mass of HFA-BDP significantly exceeded the total emitted mass of CFC-BDP ($p < 0.001$). The group mean ± SD value for HFA-BDP was 14.1 ± 1.1 μg/actuation, which is 5.8 times more than that of CFC-BDP (2.4 ± 0.8 μg/actuation). Figure 4 compares the masses of HFA-BDP and CFC-BDP captured on the exhalation filters. Slightly, but significantly more mass of HFA-BDP was collected on exhalation (2.7 ± 0.2 μg/actuation) than CFC-BDP (0.9 ± 0.4 μg) ($p < 0.001$).

Figures 5 and 6 show the cumulative mass-weighted particle size distributions under the 2 different temperature and humidity conditions. The combination of holding chamber with ETT effectively eliminated the ballistic fraction of the aerosol mass produced during MDI actuation, thus the fraction of HFA-BDP particles < 4.7 μm (and thus likely to penetrate to the deep lung) was high, at 90.8 ± 6.2% in ambient air**.** Increasing the water vapor content to near body conditions resulted in particles < 4.7 μm of 88.7 ± 1.1%, which is comparable to the value measured under ambient conditions ($p = 0.46$). However, the mass median aerodynamic diameter, which is a measure of central tendency of the distribution, was 1.2 ± 0.1 μm in ambient air, which increased to 2.8 ± 0.1 μm in humidified air. Since CFC-BDP produces larger aerosol particles than are formed with the HFA-BDP, the fraction < 4.7 μm in ambient air was only 52.0 ± 7.2%. Surprisingly, the increased moisture content at near body conditions did not significantly decrease the fraction of particles < 4.7 μm (57.2 ± 3.1%, $p = 0.30$)**,** comparable with values obtained with air at room ambient conditions. Not surprisingly, the corresponding mass median aerodynamic diameter was close to 4.6 μm under either humidity condition.

Discussion

The insertion of a rigid, small-volume AeroChamber HC MV in the inspiratory limb of the ventilator circuit, close to the Y-piece, is consistent with the goal of optimizing distal lung delivery of aerosol with the mechani-

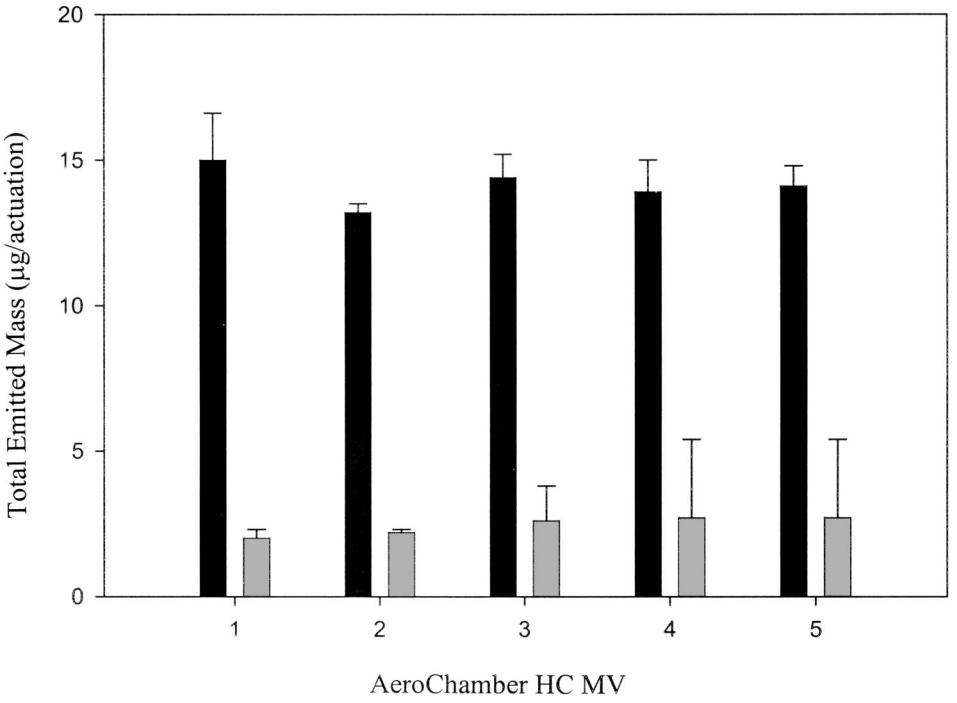

Fig. 3. Total emitted mass determined for hydrofluoroalkane-propelled (HFA) versus chlorofluorocarbon-propelled (CFC) beclomethasone dipropionate (BDP) aerosol by breathing simulator measurements. Black bars = HFA-BDP; grey bars = CFC-BDP.

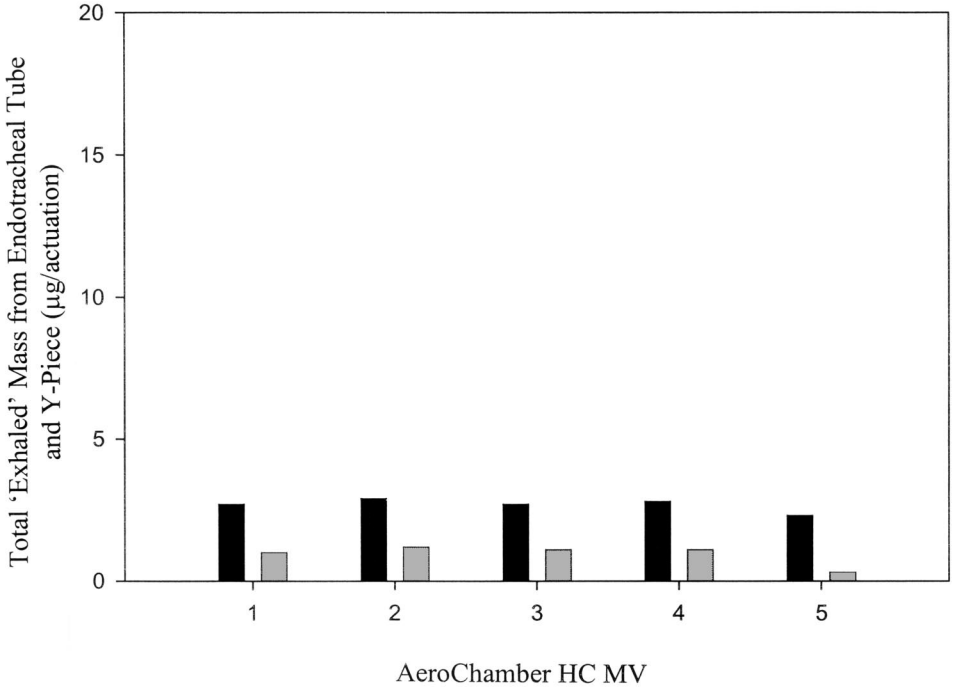

Fig. 4. Total mass of hydrofluoroalkane-propelled (HFA) versus chlorofluorocarbon-propelled (CFC) beclomethasone dipropionate aerosol (BDP) collected by exhalation filter in breathing simulator studies. Black bars = HFA-BDP; grey bars = CFC-BDP.

cally ventilated patient.[15] However, components of the circuit downstream of the AeroChamber HC MV act as baffles that trap larger particles because of the combination of turbulent deposition and inertial impaction on flow obstructions.[16] It follows that a formulation that generates an aerosol containing finer particles is likely to be deliv-

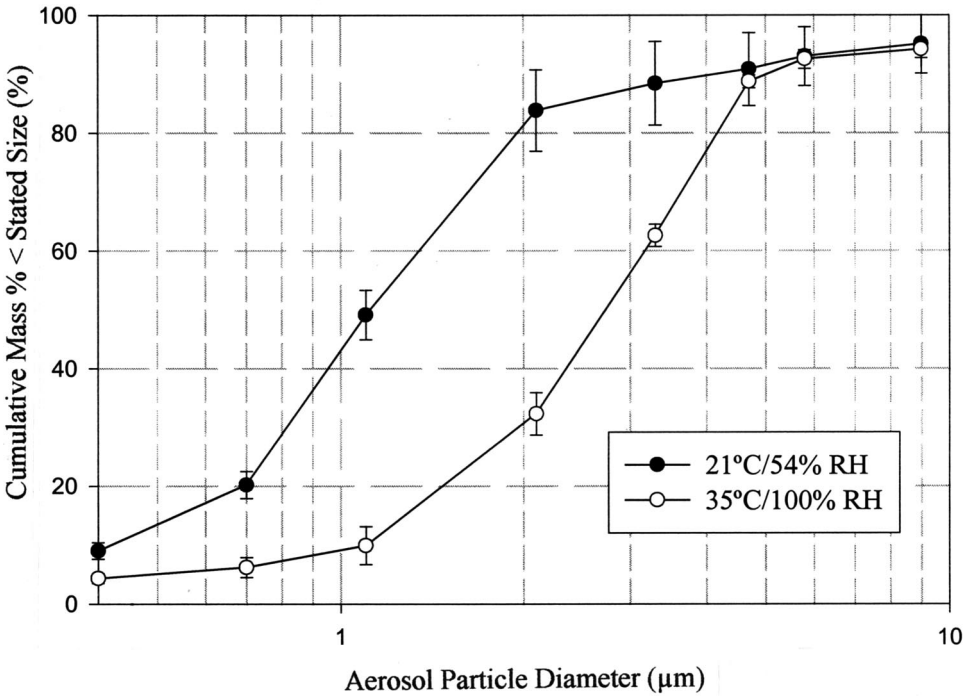

Fig. 5. Cumulative mass-weighted size distribution (measured with a cascade impactor) of beclomethasone dipropionate propelled with hydrofluoroalkane (HFA-BDP), showing the effect of humidification on aerosol particle size delivered via AeroChamber HC MV with an endotracheal tube (8 mm inner diameter) on the inspiratory limb of the ventilator circuit. RH = relative humidity.

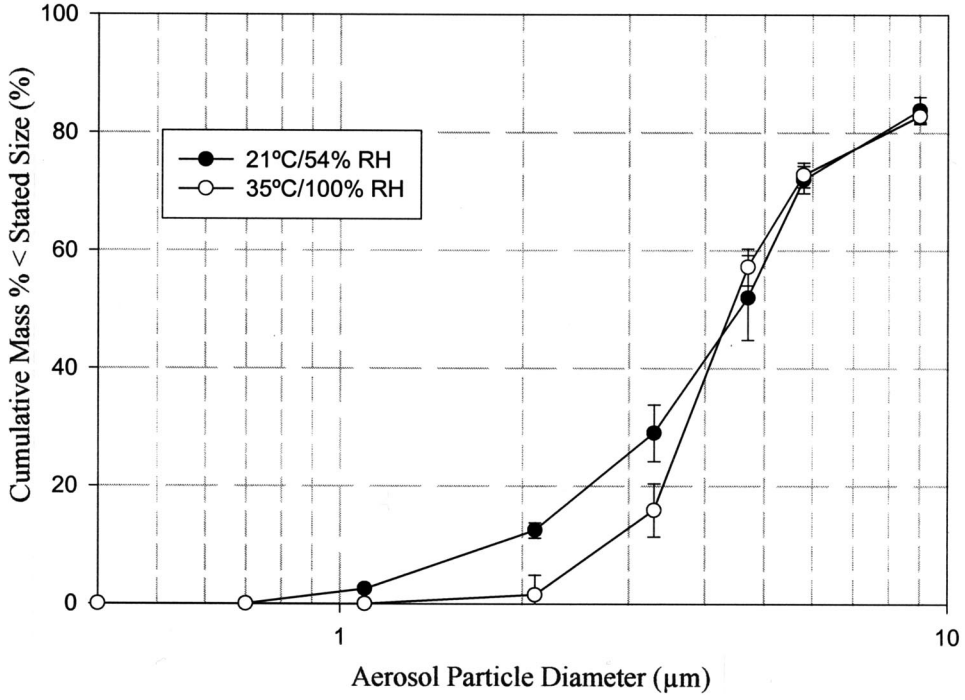

Fig. 6. Cumulative mass-weighted size distribution (measured with a cascade impactor) of beclomethasone dipropionate propelled with chlorofluorocarbon (CFC-BDP), showing the effect of humidification on aerosol particle size delivered via AeroChamber HC MV with an endotracheal tube (8 mm inner diameter) on the inspiratory limb of the ventilator circuit. RH = relative humidity.

ered more effectively from the point of generation within the HC MV to the distal end of the ETT. However, the large difference (a factor of 5.8) in total emitted mass was greater than expected (see Fig. 3), given the difference factor of 2.6 reported by Busse et al[6] and the factor of 2.0 suggested by Gross et al,[7] both based on clinical outcome measures. In explanation, the model used in the present investigation was limited to comparing total emitted mass at the distal end of the ETT . It could not therefore evaluate differences in lower respiratory tract deposition between the 2 formulations. If in the clinical situation proportionately more of the HFA-BDP were exhaled without depositing in the lungs because of its finer particle size, these particles would not be available to elicit a response. A lower ratio of HFA/CFC-BDP efficacy from clinical studies might therefore be anticipated. In this context, it should be noted that as much as 18% of the ex actuator mouthpiece mass from this formulation has been reported as being exhaled by healthy volunteers compared with 1% for CFC-BDP.[1] This argument is supported by the 3:1 ratio found in the present study for the mass/actuation of HFA-BDP and CFC-BDP recovered from the dead space within the ETT and Y-piece (see Fig 4). The present in vitro comparison therefore cannot be a substitute for clinical studies in which the total mass exhaled from both lower respiratory tract and delivery device may be assessed. However, it does provide insight into the relative performance of these formulations at the point of delivery to an intubated and mechanically ventilated adult patient.

It is interesting that only the particles finer than 4.0 to 4.5 μm aerodynamic diameter of both HFA- (see Fig. 5) and CFC-BDP (see Fig. 6) were observed to grow when the ventilator circuit was humidified. The insensitivity of the particles $>$ 4.7 μm to circuit humidification with either formulation is therefore a direct consequence of the upper size where growth was observed being finer than the size limit of 4.7 μm aerodynamic diameter chosen to define the fine drug particles. Interestingly, the greatest changes in size were generally observed in association with the finest particles of either formulation (see Figs. 5 and 6). Such an outcome is indicative of a process that is driven by available particle surface area, since the particle surface-to-volume ratio is largest for the finest particles. This growth may have occurred predominantly in the ETT, which was unheated, as it is known that the rate of change of particle diameter due to hygroscopic effects varies with the inverse of particle diameter.[17] We chose not to heat the ETT, since as much as 25–50% of its length may remain external to the patient and therefore exposed directly to room ambient conditions in a typical clinical situation.

Although it is well known that aerosol delivery is decreased when a ventilator circuit is humidified and operated at close to body temperature,[13,18] there is some uncertainty as to the underlying cause. Dolovich[19] noted that hygroscopic growth of aerosol particles brought about by absorption of condensed water vapor molecules on entering the saturated environment within the respiratory tract during oral inhalation might result in as much as a 2–3-fold increase in particle size. The magnitude of that increase depends on the initial particle size and the residence time of the particles within the saturated environment before deposition takes place.

More recently, Fink et al have suggested that water absorption is unlikely to be responsible for particle growth in a saturated environment, since particles emerging from MDIs are coated with hydrophobic surfactant (and initially, propellant).[18] It should, however, be noted that the aerosol formed from HFA-BDP does not contain surfactant, since the BDP is formulated in only ethanol and 134a HFA propellant, yet we observed similar behavior to that for CFC-BDP where surfactant (oleic acid) was present. Fink et al went on to postulate that at the high water vapor mole fraction (absolute humidity) within a typical ventilator circuit maintained at body conditions of temperature and relative humidity, the formation of a liquid water layer on the hydrophobic surfaces of the particles results in the observed growth. Whichever mechanism operates, the likelihood of losses caused by impaction of the aerosol in the HC MV and ventilator circuit increases as particle growth takes place.

More recently, Lange and Finlay have suggested that following MDI actuation, propellant evaporation may be retarded by the presence of increased water vapor molecules within a HC MV in a ventilator circuit operated at saturation and at elevated temperature.[20] Their investigation focused on finding an explanation for the increased retention of an MDI-generated aerosol that they observed within their delivery system at elevated water vapor concentrations, and was based on experience with a single formulation (HFA-albuterol sulfate). The proposal cannot therefore be extrapolated to predict how the evaporation behavior of the different propellants associated with HFA- and CFC-BDP may have influenced the particle size changes that were observed between room ambient and at near body environmental conditions in the present study.

A further possibility is particle growth caused by the interception of larger water droplets ($>$10 μm) falling through the aerosol as a result of gravitational sedimentation ('rainout'). However, it is unlikely that interception of water droplet 'rainout' would have been responsible for significant additional growth, since this type of process would be expected to be most significant with the largest particles on account of their greater cross-sectional area for collisions with falling water droplets.

Conclusions

Since the ETT bypasses the oropharyngeal region of the respiratory tract, total mass emitted at the distal end of the ETT is a reasonable metric by which to compare the dose/actuation that may be available to an intubated, mechanically ventilated patient. On this basis HFA-BDP was delivered 5.8 times more efficiently than the equivalent dose of CFC-BDP, based on comparable unit dose downstream of the metering valve (50 μg/actuation). However, being an in vitro study, this comparison did not assess the potential for greater losses of HFA-BDP to the lower respiratory tract because of nondeposition following inhalation. This effect may in part explain the higher ratio between the 2 formulations, compared to values based on clinical outcomes.

The particle size distribution measurements demonstrate that particle growth in the humidified ventilator circuit configuration used in the present study was largely confined to particles finer than about 4.5 μm. The percentage of particles $>$ 4.7 μm was therefore insensitive to the humidity difference. Since the finest particles were associated with the greatest enlargement, the underlying mechanism is believed to be growth caused by water condensation directly to the particle surface, rather than by interception ('rainout') of previously condensed water droplets.

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