

Hydrofluoroalkane- vs Chlorofluorocarbon-Beclomethasone Delivery in Neonatal Models

Cynthia H. Cole, MD, MPH¹, Jolyon P. Mitchell, PhD²,

Martin P. Foley², and Mark W. Nagel, HBSC²

¹The Floating Hospital for Children, Tufts-New England Medical Center,

Tufts University School of Medicine, Boston, MA, 02111 and

²Trudell Medical International, London, Ontario, Canada, N5V 5G4

Address correspondence to: Cynthia H Cole, MD, MPH, Division of Newborn Medicine,

Tufts-New England Medical Center, 750 Washington St., Boston, MA 02111, USA

Email: ccole@lifespan.org; Telephone: (617) 636-5322; FAX: (617) 636-1456

Disclosure: Manufacturer of chlorofluorocarbon-beclomethasone dipropionate (CFC-BDP) 50 µg/dose (Vanceril®50) was Schering, Canada Inc). Manufacturer of hydrofluoroalkane-beclomethasone dipropionate (HFA-BDP) 50 µg/dose (QVAR™50) was 3M Pharmaceuticals (Canada). Manufacturer of two holding chambers (Neonatal Chamber-Ventilator System (NCVS) and Neonatal Chamber (NC) is Trudell Medical International, London, ON, Canada. All co-authors, except for Dr. Cole, are employed by Trudell Medical International. In vitro assays were conducted in the medical aerosol laboratory of Trudell Medical International, London, Ontario, Canada. Dr. Cole has no financial arrangements and no conflict of interest with Trudell Medical International, Schering, Canada, or 3M Pharmaceuticals (Canada). The research was conducted, analyzed, and presented objectively and free of bias by Dr. Cole and biostatisticians of Tufts University School of Medicine, and by collaborators and co-authors of Trudell Medical

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Running Title: HFA- vs. CFC-BDP in Neonatal Models

Objective: To compare dose delivery of chlorofluorocarbon-beclomethasone (Vanceril®50, Shering, 50 µg/dose) vs. hydrofluoroalkane-beclomethasone (QVAR™50, 3M Canada Inc; 50 µg/dose) during five *in vitro* neonatal simulations.

Design: Beclomethasone delivery was evaluated in the following simulations: mechanical ventilation via Neonatal Chamber Ventilator System and endotracheal tube under 40% and 100% relative humidity; manual ventilation via Neonatal Chamber and endotracheal tube; spontaneous and manually assisted ventilation via Neonatal Chamber and facemask. Similar neonatal breathing parameters were used for all mechanical, manual, or spontaneous breathing simulations (PEEP 5 cm H₂O, PIP 20 cm H₂O, Flow 9 LPM, V_T 8-11.6 ml, Rate 40 bpm, I:E=1:4 to 1:4.8). Beclomethasone was measured by high-pressure liquid chromatography-ultraviolet spectrophotometry.

Outcome Measures: Total emitted dose (TED, micrograms) and efficiency (TED/labeled claim dose, %)

Results: Dose delivery (TED±SD) was greater for hydrofluoroalkane- vs. chlorofluorocarbon-beclomethasone, respectively, in each simulation: 1. mechanical ventilation (40% relative humidity) + Neonatal Chamber-Ventilator System/endotracheal tube: 4.4±0.7 vs. 0.4±0.3 micrograms; 2. mechanical ventilation (100% relative humidity) + Neonatal Chamber-Ventilator System/endotracheal tube: 1.5±0.2 vs. 0.02±0.08 micrograms; 3. manual ventilation + Neonatal Chamber/endotracheal tube: 6.5±0.6 vs. 1.3±0.5 micrograms; 4. “spontaneous breathing” + Neonatal Chamber/face mask: 4.1±1.6 vs. 2.3±0.7 micrograms; 5. manual ventilation + Neonatal Chamber/face mask: 26.6±4.3 vs. 21.6±4.3 micrograms.

Conclusions: Hydrofluoroalkane-beclomethasone was associated with greater delivery for all simulations. Manual ventilation enhanced and humidification reduced delivery.

Key Words: aerosol therapy, inhaled glucocorticoid

Introduction

Clinical trials of inhaled glucocorticoid therapy for prevention or treatment of bronchopulmonary dysplasia have demonstrated either modest or no improvements in pulmonary outcomes (1-5). The variable and limited response may result from inadequate and inconsistent delivery of inhaled glucocorticoids to neonatal lungs. Hydrofluoroalkane (HFA)-reformulation of inhaled glucocorticoids, in response to mandatory phase-out of chlorofluorocarbon (CFC) propellants (6), and new designs in holding chambers may potentially improve neonatal aerosol delivery by production of a finer aerosol particle size (7).

In vitro studies of aerosol particle size, as determined from the actuator mouthpiece of the metered dose inhaler, reported that the mass median aerodynamic diameter of the HFA-beclomethasone dipropionate QVAR™ (3M Pharmaceuticals, Canada) (HFA-BDP) was close to 1.1 micron in contrast to CFC-beclomethasone dipropionate (CFC-BDP) size of 3.4 microns. Also, the fine particle or lung targetable fraction (particle size less than 3.1 microns aerodynamic diameter) is greater for HFA-BDP compared with CFC-BDP (7-9). Radiolabeled-deposition studies of HFA-BDP vs. CFC-BDP in adults demonstrated a 10-fold increase in lung deposition of HFA-BDP (8). Clinically, HFA-BDP provided similar efficacy at half the CFC-BDP dose (10-12).

However, one cannot extrapolate *in vitro* or *in vivo* delivery data from adult studies and apply the findings to neonatal aerosol therapy without examination of the complexities and unique aerosol-device interactions and delivery technique-related factors applicable to neonates (13,14). HFA-reformulation of inhaled glucocorticoids and improvements in aerosol holding chambers require entirely new studies to understand the amount and characteristics of medications that are likely to be delivered to neonates. There are limited *in vitro* data available

comparing CFC- and HFA-formulations of inhaled glucocorticoid delivery via neonatal aerosol systems and these data are only available in abstract (Bowser L., Rhem R., Dolovich M.[abstract] Am J Respir Crit Care Med 1999;159:151A). Quantifying the dose delivered *in vitro* is a necessary first step to provide a rational basis for estimating the quantity of aerosol that might be delivered to the neonatal lung in clinically relevant scenarios. This study's objective was to measure the total emitted dose and thereby calculate the efficiency of CFC- vs. HFA-BDP delivery exiting either an endotracheal tube or facemask during five *in vitro* simulations of aerosol delivery to neonatal models. The hypothesis tested was that aerosol delivery of HFA-BDP QVAR™ is greater (in terms of absolute mass and efficiency relative to the label claim dose) than delivery of CFC-BDP in each neonatal simulation.

Methods

Inhaled Glucocorticoids: We compared two glucocorticoid formulations: CFC-BDP (Vanceril®50, Schering, Canada Inc; 50 micrograms/dose) and HFA-BDP (QVAR™50, 3M Pharmaceuticals (Canada); 50 micrograms/dose).

Neonatal Holding Chambers: We used two prototype aerosol delivery chambers (Neonatal Chamber-Ventilator System and Neonatal Chamber, Trudell Medical International, London, ON, Canada), each with 145-milliliter volume.

The Neonatal Chamber Ventilator System is intended for use solely in conjunction with a ventilator circuit and interposed between the 'y'-connector of the ventilator circuit and the endotracheal tube. One-way valves, located at either end of the chamber, direct inhalation airflow from the ventilator circuit through the chamber to the endotracheal tube, and the exhaled flow is returned to the ventilator circuit via a by-pass tube (Figure 1A). The valve located

between the chamber and endotracheal tube connection has minimal dead volume (<1 milliliter). This feature minimizes mixing of aerosol with the exhalation flow, and consequent loss of medication to the patient, and avoids reduction in oxygen content upon repeated inhalations.

The Neonatal Chamber may be attached to either an endotracheal tube (Figure 1B) or neonatal face mask at the chamber exit adapter (Figures 1C-D). The exit adapter tapers the internal diameter of the chamber smoothly to a narrow 5-millimeter diameter opening. The inlet port of the Neonatal Chamber may remain open to the atmosphere or may be connected to a resuscitation bag for manual assistance to enhance medication delivery. The metered dose inhaler normally inserts in the receptacle, and is operated in the same way as with the Neonatal Chamber Ventilator System. In the simulation of spontaneous breathing without manual assistance for this study, the integral adapter of the Neonatal Chamber for the metered dose inhaler canister was replaced with a universal adapter, and the canister was inserted in the opening on axis with the chamber using the manufacturer's actuator (Figure 1C).

Each holding chamber was pre-treated by washing with a mild ionic detergent, rinsing and drip-drying in ambient air prior to use in order to minimize any impact of electrostatic charge on performance.

Standardization for metered dose inhaler actuation and BDP measurement: The procedure for each metered dose inhaler actuation was standardized to optimize reproducible delivery with each simulation. Each metered dose inhaler (n=3 per formulation) was allocated to a particular Neonatal Chamber Ventilator System or Neonatal Chamber and then primed. Each metered dose inhaler was shaken ten times for 5 seconds prior to each actuation, which occurred at the beginning of the inspiratory cycle, followed by six complete breathing cycles. We established in a preliminary series of measurements, that more than 80% of total emitted dose

available from the Neonatal Chamber Ventilator System was recoverable after six breathing cycles (data available upon request). Three actuations of the medication (CFC-BDP or HFA-BDP) were delivered at 45-second intervals for each measurement. Total mass of beclomethasone exiting either endotracheal tube or Neonatal Chamber outlet was collected onto an absolute filter (Filtrete™, 3M, London, Ontario, Canada) in low dead-volume holder. Beclomethasone was eluted from each filter in a known volume of methanol (100% volume/volume) to permit quantitative assay for beclomethasone by high-pressure liquid chromatography-ultraviolet spectrophotometry. Mass balances were performed for all measurements.

Total emitted dose (TED, micrograms) per actuation was based on these measurements, divided by the number of actuations. Delivery efficiency (%) was calculated on a percentage basis (TED divided by label claim dose ex-metering valve). The mass of BDP delivered per actuation was measured and confirmed to be within $\pm 20\%$ labeled claim dose ex actuator mouthpiece.

Neonatal in vitro simulations: The first two simulations assessed delivery via the Neonatal Chamber Ventilator System and 2.5 millimeter endotracheal tube (Figure 1A) during mechanical ventilation at 40% and 100% relative humidity. The third simulation assessed delivery via the Neonatal Chamber and endotracheal tube during manual ventilation (Figure 1B). The fourth and fifth scenarios simulated delivery to spontaneously breathing neonates via the Neonatal Chamber attached to a facemask. Scenario 4 (Figure 1C) simulated delivery with no manual ventilation assistance, and scenario 5 (Figure 1D) simulated delivery with manual ventilation assistance using a flow-inflating resuscitation bag.

Each simulation employed ventilation parameters similar to those used with neonates: rate = 40 cycles/minute; tidal volume = 8-11.6 milliliter, positive end expiratory pressure = 5 centimeters H₂O; peak inspiratory pressure = 20 centimeters H₂O; peak inspiratory flow rate = 9 liters per minute; inspiratory/ expiratory (I/E) ratio = 1:4-1:4.8.

Data Analysis and Statistical Considerations: Comparisons of total emitted dose and delivery efficiency were made among systems for a single medication (analysis of variance) and between medication formulations within a single system (t-test). Differences were deemed significant when $p < 0.05$.

Results

Values of total emitted dose (TED, micrograms) and efficiency (%) of aerosol delivery for CFC-BDP and HFA-BDP for each of the neonatal simulations are shown in the Table. In all scenarios, HFA-BDP was associated with significantly greater aerosol delivery compared to CFC-BDP.

Delivery via endotracheal tube was more efficient using manual ventilation via the Neonatal Chamber/endotracheal tube (simulation #3) for both HFA-BDP and CFC-BDP than either mechanical ventilation simulations via Neonatal Chamber Ventilator System/endotracheal tube (simulations #1 and 2). As expected, the presence of a saturated atmosphere (100% relative humidity) compared with 40% relative humidity in the ventilator circuit significantly reduced aerosol delivery ($p < 0.001$). Simulations of delivery via the Neonatal Chamber/face mask revealed that manual ventilation with a resuscitation bag was more effective compared to delivery without assistance ($p < 0.001$) despite the use of similar breathing parameters.

Discussion

This study illustrates important differences in aerosol delivery between HFA-BDP QVAR™50 and CFC-BDP formulations and differences among techniques used within neonatal care. The finding of greater delivery of HFA-BDP vs. CFC-BDP is not surprising given the finer particle size of HFA-BDP QVAR™50 vs. CFC-BDP. Particle size distribution measurements in separate study indicate that almost all the dose available from HFA-BDP is contained in particles < 3.1 µm aerodynamic diameter and 48% is contained in submicron particles <1.0 µm. (8) (Cole CH, Mitchell JP, Foley M, Nagel MW, Doyle CC, Bates SL. [abstract]. Pediatric Research 2002; 51:356A).

Bowser *et al* provided the only other *in vitro* study to date regarding HFA-BPD delivery in ventilated neonatal and infant models (Bowser L, Rhem R, Dolovich M. *In vitro* deposition of HFA vs CFC-beclomethasone (BDP) MDI at low tidal volumes [abstract]. Am J Respir Crit Care Med 1999;159:151A). Our finding of greater HFA-BDP vs. CFC-BDP delivery at low tidal volume via a 2.5 millimeter endotracheal tube is in contrast to Bowser *et al's* observation of no difference between HFA-BDP and CFC-BDP delivery via AeroChamber® Holding Chamber for Mechanical Ventilation fitted to a 2.5, 3.0, or 3.5 millimeter endotracheal tube at a similar tidal volume (10 milliliter). However, their peak inspiratory flow rate (4.65 liters per minute) at 10 milliliter tidal volume was lower than the value 9 liters per minute estimated in the present study. Furthermore, they demonstrated significantly greater delivery of HFA-BDP vs. CFC-BDP with increasing tidal volumes (15 to 50 milliliters), associated with increasing inspiratory flow rates (6.98 to 9.30 liters per minute). Finally, the design of the holding chambers used in the present study was different from that used by Bowser *et al.*, and may be more effective for the delivery of the finer HFA-BDP at very low tidal volumes.

The difference in the dose delivered at 40% and 100% relative humidity during mechanical ventilation illustrates the effect of humidification on increasing aerosol particle size, which, in turn, reduces aerosol delivery.⁽¹⁵⁾ Hygroscopic growth results in decrease medication delivery due to inertial impaction and gravitational sedimentation of particles within the chamber and endotracheal tube. Awareness that humidification reduces aerosol delivery is clinically relevant since gas supply through ventilation circuits is normally maintained close to 100% relative humidity to avoid drying of airway mucosa.⁽¹⁶⁾ Determination of the amount of beclomethasone delivered at 40% relative humidity (representative of ambient room conditions) was performed to document the magnitude of effect that increased humidification has on aerosol delivery of HFA- and CFC-BDP via a holding chamber and endotracheal tube during mechanical ventilation.

Manual ventilation significantly enhanced aerosol delivery via endotracheal tube and facemask even though mechanical, manual, and spontaneous breaths used similar ventilation parameters. Greater aerosol delivery via endotracheal tube by manual ventilation may be influenced, in part, by lower relative humidity and differences in flow dynamics relative to actuation of the aerosol. Greater aerosol delivery with the addition of manual ventilation to spontaneous breaths via the Neonatal-Chamber/ facemask may also reflect differences in flow dynamics relative to actuation of the aerosol. Use of manual ventilation requires close attention to technique and consistency with which it is applied to minimize variability in aerosol delivery.

Delivery of inhaled medications to neonates challenges both developers of systems that are efficient at the low flow rates, such as flow rates encountered with neonates, as well as to clinicians involved with their care. These challenges are ideally addressed using formulations with delivery devices that optimize aerosol particle size and dose delivery in conjunction with

consistent good technique of aerosol administration. As drug delivery systems, both the Neonatal Chamber Ventilator System and Neonatal Chamber are designed to minimize loss of the physiologically important fine particles < 3.1 micron aerodynamic diameter to internal surfaces by directing the airflow on axis down the chamber's center towards a narrow exit, and by minimizing 'dead volume' where exhaled breath can dilute the aerosol. At the same time, the coarser non-therapeutically beneficial portion of the dose, including the ballistic fraction, is eliminated by inertial deposition to the chamber walls.

In vitro studies provide important information regarding aerosol particle size distribution and estimates of aerosol delivery with specific "medication formulation/device/technique" combinations. It is important to recognize limitations of *in vitro* models since they may overestimate the dose ultimately deposited in the lungs. *In vitro* delivery represents any aerosol that has exited the endotracheal tube or facemask and deposited on the filter, including retention of submicron particles (<1.0 micron) by the filter. For example, the comparatively high values of 53% efficiency for HFA-BDP and 43% efficiency for CFC-BDP via Neonatal Chamber and facemask relate to the quantities of glucocorticoid that will be presented to the mouth and nares of the non-intubated infant. They do not reflect the amount that will ultimately be retained and deposited in the lung. The dose delivered to the mouth and nares by facemask will be further attenuated by deposition processes that take place in the nares, oropharynx, upper airways and by swallowing. Similarly, the dose delivered to the trachea via endotracheal tube will be further attenuated by deposition into the upper and conducting airways and by exhalation of some submicron particles. *In vivo* aerosol *deposition* requires consideration of host-related factors (e.g. breathing pattern, ventilation factors, upper and lower airway anatomy, pulmonary mechanics,

and pathophysiology) in conjunction with information about medication formulation, delivery system factors, and technique.

The present *in vitro* study may influence the design of *in vivo* deposition studies, dose-response studies, and may ultimately affect the technique used to evaluate the efficacy and safety of HFA-glucocorticoid therapy in neonatal clinical trials. The availability of extra-fine HFA-glucocorticoid aerosol offers new opportunities to assess potential clinical benefits, efficacy, and safety of therapy with this class of medication in the treatment of evolving or established bronchopulmonary dysplasia.

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