Albuterol Delivery From a Metered-Dose Inhaler With Spacer Is Reduced Following Short-Duration Manual Ventilation in a Neonatal Ventilator-Lung Model

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INTRODUCTION: Albuterol aerosol is commonly administered to mechanically ventilated neonates via metered-dose inhaler (MDI) with spacer. The spacer increases the dead space in the ventilation circuit, and some institutions limit the amount of time the spacer remains in line, to minimize carbon dioxide retention and the risk of hypercarbia. However, minimizing the amount of time the spacer remains in line might also limit albuterol delivery to the patient. OBJECTIVE: To determine whether limiting the amount of time the spacer is left in line after MDI actuation significantly reduces albuterol delivery. METHODS: We conducted a bench study with a neonatal ventilator-lung model that included a Bird VIP ventilator, in a time-cycled, pressure-limited, continuous-flow mode, with settings to simulate a 1-kg infant with moderate lung disease: peak inspiratory pressure 25 cm H_2O, positive end-expiratory pressure 4 cm H_2O, respiratory rate 30 breaths/min, inspiratory time 0.35 s, tidal volume approximately 7 mL. The circuit was attached to a 3.0-mm inner-diameter endotracheal tube and a neonatal test lung. We tested 5 methods of MDI albuterol administration. The first 3 methods used a spacer attached to the ETT and either 5, 15, or 30 manual breaths (flow 6 L/min, respiratory rate 30 breaths/min, peak inspiratory pressure 25 cm H_2O) were delivered after each MDI actuation (2 actuations). The final 2 methods used an in-line spacer (placed between the circuit Y-piece and the endotracheal tube) with the spacer kept in line for 30 or 60 s after each actuation (2 actuations). A breathing filter was placed between the ETT and test lung to trap the aerosolized albuterol. RESULTS: Mean ± SD albuterol delivery was 2.3 ± 0.5%, 3.6 ± 1.8%, and 5.1 ± 1.3% after 5, 15, and 30 manual breaths, respectively ($p \leq 0.05$ for 30 breaths vs 5 and 15 breaths). Albuterol delivery was 3.7 ± 1.3% when the spacer was left in line for 30 s, versus 3.7 ± 0.6% when it was left in line for 60 s. CONCLUSIONS: Limiting the time that the spacer was left in line after each MDI actuation significantly reduced albuterol delivery in our neonatal ventilator-lung model. *Key words: albuterol, bronchodilator, respiration-artificial, administration-inhalation, metered-dose inhaler, infant-premature, intensive care units-neonatal.* [Respir Care 2004;49(9):1029–1034. © 2004 Daedalus Enterprises]

Introduction

Mechanically ventilated neonates often develop increased pulmonary resistance and reduced lung compliance as a result of chronic lung disease. In ventilated premature infants airway reactivity begins as early as day 7 of life and 25 weeks gestational age.[1–4] β-adrenergic agonists reduce pulmonary resistance and P_{CO_2} and improve pulmonary compliance, tidal volume (V_T), and oxygenation in intubated infants with respiratory distress syndrome and chronic lung disease.[1,2,4–6] Nebulization is a common method of administering aerosol to intubated neonates, but

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numerous studies show that jet nebulization is inefficient, with only 0.02–2.11% of a nebulized dose reaching the end of the neonatal endotracheal tube (ETT),[7–11] as compared with 1.5–14.5% with a metered-dose inhaler (MDI) with spacer.[11–15] Moreover, there is substantial variability between nebulizer brands.[8] Numerous studies have highlighted the advantages of MDIs over nebulizers, including more efficient drug delivery to the lung,[11] no required adjustment of ventilator settings, less risk of aerosolized bacterial contamination with nebulizer treatments,[16–18] less personnel time, and lower hospital costs and charges.[19–23]

MDI use with mechanically ventilated neonates is also increasing. A recent survey of 68 academic neonatal intensive care units found that 57% of those centers use MDI to administer albuterol to ventilated neonates.[24] Although the optimal dose of albuterol and time between actuations has not been studied, 2 puffs is the most commonly reported dose administered to ventilated neonates and most centers wait 30–60 s between actuations.[24] Ninety-five percent of the surveyed centers use a spacer with the MDI and 56% administer albuterol aerosol via manual ventilation following MDI actuation.[24] The spacer allows the high-velocity droplets of drug/propellant mixture to slow, evaporate, and produce fine (< 5 μm) aerosol particles, which are more likely (than larger particles) to penetrate to the lower respiratory tract. However, the dead space added by the spacer may be clinically important with neonates, and prolonged spacer-attachment increases the risk of rebreathing carbon dioxide and thus increasing P_{CO_2}. Concern about that added dead space has caused some respiratory therapists to limit the amount of time the spacer is in line in the ventilation circuit. Twenty-eight percent of neonatal centers allow $<$ 30 s between MDI actuations when administering aerosol via manual ventilation, and 27% remove the spacer $\leq$ 30 s after the final actuation.[24] Moreover, 18% of centers administer the aerosol with $\leq$ 5 breaths between actuations, and 38% remove the spacer after $\leq$ 5 manual breaths following the final actuation.[24] Those practices may be problematic, because reducing the amount of time between actuations or the amount of time that the spacer is left in line after the final actuation may also reduce the amount of albuterol delivered to the patient.

In vitro bench studies have been used to predict aerosol delivery to neonatal patients.[11] Bench studies are useful for identifying the variables that affect drug delivery and for generating hypotheses for clinical studies. Our objective in the present study was to determine whether limiting the duration of the spacer's presence in the ventilation circuit to $\leq$ 30 s (versus 30–60 s) after each MDI actuation significantly decreases albuterol delivery to a neonatal ventilator-lung model. Our in vitro data will help to design in vivo studies to maximize albuterol delivery and minimize the increase in P_{CO_2}.

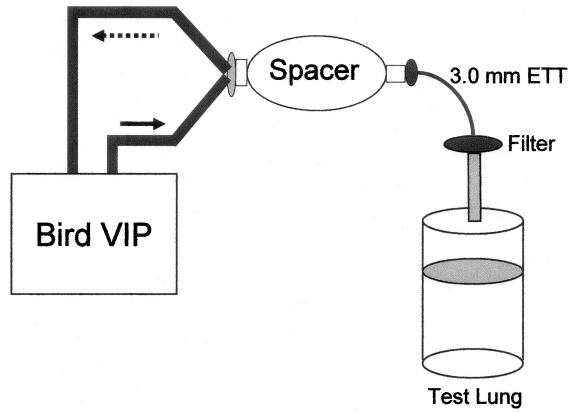

Fig. 1. Neonatal ventilator-lung model. ETT = endotracheal tube.

Methods

Lung Model

The lung model, which was designed to simulate a 1-kg premature infant with moderate lung disease, has been used in other in vitro studies of drug administration to neonates.[11] The model consisted of a 1-L cylindrical neonatal/pediatric test lung (Infrasonics, San Diego, California) partially filled with water, to create a small V_T. The test lung was connected to a 3.0-mm inner-diameter ETT (Mallinckrodt, St Louis, Missouri) that was flexed to a gradual 90° curve to simulate placement in a neonatal airway (Fig. 1). The ETT was cut to a length of 10 cm, which approximates our clinical practice in the neonatal intensive care unit. The corrugated, heated-wire neonatal ventilator circuit (Airlife, Allegiance Healthcare, McGraw Park, Illinois) was humidified (Fisher-Paykel, Auckland, New Zealand) and heated to a temperature of 35°C. The chamber control was set at −1.5°C to minimize condensation in the ventilator circuit and ETT. Before each experiment we visually inspected for condensation or coalescence in the ETT, and for fluid dripping onto the aerosol filter. If fluid was detected, adjustments were made to reduce humidity before any further experimentation.

The ventilator (VIP Bird, Bird Products, Palm Springs, California) was set to deliver time-cycled, pressure-limited, continuous-flow ventilation. Prior to each experiment we used the ventilator monitors to assure that each of the following variables were set: peak inspiratory pressure 25 cm H_2O, positive end-expiratory pressure 4 cm H_2O, respiratory rate 30 breaths/min, inspiratory time 0.35 s, continuous flow of 9 L/min, and fraction of inspired oxygen (F_{IO_2}) 0.40. Prior to each experiment the water level within the test lung was adjusted to obtain a V_T of approximately 7 mL. The model's respiratory system compliance, resistance, and V_T were measured with a computerized pneumotachograph (VenTrak, Novametrix Medical Systems,

Wallingford, Connecticut), which was placed between the ventilator circuit and the ETT. Compliance was approximately 0.6 mL/cm H_2O. Resistance was 220 cm H_2O/L/s. A low-resistance breathing filter (#002832, Sims Portex, Fort Myers, Florida) was placed between the ETT and the test lung to trap aerosolized albuterol delivered to the end of the ETT. According to the product information sheet, this breathing filter is 99.9% efficient for removing aerosolized particles that have a mean size of 1 μm.

Albuterol Administration

Albuterol MDI (Ventolin, GlaxoSmithKline, Research Triangle Park, North Carolina), which has chlorofluorocarbon propellant, was administered using 5 different methods. The first 3 methods used the cone-shaped ACE spacer (DHD Healthcare, Canastota, New York) placed horizontally between the ETT and a bag-valve-mask (E-114, Anesthesia Associates, San Marcos, California). The MDI was actuated immediately prior to an inspiratory breath, followed by 5, 15, or 30 manual breaths after each actuation (bag-valve-mask flow 6 L/min, rate 30 breaths/min, peak inspiratory pressure 25 cm H_2O). Manual ventilation was performed by one investigator, at a rate of 30 breaths/min, approximating 10 s for 5 breaths, 30 s for 15 breaths, and 60 s for 30 breaths. The investigator attempted to match the ventilator inspiratory time (0.35 s) and verified peak inspiratory pressure of 25 cm H_2O with a manometer.

The final 2 methods used an in-line ACE spacer placed horizontally between the circuit Y-piece and the ETT, with the spacer kept in line for 30 s or 60 s after each actuation.

In both experiments the ACE spacer was placed in the forward-firing position, which is the manufacturer's recommended orientation when attaching the spacer directly to the ETT, followed by manual ventilation with a resuscitation bag. All the spacers were thoroughly rinsed with water and dried prior to each experiment. Each experiment was conducted by actuating 10 different albuterol canisters twice (total 2,000 μg). Each of the canisters was primed twice prior to the series of experiments, and all MDIs were warmed in the palm of the hand and shaken vigorously for 30 s prior to actuation. Ten replicate experiments were performed for each condition.

Assay Methods

The breathing filters were rinsed 3 times with 15.0 mL of a solution of 50% methanol and 50% water (final rinse volume 45.0 mL). All samples were stored at -20°C until analyzed. Albuterol concentration was analyzed via reversed-phase, high-performance liquid chromatography (L-6200A Intelligent Pump, and AS-2000 Autosampler, Hitachi) using a 2.5-μm-particle octadecyl silane (ODS) column (250 mm $\times$ 4.6 mm) (Allsphere, Alltech, Deerfield, Illinois) with ultraviolet detection at $\lambda = 198$ nm (L-4200H UV-Vis detector, Hitachi). The mobile phase consisted of 0.07-molar potassium phosphate buffer-acetonitrile 91:9 (pH adjusted to 3.45 with phosphoric acid) and was delivered at 1.2 mL/min. Albuterol sulfate (Sigma Chemical, St Louis, Missouri) was used to prepare 7 calibration standards (range 0.1–4.0 μg/mL). Bamethane (Sigma Chemical, St Louis, Missouri) served as the internal standard. For each unknown and standard, 100-μL samples were injected onto the column in duplicate, and peak area ratios of albuterol to internal standard were determined via linear regression. Standard concentrations were linear over the concentrations studied ($r^2 \geq 0.999$). Mean accuracy for the 3 known concentrations (0.2, 1.0, and 3.0 μg/mL) measured on 7 different days ranged from 99.0% to 100.2% of theoretical. The mean interday and intraday coefficients of variation for the known concentrations were 3.5% and 1.3%, respectively ($n = 7$). Mean recovery of a known quantity of albuterol deposited on the breathing filter was 97.2% $\pm$ 3.0% ($n = 5$).

Data Analysis

The total amount of albuterol delivered to the end of the ETT was determined by multiplying the albuterol concentration by the 45.0-mL rinse volume. The percentage of albuterol delivered was determined by dividing the total amount delivered by the quantity administered by the MDI (2,000 μg) and multiplying by 100. Though the albuterol doses used in this study exceeded those used clinically, the inefficiency of aerosolized-medication delivery to mechanically ventilated infants and children required that large doses be used so that the amount of drug delivered to the filter was above the assay's lower detection limit. We report the data as percent-of-dose-delivered, to permit us to compare drug delivery after different numbers of manual breaths and for the various durations of in-line spacer placement.

A minimum sample size of 8 replicates in each group was necessary to detect a 50% difference in albuterol delivery with $\alpha = 0.05$ and $\beta = 0.20$. Groups were compared via analysis of variance and the post hoc Tukey all-pairwise comparison. Difference were considered statistically significant when $p \leq 0.05$. All data are reported as mean $\pm$ SD.

Results

Table 1 shows the results for percentage of albuterol delivered to the end of the ETT. The percent of albuterol delivered after 5 manual breaths (10 s) was 36% lower than after 15 manual breaths (30 s) and 55% lower than after 30 manual breaths (60 s) ($p \leq 0.05$). When the spacer was placed in line, there was no difference in the amount

Table 1. Albuterol Delivered to the End of the Endotracheal Tube*

Administration Method	% Delivery
5 manual breaths (10 s) after each MDI actuation	2.3 ± 0.5†‡
15 manual breaths (30 s) after each MDI actuation	3.6 ± 1.8†
30 manual breaths (60 s) after each MDI actuation	5.1 ± 1.3
In-line spacer placement: 30 s after each MDI actuation	3.7 ± 1.3
In-line spacer placement: 60 s after each MDI actuation	3.7 ± 0.6

*Albuterol administered from a metered-dose inhaler (MDI) with ACE spacer to a neonatal ventilator-lung model. Values are mean ± SD (n = 10).
†$p < 0.05$ compared to 30 manual breaths (60 s)
‡$p < 0.05$ compared to in-line spacer placement for 60 s after each MDI actuation
p values calculated with Tukey's test for all-pairwise comparison

of albuterol delivered after 30 or 60 s. However, the amount of albuterol delivered after 5 manual breaths was 38% lower than after inserting the spacer in line and waiting 30 or 60 s between actuations.

Discussion

The optimal dose of MDI albuterol to mechanically ventilated neonates has not been studied and neither has the optimal interval between actuations. Sixty-five percent of neonatal centers surveyed administer 2 puffs of albuterol via MDI-with-spacer, with the majority of centers allowing up to 1 min between actuations.[24] In our mechanically ventilated neonatal lung model the amount of albuterol delivered was significantly lower when the spacer was quickly removed after albuterol administration. Five manual breaths (administered over 10 s) after each MDI actuation delivered less than half of the amount of albuterol to the end of the ETT, compared to 30 manual breaths (administered over 60 s). Similarly, with 15 manual breaths (administered over 30 s) albuterol delivery was only 71% of that delivered with 30 manual breaths (administered over 60 s). Moreover, albuterol delivery was greater when the spacer remained in line for 30–60 s after each actuation, compared to manually administering 5 breaths after each actuation.

Our data indicate that reducing the duration of manual ventilation after MDI actuation significantly reduces albuterol delivery, but it is not known whether this in vitro phenomenon translates into significantly lower clinical efficacy.

The effects of gas flow and V_T on drug delivery with an MDI-with-spacer probably explain the positive correlation between albuterol delivery and the amount of time the spacer remains in line. Sufficient gas flow through the spacer is required to clear the aerosol from the spacer, so it is reasonable to expect that low flow will deliver less aerosol than higher flow. Accordingly, our results are not surprising, considering that the V_T (7 mL) in our neonatal lung model is < 5% of the internal volume of the ACE spacer (146 mL). Low flow might also increase the deposition of aerosol droplets inside the spacer and circuit, which is partly due to electrostatic attraction between the aerosol particles and the spacer's internal surface. Circuit deposition from electrostatic charge can be minimized by pretreating the inside of the spacer with ionic detergent.[25]

The results of the present study indicate that 5 breaths and 15 breaths (cumulative V_T of 35 mL and 105 mL, respectively) are insufficient to maximize albuterol aerosol delivery. These results apply to extremely-low-birthweight premature infants who weigh approximately 1-kg and who have a V_T of approximately 7 mL/kg, but they may not apply to larger infants, because they have larger V_T, which would be associated with greater aerosol delivery.

Our findings are consistent with the limited number of published in vitro neonatal lung studies. Our present results for when the spacer was left in line for 30–60 s after each actuation are similar to the results from our previous study (3.82–5.66%) that used an in vitro neonatal lung model and an MDI with ACE spacer.[11] Avent et al[26] used an Aerochamber spacer with an in vitro infant lung model and they reported 2.17% albuterol (Ventolin) delivery.

In the present study we did not address the risk of hypercarbia from having the spacer in line for a prolonged period. Recent studies indicate that the risk of hypercarbia is low when the spacer is attached to a neonate's ETT for a limited period of time. Lugo et al[27] found that carbon dioxide accumulation in the spacer depended on the patient's V_T, the type of spacer used, and amount of time the spacer was in the circuit.[27] In that study carbon dioxide accumulation in the ACE spacer peaked at 4 min and was < 12 mm Hg. In 2 min (the amount of time a spacer is usually kept in line to administer the usual dose of albuterol) the carbon dioxide accumulation in the spacer was approximately 2.0 mm Hg with a V_T of 7.5 mL, and 10.0 mm Hg with a V_T of 15.0 mL.[27] Those in vitro data suggest that keeping the ACE spacer in line for several minutes to optimize albuterol administration does not substantially increase the risk of hypercarbia in mechanically ventilated premature neonates.

Liu and Heldt[28] conducted an in vivo safety study to measure the increase in P_{CO_2} after beclomethasone administration in mechanically ventilated neonates. They observed a transient 4–10 mm Hg increase in P_{CO_2}, which returned to baseline in 30 min. In contrast, Lee et al[2] reported a significant decrease in P_{CO_2} 30 min after administering albuterol via MDI. Fok et al[29] observed no significant change in transcutaneously measured P_{aCO_2} 30 min after administering albuterol via MDI. Our view of the results of the latter studies is that adding a spacer to the end of the ETT for a limited period of time is associated

with a low risk of inducing hypercarbia in mechanically ventilated neonates.

The Aerochamber valved holding chamber is commonly used to administer aerosolized medication to mechanically ventilated patients;[26,30–32] however, we used the ACE spacer, because albuterol delivery is greater with the ACE (4.1%) than with either the Aerochamber-MV (1.2%) or Aerovent (1.5%) when tested with our neonatal lung model.[15] It is noteworthy that our in-line placement of the ACE spacer was different than the manufacturer's recommended in-line position for mechanically ventilated adults. The ACE product information sheet recommends placing the ACE spacer in the inspiratory limb of the circuit, proximal to the Y-piece, and in the reverse-firing position. However, with neonates who require time-cycled, pressure-limited ventilation there is no specific recommendation, and the reverse-firing position would significantly increase drug loss through the expiratory limb because of the continuous gas flow.[33] To minimize that effect, most neonatal clinicians place the spacer between the ETT and the Y-piece, or attach the spacer to the ETT and administer aerosol via manual ventilation.[24] The manufacturer of the ACE spacer recommends the forward-firing position when attaching the ACE spacer directly to the ETT, and administering the aerosol via manual ventilation. That avoids firing the aerosol backwards into the resuscitation bag, where drug would be lost. Similarly, to avoid firing the aerosol backwards into the continuous flow of gas in the circuit, we inserted the ACE spacer in the forward-firing position when placing it in line between the Y-piece and ETT.

With regard to delivering aerosolized albuterol to mechanically ventilated neonates, it may be more important to provide consistent, reproducible drug delivery than it is to maximize the percent of drug delivered, particularly since albuterol is relatively inexpensive and the dose can be easily titrated to the desired effect. However, the results of the present study underscore the potential for dose-to-dose variability in aerosol delivery when there is inconsistency in respiratory therapists' methods of administering MDI albuterol. That practice variability could cause adverse effects and erroneous conclusions regarding dosage requirements and patient response. For those reasons we recommend standardizing the MDI administration method within a facility.

The present study was limited by the lack of validation of the in vitro neonatal model; it is unknown how well our model predicts in vivo drug delivery. However, that concern is mitigated by a recent study in adults, which found close agreement between in vitro models and in vivo scintigraphy findings, when the effects of circuit humidity and exhaled aerosol were taken into account.[34] In addition, O'Riordan et al[33] reported that in vitro bench models of neonatal ventilation resulted in drug deposition that is proportional to that detected in the lung. It should be noted, however, that conclusions derived from models (including the present study) are specific to the stated conditions and cannot be extrapolated to a broad neonatal population in which V_T, respiratory rate, and other variables are different than those described in the in vitro study. Our results are best applied to extremely-low-birthweight infants who have ventilator settings and V_T similar to those we used in our experiments.

Conclusions

In our neonatal-ventilator lung model, albuterol delivery from an MDI-with-spacer was significantly reduced by removing the spacer from the ETT after 5 or 15 manual breaths (10 or 30 s, respectively), compared to 30 manual breaths (60 s) between MDI actuations. Similarly, removing the spacer from the ETT after 5 manual breaths (10 s) caused significantly less albuterol to be delivered than did leaving the spacer in line for 30–60 s between and after actuations. With in-line albuterol administration, 30 s between actuations appeared to deliver the same amount of albuterol as 60 s; therefore, in order to minimize the risk of hypercarbia, 30 s between actuations may be preferable. The clinical implications of these findings should be considered cautiously, because no clinical correlate to these in vitro findings has been published. Nonetheless, these data should alert practitioners to the risk of reduced albuterol delivery, and therefore less pharmacologic effect, when the spacer is quickly removed from the ETT following MDI actuation. Furthermore, consistency in the method of administration may help reduce the variability of albuterol delivery. These in vitro data provide the basis for future clinical studies to determine the optimal amount of time that a spacer should be left in line to maximize aerosol delivery and minimize the increase in P_{CO_2}.

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