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Diagnostic and Therapeutic Methods

# Jet Nebulization of Budesonide Suspension Into a Neonatal Ventilator Circuit: Synchronized Versus Continuous Nebulizer Flow

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**Summary.** To determine the dose of inhaled budesonide suspension in the treatment of preterm infants with ventilator-dependent lung disease, we measured the dose of nebulized budesonide delivered through an endotracheal tube (ETT), using a test lung and filters. The effect of delivering the nebulized aerosol to two different locations in the same ventilatory circuit was evaluated. In addition, a new synchronized jet nebulizer was tested.

The median drug delivery to the test lung was 0.3% (range, 0–0.4%) of the nominal dose when the nebulizer activated by continuous gas flow was inserted into the inspiratory line of the circuit. Drug delivery could be increased to 0.7% (range, 0.5–0.8%) by delivering the nebulizer output directly to the ETT. When using the synchronized jet nebulizer, drug delivery was 1.1% (range, 0.8–1.6%). The particle size of aerosol emerging from the ETT was 2.14 μm. The nebulization time with the synchronized nebulizer set-up was 38 min, while the other set-ups delivered an equal volume of solution in 6–7 min. Drug delivery of 0.3–1.1% to the test lung illustrates the problems encountered in aerosol treatment of intubated neonates. We conclude that the delivery of budesonide to the test lung can be increased by delivering the nebulizer output to the ETT directly. Using synchronized nebulization during inspiration only can achieve further increases in drug delivery, and wastage of drug during expiration is decreased. Synchronized nebulization may, therefore, have an important place in the delivery of expensive aerosolized drugs. **Pediatr. Pulmonol. 1997; 24:282–286.** 

**Key words: neonates; artificial ventilation; inhalation therapy; budesonide.**

## INTRODUCTION

Dexamethasone treatment in infants with CLD has shown short-term benefits by improving lung compliance and shortening the duration of artificial ventilation.[1–6] However, high doses and prolonged exposure to systemic GCs are associated with significant side effects.[1–7] Inhaled GCs, as used in the treatment of asthma, may reduce the severity of CLD by reducing inflammation and tissue damage and pose low risks compared with systemic GCs.[8] The amount of aerosolized drug delivered to intubated babies depends on a number of variables, such as the choice of flow pattern and the point in the ventilatory circuit at which the aerosolized output of the nebulizer is delivered.[9–12] Generally, the respiratory circuit and the ETT markedly reduce the delivered dose of nebulized drugs, especially when continuous flow patterns are used.[10,13–15]

The aim of this in vitro study was to determine the dose of nebulized budesonide that is delivered through an ETT to a test lung and filters. The primary objective was to evaluate the benefits of synchronizing aerosolization of drug to inspiration only in comparison with continuous nebulization on the dose of budesonide delivered through the ETT. The second objective was to evaluate



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the effect of the point in the ventilator circuit at which the aerosolized drug was delivered on the dose delivered to the test lung.

## MATERIALS AND METHODS

### Equipment

An in vitro set-up was used to compare three different methods of delivering budesonide aerosol through an ETT (Fig. 1). To imitate the treatment situation of a ventilated premature neonate, a rubber silicone test lung with a compliance of 9.6 mL/kPa (Dräger, Germany) and a time-cycled, pressure-limited ventilator with a continuous gas flow of 12 L/min (Baby Bird, Bird Corporation, USA) were used. The inspiratory pressure was set to 18 $cmH_2O$ with a positive end-expiratory pressure of 2 $cmH_2O$. The ventilation frequency was set at 40/min, tidal volume was 15 mL, and the minute volume was 0.6 L/min. The duration of inspiration was 0.4 s and the total respiratory cycle was 1.5 s, giving an inspiratory-to-expiratory time ratio of 0.27. The settings were adjusted and monitored by using a P-7 scanner monitor/alarm system (Bird Corporation, USA). A 3.0 mm outer diameter and 11 cm long ETT (Portex, UK) was connected to the circuit. No humidifier was used.

A dose of 1 mg budesonide suspension in a 2 mL volume was placed into the nebulizer cup of the sidestream jet nebulizer (Medic-Aid Ltd, Pagham, UK). The sidestream nebulizer was operated at a flow of 4.5 L/min. Budesonide suspension was nebulized into the ventilator circuit under three different conditions. Budesonide was collected on two filters (Marquest Respirgard-II filter, Marquest Medical Products, USA), one placed between the tip of the ETT (inspiratory filter) and the test lung, and the other in the expiratory line of the ventilator circuit at a distance of 8 cm from the ETT (expiratory filter). The amount of drug on the inspiratory filter in this set-up was considered to be equal to the amount of drug delivered to the lung plus the exhaled fraction in an in vivo situation.[15] Budesonide was eluted from the filters with ethanol, and the total dose deposited was determined by liquid chromatography (Astra Draco AB, Lund, Sweden).

The total budesonide output from the sidestream nebulizer was 39% of the amount placed into the nebulizer cup, as measured in our laboratory (Astra Draco AB). The sidestream nebulizer produced a droplet size with an MMD of 3 μm when the nebulizer was run with a Portaneb 50 compressor (Medic-Aid Ltd), and about 85% of the aerosol was in droplets <5 μm (Malvern Mastersizer, Malvern, UK).[16] The aerosol emerging from the end of the endotracheal tube had droplets with an MMD of 2.14 μm; about 80% of the aerosol was in droplets <5 μm.

Abbreviations

| | |
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| CLD | Chronic lung disease |
| ETT | Endotracheal tube |
| GC | Glucocorticoid |
| MMD | Mass median diameter |

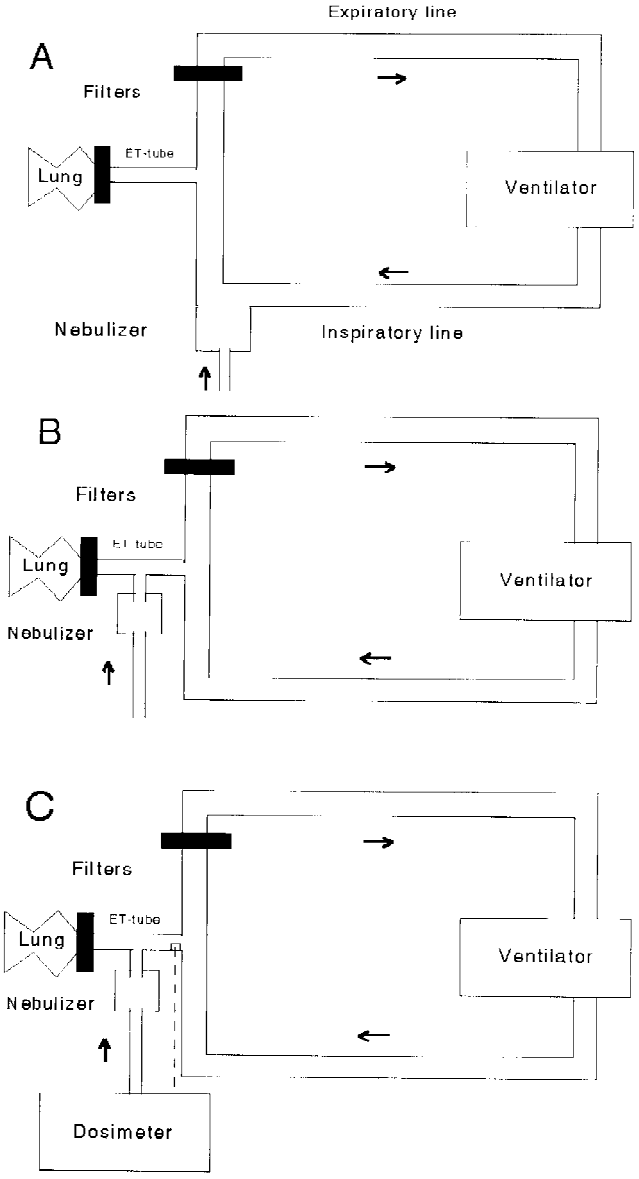


**Fig. 1. The experimental set-ups. Nebulizer output was connected to the inspiratory line in set-up A and to the ETT in set-ups B (continuous flow) and C (synchronized flow). Arrows indicate the direction of the gas flow and black bars the positions of the filters.**

### Test Set-ups

Three different jet nebulizer set-ups were built (Fig. 1). In all of these set-ups the nebulizer was connected by a T-piece connector (BabyBird®, USA) to the circuit. The

T-piece dead space volume was 5 mL. A driving pressure of 1.5 bar was used for all three set-ups, resulting in a continuous flow of 4.5 L/min through the nebulizer.

In *set-up A* (Fig. 1A), the sidestream nebulizer delivered its aerosol into the inspiratory line of the ventilator circuit at a distance of 8 cm upstream from the ETT connector. The sidestream nebulizer was used in a constant flow mode. In *set-up B* (Fig. 1B), the sidestream nebulizer was connected directly to the ETT and was used in a constant flow mode. In *set-up C* (Fig. 1C), the sidestream nebulizer was connected directly to the ETT. The nebulizer was used in a synchronized flow mode so that the nebulizer was triggered at the beginning of an inspiration to generate aerosol for only 0.3 s during each inspiration. A modified Spira E4 synchronizer (Respiratory Care Center, Hämeenlinna, Finland) was used.

Ten experiments were performed with each set-up. The same jet nebulizer was used in all experiments. The nebulizer cup was filled with 1 mg budesonide suspension in a 2 mL volume, and nebulization was stopped at a gravimetric output of 1.5 mg, i.e., 75% of the volume in the cup. The duration of nebulization was recorded. Between the tests, the nebulizer cup was washed with ethanol (96%) and dried.

### Statistical Methods

Differences between set-ups A and B were analyzed using the Kruskal Wallis one-way analysis of variance test. The same analysis was used to detect a difference between set-ups B and C.

## RESULTS

The median amounts of budesonide delivered to the *inspiratory* filters were 3 μg (range, 0–4) with set-up A, 7 μg (range, 5–8) with set-up B, and 11 μg (range, 8–16) with set-up C. The differences in median dose between set-ups A and B, and between set-ups B and C were statistically significant ($P < 0.05$, Fig. 2).

The median amounts of budesonide on the *expiratory* filters were 156 μg (range, 140–207) with set-up A, 164 μg (range, 123–177) with set-up B, and 114 μg (range, 76–154) with set-up C. The difference in median amounts on the filters between set-ups A and B was not significant. However, the difference between set-ups B and C was significant ($P < 0.01$, Fig. 2).

The median duration of nebulization was 6 min 46 s (range, 6 min 16 s to 7 min 43 s) for set-up A, 6 min 43 s (range, 6 min 17 s to 7 min 41 s) for set-up B, and 38 min 25 s (range, 31 min 33 s to 42 min 30 s) for set-up C. The difference in nebulization time between set-ups A and C ($P < 0.05$) and set-ups B and C ($P < 0.01$) were statistically significant.

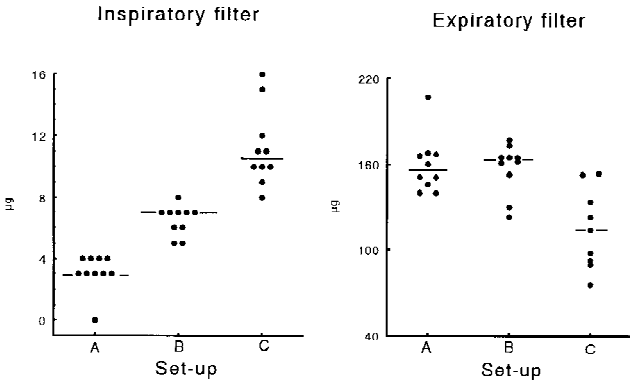


**Fig. 2. The mass of budesonide in the inspiratory and expiratory filters. The nominal dose of budesonide was 1 mg. Medians are expressed as horizontal lines.**

## DISCUSSION

Aerosol delivery measured on filters in an in vitro bench model has been found to be proportional to the delivery detected in the animal lung.[15] Thus, these in vitro models can be used in preliminary testing of aerosol delivery systems. However, comparisons between the in vivo and in vitro models have shown that the in vitro systems, similar to the set-ups in our study, overestimate drug delivery; the filter captures the total amount of aerosolized drug during inspiration including the part of aerosol that would be exhaled during expiration. This has been observed in various set-ups including those using anti-microbial agents or GCs in ventilated and non-ventilated subjects.[17–21]

Drug delivery to the neonatal lung varies from 0.02 to 2.7%, using different jet nebulizers and different set-ups.[9,10,12,22–26] Because of the wide variations in the set-ups, these data cannot directly be compared with the present findings. In our study, drug delivery to the test lung was only 0.3% when a constant flow nebulizer was used. Drug delivery to the test lung could be doubled by connecting the nebulizer output directly to the ETT. This was due to the shorter distance between the site of entrance of the aerosol into the ventilator circuit and the test lung. The length of tubing through which an aerosol has to pass has been shown to be an important determinant for the delivery of nebulized drugs.[11,13] The use of a connector increased dead space by 5 mL in our model. Functionally, however, this increase may be compensated for by the flow of fresh gas to the connector. Our findings of increased drug delivery to the test lung when the nebulizer was connected directly to the ETT is in line with previous in vitro studies.[11,15] In other studies,[10,23] in which delivery of nebulizer output to different positions in the ventilator circuit were tested, no significant differences were observed. However, because of the differences in the overall set-ups, these results cannot be compared with our observations. Our data of 0.3–1.1% drug

delivery to the test lung illustrate the difficulties in aerosol delivery to intubated babies and are in keeping with previous studies.[9,10,22–26] Most of the drug remains in the nebulizer cup and in the tubing.[27] Drug delivery is dramatically affected by the diameter of the ETT; the use of a 6 mm ETT instead of a 3 mm tube resulted in a fourfold increase in drug delivery.[28] We used a 3 mm ETT that is commonly used in mechanical ventilation of preterm infants.

The constant flow of the ventilator circuit delivers a significant amount of the drug to the expiratory line; in our study 11.4–16.4% of the drug was found on the expiratory filters. With synchronized nebulization, deposition on the expiratory filter was significantly lower than with constant gas flow to the nebulizer. One explanation could be a more local deposition of the drug at the site of nebulization. Interestingly, budesonide delivery to the expiratory filter was equal to the deposition of the radiolabeled human serum albumin observed previously.[27]

Theoretically, nebulization restricted to inspiration only markedly decreases the wastage of the drug during expiration and increases total drug delivery through the ETT. In the present study, medication delivery was increased 1.6-fold (to 1.1%) when the synchronizer set-up was used. Accordingly, the ratio between the constant and synchronizer set-ups was similar to previous studies in non-intubated children[29] and adults.[30] The use of higher concentrations of drug in lower volumes would reduce the long duration of nebulization observed in our synchronized flow study.

Drug delivery from metered-dose inhalers via a spacer device connected to an ETT has been suggested to be more efficient than jet nebulization.[9,22,26,31] There are, however, great differences in drug delivery, and it may range from 1.7 to 14.2%.[22,26] The spacer also increases dead space significantly, which may lead to accumulation of $CO_2$, especially when low tidal volumes are used.[32]

The nebulizer with continuous flow connected directly to the ETT is simple to use and results in rapid nebulization of drug. Although drug delivery for budesonide suspension was only 0.7%, the particle size was ideal. In adults, budesonide suspension nebulized with constant flow gives a lung deposition of about 15%.[33] Accordingly, a high nominal dose of 1,000 μg results in a deposition of 150 μg in the lungs, corresponding to 86 $\mu g/m^2$ skin surface. In preterm infants weighing 1,000 g, the skin surface area is about 0.12 $m^2$. When these babies are treated with 1,000 μg of budesonide, the lung deposition should be about 10 μg (86 $\mu g/m^2$). If the drug delivery is 0.7%, the nominal dose should be as high as 1,429 μg. If the drug delivery is 1.1% (synchronized system), the nominal dose should be 938 μg. Whatever the system, the nominal dose of budesonide should be adjusted to the flow pattern of the nebulizer and to the point in the ventilator circuit at which the nebulizer delivers the aerosol. In ventilated and spontaneously breathing subjects, 50–70% of aerosol inhaled will be retained by the lung, the other part being exhaled.[21] Thus, compared with in vivo set-ups, our in vitro deposition overestimates drug delivery because the filter measures the total amount inhaled (i.e., there is no exhalation from an absolute filter).[15]

In conclusion, the delivery of budesonide to the test lung could be increased by directing the nebulizer output directly to the ETT. The use of synchronized nebulization during inspiration only further increased drug delivery and decreased wastage of drug during expiration. Synchronous nebulization may, therefore, have an important role, especially in the delivery of expensive drugs.

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