

An Investigation of Nebulized Bronchodilator Delivery Using a Pediatric Lung Model of Spontaneous Breathing

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BACKGROUND: The literature lacks comparative data on nebulizer aerosol delivered via mask versus T-piece, to spontaneously breathing pediatric subjects. **PURPOSE:** To compare total inhaled drug mass delivered via standard pediatric aerosol mask versus via T-piece, with increasing distance. **METHODS:** We used a sample of 5 nebulizers, operated under manufacturers' conditions, with a standard pediatric aerosol mask and with a T-piece capped at one end, at 0 cm, 1 cm, and 2 cm from an inhalation filter placed at the inlet of a pediatric test lung. Inhaled drug mass was analyzed with spectrophotometry. Aerosol particle size was measured separately from the breathing simulations, using a laser particle sizer to determine fine-particle mass (particles < 4.7 μm) and fine-particle fraction as percent of total mass. The fine-particle fraction was used to estimate the fine-particle mass. **RESULTS:** The mean \pm SD values for inhaled drug mass as a percentage of nominal dose, at 0 cm, 1 cm, and 2 cm, with the mask were $2.88 \pm 0.79\%$, $1.61 \pm 0.65\%$, and $1.3 \pm 0.42\%$, respectively, and with the T-piece were $4.14 \pm 1.37\%$, $3.77 \pm 1.04\%$, and $3.47 \pm 0.64\%$, respectively. There was a statistically greater inhaled drug mass with T-piece than with mask, overall ($p < 0.01$), and a significant decrease with mask or T-piece as distance increased ($p < 0.01$). The difference between mask and T-piece for inhaled drug mass at 2 cm was statistically significant ($p < 0.018$). The mean \pm SD values for fine-particle mass estimated as a percentage of total drug mass at 0, 1, and 2 cm, with the mask were $1.39 \pm 0.36\%$, $0.78 \pm 0.29\%$, and $0.64 \pm 0.20\%$, respectively, and with the T-piece were $2.1 \pm 0.63\%$, $1.84 \pm 0.45\%$, and $1.71 \pm 0.27\%$, respectively. **CONCLUSION:** Inhaled drug mass was greater with T-piece than with a standard pediatric aerosol mask under the conditions studied. *Key words:* aerosol, infant, toddler, pediatric, mask, T-piece. [Respir Care 2006;51(1):56–61. © 2006 Daedalus Enterprises]

Introduction

Aerosol therapy is a common modality for the treatment of respiratory symptoms. Evidence has clearly demon-

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strated that most pediatric patients, regardless of age, respond to bronchodilator therapy.¹ Although a more comprehensive understanding of aerosol therapy has been developed, in vitro studies have demonstrated that only a small proportion of aerosolized drug reaches the lungs of spontaneously breathing children.^{2–10}

An important disadvantage of aerosol therapy with jet nebulizers in pediatric patients is the poor tolerance often demonstrated, because of noise of operation, "lengthy" treatment periods, and the need for a tight-fitting mask.² The absence of a tight seal between the mask and the patient's face results in a decrease in the amount of medication available for inhalation.¹¹ The typical pediatric patient does not tolerate a mask applied to the face, and agitation and crying are frequently observed. The efficacy of aerosol therapy administered to a combative toddler is known to be negligible.^{12,13} Changes in respiratory patterns during nebulization have also been shown to ad-

versely impact the delivery of aerosolized medication.¹⁴ Often the mask is simply held near the face, a technique known as “blow-by.”

An alternative technique for aerosol delivery to the pediatric patient is the use of a T-piece, with one port of the “T” capped so the aerosol stream is directed toward the patient’s face. This technique facilitates the delivery of aerosol to the patient’s face and may be better tolerated than mask therapy, as mask application is avoided. There are few data available on how much drug is actually inhaled with the use of blow-by when a mask or T-piece is used. Everard et al measured the amount of inhaled sodium cromoglycate delivered to a pediatric lung model, with a mask held 0 cm, 1 cm, and 2 cm away from an inhalation filter.³ However, we could find no similar data for inhaled albuterol with a mask or T-piece used with blow-by. The purpose of this study was to investigate these 2 methods of aerosol delivery in a model of a spontaneously breathing pediatric patient. Two research questions were the focus of this study:

1. Is there a difference in inhaled drug mass between mask and T-piece?
2. What is the effect of the distance between the delivery device and the inhalation filter on inhaled drug mass?

Methods

Lung Model

An *in vitro* model to simulate spontaneous breathing in a toddler was constructed, using a dual-chamber test lung (adult/infant TTL model 2601I, Michigan Instruments, Grand Rapids, Michigan). A bar was used to connect the adult and infant test-lung chambers. A ventilator (Bennett MA-2, Puritan Bennett, Pleasanton, California) was used to power the adult side of the test lung, and the infant side served as the breathing simulator in both the inspiratory and expiratory phases.

The adult side of the test lung was powered with a square-wave flow pattern at a suitable volume, rate, and flow to create an inspiratory tidal volume of 60 mL at a respiratory rate of 20 breaths/min in the infant side. The inspiratory-to-expiratory ratio was set at 1:2, giving an average flow of 3.6 L/min. The tidal volume was read from the displacement line marker on the infant test lung, and verified using a respiratory mechanics monitor (Vent-Check, Novamatrix, Wallingford, Connecticut).

An inhalation filter (2-way, nonconductive anesthesia filter, model 1T0241, Baxter Healthcare, Valencia, California) was connected to the 15-mm adapter located at the infant test-lung inlet, to collect the “inhaled” aerosol. For the nebulizer trials conducted at a 0-cm distance between the aerosol mask and the filter, we used a 10×10-cm piece of waterproof film (Parafilm M, American National Can,

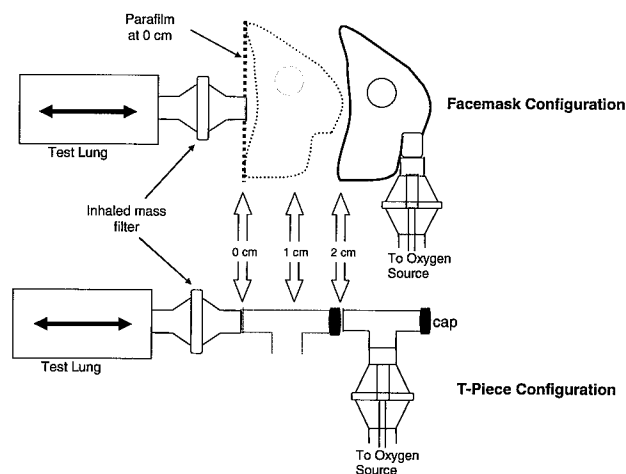


Fig. 1. Configuration of equipment for simulation of spontaneous pediatric breathing and delivery of nebulizer aerosol via either face mask or T-piece at 0 cm, 1 cm, and 2 cm from the filter at the inhalation port.

Greenwich, Connecticut) to create a “face-mask seal” by stretching the film from the edges of the aerosol mask to the edge of the inlet of the inhalation filter. The T-piece was placed directly at the filter inlet for the 0-cm distance. The film was removed for measurements at 1 cm and 2 cm, because the face seal was not necessary (Fig. 1). Each nebulizer was held vertical with a metal holder and a clamp to minimize the risk of error that could be caused by misalignment. Both mask and T-piece were placed at right angles to the inhalation filter/inlet.

Study Design

Five samples of the nebulizer (Misty-Neb, Baxter Healthcare, Valencia, California) were attached, in paired fashion, to either a pediatric aerosol mask (Allegiance Healthcare, McGaw Park, Illinois) or a T-piece that had its distal opening obstructed with a cap, in alternating order. The open ports in the aerosol mask were not blocked in any way. The distance between the aerosol-delivery device and the inhalation filter was increased from 0 cm to 2 cm, in 1-cm increments. This resulted in a total of 30 trials (6 trials with each of the 5 nebulizers). The nebulizers were powered by 50-psi oxygen at 8 L/min and were run to the onset of sputter, with no tapping of the nebulizer. For each trial the nebulizer was filled with 3.0 mL of a unit dose vial that contained 3.0 mg of albuterol sulfate, which is equivalent to 2.5 mg of albuterol base.

Measures

In each trial the inhaled drug mass and the residual drug in the nebulizer apparatus were collected and measured.

Based upon previous measures, a negligible amount of drug is left in the unit dose vial, and this was not analyzed in the present study. Because of the open nature of the model, with distance between the the inhalation filter and mask or T-piece, the drug mass lost to the ambient air could not be collected and measured. Exhaled/ambient loss of drug was estimated by subtracting the inhaled drug mass and the residual nebulizer drug mass from the total starting (nominal) dose of albuterol sulfate.

The total inhaled drug mass was measured by collecting the aerosolized medication captured on the inhalation filter during simulated spontaneous breathing. The drug remaining in the nebulizer system was collected by washing the components with a 0.1 N hydrochloric-acid solution. Each nebulizer was weighed empty, after filling, and at the end of nebulization, to calculate the volume left, as described previously by us¹⁵ and by Coates et al.¹⁶ Solvent was added to the calculated volume, drug concentration was determined with spectrophotometry, and the drug mass was calculated.

All drug amounts were analyzed with a spectrophotometer (Beckman Instruments, Fullerton, California) at a wavelength of 276 nm. The solvent was 0.1 N hydrochloric acid (JT Baker, Phillipsburg, New Jersey). Collecting filters were washed for 1 min with gentle agitation; longer washing did not yield additional drug. The spectrophotometer was calibrated prior to trials, using a holmium oxide filter (Beckman Instruments, Fullerton, California) to determine wavelength accuracy, and set to zero, using the solvent alone, before each analysis. A regression curve and prediction equation was developed from a known albuterol sulfate solution (Sigma, St Louis, Missouri). Concentrations of sample solutions, and thereby drug amount of albuterol, were calculated from this known concentration/absorbency relationship.

Particle-size measurements were made separately from the trials conducted with the lung model. Particle-size distribution for each of the 5 nebulizers, with no T-piece or mask, was determined as a static measurement, using a laser diffractometer (Mastersizer X, Malvern Instruments, Worcestershire, United Kingdom), operated with a 100-mm lens. Five replicate measurements were made per device, using 3.0 mL of albuterol sulfate, with the nebulizer powered at 8 L/min. The fine-particle fraction was determined as the percentage of particles that were less than 4.8 μm (fine-particle mass/total mass \times 100). The geometric standard deviation was calculated as the ratio of particle diameter at 84% of the cumulative distribution divided by the diameter at 50% of the cumulative distribution. The portion of the inhaled drug mass in the fine-particle range was indirectly estimated as the product of fine-particle fraction and total inhaled drug mass.

Table 1. Drug Mass on the Collecting Filter, Left in the Nebulizer, and Estimated As Ambient Loss, Expressed As a Percentage of the Beginning Nominal Dose

	Distance (cm)	Drug Mass (mean \pm SD percent)	
		Mask*	T-Piece*
Inhalation Filter (measured)	0†	2.88 \pm 0.79	4.14 \pm 1.37
	1†	1.61 \pm 0.65	3.77 \pm 1.04
	2†	1.30 \pm 0.42‡	3.45 \pm 0.62‡
Nebulizer Loss (measured)	0	68.3 \pm 3.71	66.78 \pm 1.69
	1	68.89 \pm 2.38	67.4 \pm 6.02
	2	64.96 \pm 5.6	64.87 \pm 4.39
Ambient Loss (estimated)	0	28.83 \pm 3.06	29.08 \pm 1.53
	1	29.5 \pm 1.83	28.84 \pm 5.4
	2	33.74 \pm 5.53	31.65 \pm 4.28

*Significant difference overall ($p < 0.01$) for mask versus T-piece

†Significant distance overall ($p < 0.01$) across distances

‡ $p = 0.018$

Statistical Analysis

A randomized block factorial analysis of variance for repeated measures was performed for devices and distances, with an alpha level of 0.05.¹⁷ Follow-up comparisons were performed using a paired t test for drug delivery between devices at each distance, as well as between distances, and a Bonferroni-adjusted probability was calculated for each test.

Results

Table 1 lists the mean \pm SD values for total drug mass, nebulizer residual drug mass, and estimated ambient drug loss as a percentage of nominal dose for each type of device at 0 cm, 1 cm, and 2 cm.

Randomized block factorial analysis of variance for device and distance indicated a statistically greater inhaled drug mass with T-piece than with mask ($p < 0.01$), and significant decrease as distance increased ($p < 0.01$). The Bonferroni-adjusted probabilities for inhaled drug mass with mask versus T-piece were 1.0, 0.14, and 0.018, at 0 cm, 1 cm, and 2 cm, respectively, indicating a statistically significant difference only at 2 cm. With the mask, the probabilities for differences in inhaled drug mass between 0 cm and 1 cm, 0 cm and 2 cm, and 1 cm and 2 cm were 0.054, 0.063, and 1.0, respectively, indicating no difference in inhaled drug mass, although the differences between 0 cm and 1 cm, and between 0 cm and 2 cm, approached significance. Changes in inhaled drug mass with the T-piece were not significantly different between any of the distances measured.

Table 2. Particle-Size Data From the 5 Tested Nebulizers*

Nebulizer	Volume Median Diameter (mean \pm SD μm)	Fine-Particle Fraction (mean \pm SD%)	Geometric Standard Deviation (mean \pm SD)
1	7.19 \pm 0.49	47.96 \pm 1.88	2.1 \pm 0.1
2	6.09 \pm 0.37	47.55 \pm 1.03	2.1 \pm 0.0
3	6.89 \pm 0.40	55.09 \pm 0.75	2.0 \pm 0.0
4	5.95 \pm 0.18	48.37 \pm 0.89	2.1 \pm 0.2
5	6.33 \pm 0.03	49.29 \pm 0.96	2.1 \pm 0.1

*Based on 5 replicate measurements. See Methods section for details of measurement.

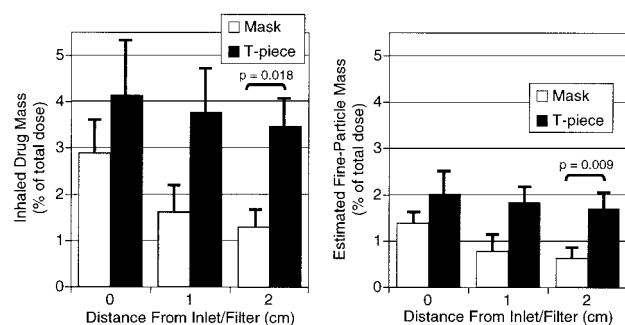


Fig. 2. Mean \pm SD values for measured inhaled drug mass and estimated fine-particle mass for mask and T-piece at 0 cm, 1 cm, and 2 cm from the filter at the inhalation port. The difference between mask and T-piece was significant at 2 cm for both inhaled drug mass and fine-particle mass. See text for details on calculation of estimated fine-particle mass.

Table 2 lists the mean \pm SD values for the particle-size measurements with each of the 5 nebulizers tested, without a mask or T-piece attached.

Figure 2 shows the mean \pm SD values for the total inhaled drug mass as a percentage of the nominal dose, for both mask and T-piece, at each of the 3 distances tested. Figure 2 includes the estimated fine-particle mass percent, calculated as the product of the measured fine-particle fraction and the measured inhaled drug mass. There was a significant difference in the estimated fine-particle mass percent between the mask and T-piece ($p < 0.01$), and with changes in distance from the filter ($p < 0.01$).

Bonferroni-adjusted probabilities for fine-particle mass percent between mask versus T-piece were significant at 2 cm ($p = 0.009$). Differences in fine-particle mass percent for the mask alone or for the T-piece alone were not significant at the 3 distances tested ($p > 0.05$).

Discussion

Despite a recommendation by Friegang to consider an alternative method for aerosol delivery to children less than 4 years of age, no substantial changes have been

undertaken in the techniques for nebulizer-aerosol delivery to pediatric patients.¹⁸ In the present study the T-piece gave greater inhaled drug mass than did the mask at all 3 distances measured, with a significant difference at 2 cm. Results were similar for the estimate of fine-particle mass percent. However, all inhaled drug amounts were considerably lower than those with adults receiving aerosol from a small-volume nebulizer.¹⁹

Everard et al investigated the inhaled mass with 40 mg of sodium cromoglycate (10 mg per mL) via face mask, using a similar in vitro technique.³ In Everard's study, at 0 cm, 1 cm, and 2 cm the mean deposition on the filter was 1.25 mg, 0.49 mg, and 0.18 mg, respectively. Expressed as a percentage, this is 3.13%, 1.2%, and 0.45%, respectively. These values compare well with the inhaled mass percentages in the present study with the mask, which were 2.88% at 0 cm, 1.61% at 1 cm, and 1.30% at 2 cm. Everard et al used a set tidal volume of 50 mL, whereas we used a set tidal volume of 60 mL, but that difference in tidal volume does not appear to have been a source of significant difference.³

A study by Amirav et al, which compared nebulizer delivery to infants via aerosol mask versus via a prototype hood, found a mean lung deposition of 2.4% of the nominal dose with the aerosol mask.²⁰ In that study the mask was fitted to the infant's face, so that 2.4% value is comparable to the value at 0 cm in our study, which was 2.88% of the total dose. The fine-particle mass in our study (1.42%) was actually lower than the lung deposition in the study by Amirav et al, which may be because they used a different nebulizer (Hudson Micromist) or because of other differences between an in vitro and in vivo study.

Though the aerosol mask values from the Everard et al study and those from the present study are very similar, it is important to note the performance of the T-piece at all measured distances. In the present study the inhaled drug mass percentage values with the T-piece were 4.14%, 3.77%, and 3.47%, at 0 cm, 1 cm, and 2 cm, respectively, and the T-piece performance was superior to the aerosol mask. At 0 cm, T-piece use increased the inhaled drug mass by 44%, compared to aerosol mask use. A 134% increase was observed at 1 cm, and a 167% increase was observed at 2 cm.

The superior performance of the T-piece may be associated with its physical design. The T-piece is constructed with a 90-degree "T" shape. Conventional nebulizers attach at the base of the "T." In the presence of an occluded distal port, this technique directs the aerosol stream toward the patient's face (the filter in the study) and could explain a substantially higher amount of inhaled drug mass by simple impaction. Beyond the face, aerosol delivery is an open question. It is possible that a more standard adaptor (L-shaped) can suffice or that the adaptor may be com-

pletely unnecessary. However, the alignment of the nebulizer under these last conditions may change and affect the available inhaled drug mass. The design of the standard pediatric aerosol mask is such that the aerosol leaving the nebulizer is directed vertically into the mouth and nose areas of the mask. The movement of aerosol toward the patient's face depends on the adequacy of the mask seal and the patient's inspiratory effort. The side holes found on standard pediatric aerosol masks are a source of aerosol loss, contributing to a decrease in the amount of medication available to the patient. It is important to note that the side port holes were not occluded in any way during the nebulizer trials.

The data generated in this research indicate that the nebulizer drug loss (drug remaining in the nebulizer following termination of the trial) ranged from 59.70% to 77.26% of the total drug volume present at the initiation of each trial. These measurements are in agreement with previously published studies of nebulizer-apparatus loss.^{19,21}

There are several limitations to the present study. First, we did not have a direct measure of particle-size distribution during the simulated breathing trials. It is difficult to obtain accurate particle-size measurements while simulating breathing without influencing the aerosol or the inhalation properties. In addition, measurements of fine-particle mass may not be as representative of potential lung deposition with infants as they are with adults. The use of separate measurements of particle size was intended to give some indication of the efficiency of the nebulizers tested in producing smaller particles.

A second limitation was the lack of a true mass-balance measure. With the open system (ie, space between the inhalation filter and T-piece or mask), it was not practical to capture aerosol lost to the ambient air.

A third limitation is that the T-piece measurement of inhaled drug mass and fine-particle mass at 0 cm must be acknowledged as somewhat unrealistic. It is very unlikely to occur clinically, because it is extremely difficult to establish and maintain a T-piece positioned at 0 cm from the mouth of an infant or toddler.

Although the steady-state nature of an *in vitro* study does not reflect the potential differences one might expect if studying live subjects, the major advantage of using a lung model to simulate actual respiratory patterns is the minimization of the substantial intra- and inter-subject variability that is common in toddlers. Finally, our use of auditory pitch changes (nebulizer sputter), rather than a timer, to determine the termination point for each trial resulted in inconsistent aerosolization periods. This could result in differences in "dead volume" with each nebulizer, as well as differences in inhaled drug mass in each trial. However, we found no data to show that nebulizer treatments are given clinically for a pre-set time period. By

nebulizing to sputter, this study yielded data more representative of actual clinical use.

Aerosol studies performed by Everard et al² and by Amirav and Newhouse¹¹ examined the use of valved holding chambers with aerosol-delivery devices. The importance of the face-mask seal has been established, as has the efficacy of metered-dose inhalers. Further research on pediatric aerosol delivery should be performed to improve the efficacy of pediatric aerosol delivery. A randomized controlled *in vivo* study is needed to compare patient response with aerosol mask versus T-piece and truly identify the clinical importance, if any, of the T-piece values from the present study. Additional studies should be undertaken to compare the efficacy of design modifications in a standard pediatric aerosol mask versus the more traditional, slightly modified pediatric mask devices marketed specifically for aerosol delivery.

Conclusion

Our study shows that the use of a T-piece for aerosol administration is probably superior to the use of a standard pediatric aerosol mask under the conditions tested. The use of a T-piece with conventional nebulization is likely to optimize the inhaled drug mass for infants and toddlers.

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