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Pressurized Metered-Dose Inhalers Versus Nebulizers in the Treatment of Mechanically Ventilated Subjects With Artificial Airways: An In Vitro Study

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BACKGROUND: The primary focus of previous aerosol research during mechanical ventilation was the endotracheal tube (ETT). Consequently, there are limited data in the literature on the delivery of inhaled medications administered with different aerosol devices in mechanically ventilated patients with a tracheostomy tube (TT). The purpose of this study was to quantify and compare the efficiency of aerosol devices in a lung model of an intubated and mechanically ventilated adult with a TT. METHODS: An in vitro lung model was constructed to simulate a ventilator-dependent adult with a Portex TT and a Mallinckrodt ETT (8-mm inner diameter). Aerosol was collected distal to the bronchi of an adult mannikin on a filter attached to a passive test lung. A ventilator delivered adult breathing parameters (tidal volume 450 mL, breathing frequency 20 breaths/min, peak expiratory flow 40 L/min, and inspiratory-expiratory ratio 1:3) to the airway. A jet nebulizer and pressurized metered-dose inhaler (pMDI) were placed in the inspiratory limb of the circuit 15 cm from the Y-adapter. The jet nebulizer was operated at 8 L/min to deliver albuterol sulfate (2.5 mg/3 mL), whereas an albuterol pMDI was actuated 4 times with a spacer. Drug was eluted from the filter and analyzed by spectrophotometry. RESULTS: Drug delivered via a TT was marginally greater compared with an ETT using the jet nebulizer and pMDI ($P = .10$ and .046, respectively). Although delivery efficiency with the pMDI was 3-fold greater than with the jet nebulizer with both a TT and an ETT ($P = .001$ and .002, respectively), the jet nebulizer delivered greater drug mass compared with the pMDI with either a TT ($P = .01$) or an ETT ($P = .005$). CONCLUSIONS: Aerosol drug delivery via a TT was greater than with an ETT, whereas the delivery efficiency of a pMDI via either airway was greater than that of a jet nebulizer. *Key words: aerosols; nebulizers; metered-dose inhalers; mechanical ventilation; tracheostomy; endotracheal tube.* [Respir Care 0;0(0):1–•. © 0 Daedalus Enterprises]

Introduction

Ventilator-dependent patients with artificial airways frequently need aerosol therapy. Inhaled bronchodilators are commonly administered with both pressurized metered-dose inhalers (pMDIs) and jet nebulizers to patients with tracheostomy tubes (TTs) or endotracheal tubes (ETTs) suffering from acute or chronic respiratory distress. However, providing effective aerosol therapy is a complex procedure that is influenced by many factors.[1-5] Achieving success in aerosol therapy in patients with artificial air-

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ways depends on both the efficiency of aerosol devices and the type of artificial airways used.

Because the primary focus of previous research on aerosol delivery during mechanical ventilation was the ETT,[6-16] there are limited data in the literature on the delivery of inhaled medications administered with different aerosol devices in mechanically ventilated patients with TTs. Consequently, the difference between TTs and ETTs in drug delivery to ventilator-dependent patients is not clear, and determining the most efficient aerosol device for critically ill patients with a tracheostomy is essential to optimize effectiveness of drug delivery to this patient population. The purpose of this study was to quantify the efficiency of aerosol devices in a lung model of an intubated and mechanically ventilated adult with both types of artificial airways. Upon review of the literature, the following research questions arose. (1) What is the amount of drug deposition with a jet nebulizer and pMDI in simulated mechanically ventilated adult models with TTs and ETTs? (2) What is the difference between a jet nebulizer and pMDI in delivery efficiencies in simulated ventilator-dependent adults with artificial airways? (3) How does aerosol delivery via a TT differ compared with an ETT in a lung model of adult mechanical ventilation?

QUICK LOOK

Current knowledge

Aerosol delivery in mechanically ventilated patients is impacted by ventilator settings, aerosol delivery device, device placement, humidification, and the artificial airway. Previous research has predominately evaluated the impact of the endotracheal tube on aerosol delivery.

What this paper contributes to our knowledge

Aerosol drug delivery in an adult lung model was reduced with an endotracheal tube compared with a tracheostomy tube. Aerosol delivery using either airway was greater with a pressurized metered-dose inhaler than with a jet nebulizer. The clinical relevance of these findings remains to be elucidated.

Methods

Lung Model

As shown in Figure 1, an in vitro lung model was constructed to simulate mechanically ventilated adults with artificial airways such as a TT or an ETT. An anatomic teaching mannikin was intubated with either an 8-mm inner diameter TT (Portex, Smiths Medical, Hythe, Kent, United Kingdom) or ETT (Mallinckrodt, Covidien, Mansfield, Massachusetts). Each main bronchus of the mannikin was connected to a bifurcated adapter, which was attached to a collecting filter (Respirgard II, Vital Signs, Totowa, New Jersey) in line with a passive test lung. Using a heated humidifier with a 22-mm inner diameter heated-wire ventilator circuit, a ventilator (Esprit, Philips Respironics, Murrysville, Pennsylvania) was heated and humidified until the temperature was stable at 35 ± 2°C to ventilate the model, and adult breathing parameters were delivered (tidal volume 450 mL, breathing frequency 20 breaths/min, and inspiratory-expiratory ratio 1:3).

Albuterol sulfate was administered via a jet nebulizer (eValueMed, Tri-anim, Dublin, Ohio) and pMDI (ProAir HFA, Teva Specialty Pharmaceuticals, Atlanta, Georgia) placed in the inspiratory limb of the circuit proximal to the intubated model. The jet nebulizer and pMDI with a spacer (AeroVent, Monaghan Medical, Plattsburgh, New York) were placed 15 cm from the Y-adapter in the inspiratory limb of the ventilator circuit (see Fig. 1) for administration of aerosol during mechanical ventilation. The jet nebulizer was operated continuously at 8 L/min to deliver albuterol sulfate (2.5 mg in 3 mL of normal saline) and run until sputter, whereas a primed pMDI with a spacer was actuated at > 15-s intervals to deliver 4 puffs (108 μg/puff). We synchronized the pMDI actuations with the beginning of inspiration. All runs were completed by the same operator to prevent inter-operator variability. Aerosol drug delivery distal to the bronchi was measured by eluting drug from the collecting filter after each treatment. Each condition was repeated in triplicate.

Data Collection and Analysis

Deposited drug was eluted from the filter with 0.1 N hydrogen chloride, analyzed by spectrophotometry at 276 nm (Beckman Coulter, Fullerton, California) to quantify inhaled drug mass, and expressed as mean ± SD mass of drug and percentage of the nominal dose delivered with each aerosol generator. Comparisons of inhaled dose percentages between aerosol devices with each airway were made using independent *t* tests. *P* of < .05 was considered statistically significant.

Results

Table 1 shows the mean ± SD inhaled mass (μg) and lung dose percentage of the emitted (pMDI) and nominal (jet nebulizer) dose delivered distal to the trachea with each device. Drug delivery distal to the bronchi trended higher with a TT than with an ETT with both devices, but only the pMDI was significant ($P = .046$), not the jet

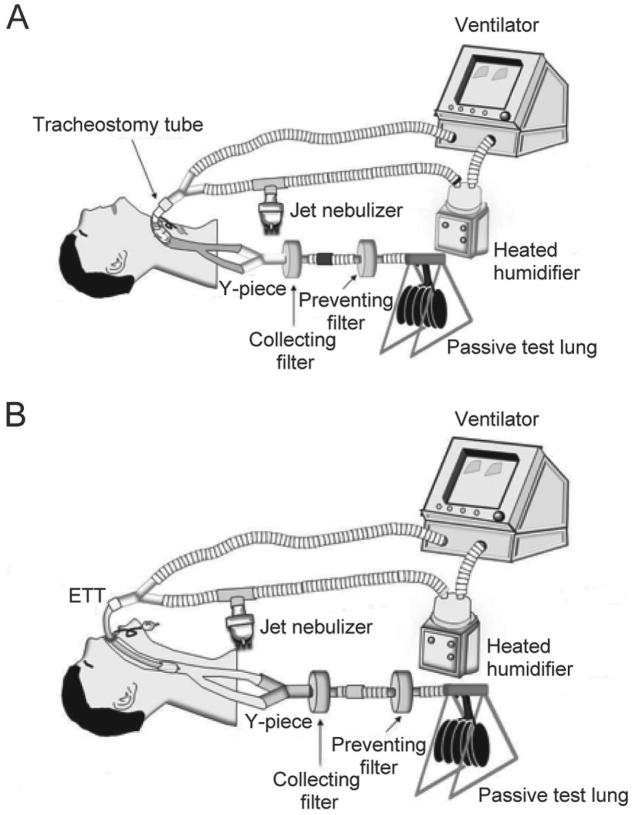

Fig. 1. Model to simulate mechanically ventilated adults with artificial airways. A: Tracheostomy tube. B: Endotracheal tube (ETT). Aerosol was generated by a pMDI and jet nebulizer placed proximal to the airway in the inspiratory limb of a heated humidified ventilator circuit attached to the artificial airway placed orally or tracheally in an adult teaching mannikin. A collecting filter placed distal to the bronchi was attached to a passive test lung.

nebulizer ($P = .10$). Although the delivery efficiency of aerosols with the pMDI and spacer was up to 3-fold greater compared with the jet nebulizer with both a TT and an ETT ($P = .001$ and .002, respectively), the jet nebulizer delivered more drug than the pMDI with both a TT ($P = .01$) and an ETT ($P = .005$). Regardless of the type of aerosol device used in this study, inhaled mass obtained with a TT was greater compared with an ETT ($P < .05$).

Discussion

The study shows that aerosol delivery is influenced by the type of artificial airway and aerosol device used for treatment in our model of ventilator-dependent patients. Lung dose via a TT was marginally greater compared with an ETT regardless of the type of aerosol device used for aerosol therapy in simulated ventilator-dependent patients. The pMDI had a greater efficiency than the jet nebulizer with both a TT and an ETT. During mechanical ventilation of this in vitro model, aerosol delivery to filters distal to the bronchi of the model ranged from 3.18 to 14.73% of the emitted (pMDI) or nominal (jet nebulizer) dose.

For airways with the same internal diameter, drug delivery was greater with a TT than with an ETT. The difference in aerosol deposition between the TT and ETT may be due in part to the length of the TT compared with the ETT. Poiseuille's law teaches that, in laminar systems, the diameter of the airway is associated primarily with the resistance through a tube, whereas the length of a tube is a secondary factor. Consequently, the shorter artificial airway of the same internal diameter would have less resistance to flow and possibly lower levels of transitional flow and turbulence-associated impaction losses of aerosol in transit.

These findings are consistent with our previous research comparing delivery of aerosol via TTs and ETTs using different interfaces in a model of a spontaneously breathing patient.[17] We reported that aerosol delivery was more efficient with a TT than with an ETT with a jet nebulizer and pMDI (18% and 21%, respectively, compared with the 22% and 27% found in this study). The difference may be due in part to differences between the inspiratory-expiratory ratios (1:2 used for spontaneous ventilation vs 1:3 for mechanical ventilation) and the resulting increase in inspiratory flows used in this study. In the previous study,[17] aerosol was administered to the simulated spontaneously breathing patient under ambient conditions without additional heat and humidification; nevertheless spontaneous breathing with a jet nebulizer via a T-piece to the TT was 3-fold greater than simulated aerosol delivery to a ventilator-dependent patient using a heated humidified ventilator circuit during mechanical ventilation.

Others have reported greater aerosol deposition during spontaneous breathing than during active mechanical ventilation or positive-pressure ventilation.[18,19] This reduction may be explained in part by less turbulent flow and subsequent inertial impaction by active inspiration during spontaneous breathing. Moreover, it has been well documented that aerosol delivery is decreased by up to 40% in heated humidified ventilator circuits compared with unheated and non-humidified circuits.[1,5,10,12,20-22] Because ventilator-dependent patients with artificial airways are commonly provided heated humidified gas during mechanical ventilation, we used humidification in the adult lung model in this study.

Multiple investigators have reported in vitro studies that drug delivery to simulated ventilator-dependent subjects ranges from 1 to 37% depending on the type of aerosol device, interface, placement and, ventilator parameters used during mechanical ventilation.[7-10,12,13-16,23] This is consistent with the dose efficiency we obtained with each device and airway used in this study, which ranged from 3 to 15%.

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Table 1. Mean Inhaled Mass and Lung Dose as Percent of Nominal Dose Delivered Distal to the Trachea With Each Aerosol Device

	TT			ETT		
	Jet Nebulizer	pMDI	*P*	Jet Nebulizer	pMDI	*P*
Inhaled mass, mean ± SD μg	97.3 ± 14.0*	63.6 ± 0.4†	.01	79.6 ± 3.8	50.1 ± 8.2	.005
Lung dose, mean ± SD %	3.9 ± 0.5‡	14.7 ± 0.1§	.001	3.2 ± 0.1	11.6 ± 1.9	.002

* The difference between a tracheostomy tube (TT) and an endotracheal tube (ETT) in inhaled mass using a jet nebulizer ($P = .10$).
† The difference between a TT and an ETT in inhaled mass using a pressurized metered-dose inhaler (pMDI; $P = .046$).
‡ The difference between a TT and an ETT in lung dose using a jet nebulizer ($P = .10$).
§ The difference between a TT and an ETT in lung dose using a pMDI ($P = .046$).

Our findings of aerosol delivery via an ETT are consistent with previous findings of Ari et al[22] using the same aerosol devices under similar conditions. Aerosol delivery efficiency with a jet nebulizer and pMDI in our 2010 study was 3.6% and 17%, respectively.[22] In contrast, this study showed that aerosol deposition obtained with a jet nebulizer was 3.18% using an ETT compared with 11.59% with a pMDI. The small difference in aerosol delivery between these studies may be explained by differences in the model, with collection of aerosol at the tip of the ETT in the earlier study[22] versus measurement distal to the bronchi, where anatomic structures beyond the tip of the ETT may have incurred additional impactive losses of aerosol. In addition, this study confirmed that a pMDI can be a more efficient alternative to a jet nebulizer, as the dose delivery efficiency with the pMDI was 3-fold more than with the jet nebulizer in our simulated ventilator-dependent patients with artificial airways. The 3-fold greater efficiency of the pMDI compared with the jet nebulizer during conventional mechanical ventilation with both a TT and an ETT is offset by the greater mass of drug delivered by the jet nebulizer. Several studies reported that pMDIs offer equivalent therapeutic effect with greater convenience compared with jet nebulizers.[24-26] Dhand et al[27] and Duarte et al[28,29] demonstrated similar comparable bronchodilator effects with the devices and doses used in this study in ventilated subjects.

In an in vitro study conducted by Piccuito and Hess,[30] aerosol delivery via a jet nebulizer and pMDI using different interfaces was compared in a spontaneously breathing adult lung tracheostomy model. Although the delivery efficiency of the pMDI with a valved holding chamber was greater compared with the jet nebulizer, the authors reported that the absolute dose obtained with the jet nebulizer was more than with the pMDI because of the greater nominal dose placed in the nebulizer cup. Piccuito and Hess[30] used a spontaneously breathing active adult lung model as opposed to the passive ventilator-dependent lung model used in our study.

This is the first study to show that aerosol deposition via a TT was greater than with an ETT regardless of the type of aerosol device used in our model of ventilator-dependent patients. Clinicians should be aware of these differences to achieve effective aerosol drug therapy in critically ill patients. The lower efficiency with the jet nebulizer during mechanical ventilation is associated with several other disadvantages, such as the introduction of gas flow into the circuit and the associated interference with ventilator parameters and need for adjustment of alarm settings both during and after nebulization. In addition, a jet nebulizer requires more preparation to set up, more time for administration, and more cleaning and maintenance than a pMDI.

Our findings suggest that although drug delivery may be greater via a TT than with an ETT, the differences would not likely be clinically important with administration of bronchodilators such as albuterol, which has a steep response curve. However, for other drugs such as antibiotics, mucokinetics, and anti-inflammatory agents, in which the therapeutic effect is dependent on achieving a specific threshold lung dose, the 22–27% increase in aerosol drug delivery may have an impact on clinical response in a ventilated patient with a tracheostomy. Most drugs approved for inhalation were based on clinical studies in ambulatory subjects using aerosol delivery systems with deposition ranging from 8 to 14%. Our data suggest that aerosol delivery with a pMDI is more consistent with inhaled dose and label claim (at 11.59–14.7%) compared with a jet nebulizer (3.2–3.9%). Drug administered by a jet nebulizer with either an ETT or a TT may require a > 3-fold greater dose to achieve approximate lung deposition achieved in the registration studies. To that end, our findings provide one more piece of the puzzle to inform clinicians of how to more effectively dose inhaled drugs to mechanically ventilated patients.

Several research questions remain unanswered. How does the size of artificial airways influence aerosol delivery to critically ill patients? What is the impact of different ventilator parameters on lung dose in ventilator-dependent patients with artificial airways? What is the difference between pMDIs and new aerosol devices such as mesh nebulizers in drug delivery to mechanically ventilated patients?

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Conclusions

Aerosol drug delivery via an ETT was less compared with a TT, whereas the delivery efficiency of a pMDI via either airway was greater than that of a jet nebulizer in this simulated model of mechanically ventilated adults. Clinical studies are warranted to determine whether differences in aerosol delivery via a TT in vivo are clinically relevant in the treatment of ventilator-dependent patients with TTs or ETTs.

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