IN VITRO COMPARISON OF NEBULIZERS FOR AEROSOL DELIVERY DURING MECHANICAL VENTILATION

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ABSTRACT

Introduction: Aerosol delivery using small volume nebulizers (SVN) during controlled mechanical ventilation (CMV) delivers < 3% of dose.

Methods: The Aeroneb® Professional Nebulizer System (APNS) and three SVNs (Puritan Bennett Raindrop® [PBRD], AirLife Misty-Neb™ [AMN] and Salter 8900 [S8900]) were used in this study. Albuterol sulfate (2.5mg in 3mL) was nebulized during MV of an intubated adult model under humidified conditions. Drug deposited on a filter distal to an 8 mm endotracheal tube was determined by HPLC. Mass median aerodynamic diameter (MMAD) and fine particle fraction (FPF) (particles < 5 µm) were determined by cascade impaction. Residual volume in the nebulizer was determined gravimetrically.

Results: Results are expressed as averages (n=3) with* indicating difference from all three SVNs, p<0.05.

Device	MMAD	FPF (<5 µm)	Residual (mL)	Deposited (µg)	Deposited (%)
APNS	2.1	83%*	0.4 mL*	315 *	13*
S8900	3.1	62%	1.7 mL	19	0.8
AMN	2.5	73%	1.1 mL	68	2.7
PBRD	2.7	67%	1.3 mL	52	2.1

Summary: The Aeroneb® Professional Nebulizer System delivered greater than four times more drug than any of the three small volume nebulizers tested.

Conclusion: The Aeroneb® Professional Nebulizer System provides more effective aerosol delivery during mechanical ventilation.

INTRODUCTION

For aerosol delivery of expensive medications (e.g., antibiotics, proteins and surfactants) to be practical for use in the critical care environment, a large proportion of the nominal dose needs to be delivered to the lungs with minimal waste. Controlled mechanical ventilation (CMV) poses challenges to aerosol delivery with 1-3% deposition of doses reported with pneumatic small volume nebulizers (SVN).[1]

The Aeroneb® Professional Nebulizer System, or Aeroneb Pro, (Figure 1) designed for continuous aerosolization with mechanical ventilators, utilizes a micro-pumping action with an aerosol generator (Figure 2) that creates fine-droplet, low-velocity aerosols of specific particle sizes without propellants or compressors.

Figure 1. The Aeroneb® Professional Nebulizer System

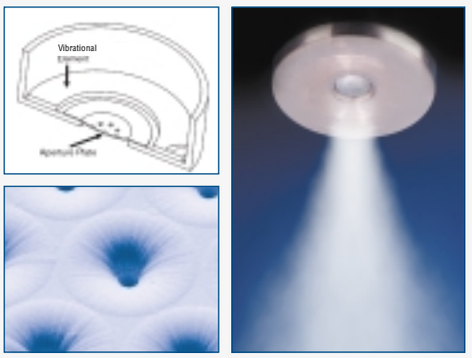

Figure 2. Aerogen's aerosol generator with diagram of aerosol generator components (top left), microscopic view of aperture plate (bottom left) and picture of aerosol generator (right).

The Aeroneb Pro was compared to several ultrasonic and pneumatic small volume nebulizers to determine *in vitro* performance and drug delivery efficiency during CMV. In an additional experiment, we determined the effect of particle size on aerosol delivery utilizing Aeroneb Pro nebulizers modified to produce particles ranging from 3.4 – 5.4 µm.

METHODS

Testing was conducted with one unit each of the Aeroneb Pro, the ultrasonic Siemens Ultra Nebulizer 145™ (SUN 145), the ultrasonic Puritan Bennett Easy Neb™ (PBEN), the pneumatic Salter 8900 nebulizer (S8900), the pneumatic AirLife Misty-Neb™ (AMN) and the pneumatic Puritan Bennett Raindrop® (PBRD). Residual medication left in the cup after nebulization was determined gravimetrically and reported in mL. Volumetric median diameter (VMD) and geometric standard deviation (GSD) were determined for all devices by laser diffraction with the Spraytec™ (Malvern / INSITEC, San Ramon, CA).

Each nebulizer was placed in the inspiratory limb of a humidified ventilator circuit, connecting a PB 760 ventilator (Puritan Bennett, Carlsbad, CA) to an endotracheal tube (8.0 mm ID), an absolute filter and a test lung (Figure 3). To determine the amount of aerosol delivered during CMV, each nebulizer was filled with albuterol sulfate inhalation solution (3.0 mL of 0.083% solution) and operated in the circuit with active humidification and adult ventilator settings (tidal volume 800 mL, rate 12, inspiratory flow 60 L/min) until sputter (SVN) or end of aerosol generation.

In a separate experiment, small doses of albuterol sulfate inhalation solution (0.5 mL of 0.5% solution) were pipetted into Aeroneb Pro units that were modified to produce aerosols ranging from 3.4 and 5.4 mm VMD. In this experiment, lower volumes and flow rates were used (tidal volume 500 mL, rate 15, inspiratory flow 40 L/min), with a descending (ramp) flow pattern, resulting in an inspiratory:expiratory ratio of 1:3. Albuterol was collected on an absolute filter distal to the endotracheal tube.

In both experiments, drug was eluted from the filter and measured by reverse phase HPLC with isocratic elution and UV detection at 275 nm. Results were reported as percent of input dose delivered to the absolute filter. Each experiment was performed in triplicate.

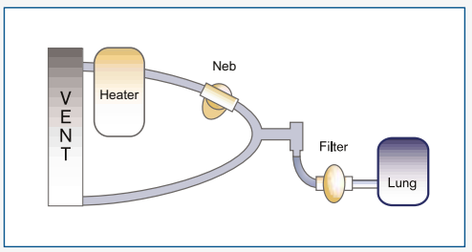

Figure 3. Model used for measuring aerosol delivery during mechanical ventilation

RESULTS

During administration of 3 mL of albuterol sulfate solution during CMV, the SUN 145 and Aeroneb Pro delivered the largest deposited doses, and the residual volume was smaller in the Aeroneb Pro than any of the other nebulizers tested (Table 1). All devices tested completed nebulization in <15 minutes.

TABLE 1. COMPARISON OF VOLUME MEDIAN DIAMETER (VMD), RESIDUAL VOLUME AND DEPOSITED DOSE

Device	VMD (µm)	GSD	Residual Volume (mL)	Dose Deposited (%±SD)
Aeroneb Pro	5.2	2.2	0.4	13±1.2
SUN 145	4.6	1.9	1.4	14±0.9
PBEN	4.6	2.1	1.4	9±1.1
S8900	6.3	2.7	1.7	0.8±0.3
AMN	4.8	2.6	1.1	2.7±0.5
PBRD	5.1	2.5	1.3	2.1±0.6

With doses of 0.5 mL, the residual volume in Aeroneb Pro units ranged from 0.02 – 0.06 mL. The percent of the total 0.5 mL dose deposited on the absolute filter distal to the endotracheal tube for each VMD tested was inversely proportional to mean aerosol size (Table 2). Nebulization time was less than 2 minutes with each device.

TABLE 2. AEROSOL SIZE DISTRIBUTION AND DEPOSITED DOSE (MODIFIED AERONEB PRO)

VMD (µm)	3.4	4.0	4.6	4.9	5.4
Deposition (%±SD)	39.6±3.9	37.6±4.5	36.0±2.3	26.5±4.5	19.0±4.1

DISCUSSION

The Aeroneb® Professional Nebulizer System and the SUN 145 delivered greater than four times more drug than the other pneumatic small volume nebulizers when delivering 3 mL doses of albuterol. The efficiency of the Aeroneb Pro improved with the smaller dose volume. An inverse correlation ($p<0.05$, least squares analysis) was observed between deposition of drug and aerosol particle size across the range of particle sizes tested. The efficient deposition (19 – 40%) of the 0.5 mL dose of albuterol is due in part to the low residual volume of the Aeroneb Pro.

CONCLUSION

Small residual volumes and decreasing mean aerosol particle size improved the efficiency of drug delivery during CMV. Using the modified Aeroneb Pro during CMV, low residual volume and smaller aerosol particles combined to increase delivered dose up to 40% *in vitro*. Further studies are warranted to better understand and confirm this effect *in vivo*.

REFERENCE

[1]Dhand R, Tobin MJ: Inhaled bronchodilator therapy in mechanically ventilated patients. American Journal Respiratory Critical Care Medicine 156:3, 1997.

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