

DOES USE OF A NEBULIZER RESULT IN AN INCREASE IN DRUG CONCENTRATION?

Fink JB, Simon M, Heramia M, Uster P

Aerogen, Inc., Sunnyvale, California

As presented at the 47th International Respiratory Congress •
December 2001 • San Antonio, Texas



ABSTRACT

Increasing drug concentrations during the process of nebulization has been identified with use of ultrasonic nebulizers, but has not been well defined with other types of nebulizers. We measured the concentration of drug remaining in each of five pneumatic nebulizers (Pari LC Plus, Monaghan AeroEclipse, DeVilbiss Model 800, Allegiance Airtle Misty-Neb and Salter 8900) and a novel nebulizer (Aerogen's Aeroneb™ Portable Nebulizer System) after aerosol generation was complete. Each nebulizer was filled with 2.5 mg (3 mL of 0.083%) albuterol sulfate. Upon completion of aerosol flow, the residual drug volume was determined gravimetrically while residual mass (mg) and concentration (percent of initial concentration) were determined using an HPLC method. Significant differences ($p < 0.05$) were determined by ANOVA.

RESULTS:

Device	Residual Volume (mL)	Residual Volume (%)	Residual Mass (mg)	Concentration Change (%)
Pari LC Plus w/ ProNeb Turbo	1.4	46	1.3	+112
Monaghan AeroEclipse w/ 50 psi	1.1	36	1.3	+234
DeVilbiss 800 w/ Compressor	2.1	70	1.8	+48
Airtle Misty-Neb w/ 50 psi	1.0	33	1.2	+230
Salter 8900 w/ 50 psi	1.7	62	1.7	+163
Aerogen Aeroneb Nebulizer™	0.4	13	0.3	-20

Residual volume, % of residual volume, residual mass, and change in concentration all are statistically significantly lower with the Aeroneb Portable Nebulizer System, compared with use of any of the other nebulizers.

DISCUSSION: All of the pneumatic nebulizers increased concentration of residual albuterol. Increased residual concentration was inversely related to the residual volume. In contrast, the Aeroneb Portable Nebulizer System did not increase residual concentration, despite a lower residual volume and mass than those resulting from the use of the pneumatic nebulizers.

CONCLUSION: Concentration of residual medication increases during operation of pneumatic nebulizers, but not with the Aeroneb Portable Nebulizer System.

INTRODUCTION

Increasing residual drug concentration during the process of ultrasonic nebulization has been identified, but has not been well defined with pneumatic nebulizers, or the novel Aeroneb™ Portable Nebulizer System. The purpose of this

INTRODUCTION (cont.)

study was to quantify changes in medication concentration at the end of treatment using the Aeroneb Portable Nebulizer System and a variety of other commercially available pneumatic nebulizers. In addition, we examined and compared aerosol parameters and performance of these nebulizers during simulated breathing.

The Aeroneb Portable Nebulizer System is a portable, hand-held nebulizer (Figure 1) utilizing Aerogen's aerosol generator (Figure 2). The aerosol generator consists of a domed aperture plate with precision-formed holes of a discrete shape and size and a vibrational element that creates a micro-pumping action to produce a fine droplet, low-velocity aerosol using no propellants or compressors. Aerosol particle size, flow rate and fine particle fraction are functions of the aperture exit diameter.



Figure 1. Aeroneb Portable Nebulizer System.

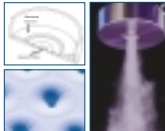


Figure 2. Aerogen's aerosol generator with diagram of aerosol generator components (top left), microscopic view of aperture plate (bottom left), and picture of aerosol generator (right).

METHODS

Aerogen's Aeroneb Portable Nebulizer System and a variety of pneumatic nebulizers including the DeVilbiss® Model 800, the Allergiance AirLife Misty-Neb®, the Salter 8900 Ultramist continuous nebulizer, the Pari LC Plus™ breath enhanced nebulizer and the Monaghan AeroEclipse® breath actuated nebulizer were tested. Each nebulizer was operated according to the manufacturer's specifications. The Pari LC Plus and DeVilbiss nebulizers were operated using their recommended compressors, while the AeroEclipse, AirLife and Salter nebulizers were operated with 6 L/min of oxygen at 50 psi. Each nebulizer was filled with 2.5 mg (3 mL of 0.083%) albuterol sulfate and tested.

AEROSOL CHARACTERISTICS AND PERFORMANCE DURING SIMULATED BREATHING (TABLES 1 & 2)

Aerosol characteristics and respirable mass available from the Aeroneb Portable Nebulizer System and the four continuous pneumatic nebulizers were compared. Volume median diameter (VMD), geometric standard deviation (GSD) and fine particle fraction 1-7µm (FPF₁₋₇) were determined by laser diffraction (Spraytech®, Malvern).

Inhaled drug was collected on filters (Respigard II 303, Vital Signs, Englewood, CO) placed between the nebulizer and a breath simulator (Hans Rudolph, Series 1101, Kansas City, MO) that generated an adult breathing pattern (tidal volume 500 mL, rate 15 breaths/min, and inspiratory-expiratory ratio of 1:3) (Figure 3). Drug was eluted from filters and analyzed by reverse phase HPLC with isocratic elution and UV detection at 275 nm.

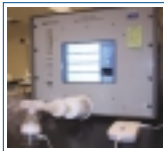


Figure 3. Breath simulator with Aeroneb Portable Nebulizer System.

METHODS (cont.)

DRUG CONCENTRATION (TABLE 3)

The concentration of drug remaining in each of the nebulizers was measured after aerosolization ended. Each nebulizer was filled with 2.5 mg (3 mL of 0.083%) albuterol sulfate. Upon completion of aerosolization, the residual drug volume was determined gravimetrically while residual mass (mg) and concentration of drug remaining in the nebulizer were determined using an HPLC method in triplicate. Significant differences (p<0.05) were determined by ANOVA. Fishers PLSD (Statview).

RESULTS

Aerosol Characteristics

TABLE 1. VMD, GSD, AND %FPF OF THE SIX NEBULIZERS TESTED (N=5).

Nebulizer	VMD	GSD	FPF ₁₋₇
Aerogen Aeroneb Portable Nebulizer System	5.2	1.9	66%
Pari LC Plus with ProTech Turbo	4.8	2.3	70%
Monaghan AeroEclipse	3.8	2.3	70%
DeVilbiss Model 800	5.4	2.6	58%
Allergiance AirLife Misty-Neb	4.5	2.7	62%
Salter Labs Ultramist Neb	6.3	2.7	49%

Performance Characteristics

TABLE 2. PERFORMANCE PARAMETERS OF THE FIVE CONTINUOUS NEBULIZERS DURING SIMULATED ADULT BREATHING.

Nebulizer	Treatment Time (min)	Flow Rate (mL/min)	Inhaled Mass (µg)	Respirable Mass (µg)	Respirable Mass (%)
Aerogen Aeroneb Portable Nebulizer System	6.4	0.01	0.52	0.36	13.5
Pari LC Plus	7.9	0.21	0.62	0.30	11.9
DeVilbiss Model 800	5.9	0.20	0.26	0.16	5.6
Allergiance AirLife Misty-Neb	6.7	0.21	0.35	0.22	8.7
Salter Labs Ultramist Neb	3.6	0.26	0.20	0.10	3.9

Treatment time = minutes required to deliver a complete dose

Flow rate (mL/min) = emitted dose / treatment time

Inhaled mass = amount of drug "inhaled" and deposited on the filter

Respirable mass = inhaled mass x % FPF

Respirable mass % = respirable mass expressed as % of inhaled dose

RESULTS (cont.)

Drug Concentration

TABLE 3. COMPARISON OF VOLUME AND MASS OF DRUG REMAINING IN NEBULIZERS AT THE COMPLETION OF AEROSOLIZATION, AND CHANGE IN RESIDUAL DRUG CONCENTRATION.

Nebulizer	Residual Volume (mL)	Residual Volume (% of dose)	Residual Mass (mg)	Concentration Change (%)
Aerogen Aeroneb Portable Nebulizer System	0.4*	13*	0.2*	-2*
Pari LC Plus w/ ProHalo Turbo	1.4	44	1.3	+12
Monaghan Aero-Eclipse w/ 50 psi	1.1	34	1.3	+31
Driftless Model 800 w/ Compressor	2.1	70	1.8	+6
Alegiance Airflo Misty Neb w/ 50 psi	1.0	33	1.2	+31
Salter Labs 8900 w/ 50 psi	1.7	52	1.3	+16

Residual volume = volume of drug remaining in the nebulizer at conclusion of aerosolization

Residual volume (% of dose) = residual volume / initial dose volume

Residual mass = mass of albuterol (mg) remaining in the nebulizer at conclusion of aerosolization

Concentration change (%) = final concentration / initial concentration

*Significantly lower than other nebulizers tested p<0.05

SUMMARY

Similar to previous reports with ultrasonic nebulizers, the residual concentration of albuterol increased in all of the pneumatic nebulizers tested, with residual concentration inversely related to the residual volume. In contrast, the Aeroneb Portable Nebulizer System did not increase the concentration of residual medication during therapy.

Our findings suggest that concentration of drug delivered increases over time with the pneumatic nebulizers but not the Aeroneb Portable Nebulizer System. A change in concentration may be undesirable when aerosols are administered continuously for prolonged periods of time.

CONCLUSION

Concentration of residual medication increased during operation of pneumatic nebulizers, but not during operation of the Aeroneb Portable Nebulizer System. Additional studies are required to better understand the implications of these findings.