AEROECLIPSE® XL
Reusable Breath Actuated Nebulizer

Study Summary

FOREWORD

Monaghan Medical and its affiliate company Trudell Medical have an enviable history of strong leadership in creating innovative medical devices that enhance the quality of life for people of all ages. We focus our efforts on the well-being of our employees and customers, and provide safe, valuable and easy to use devices for a global market.

Monaghan Medical Corporation designs, develops and manufactures innovative aerosol drug delivery devices for human health applications. We supply the pharmaceutical and healthcare industry with devices and solutions to help ease the burden that respiratory challenges bring to patients and their caregivers. With a dedication to providing unsurpassed quality products, we take our role within respiratory disease management very seriously.

The AEROECLIPSE® XL Reusable Breath Actuated Nebulizer (R BAN) is designed to deliver superior aerosol performance in a home or clinic setting for up to 6 months of continuous use. Clinicians can be confident of delivered dose since aerosol is only generated in response to the patient's inspiratory maneuver – for true on-demand therapy.

Using proprietary technology, the AEROECLIPSE® XL R BAN emits significantly lower levels of fugitive emissions (compared to continuous nebulizers) during exhalation or at rest which may provide for a safer patient environment and less wasted medication.

This may be of considerable interest to clinicians wishing to minimize medication exposure of caregivers in the home.

The AEROECLIPSE® XL R BAN is designed and manufactured under strict ISO 13485:2016 controls in a Class 8 Cleanroom Environment.

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AEROECLIPSE® XL BAN

Summary by Active Pharmaceutical Ingredient

Albuterol Sulfate/Salbutamol Sulfate (Ventolin†, GSK† Inc.)

DELIVERY OF INHALED MEDICATION IS MAINTAINED BY A BREATH-ACTUATED NEBULIZER WHEN USED BY PATIENTS WITH DIFFERING INHALATION/EXHALATION RATIOS: A LABORATORY STUDY USING ALBUTEROL SULFATE SOLUTION FOR NEBULIZATION.

J Suggett, M Nagel, V Avvakoumova, V Wang, D Coppolo, JP Mitchell. American Journal of Respiratory and Critical Care Medicine 2016;193:A5843.

Rationale: Breath actuated pneumatic nebulizers (BANs) only deliver aerosolized medication during the inhalation component of each tidal-breathing cycle. In contrast, continuous output (CONs) and breath enhanced nebulizers (BENs), continue to deliver aerosol during exhalation. The inspiratory:expiratory (I:E) ratio may vary from 1:1 to as much as 1:4 in the presence of obstructive lung disease. This laboratory study sought to compare the output of nebulizers at different I:E ratios simulating potential real patient breathing pattern. **Methods**: Measurements were undertaken with the following nebulizer systems: AEROECLIPSE® XL BAN with *OMBRA*® Table Top Compressor, Monaghan Medical Corp.; PROBASICS† Rite-Neb 3† CON with compressor, PMI; Mini nebulizer CON with compressor, Roscoe Medical Inc.; SideStream† Plus BEN with InnoSpire Essence compressor, Phillips Healthcare. Each nebulizer (n = 3/group) was filled with 3.0 mL fill of 2.5 mg albuterol sulfate (AS) and the mouthpiece connected to a breathing simulator (ASL 5000, IngMar Medical). Tidal volume (V_t) was fixed at 500-ml to mimic adult use, but I:E ratio and rate/minute were varied as presented in **Table 1**. Emitted droplets were collected at minute intervals to first sputter by a filter positioned at the mouthpiece; AS recovered from the filter was assayed by HPLC-UV spectrophotometry. **Results**: Measures of total emitted mass (TEM (µg); mean ± SD) are summarized in the Table. TEM from the BAN was unaffected by changes in breathing pattern (1-way ANOVA, p = 0.97), whereas the output from the other nebulizers was lower generally and decreased with increasing I:E ratio (1-way ANOVA for each nebulizer-compressor, p < 0.001).

Table 1: Total Emitted Mass from Nebulizers at Different Tidal Breathing Patterns

Nebulizers/ Compressors	I:E ratio/rate per minute 1:1/15	1:2/10	1:3/7	1:4/6
AEROECLIPSE® XL BAN/*OMBRA*® Compressor	985 ± 93	964 ± 81	960 ± 80	979 ± 37
PROBASICS† Rite-Neb 3† CON/compressor	673 ± 26	528 ± 6	354 ± 4	302 ± 15
Mini nebulizer CON/compressor	441 ± 8	301 ± 14	245 ± 14	176 ± 30
SideStream† Plus BEN/InnoSpire† Essence†	467 ± 23	344 ± 10	270 ± 9	231 ± 11

Conclusions: A more consistent dose delivery was achieved across the range of I:E ratios tested with the BAN rather than the other nebulizer types. The ability to conserve medication for delivery only when the patient inhales, would result in more consistent therapy if I:E ratio was to change in association with disease progression. .

VERSATILITY OF A NEW RE-USABLE BREATH-ACTUATED NEBULIZER (RBAN) INTENDED FOR DOMICILIARY USE WITH ITS TABLE-TOP COMPRESSOR: *IN VITRO* COMPARISON IN BREATH-ACTUATED AND CONTINUOUS DELIVERY MODES WITH A CONTINUOUS HIGH OUTPUT JET NEBULIZER.

D Coppolo, J Mitchell, V Avvakoumova , R Ali , H Schneider , M Nagel. American Journal of Respiratory and Critical Care Medicine 2013;187:A2607.

Rationale: It can be helpful in the home-based situation to be able to provide rapid bronchodilator therapy by nebulizer during exacerbations of obstructive lung disease. A new re-usable rBAN (AEROECLIPSE® rBAN, Monaghan Medical Corp. (MMC)) does not waste medication during exhalation, but can be converted to continuous output by rotating the green selector button in the center of the nebulizer cap when the patient cannot operate the device in breath-actuated mode and/or to shorten overall treatment time. We evaluated this device operated in both modes using its table-top compressor (*OMBRA*®, MMC), and comparing performance with that of a reusable high output venturi jet nebulizer (SideStream†, Respironics† Inc., Pittsburgh, PA) equipped with Inspiration Elite† table-top compressor, chosen as a benchmark. **Methods**: The nebulizer-on-test (n = 5/group) was filled with 2.5-mL, 1.0 mg/mL albuterol solution (Ventolin†, GSK† Canada Inc.),

and connected to a breathing simulator (ASL5000, IngMar Medical, Pittsburgh, PA), mimicking adult tidal breathing (V_t = 600-mL; duty cycle = 33%; rate = 10 cycles/min). The rBAN was first operated in breath-actuated mode, and testing was subsequently repeated with the same nebulizer set to continuous operation. Emitted aerosol was captured on a filter located at the mouthpiece, replaced at minute intervals until onset of sputtering, defining run time. Recovery/assay of salbutamol was undertaken by HPLC-UV spectrophotometry. Fine droplet fraction ($FDF_{<4.7\mu m}$) and mass median droplet diameter (MMD) were determined by laser diffractometry in a parallel study. Total fine droplet mass ($FDM_{<4.7\mu m}$) was the product of total mass and $FDF_{<4.7\mu m}$ Comparative measurements were reusable SideStream† nebulizers. **Results**: **Table 1** summarizes the outcomes from these measurements.

Table 1: Performance Measures (mean ± SD) for the Nebulizer-Table-Top Compressor Systems Evaluated

System	rBAN/Ombra®		SideStream†/Inspiration Elite†
Operating Mode	Breath-Actuated	Continuous	Continuous
$FDF_{<4.7\mu m}$ (%)	70.8 ± 1.0		68.6 ± 1.5
MMD (µm)	3.39 ± 0.05		3.43 ± 0.11
$FDM_{<4.7\mu m}$ (µg)	503 ± 39	349 ± 13	233 ± 6
Run time (min)	10	7	10

Conclusions: Treatment time with the AEROECLIPSE® rBAN/*OMBRA*® compressor was reduced by 36%, when used in continuous mode, significantly shorter than the 10 minutes required by the SideStream†/Inspiration Elite† system. The longer run time for the rBAN/*OMBRA*® system in the breath-actuated mode reflects the fact that aerosol is only delivered during inhalation and not wasted to the environment. Both systems provided highly respirable aerosol with values of $FDF_{<4.7\mu m}$ close to 70%, but $FDM_{<4.7\mu m}$ from the rBAN/*OMBRA* system in either mode of operation was significantly greater than the equivalent measure from the benchmark system (1-way ANOVA, $p < 0.001$).

EXTENDING THE CAPABILITY OF A BREATH-ACTUATED JET NEBULIZER FOR HOME AS WELL AS HOSPITAL USE – *IN VITRO* STUDIES TO CHARACTERIZE PERFORMANCE.

J Malpass, J Mitchell, M Nagel, V Avvakoumova, Cathy Doyle, Rubina Ali. American Journal of Respiratory and Critical Care Medicine 2012;185:A5626.

Rationale: It is desirable that patients prescribed a breath-actuated nebulizer (BAN) in hospital can continue its use at home. However, domiciliary compressors typically operate at pressures < 3.4 bar associated with hospital wall outlet gas supplies. The AEROECLIPSE® XL BAN (Trudell Medical International, London, Canada), has been developed to meet this need. This laboratory investigation was undertaken to guide transitioning patients to the new nebulizer. **Methods**: A simulator (ASL5000, Ingmar Medical, Pittsburgh, PA) was used to generate adult breathing (tidal volume = 600-mL; duty cycle = 33%; rate = 10-cycles/min). The nebulizer-on-test was coupled to the simulator via its mouthpiece and evaluated with 2.5-mL fill of salbutamol (0.1% w/v). AEROECLIPSE® XL BANs (n = 5) were operated by table-top or portable compressor (*OMBRA*®, Trudell Medical International)) at ca. 1.5 and 1.2 bar respectively. Total emitted mass (TEM) of salbutamol was determined on a minute-by-minute basis to sputter by filter collection of the aerosol at the mouthpiece. The same procedure was undertaken for LC† Sprint breath-enhanced nebulizers (n = 5) powered by PARI BOY† SX and BOY† mobile S compressors at ca. 1.5 and 1.0 bar respectively (PARI Pharma GmbH, Starnberg, Germany), as benchmarks. Salbutamol assay was undertaken by HPLC-UV spectrophotometric analysis. In parallel experiments, fine droplet fraction <4.7 µm diameter ($FDF_{<4.7\mu m}$) was determined for each nebulizer-compressor combination by laser diffractometry (Spraytec, Malvern Instruments, UK). The performance metrics were fine droplet mass <4.7 µm ($FDM_{<4.7\mu m}$) as the product of TEM and ($FDF_{<4.7\mu m}$) and run time (t), with delivery rate/min calculated from the ratio ($FDM_{<4.7\mu m}$)/t. **Results**: $FDF_{<4.7\mu m}$ (mean ± SD) for the AEROECLIPSE® XL BAN with table-top and portable compressors were 70.8 ± 1.0 and 68.1 ± 0.9 % respectively. $FDF_{<4.7\mu m}$ for the LC† Sprint with BOY† SX and BOY† mobile S compressors were 57.9 ± 3.1 and 52.0 ± 0.7% respectively. The variation of $FDM_{<4.7\mu m}$ with run time for all systems is illustrated in the Figure. Average $FDM_{<4.7\mu m}$/min were 43.5 and 50.4 µg/min for the AEROECLIPSE® XL BAN with Portable and Table-Top compressors respectively, whereas equivalent rates for the LC† Sprint nebulizers were 37.8 and 56.3 µg/min with the PARI BOY† mobile S and SX compressors respectively. Treatment times for all combinations were approximately the same. **Conclusions**: The AEROECLIPSE® XL BAN has superior performance to the LC† Sprint nebulizer based on $FDF_{<4.7\mu m}$, but is equivalent in terms of $FDM_{<4.7\mu m}$/min. However, the breath-actuation feature ensures compliance and a safe environment, because medication is only nebulized when the patient performs the inhalation maneuver.

COMPARATIVE *IN VITRO* PERFORMANCE OF A NEW RE-USABLE BREATH-ACTUATED NEBULIZER (BAN) WITH HIGH PERFORMANCE AIR ENTRAINMENT (AEN) NEBULIZER SYSTEMS INTENDED FOR DOMICILIARY USE: TABLE TOP AND PORTABLE COMPRESSOR SYSTEMS.

J Mitchell, V Avvakoumova, H Schneider, R Ali, M Nagel. Journal of Aerosol Medicine and Pulmonary Drug Delivery 2012;26(5):189-192.

Summary: We evaluated a new, reusable BAN (AEROECLIPSE® XL, Trudell Medical International, London, Canada), optimized with both its table-top and portable (*OMBRA*®) compressor systems. We compared *in vitro* performance for delivery of salbutamol solution for nebulization, with that of a high output air entrainment nebulizer ((AEN) LC† Sprint, PARI GmbH, Starnberg, Germany) with equivalent compressors as benchmark systems. Adult tidal breathing was simulated by means of a test lung-driven system with the aerosol collected at the nebulizer mouthpiece to provide measures of total mass of salbutamol. In parallel studies, the droplet size distribution of aerosol from each nebulizer-compressor system was determined by laser diffractometry, so that the mass median droplet diameter (MMD) and fine droplet fraction < 4.7 µm diameter ($FDF_{<4.7\mu m}$) could be determined. Values of MMD and $FDF_{<4.7\mu m}$ for the BAN-generated droplets were near to 3.5 µm and 70% respectively with either compressor system, and likely to be sufficiently fine for efficient medication delivery to patients with narrowed airways. These investigations also confirmed that for either table-top or portable compressor systems, despite generating aerosol droplets only during 33% of each simulated breathing cycle, the BAN provided comparable therapeutically beneficial fine droplet delivery of salbutamol to the benchmark AEN. The delivery rate/minute of fine droplets was near to constant for the first 6-minutes of delivery with the BAN, irrespective of compressor type, suggesting that the dosimetric capability of this device is available when used with the domiciliary compressors sold with this product. **Introduction**: Treatments with portable compressor/nebulizer systems can offer very different time-dependent delivery profiles based on fine droplet mass, depending upon compressor type [1], and also compared with the profile that would be obtained with compressed air driven at a typical hospital wall-outlet pressure of 50 psig (340 kPa) [2]. We evaluated in the laboratory a new, reusable BAN (AEROECLIPSE® XL, Trudell Medical International, London, Canada) optimized with its table-top and portable (*OMBRA*®) compressor systems. We compared its performance in terms of delivery of a beta-2 adrenergic agonist, salbutamol solution for nebulization, with that for a high output air entrainment nebulizer (LC† Sprint, PARI GmbH, Starnberg, Germany) also with the equivalent table-top and portable compressors, to represent benchmark systems that are in widespread domiciliary use [3]. **Materials and Methods**: In the first part of the investigation, we operated each BAN with its associated *OMBRA*® table-top compressor and comparative measurements were made with the AEN and PARI BOY† SX table-top compressor **(Figure 1)**. In the second part, we operated each BAN with its *OMBRA*® portable compressor and compare performance with the AEN in association with the PARI BOY† mobile S portable compressor **(Figure 2)**. We filled the nebulizer-on-test (n = 5/group) with 2.5-mL, 1.0 mg/mL salbutamol solution (Ventolin†, GSK† Canada Inc.) for both parts of the investigation, and connected it to a breathing simulator (ASL5000, IngMar Medical, Pittsburgh, PA), mimicking adult tidal breathing (tidal volume (V_t) = 600-mL; duty cycle = 33%; breathing rate = 10 cycles/min). We captured the emitted aerosol on a filter located at the mouthpiece, replaced at minute intervals until onset of sputtering, defining the run time, t_{run} **(Figure 3)**. Recovery/assay of salbutamol was undertaken by HPLC-UV spectrophotometry. In parallel measurements, we also determined the fine droplet fraction < 4.7 µm diameter ($FDF_{<4.7\mu m}$) and mass median droplet diameter (MMD) by laser diffractometry **(Figure 4)**. We subsequently calculated the fine droplet mass ($FDM_{<4.7\mu m}$) as the product of total mass (TM) and fine droplet fraction ($FDF_{<4.7\mu m}$). **Results and Discussion**: We observed that all droplet particle size distributions were uni-modal, making it possible to calculate MMD from the LD-measured distributions as the size that corresponded to the 50th volume (mass) percentile reported by the Spraytec LD. The performance metrics: $FDF_{<4.7\mu m}$, MMD, $FDM_{<4.7\mu m}$, trun are summarized in **Table 1**. We also calculated the range for fine droplet delivery rate based on the averages for the first 2 minutes (upper limit) and 6 minutes (lower limit) of operation. The variation in $FDM_{<4.7\mu m}$ as a function of elapsed time from start of nebulization to the onset of sputter is illustrated in **Figures 5** and **6** for the nebulizer-table-top and nebulizer-portable compressor systems respectively. Each compressor-type nebulizer system is a unique combination in terms of its pressure-gas flow relationship [4]. In this study, we found that both the benchmark and BAN systems had comparable and near-to-linear values of $FDM_{<4.7\mu m}$ delivery rate as a function of elapsed time, whether the table-top or portable compressor options were chosen. The slightly lower delivery rates for both BAN and AEN devices with their respective portable compressor is a reflection of the fact that these air supply systems are battery-driven rather than powered from a wall outlet ("mains" electricity), and therefore operate at slightly lower pressure. It is also important to note that whereas the AEN generates aerosol continuously, albeit at a lower rate during exhalation **(Figure 7a)**, the BAN only generates aerosol during the inhalation portion of each breathing cycle **(Figure 7b)**. This outcome has the advantage that medication in the reservoir is conserved for a longer treatment time, if needed, and also that fugitive emissions of drug product to the ambient environment surrounding the patient are minimized during each exhalation [5]. The significantly finer measures we observed for MMD of droplets from the BAN compared with AEN in association with either compressor type (un-paired t-test $p \leq 0.005$), were associated with relatively high values of $FDF_{<4.7\mu m}$ close to 70%. Such aerosols may be beneficial for patients whose airways are physiologically narrow, such as those of children [6,7] or narrowing caused by obstructive lung disease [8,9].

Table 1: *In Vitro* Performance Measures for Evaluated Nebulizer-Compressor Systems

Metric	Table Top Compressor Systems		Portable Compressor Systems	
	BAN/*OMBRA*®	AEN/BOY† SX	BAN/*OMBRA*®	AEN/BOY† mobile S
$FDF_{<4.7\mu m}$ (%)	70.8 ± 1.0	57.9 ± 3.1	68.1 ± 0.9	52.0 ± 0.7
MMD (µm)	3.39 ± 0.05	4.13 ± 0.21	3.53 ± 0.04	4.55 ± 0.05
$FDM_{<4.7\mu m}$ (µg)	530 ± 22	408 ± 22	474 ± 32	344 ± 20
t_{run} (min)	11	8	12	9
$FDM_{<4.7\mu mrate}$‡ (µg/min)	58-63	60-64	48-55	43-45

Conclusions: We confirmed by these laboratory studies that for each class of compressor system (table-top or portable), the BAN provided comparable therapeutically beneficial fine droplet delivery of salbutamol to the benchmark AEN, despite generating aerosol droplets only during 33% of each simulated adult tidal-breathing cycle. The delivery rate of fine droplets was near to constant for the first six minutes of delivery with the BAN, irrespective of compressor type, suggesting that dosimetric delivery is possible with this device when operated by compressor, rather than via a higher pressure wall outlet air supply.

References: 1 Reisner C, Katial RK, Bartelson BB, Buchmeir A, Rosenwasser LJ, Nelson HS. Characterization of aerosol output from various nebulizer/compressor combinations. Annals of Allergy, Asthma & Immunology 2001;86(5):566-574. 2 Leung K, Louca E, Coates AL. Comparison of breath-enhanced to breath-actuated nebulizers for rate, consistency, and efficiency. CHEST 2004;126(5);1619-1627. 3 PARI GmbH. Effective aerosol therapy devices for respiratory disease management – practical considerations key to successful treatment. US Respiratory Disease 2007;Issue 1. Available at: http://www.touchbriefings.com/pdf/2901/PARI_tech.pdf. 4 Standaert T, Bohn SE, Aitken ML, Ramsey B. The equivalence of compressor pressure-flow relationships with respect to jet nebulizer aerosolization characteristics. Journal of Aerosol Medicine 2001;14(1):31-42. 5 Mitchell JP. Delivery of inhaled bronchodilators by breath-actuated jet nebulizer: The potential for improved adherence with clinical guidelines. Inhalation, 2011;5(4):20-23. 6 Schüepp KG, Straub D, Möller A, Wildhaber JH. Deposition of Aerosols in Infants and Children. Journal of Aerosol Medicine 2004;17(2):153-156. 7 Newhouse MT. The current laboratory determination of "respirable mass" is not clinically relevant. Journal of Aerosol Medicine 1998;11S1:S122-S132. 8 Rees PJ, Clark TJ, Moren F. The importance of particle size in response to inhaled bronchodilators. European Journal of Respiratory Diseases 1982;119(S):73–78. 9 Labiris NR, Dolovich MB. Pulmonary drug delivery. Part I: Physiological factors affecting therapeutic effectiveness of aerosolized medications. British Journal of Clinical Pharmacology 2003;56(6):588–599.

COMPARATIVE *IN VITRO* PERFORMANCE OF A NEW RE-USABLE BREATH-ACTUATED NEBULIZER (BAN) WITH OTHER HIGH PERFORMANCE SYSTEMS INTENDED FOR DOMICILIARY USE – 1: TABLE-TOP COMPRESSORS.

J Malpass, M Nagel, V Avvakoumova, R Ali, H Schneider, J Mitchell. European Respiratory Journal 2012;40(56):P2181.

Rationale: Treatments by portable compressor/nebulizer systems can offer very different delivery characteristics. We evaluated a new, reusable BAN (AEROECLIPSE® XL, Trudell Medical International) optimized with its table-top (*OMBRA*®) compressor. **Methods**: Each nebulizer (*n* = 5/group) was filled with 2.5-mL, 1.0-mg/mL albuterol (Ventolin†, GSK† Canada Inc.), and connected to a breathing simulator (ASL5000, IngMar Medical, Pittsburgh, PA) mimicking adult tidal breathing (V_t = 600-mL; duty cycle = 33%; rate = 10 cycles/min). Emitted aerosol was captured on a filter at the mouthpiece, replaced every minute until onset of sputtering, defining run time. Recovery/assay of salbutamol was undertaken by HPLC-UV spectrophotometry. Fine droplet fraction ($FDF_{<4.7\mu m}$) and mass median droplet diameter (MMD) were determined by laser diffractometry. Total fine droplet mass ($FDM_{<4.7\mu m}$) was the product of total mass and $FDF_{<4.7\mu m}$. Comparative measurements were made with the LC† Sprint (PARI, Germany) and reusable SideStream† (Philips Respironics†, Germany) air entrainment nebulizers using PARI BOY† SX and Inspiration Elite† table-top compressors respectively. **Results**: **See Table**.

Nebulizer/Table-Top Compressor Performance Data

MEAN ± SD	BAN	LC† Sprint	SideStream†
$FDF_{<4.7\mu m}$ (%)	70.8 ± 1.0	57.9 ± 3.1	68.6 ± 1.5
MMD (µm)	3.39 ± 0.05	4.13 ± 0.21	3.43 ± 0.11
$FDM_{<4.7\mu m}$ (µg)	530 ± 22	408 ± 22	233 ± 6
Run Time (min)	11	8	10

Conclusions: The BAN/*OMBRA*® system provided highly respirable aerosol with $FDM_{<4.7\mu m}$ greater than the benchmark systems. Its run time reflects the fact that aerosol is only delivered during inhalation and not wasted to the environment.

COMPARATIVE *IN VITRO* PERFORMANCE OF A NEW RE-USABLE BREATH-ACTUATED NEBULIZER (BAN) WITH OTHER HIGH PERFORMANCE SYSTEMS INTENDED FOR DOMICILIARY USE – 2: PORTABLE BATTERY-COMPRESSOR.

J Malpass, M Nagel, V Avvakoumova, R Ali, H Schneider, J Mitchell. European Respiratory Journal 2012;40(56):P2148.

Rationale: Treatments with home based compressor/nebulizer systems can offer very different delivery characteristics. We evaluated a new, reusable BAN (AEROECLIPSE® XL, Trudell Medical International) in breath-actuated mode with its portable (*OMBRA*®) battery-compressor. **Methods**: The nebulizer-on-test (*n* = 5/group) was filled with 2.5-mL, 1.0 mg/mL

albuterol (Ventolin†, GSK† Canada Inc.), and connected to a breathing simulator (ASL5000, IngMar Medical, Pittsburgh, PA) mimicking adult tidal breathing (V_t = 600-mL; duty cycle = 33%; rate = 10 cycles/min). Emitted aerosol was captured on a filter at the mouthpiece, replaced at minute intervals until onset of sputtering, defining run time. Recovery/assay of salbutamol was undertaken by HPLC-UV spectrophotometry. Fine droplet fraction ($FDF_{<4.7\mu m}$) and mass median droplet diameter (MMD) were determined by laser diffractometry. Total fine droplet mass ($FDM_{<4.7\mu m}$) was the product of total mass and $FDF_{<4.7\mu m}$. Comparative measurements were made with the LC† Sprint (PARI, Germany) and MicroPlus† (Philips Respironics†, Germany) nebulizers using PARI BOY† mobile S and Inspiration MicroElite† portable compressors respectively. **Results**: **See Table**.

MEAN ± SD	BAN	LC† Sprint	MicroPlus†
$FDF_{<4.7\mu m}$ (%)	68.1 ± 0.9	52.0 ± 0.7	52.8 ± 2.8
MMD (µm)	3.53 ± 0.04	4.55 ± 0.05	4.46 ± 0.23
$FDM_{<4.7\mu m}$ (µg)	474 ± 32	344 ± 20	297 ± 20
Run Time (min)	12	9	11

Conclusions: The BAN/*OMBRA*® system provided highly respirable aerosol with $FDM_{<4.7\mu m}$ substantially greater than the benchmark systems. Its run time reflects the fact that aerosol is only delivered during inhalation and not wasted to the environment.

Budesonide (Pulmicort†, AstraZeneca†)

CONSISTENT DELIVERY OF INHALED MEDICATION IS MAINTAINED BY A BREATH ACTUATED NEBULIZER WITH DIFFERING INHALATION/EXHALATION RATIOS: A STUDY USING BUDESONIDE SUSPENSION FOR NEBULIZATION.
D Coppolo, J Suggett, M Nagel, C Doyle, R Ali, J Mitchell. Presented at the Association of Asthma Educators Conference 2015.

Background: In adult asthma, the Inhalation/Exhalation (I:E) ratio may vary due to collapse of the bronchiolar airways during exhalation. This study sought to investigate if I:E ratio changes affect medication delivery. Introduction: Patients receiving inhaled medications via nebulizer are often quite sick and therefore breathe tidally, rather than being asked to execute a forced breathing maneuver, such as a long slow inhalation followed by a breath hold. The I:E ratio, along with tidal volume and respiration rate, is an important descriptor of tidal breathing. Typically, nebulizers are evaluated in the laboratory, mimicking a patient having a fixed I:E ratio. However, in severe obstructive disease, such as asthma, this ratio can shift with disease progression. Breath Actuated Nebulizers (BANs) only deliver medication during the inhalation portion of each breathing cycle **(Figure 1)**. This study sought to confirm the hypothesis that if the portion of each breathing cycle involved with exhalation increases, the medication is conserved and not vented to the local environment, as would be the case with Breath Enhanced Nebulizers (BENs), whose output of medication does not fall to zero during exhalation **(Figure 2)**. **Methods**: Measurements were undertaken with the following pneumatic nebulizers, using a 2 x 2.0 mL fill of 0.25 mg/mL budesonide (Pulmicort†, AstraZeneca† Inc., Canada):

- AEROECLIPSE® XL BAN/*OMBRA*® Table Top Compressor Monaghan Medical Corp., Plattsburgh, NY – in Breath Actuated Mode (AE+)
- LC PLUS† BEN/PARI BOY† SX Table Top Compressor PARI Respiratory Equipment, Midlothian, VA (LC+)
- LC† Sprint BEN/PARI BOY† SX Compressor (LC*)
- SideStream† Plus BEN/Inspiration Elite† Table Top Compressor Philips Healthcare, Andover, MA (SS+)

Each nebulizer (*n* = 5/group) was connected to a breathing simulator (ASL5000, IngMar Medical, Pittsburgh, PA) set at a constant tidal volume of 500 mL and rates of 15, 10 and 7 cycles/min with I:E ratios of 1:1, 1:2 and 1:3 respectively. Budesonide mass was determined by HPLC-UV spectrophotometry using a validated procedure. **Results**: Values of Total Mass of budesonide delivered (TM_{bud}) (mean ± SD) from start-of-nebulization until first-sputter are summarized in **Figure 3**. Average TM_{bud} from the AE+ BAN was ~300 µg irrespective of I:E ratio. Kruskal-Wallis 1-way analysis of ranks (p = 0.264). Average decreases of 38%, 37% and 32% were observed for the LC+, LC* and SS+ BENs respectively. The change between I:E of 1:1 to 1:2 and 1:1 to 1:3 were significant (1-way ANOVA; $p \leq 0.011$).

Conclusions: Consistent delivery was achieved by BAN across the range of I:E ratios, reflecting its conservation of medication during exhalation. Educators should be aware that the BANs ability to conserve medication for delivery only when the patient inhales, provides greater assurance of dose consistency, resulting in more consistent therapy if I:E ratio changes with disease progression.

Figure 1: Medication Delivery Profile from a BAN

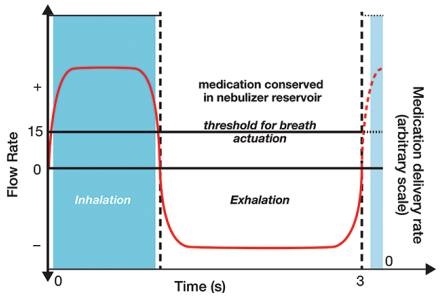


Figure 2: Medication Delivery Profile from a BEN

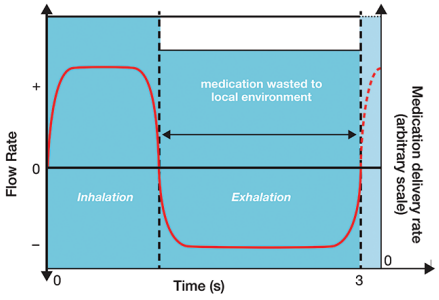
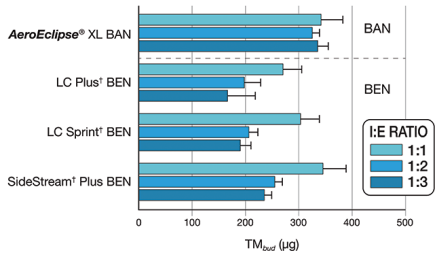


Figure 3: TM_{bud} for the Various Nebulizers Evaluated as a Function of I:E Ratio



DELIVERY OF MEDICATION BY BREATH-ACTUATED NEBULIZER (BAN) IS SIMILAR WHEN USED WITH DIFFERING INHALATION/EXHALATION RATIOS: A CONTRAST TO BREATH ENHANCED NEBULIZER (BEN) BEHAVIOR.

J Suggett, M Nagel, C Doyle, R Ali, J Mitchell. European Respiratory Journal 2014;44(S58):3819.

Rationale: BANs only deliver medication during inhalation. BENs continue to deliver aerosol (at a lower rate) during exhalation. If the inspiratory/expiratory (I/E) ratio of a patient decreases in obstructive lung disease, drug delivery efficiency by BEN may reduce. We compared the delivery of a corticosteroid by both types of nebulizer in a lab study. Methods: These nebulizer/table-top compressor systems (*n* = 5/group) were evaluated: (a) AEROECLIPSE® XL BAN/*OMBRA*® (TMI); (b) LC PLUS† BEN/PARI BOY†; (c) LC† Sprint BEN/PARI BOY† SX (PARI Respiratory Equipment); (d) SideStream† Plus BEN/ Inspiration Elite† (Philips Respironics†). Each device was evaluated with 2 x 2.0-mL fill of 0.25 mg/mL budesonide (AstraZeneca†). The nebulizer was connected to a simulator (ASL5000, IngMar Medical) mimicking adult (tidal volume=500-ml) tidal breathing, with I/E ratios of 1:1, 1:2 or 1:3. Emitted aerosol was captured by filter at 1-minute intervals until sputtering to determine total mass budesonide delivered (TM_{bud}), as percentage of TM_{bud} at I/E ratio=1:1. Budesonide assay was undertaken by HPLC-UV spectrophotometry. **Results**: Average TM_{bud} at extended I/E ratios as percentage of TM_{bud} are in the Table.

Nebulizer	AEROECLIPSE® XL	LC PLUS†	LC† Sprint	SideStream† Plus
Type	BAN	BEN	BEN	BEN
I/E ratio = 1:1	100.0	100.0	100.0	100.0
I/E ratio = 1:2	95.3	73.3	68.0	73.9
I/E ratio = 1:3	98.2	61.5	62.7	68.1

Conclusions: More consistent dose delivery was achieved by BAN. Clinicians should be aware of the opportunity to more confidently titrate patients to the lowest effective dose. The risk of potential under-dosing as disease progresses is also removed.

DELIVERY OF INHALED MEDICATION IS MAINTAINED BY A BREATH ACTUATED NEBULIZER WHEN USED BY PATIENTS WITH DIFFERING INHALATION/EXHALATION RATIOS: A LABORATORY STUDY USING BUDESONIDE SUSPENSION FOR NEBULIZATION.

J Suggett, M Nagel, C Doyle, R Ali, J Mitchell. Respiratory Drug Delivery 2014;3:573-576.

Background: Breath Actuated Nebulizers (BANs) only deliver aerosolized medication during the course of the inhalation component of each tidal-breathing cycle. In contrast, Breath Enhanced Nebulizers (BENs), although utilizing entrained air to enhance the output of medication when the patient inhales, continue to deliver aerosol (at a lower rate) during exhalation and between breaths. The following benefits apply for the BAN. Medication delivery is optimized by the near elimination of aerosol emitted by the nebulizer during exhalation, that would otherwise be wasted to the local environment, resulting in the potential for unnecessary caregiver exposure. Dosimetric delivery is possible, an advantage for drugs that are expensive or that have narrow therapeutic indices. In obstructive lung diseases, such as COPD, the tendency exists for the inhalation:exhalation ratio (I:E ratio) to be increased from 1:2 in the normal adult, to 1:3 or beyond. This behavior arises due to the loss of connective tissue typical of these diseases, resulting in the collapse of the bronchiolar airways during exhalation, thereby delaying this part of the respiratory cycle. There is also anecdotal evidence from caregivers in various healthcare settings, that patients during a treatment period occasionally remove the nebulizer mouthpiece from their lips in order to engage in conversational activity or to have a self-administered pause in therapy. Under these circumstances, medication delivered by a BAN will be conserved, whereas waste will inevitably occur with BEN-administered therapy. **Study Rationale**: A laboratory study was therefore undertaken to compare data obtained with a BAN/compressor system with results from a variety of BENs. A widely prescribed formulation for nebulization budesonide (Pulmicort†, AstraZeneca† Inc., Canada) was

chosen as the test product. **Materials and Methods**: Measurements were undertaken with nebulizer-compressor systems (*n* = 5 devices/group). Each nebulizer was tested with a 2 x 2.0-mL fill of 0.25 mg/mL budesonide. The BAN group were operated in breath actuated mode. Each nebulizer-on-test was connected to a breathing simulator set to mimic adult tidal breathing patterns (ASL5000, IngMar Medical, Pittsburgh, PA). The tidal volume was held at 500 mL. The emitted aerosol was captured on a filter located at the mouthpiece that was replaced at one-minute intervals until the onset of sputtering occurred. Recovery and subsequent assay of budesonide was undertaken by an HPLC-UV spectrophotometric procedure.

Nebulizer Systems Assessed

Nebulizer	Type	Compressor	Manufacturer
AEROECLIPSE® XL	BAN	*OMBRA*® Table Top	Trudell Medical International
LC PLUS†	BEN	PARI BOY† SX Table Top	PARI
LC† Sprint	BEN	PARI BOY† SX Table Top	PARI
SideStream† Plus	BEN	Inspiration Elite† Table Top	Philips Respironics†

Adult Breathing Patterns Simulated

Rate (cycles/min)	Minute Volume (mL)	I:E Ratio
15	7500	1:1
10	5000	1:2
7	3500	1:3

Results: Total mass of budesonide delivered (TM_{bud}) (mean ± SD) from start of nebulization until first audible sputter are summarized below.

Nebulizer	AEROECLIPSE® XL	LC PLUS†	LC† Sprint	SideStream† Plus
Type	BAN	BEN		
I/E ratio = 1:1	100.0	100.0	100.0	100.0
I/E ratio = 1:2	95.3	73.3	68.0	73.9
I/E ratio = 1:3	98.2	61.5	62.7	68.1

Average TM_{bud} from the AEROECLIPSE® XL BAN was maintained at a constant level across the three I:E ratios, whereas average decreases of 38%, 37% and 32% were observed for the LC PLUS†, LC† Sprint and SideStream† Plus BENs, respectively. Byrne et al.1, in a similar study observed that for two different BENs (LC PLUS† and LC† Sprint), the total mass of colistimethate sodium ($TM_{c\text{-}m}$) decreased as the I:E ratio increased mimicking adult tidal breathing with tidal volume and I:E ratios. In contrast, they found that the Adaptive Aerosol Delivery (AAD) nebulizer (I-neb, Philips Respironics†) like the AEROECLIPSE® XL BAN, only delivers medication during the inspiratory portion of each breathing cycle, providing constant delivery regardless of chosen I:E ratio. **Conclusions**: A more consistent dose delivery was achieved across the range of I:E ratios tested with the BAN rather than BEN nebulizers. This study reflects the greatly reduced loss of medication from the BAN device since aerosol is only produced during inhalation and therefore ensures that there is no risk of under-dosing. Since the operation of the BAN is purely mechanical, it is a significant low cost alternative to AAD-based nebulizers. The ability to conserve medication for delivery only when the patient inhales, provides a greater assurance of dose consistency and therefore would result in more consistent therapy if I:E ratio was to change with disease progression.

Reference: 1 Byrne, S., Jeffrey, D. and Hatley, R.H.M. (2013) The effect of inhalation: exhalation (I:E) ratio on the delivered dose of colistimethate sodium from 3 nebulizers, Proc. 19th Congress International Society for Aerosols in Medicine, Chapel Hill, NC, USA. (Abstract).

Colistimethate Sodium (Colomycin†, Forest Laboratories UK† Ltd.)

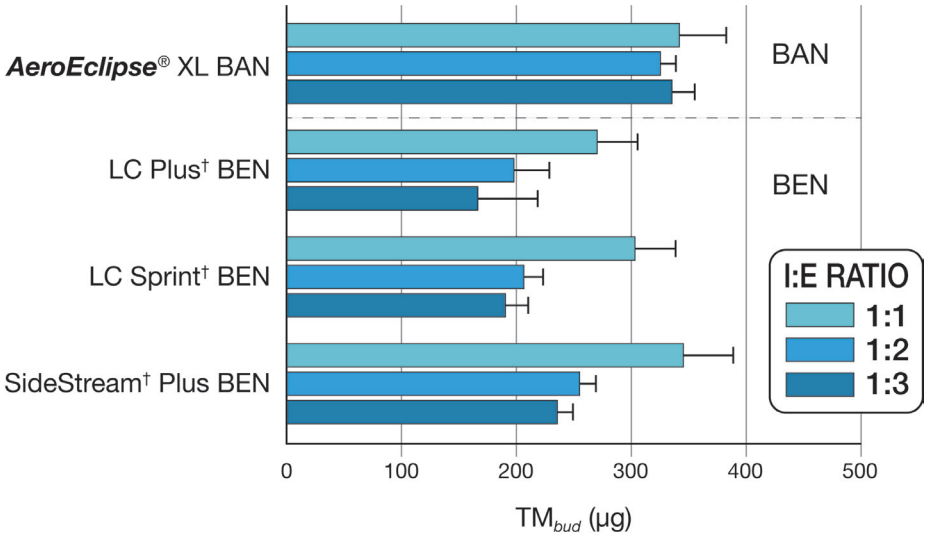
AN *IN VITRO* INVESTIGATION OF INHALED MEDICATION DELIVERY FROM A BREATH ACTUATED NEBULIZER COMPARING A SLOW, DEEP INHALATION WITH TIDAL BREATHING – DOES BREATHING PROFILE MATTER?

MW Nagel, JA Suggett, R Ali, V Wang, JP Mitchell. Respirable Drug Delivery 2016;3:533-538.

Introduction: Breath-actuated operation of a nebulizer only during inhalation affords the prospect for reduced wasted medication when the patient exhales [1]. There is also the prospect of optimizing delivery and shortening treatment time where the patient is capable of performing a trained maneuver, such as a slow deep inhalation followed by a breath-hold, known to be associated with improved lung deposition [2], rather than simply tidal breathing. Whereas inhalation technique is a focus for dry powder and pressurized metered dose inhaler administration, little if any mention is made of the importance of good inhalation technique when using small volume nebulizers (SVNs). However, slow and deep

inhalation using adaptive aerosol delivery devices such as the Akita† or the I-neb† AAD System has been shown to improve lung deposition [3, 4]. In addition, a shorter treatment time would be a highly desirable goal for many patients undergoing nebulizer-based treatments, particularly those with cystic fibrosis (CF), who must spend a significant proportion of each day receiving therapy [5]. We report an *in vitro* study in which an antibiotic representative of those given by inhalation to patients with CF, was used to investigate medication delivery from a pneumatic breath actuated nebulizer (BAN) to an adult, comparing the simulation of a slow deep inhalation with tidal breathing. **Materials and Methods**: AEROECLIPSE® XL BAN (*n* = 5 devices, Trudell Medical International, London, Canada), each filled with 4 mL of colistimethate sodium solution (160 mg/mL, 2 million IU, Forest Laboratories UK†), were operated at 7-8 L/min with medical air (50 psi). The mouthpiece from the nebulizer on test was connected to a breathing simulator (ASL5000, IngMar Medical Ltd., Pittsburgh, PA, USA) via an electret bacterial/viral filter upon which the "inhaled" aerosol deposited **(Figure 1)**. The aerosol filters were replaced at one minute intervals to prevent overloading and to provide time-dependent information. Colistimethate sodium content collected on the filter was subsequently assayed by UV spectrophotometry. The parameters defining the adult tidal breathing pattern simulated for the first part of the study **(Figure 2)** were: (a) tidal volume (V_t) = 600 mL; (b) rate/min = 10 cycles; (c) duty cycle = 33% (inspiratory/expiratory ratio = 1:2). For the second part of the investigation, an adult volunteer was instructed to exhale fully, inhale slowly and deeply, at the same time focusing on keeping the green inhalation feedback indicator on top of the breath actuated nebulizer lowered for as long as possible. A recorded representative inhalation pattern **(Figure 3)** was subsequently played back through the breathing simulator at a rate of four cycles per minute as this was shown to be a comfortable rate in which the volunteer had sufficient time to rest in between the slow, deep inhalations. In both cases, the nebulizer-on-test was operated until first sputter. The fine droplet fraction ($FDF_{<4.7\mu m}$) of the emitted size distribution from the BAN contained in aqueous droplets <4.7 µm in diameter was determined in a separate series of measurements by laser diffractometry (Spraytec, Malvern Instruments, Malvern, UK). The mass of those droplets (fine droplet mass (FDM) was calculated as the product of the FDF multiplied by the mass of colistimethate recovered from each filter. **Results**: The cumulative delivery of colistimethate as mass contained in fine droplets ($FDM_{<4.7\mu m}$) versus number of breaths is illustrated in Figure 4 for both the tidal breathing and slow deep inhalation, respectively. $FDF_{<4.7\mu m}$ was determined to be 82%. Total $FDM_{<4.7\mu m}$ delivered to sputter by either breathing profile was comparable and close to 50 mg, however, only six minutes (24 deep inhalations) was required to achieve this delivered mass using the slow deep inhalation, compared with 10 minutes (100 breathing cycles) by tidal breathing.

Figure 4: Delivery of colistin as fine droplets <4.7µm from the AEROECLIPSE® XL BAN (*n* = 5/group) as a function of the number of breaths.



Discussion: The present investigation has shown the potential for shortening BAN-based therapy if the patient is capable of achieving a long slow inhalation (aided by concentrating on the inhalation feedback indicator on the device), rather than merely tidal breathing, as is usual with such drug delivery devices. Poor inhalation technique is known to result, in some cases, in less than ideal control of lungs disease [6]. The European-based Aerosol Drug Management Improvement Team (ADMIT) group has therefore suggested that devices which provide reassurance to patients and their physicians when inhalation is performed correctly could help improve patient compliance [7] offering the prospect of better disease management. It follows that if patients are willing to be engaged in their treatment and are capable of executing the ideal maneuver of a long, slow inhalation followed by a breath-hold for fine droplet deposition to the lungs [8], the use of a pneumatic BAN could lead to reduced treatment times and potentially better disease management. **Conclusions**: This

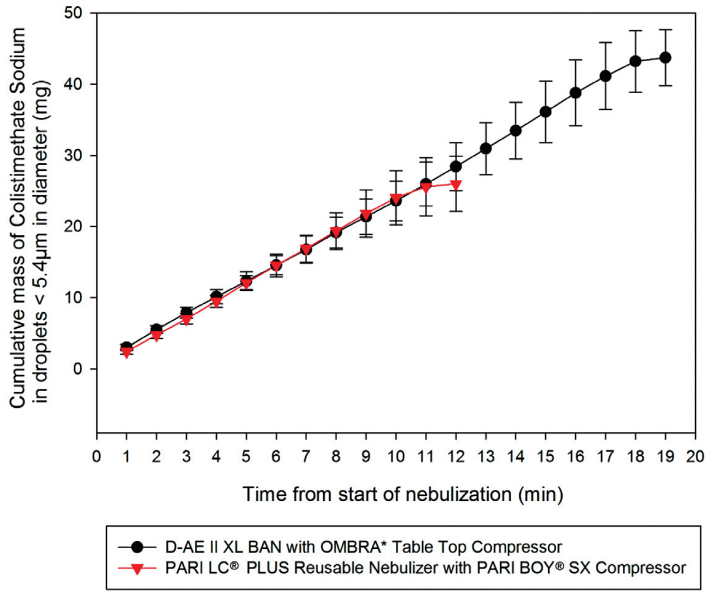
study has demonstrated that the AEROECLIPSE® XL BAN has the potential to significantly reduce overall therapy time based on patients achieving a slow, deep inhalation, as an alternative to tidal breathing. Consequently, this could lead to potential improved patient compliance and healthcare costs of nebulizer treatments.

References: 1 Arunthari V, Bruinsma RS, Lee AS, Johnson MM: A prospective, comparative trial of standard and breath-actuated nebulizer: efficacy, safety, and satisfaction. Respiratory Care 2013: 57(8): 1242-47. 2 Brand P, Hederer B, Austen G, Dewberry H, Meyer T: Higher lung deposition with Respimat† Soft Mist† Inhaler than HFA-MDI in COPD patients with poor technique. International Journal of Chronic Obstructive Pulmonary Disease 2008: 3(4): 763-70. 3 Köhler E, Sollich V, Schuster-Wonka R, Jorch G: Lung deposition after electronically breath-controlled inhalation and manually triggered conventional inhalation in cystic fibrosis patients. Journal of Aerosol Medicine 2005: 18(4): 386-95. 4 Denyer J, Nikander K, Smith NJ: Adaptive aerosol delivery (AAD) technology. Expert Opinion on Drug Delivery 2004: 1(1): 165-76. 5 Sawick GS, Sellers DE, Robinson WM: High treatment burden in adults with cystic fibrosis: Challenges to disease self-management. Journal of Cystic Fibrosis 2009: 8: 91-96. 6 Melani AS, Bonavia M, Cilenti V, Cinti C, Lodi M, Martucci P, Serra M, Schichilone N, Sestini P, Aliani M, Neri M: Inhaler mishandling remains common in real life and is associated with reduced disease control. Respir Med 2011: 105: 930-38. 7 Crompton GK, Barnes PJ, Broeders M, Corrigan C, Corbetta L, Dekhuijzen R, Dubus JC, Magnan A, Massone F, Sanchis J, Viejo JL, Voshaar T: The need to improve inhalation technique in Europe: A report from the Aerosol Drug Management Improvement Team. Respiratory Medicine 2006: 100: 1479-94. 8 Sanchis J, Corrigan C, Levy ML, Viejo JL: Inhaler devices: From theory to practice. Respiratory Medicine 2013: 107: 495-502.

INHALED ANTIBIOTIC DELIVERY BY PNEUMATIC NEBULIZATION: CASE STUDY COMPARING BREATH ACTUATED WITH BREATH ENHANCED NEBULIZERS FOR COLISTIMETHATE SODIUM.

JA Suggett, MW Nagel, H Schneider, CC Doyle, RS Ali, JP Mitchell. Respiratory Drug Delivery 2014;3:581-584.

Background: Inhaled colistimethate sodium is a polymixin antibiotic that is indicated for treating lung infection with pseudomonas aeruginosa in cystic fibrosis. Although dry powder inhaler-based products are available, this therapeutic agent is often given by pneumatic nebulization. To ensure optimal dosing, the possibility of using such products in conjunction with a Breath Actuated Nebulizer (BAN) may be of interest, as this type of nebulizer conserves medication during exhalation rather than allowing it to escape and disperse into the local environment. The present laboratory investigation was designed to evaluate colistimethate sodium output from a BAN configuration able to be used in either the hospital or home environment. Comparison measurements were also gathered for a continuous Breath Enhanced Nebulizer (BEN), to provide benchmark data. **Materials and Methods**: BAN group (*n* = 5 devices) AEROECLIPSE® XL with *OMBRA*® Table Top Compressor; AE-XL, Trudell Medical international, London, ON, Canada. BEN group (*n* = 5 devices) LC PLUS† with PARI BOY† SX compressor; PARI Respiratory equipment, Midlothian, VA, USA. 4.0 mL fill colistimethate sodium from ampoule (Colomycin† for injection, Forest Laboratories UK† Ltd.) equivalent to 160 mg colistimethate sodium, representative polymyxin antibiotic (polymyxin E). Adult patient tidal-breathing simulation with ASL5000 Test Lung (IngMar Medical, Pittsburgh, PA), Tidal volume = 600 mL, Duty cycle = 33%, Rate = 10 breathing cycles/min. Filter collection at mouthpiece of nebulizer at 1-min intervals from start to onset of sputter. Colistimethate sodium recovered quantitatively and assayed by HPLC-UV spectrophotometry to determine total mass of colistimethate sodium (TM_{cs}) at each time interval. The BANs were operated in the breath actuated mode for this part of the study. Medication is only delivered during the inspiratory portion of each breathing cycle. There is negligible waste of medication to the ambient surroundings during exhalation. The measurements were subsequently repeated with the same nebulizers sampling continuously at 15 L/min to determine droplet size distribution by Next Generation pharmaceutical Impactor (NGI). Fine Droplet Fraction < 5.4 µm diameter ($FDF_{<5.4\ \mu m}$) determined in accordance with USP Chapter 1601 (2013). Fine particle mass delivery profiles for colistimethate sodium aerosols were constructed on a minute by minute basis from the product of TM_{cs} and $FDF_{<5.4\ \mu m}$. **Results**: The figure summarizes the time dependent delivery of colistimethate sodium from BAN and BEN groups as Fine Particles <5.4µm aerodynamic diameter.



Fine particle mass delivery rates during the first 10 minutes from start of nebulization for both BAN and BEN systems were comparable. This outcome might be anticipated, since both nebulizers operate as breath entrainment devices having similar droplet aerodynamic particle size distributions. TM delivered to sputter was appreciably higher for the AEROECLIPSE® XL BAN. **Conclusions**: Conservation of medication and associated avoidance of environmental losses from fugitive emissions with the BAN nebulizer system was evident by the increased fine particle mass, compared with the BEN nebulizer system. Mean delivery rates of the therapeutically beneficial fine droplets were, however, comparable at ca. 2.4 mg/min for both nebulizer-compressor systems. In this particular instance, the caregiver therefore has the option of stopping treatment after 12 minutes with the BAN if a similar dose or run time to the BEN is desired, or can continue to deliver additional dose in the same treatment session if it is considered clinically desirable to maximize delivered dose. This additional dose is well within the safe and effective daily dose range reported from a colistimethate sodium marketed product registration information[1].

Reference: 1 Summary of Product Characteristics, Colomycin† Injection (Aerosol Inhalation), Forest Laboratories UK† Ltd.

Dornase Alfa (Pulmozyme†, Genentech† Inc.)

USE OF A BREATH-ACTUATED JET NEBULIZER TO DELIVER DORNASE ALFA FOR THE TREATMENT OF CYSTIC FIBROSIS: *IN VITRO* ASSESSMENT USING ADULT TIDAL BREATHING SIMULATION.

P Mitchell, D Coppolo, M Nagel. Pediatric Pulmonology 2013;48(S36):418.

Background: Dornase alfa recombinant human deoxyribonuclease I enzyme (Pulmozyme†, Genentech† Inc., South San Francisco, CA) is indicated in the management of cystic fibrosis to improve lung function. This inhaled biotherapeutic is typically delivered by continuous nebulization to tidal-breathing patients, but during the exhalation phase, medication is discharged into the environment. Breath-actuated nebulizers such as the AEROECLIPSE®-rBAN (Monaghan Medical Corporation, Syracuse, NY) only operate during inhalation, thereby mitigating contamination of the local environment and exposure burden of caregivers. **Study Objective**: This study was designed to evaluate medication output from an rBAN with table-top compressor (rBAN/*OMBRA*®) that is capable of being used in either the hospital or home environment, comparing its performance with that of a continuous nebulizer-compressor (LC PLUS†/BOY† SX compressor (LC+/BOY† SX), PARI Respiratory Equipment Inc., Midlothian, VA) that could be used for this therapeutic modality. **Methods**: Each nebulizer group (10 devices) was filled with a 2.5 mL Pulmozyme† ampoule (1 mg/mL dornase alfa) and run until onset of sputtering. Aerosol was captured by a filter at the mouthpiece, and the nebulizer connected to a breathing simulator (tidal volume = 600 mL; duty cycle = 33%; rate = 10 cycles/min). Fine droplet mass (μg < 5.4 μm diameter (FM_{pulm})) and fine droplet mass fraction (% < 5.4μm, (FMF_{pulm})) were determined by Next Generation Impactor operated at 15 L/min with assay for dornase alfa by isocratic size exclusion high performance liquid chromatography. Results: Comparative measures of the therapeutically beneficial FMF_{pulm} and FM_{pulm} are summarized in the Table.

Delivery of Dornase Alfa by Nebulizer-Compressor (values are mean ± SD)

System	FMF_{pulm} (%)	FM_{pulm} (μg)
rXL/*OMBRA*®	83.3 ± 2.2	428 ± 40
LC+/BOY† SX	83.8 ± 2.2	349 ± 62

Conclusions: Both nebulizer-compressor systems offer similar aerosol quality in terms of FMF_{pulm} and FM_{pulm} for delivery of Pulmozyme†. However, clinicians should be aware that, since the operation of the rBAN only occurs due to patient inhalation nearly all fugitive emissions are eliminated and delivery of all the FM_{pulm} leaving the nebulizer to the patient is assured.

DELIVERY OF DORNASE ALFA VIA BREATH-ACTUATED NEBULIZER: *IN VITRO* MEASURES OF PERFORMANCE.

J Suggett, J Mitchell, H Schneider, R Ali, M Nagel. European Respiratory Journal 2013;42:P1186.

Rationale: Pulmozyme† is indicated in the management of cystic fibrosis to improve lung function and is typically delivered by continuous nebulization to tidal-breathing patients. During the exhalation phase medication is discharged into the environment. Breath-actuated nebulizers (BANs) only operate during inhalation. This study was designed to evaluate medication output from a BAN configuration (AEROECLIPSE® XL/Ombra® compressor (AE-XL); TMI) compared with a continuous nebulizer configuration (PARI LC PLUS†/PARI BOY† SX compressor (LC+)). **Methods**: Each nebulizer was filled with a 2.5 mL Pulmozyme† ampoule (1 mg/mL dornase alfa) and run until onset of sputtering. Aerosol was captured by a filter at the mouthpiece, and the nebulizer connected to a breathing simulator (tidal volume = 600 mL; duty cycle = 33%; rate = 10 cycles/min). Fine droplet mass (μg < 5.4 μm diameter (FM_{pulm})) and fine droplet fraction (% < 5.4μm, (FMF_{pulm}) were determined by Next Generation Impactor operated at 15 L/min with assay for dornase alfa by HPLC.

Results

Device (n = 10)	FMF_{pulm} (%)	FM_{pulm} (mg)
AE-XL /*OMBRA*®	83.3 ± 2.2	428 ± 40
LC+/ PARI BOY† SX	83.8 ± 2.2	349 ± 62

Conclusions: The AE-XL BAN exhibited a little higher delivery of Pulmozyme† to the LC+, although well within the demonstrated patient tolerability (Pulmozyme† Nebuliser solution SPC, Roche). In addition, clinicians should be aware that, unlike the LC+, the operation of the BAN only occurs due to patient inhalation thereby eliminating nearly all fugitive emissions and ensuring delivery to the patient at their own pace.

Hypertonic Saline

USE OF AN OSCILLATING POSITIVE EXPIRATORY PRESSURE (OPEP) DEVICE WITH A BREATH ACTUATED NEBULIZER FOR THE DELIVERY OF HYPERTONIC SALINE.

DP Coppolo, JA Suggett, MW Nagel, JP Mitchell. Pediatric Pulmonology 2016;S45(51):S194-S485.

Background/Objective: Hypertonic saline is associated with increased mucociliary clearance of secretions. OPEP therapy helps to mobilize secretions mechanically. This laboratory investigation examined the performance of a breath-actuated nebulizer (BAN) in conjunction with OPEP for the delivery of hypertonic saline to see if the OPEP affected the emitted aerosol size distribution. **Methods**: The AEROECLIPSE® XL BAN (MMC, n = 5 devices) with tabletop compressor (*OMBRA*®) was evaluated for the delivery of hypertonic saline (4 mL, 7% v/w NaCl aq.) with and without the OPEP device (Aerobika®, MMC) inserted between the mouthpiece and nebulizer. Aerosol from the BAN was "inhaled" via a vacuum source operated at 28.3 L/min, and sized by a laser diffractometer (Malvern Spraytec, Malvern, UK). Comparative measurements were also made with a widely encountered breath enhanced nebulizer (LC PLUS†, PARI Respiratory Equipment, Midlothian, VA; n = 5 devices) operated by tabletop compressor (BOY-SX). **Results**: Measures of the aerosol size distribution were volume median diameter (VMD) and fine droplet fraction defined as the % < 4.7 µm diameter ($FDF_{<4.7µm}$), and are summarized in The Table. **Conclusions**: The addition of the OPEP device marginally reduced droplet size (paired t-test for each metric, p < 0.001), but the effect was small and likely unimportant, given that the finer droplets are more likely to penetrate further into the airways of the lungs, especially when restricted by secretions. The comparator BEN device produced similar, if slightly larger, droplet size results. Use of the AEROECLIPSE® XL with tabletop compressor, either with or without the concurrent use of the Aerobika® OPEP device, would appear to be an effective method of delivering hypertonic saline to the lungs for the purpose of mucociliary clearance.

Ipratropium Bromide (Atrovent†, Boehringer Ingelheim†)

A LABORATORY STUDY COMPARING BREATH ACTUATED AND BREATH ENHANCED NEBULIZER DEVICES AT VARIOUS DUTY CYCLES ASSOCIATED WITH COPD.

JA Suggett, H Schneider, R Ali, M Nagel, J Mitchell. American Journal of Respiratory and Critical Care Medicine 2014;189: A3035.

Background: Breath-actuation of a nebulizer only during patient inhalation conserves medication that would otherwise go to waste as fugitive emissions during exhalation. Similarly, medication is conserved if the patient interrupts their treatment by removing the mouthpiece temporarily. This laboratory study compared the delivery of an anticholinergic [Ipratropium Bromide (IPR)] solution widely used in the treatment of COPD by a breath actuated jet nebulizer (AEROECLIPSE® II XL with *OMBRA*® Table Top compressor (Trudell Medical International, London, Canada) with widely used breath enhanced nebulizer (BEN)-compressor systems in home-based therapy for COPD at various duty cycles (50%, 33%, 25% and 20%). **Methods**: The breath actuated nebulizer (BAN) group (n = 5 devices/group) were evaluated with an adult tidal breathing waveform (tidal volume = 500 mL) with duty cycles = 50%, 33%, 25% and 20% with 15, 10, 7 and 6 breaths/min respectively, delivered by breathing simulator (ASL 5000, IngMar Medical, Pittsburgh, PA). An electret filter at the mouthpiece of the nebulizer captured emitted aerosol containing 5000 ug ipratropium bromide in a 2-mL fill (UDV; Ratiopharm Inc., Canada) at minute intervals until onset of sputter. Total mass delivered (TM) was calculated after assaying for IPR by a validated HPLC-based procedure. Similar measurements were undertaken with an identical number of BENs (LC PLUS† and LC† Sprint with PARI BOY† SX compressor; PARI Respiratory Equipment, Midlothian, VA; SideStream† Plus with Inspiration Elite† compressor; Philips Respironics†, Murrysville, PA). **Results**: TM values are reported in **Table 1**. Significantly less medication (1-way ANOVA, p < 0.001) was delivered per treatment by each BEN group with decreasing duty cycle, due to wastage during each exhalation. In contrast, BAN-based delivery was unaffected (p = 0.722), because medication was conserved during exhalation.

Table 1: Nebulizer-Based Delivery (TM µg mean ± SD) of IPR from BAN and BEN Devices Simulating Adult Tidal-Breathing in COPD with Differing Duty Cycles

Duty Cycle		50%	33%	25%	20%
Nebulizer/Compressor		TM_{ipr} (µg)			
BAN	AE XL/OMBRA	102.9 ± 9.0	98.9 ± 8.5	105.7 ±16.5	97.1 ± 15.6
	LC† Sprint/ PARI BOY† SX	135.1 ± 5.7	107.0 ±9.9	84.7 ± 10.0	68.6 ± 4.1
BEN	LC PLUS†/ PARI BOY† SX	94.8 ± 13.9	76.4 ±12.2	53.3 ± 11.5	37.1 ± 8.6
	SideStream† PLUS†/ Inspiration Elite†	144.5 ±12.4	108.4 ±7.5	81.0 ± 7.1	76.3 ± 3.6

Conclusions: Wasted medication during exhalation can markedly reduce delivery via BEN to the patient, especially at short duty cycles, and can be avoided by the use of a BAN. The BAN therefore provides assurance of dose consistency independent of the patient's duty cycle and prevents potentially harmful fugitive emissions.

Tobramycin (TOBI†, Novartis Pharmaceuticals Corporation†)

DELIVERY OF TOBRAMYCIN VIA PNEUMATIC NEBULIZER: A LABORATORY STUDY COMPARING BREATH-ACTUATED AND BREATH-ENHANCED DEVICES.

JA Suggett, H Schneider, M Nagel, J Mitchell. American Journal of Respiratory and Critical Care Medicine 2014;189: A2847.

Rationale: Pneumatic nebulization is the mainstay of care of patients requiring inhaled antibiotic therapy in association with pulmonary diseases such as cystic fibrosis and chronic obstructive pulmonary disease. Breath-actuated nebulizers (BANs) offer the opportunity to provide such therapy without emission of fugitive emissions to caregivers during exhalation, as well as conserving medication if the patient chooses to interrupt therapy. This bench study was undertaken to determine the delivery of tobramycin using a BAN, with data from a breath-entrained nebulizer (BEN) as a benchmark. **Methods**: The BAN (AEROECLIPSE® XL BAN with *OMBRA*® Table Top compressor (AE-XL, Trudell Medical International, London, ON) was evaluated with an adult tidal breathing waveform (tidal volume = 600 mL; duty cycle = 33%; rate/min = 10 breaths) delivered by breathing simulator (ASL 5000, IngMar Medical, Pittsburgh, PA). An electret filter at the mouthpiece of the nebulizer captured emitted aerosol containing 300 mg tobramycin in a 5-mL fill (TOBI†; Novartis Pharmaceuticals Corporation†, East Hanover, NJ) at minute intervals until onset of sputter. Average delivery rate/min (DR_{min}) was calculated after assaying for tobramycin by a validated HPLC-based procedure. Similar measurements were undertaken with an identical number of BENs (LC PLUS† with PARI BOY† SX compressor; PARI Respiratory Equipment, Midlothian, VA). Parallel measurements of fine droplet fraction < 5.4 µm diameter ($FDF_{<5.4µm}$) were made with each nebulizer, sampling the emitted aerosol via a Next Generation Pharmaceutical Impactor at 15 L/min in accordance with the pharmacopeial procedure. Fine droplet mass delivery/min ($FDM_{<5.4µm/min}$) was determined as the product of DR_{min} and $FDF_{<5.4µm}$. Total mass delivered (TM) was also determined. **Results**: **Table 1** summarizes the results for DR_{min}, $FDF_{<5.4µm}$, $FDM_{<5.4µm/min}$ and TM. DR_{min} data was similar for the two nebulizer/compressor systems however the $FDM_{<5.4µm/min}$ delivery rate was a little higher with the BAN than with the BEN, as a result of the higher FDF. The TM delivered to sputter was appreciably higher for the BAN (140.9 mg compared to 83.4 mg).

Table 1: Nebulizer-Based Delivery of Tobramycin from BAN and BEN Devices Simulating Adult Tidal-Breathing mean ± SD) (*n* = 5 devices/group)

Type	Nebulizer	DR_{min} (mg/min)	$FDF_{<5.4µg}$ (%)	$FDFM_{<5.4µg/min}$ (mg/min)	TM (mg)
BAN	AE-XL/*OMBRA* compressor	4.14 ± 0.18	72.1 ± 1.9	2.99 ± 0.13	140.9 ± 6.2
BEN	LC PLUS†/ PARI BOY† SX compressor	4.17 ± 0.34	63.7 ± 2.0	2.66 ± 0.22	83.4 ± 6.9

Conclusions: The delivery rate of tobramycin using the BAN and BEN/compressor systems was similar with evidence of a slightly higher fine particle delivery rate for the BAN. The more significant difference related to the total mass delivered and is somewhat expected given the higher delivery efficiency with a breath actuated nebulizer. The potential to adjust total delivery, if required, exists through the adjustment of either delivery time or fill volume.

COMBINED THERAPY

USE OF AN OSCILLATING POSITIVE EXPIRATORY PRESSURE (OPEP) DEVICE WITH A BREATH ACTUATED NEBULIZER FOR THE DELIVERY OF HYPERTONIC SALINE.

DP Coppolo, JA Suggett, MW Nagel, JP Mitchell. Pediatric Pulmonology 2016;S45(51):S194-S485.

Background/Objective: Hypertonic saline is associated with increased mucociliary clearance of secretions. OPEP therapy helps to mobilize secretions mechanically. This laboratory investigation examined the performance of a breath-actuated nebulizer (BAN) in conjunction with OPEP for the delivery of hypertonic saline to see if the OPEP affected the emitted aerosol size distribution. **Methods**: The AEROECLIPSE® XL BAN (MMC, *n* = 5 devices) with tabletop compressor (*OMBRA*®) was evaluated for the delivery of hypertonic saline (4 mL, 7% v/w NaCl aq.) with and without the OPEP device (Aerobika®, MMC) inserted between the mouthpiece and nebulizer. Aerosol from the BAN was "inhaled" via a vacuum source operated at 28.3 L/min, and sized by a laser diffractometer (Malvern Spraytec, Malvern, UK). Comparative measurements were also made with a widely encountered breath enhanced nebulizer (LC PLUS†, PARI Respiratory Equipment, Midlothian, VA; *n* = 5 devices) operated by tabletop compressor (BOY-SX). **Results**: Measures of the aerosol size distribution were volume median diameter (VMD) and fine droplet fraction defined as the % < 4.7 µm diameter ($FDF_{<4.7\mu m}$). **Conclusions**: The addition of the OPEP device marginally reduced droplet size (paired t-test for each metric, $p < 0.001$), but the effect was small and likely unimportant, given that the finer droplets are more likely to penetrate further into the airways of the lungs, especially when restricted by secretions. The comparator BEN device produced similar, if slightly larger, droplet size results. Use of the AEROECLIPSE® XL with tabletop compressor, either with or without the concurrent use of the Aerobika® OPEP device, would appear to be an effective method of delivering hypertonic saline to the lungs for the purpose of mucociliary clearance.

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