REFERENCE MATERIAL

BAUR OUTPUT AND AEROSOL PROPERTIES OF 5 NEBULIZER COMPRESSOR SYSTEMS WITH ARFORMOTEROL INHALATION SOLUTION

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Output and Aerosol Properties of 5 Nebulizer/Compressor Systems With Arformoterol Inhalation Solution

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BACKGROUND: Arformoterol, the (R,R) isomer of formoterol, is approved as an inhalation solution for the treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease. Multiple nebulizer systems are commercially available. Different nebulizers can differ significantly in drug output, which may impact drug delivery and clinical efficacy. This study compared the aerosol properties of arformoterol delivered via 5 commonly used nebulizer systems for the home-care market. METHODS: The delivered dose of arformoterol inhalation solution (15 μg/2 mL) was collected in a glass Dreschel-type apparatus. The delivered amount in fine-droplet fraction was assessed with an Andersen cascade impactor, and droplet size (average median diameter and average percent < 5 μm) was evaluated via laser diffraction. Compressor flow rate measurements were taken after 1 min and 6 min by placing the flow meter in line with each system. RESULTS: The Pari LC Plus, Updraft II Opti-Neb, and NebuTech systems delivered similar amounts of the 15-μg nominal dose (from 23% to 25%). The Pari LC Star and Sidestream systems delivered slightly higher doses (31% and 35%, respectively). The nebulizer/compressor systems differed somewhat with respect to droplet size. The NebuTech delivered the lowest fine-droplet fraction (61%) via Andersen cascade impactor, and the smallest percent of droplets < 5 μm (40%) via laser diffraction. The Pari LC Star and Sidestream delivered the highest fine-droplet fraction (100% and 93%, respectively), and the greatest percent of droplets < 5 μm (84% and 88%). The fine-droplet fractions for the Updraft II Opti-Neb and Pari LC Plus were 93% and 89%, respectively, and the percent of droplets < 5 μm was about 67%. Compressor flow rates ranged from 3.2 L/min (Pari LC Plus) to 5.4 L/min (NebuTech). CONCLUSIONS: The results of this study demonstrate that the choice of nebulizer/compressor system can influence the aerosol properties of arformoterol inhalation solution and should be considered when prescribing nebulized medications.
Key words: arformoterol, nebulizer, compressor, aerosol, delivered dose, droplet-size distribution, Andersen cascade impactor, laser diffraction. [Respir Care 2009;54(10):1342–1347.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by incompletely or poorly reversible airway obstruction resulting from chronic airway inflammation and disruption of airway support structures. Evidence-based guidelines recommend the use of long-acting bronchodilators for treating patients with COPD.[1,2] Long-acting β_2 agonists that act for at least 12 hours are used extensively in the treatment of symptoms of COPD.

Until recently, inhaled long-acting β_2 agonist treatment options included primarily metered-dose inhalers or dry-powder inhalers. However, some COPD patients

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have difficulty using these inhalers,[3] leading to ineffective drug delivery or adherence to treatment regimens. Nebulized inhalation of a short-acting bronchodilator is used by approximately 25% of patients with COPD.[3] Recently, arformoterol, the (R,R) isomer of the long-acting β_2 agonist, formoterol, was developed and approved as a nebulized therapy for the maintenance treatment of bronchoconstriction in COPD.[4,5]

A large number of nebulizer systems are commercially available. It is known that the nebulizer systems differ from one another in their effect upon the aerosol properties of a given medication,[6-9] which, in turn, may affect treatment outcomes.[8] Nebulizer design, flow rate requirements, solution properties, and breathing patterns are all key variables that affect nebulized delivery of a drug.[10] There are 2 broad categories of nebulizers: traditional constant-output nebulizers and breath-enhanced nebulizers. Constant-output nebulizers produce aerosol throughout the respiratory cycle so that a large proportion of the nebulizer output occurs at a time during the respiratory cycle when the patient is not inhaling, and is thus not delivered to the airways.[11] In contrast, breath-enhanced nebulizers have a set of inspiratory and expiratory valves that allow ambient air to be entrained into the nebulizing chamber only during the inspiratory phase, when the patient's flow exceeds the driving flow of the device.[11] The valve system closes during expiration; therefore, drug delivery occurs only during inspiration, resulting in less medication loss. The breath-enhanced nebulizers are usually designed to be reusable.

This paper describes the results from in vitro experiments comparing the delivered dose and droplet-size distribution of arformoterol by 5 nebulizer systems: NebuTech, Updraft II Opti-Neb, Pari LC Plus, Pari LC Star, and Sidestream. The Pari LC Plus nebulizer was used in phase III arformoterol trials,[4,5] and the other 4 nebulizers were chosen because they are commonly prescribed by physicians and used by patients with COPD. For aqueous solutions, laboratory studies measuring differences in the quantity and aerosol properties of drug delivered to the mouth by a nebulizer system can accurately predict differences in aerosol inhaled and deposited in patient airways.[12,13] The purpose of this study was to determine whether the aerosol output and droplet-size distribution of arformoterol inhalation solution are impacted by these different nebulizer systems.

Methods

Nebulizers and Drug

The following nebulizers and compressor systems were tested in this study:

- Pari LC Plus nebulizer and Duraneb 3000 portable aerosol system (both Pari Respiratory Equipment, Midlothian, Virginia)
- Pari LC Star nebulizer and Pari Trek compressor (both Pari Respiratory Equipment, Midlothian, Virginia)
- Reusable Sidestream nebulizer (Respironics, Parsippany, New Jersey) and Invacare Envoy compressor (Invacare Corporation, Elyria, Ohio)
- Reusable NebuTech HDN nebulizer and NebuTech Aire Plus compressor (both Salter Labs, Arvin, California)
- Updraft II Opti-Neb nebulizer and Hudson Mini-Neb compressor (both Hudson RCI, Durham, North Carolina)

Nebulizer and compressor systems that were used in this study are marketed for use together, and were operated according to the manufacturer's specifications. The driving pressure for each nebulizer was supplied by the corresponding compressor at ambient conditions. The Pari LC Plus, the Pari LC Star, and the NebuTech HDN are reusable breath-enhanced nebulizers. The Sidestream enhances the amount of drug nebulized; an inlet vent draws air into the nebulizer, which increases the rate of flow of nebulized drug. The Updraft II Opti-Neb is a constant-output T-mouthpiece nebulizer.

Each nebulizer was loaded with 2 mL of arformoterol tartrate nebulizing solution (15 μg/2 mL) (Brovana, Sepracor, Marlborough, Massachusetts). Nebulizers were held in upright position by a ring stand and were connected with an adapter to the Andersen cascade impactor or delivered dose apparatus. The collection time for delivered dose and cascade impaction was 6 min, the time recommended by the arformoterol prescribing instructions for nebulization. All experiments were performed in an average relative humidity of 33.9 $\pm$ 3.1%.

Drug Assay

Chemical analysis of arformoterol was performed via high-pressure liquid chromatography. The technique used 16:84 (v/v) acetonitrile: 50 mM KH_2PO_4, pH 3.85, as mobile phase with a YMC Pack Pro C18 column (Waters, Milford, Massachusetts). The flow rate was set at 1.5 mL/min. Electrochemical detection (ESA Coulochem II, ESA, Chelmsford, Massachusetts) was used for quantifying arformoterol. The limit of quantitation for this method was 5 ng/g.

Aerosol Output Analysis

The aerosol output was collected in a glass Dreschel-type apparatus, commonly used for aerosol collection. Neb-

ulized solution was collected (minus mouthpiece) for 6 min at a vacuum-assisted constant flow rate of 28.3 L/min (per United States Pharmacopoeia monograph 601, Aerosols, Nasal Sprays, Metered-Dose Inhalers and Dry-Powder Inhalers[14]). High-pressure liquid chromatography mobile-phase solution was used to extract arformoterol from the Dreschel-type apparatus, and the amount extracted was measured via high-pressure liquid chromatography. The residual amount of arformoterol contained in the nebulizer bowl was extracted and also determined via high-pressure liquid chromatography. The remaining volume in the nebulizer bowl after extraction was measured via weight. Duplicate delivered dose experiments were performed on 3 different nebulizer/compressor systems per brand, resulting in 6 independent experiments for each nebulizer/compressor system. The aerosol output in micrograms and in percent of the nominal dose (amount of drug per vial 15 μg), the retained dose in the nebulizer in micrograms, the mass balance (total recovery of drug) in percent, and the emitted nebule solution weight in grams were determined. The mass balance was calculated by dividing the total recovered drug (Dreschel-type apparatus, mouthpiece, and nebulizer bowl) by the drug initially placed into the nebulizer bowl.

Cascade Impaction

Aerodynamic particle size distribution was determined using an Andersen cascade impactor (Thermo Andersen Instruments, Waltham, Massachusetts) at a flow rate of 28.3 L/min, minus mouthpiece (per United States Pharmacopoeia monograph 601, Aerosols, Nasal Sprays, Metered-Dose Inhalers and Dry-Powder Inhalers[14]) over a 6 min period. High-pressure liquid chromatography mobile phase was used to extract arformoterol from the various stages of the cascade impactor. Duplicate cascade impaction experiments were performed on 2 different nebulizer/compressor systems per brand, resulting in 4 individual independent experiments for each nebulizer/compressor system. The fine-droplet fraction is calculated by the sum of the arformoterol dose on stages 3 through "filter" divided by the sum of the arformoterol dose on "throat" through "filter" of the cascade impactor, and includes droplets < 4.7 μm. In addition, the fine-droplet dose in nominal dose [(delivered dose $\times$ fine-droplet fraction)/100] was calculated. The ambient humidity was recorded and ranged from 30% to 43% relative humidity, with an average and standard deviation of 33.9 $\pm$ 3.1% relative humidity.

Laser Diffraction

Droplet-size distribution was determined for each nebulizer and compressor combination via laser diffraction, using a Sympatec Helos laser diffraction system with the inhaler adapter (Sympatec, Lawrenceville, New Jersey). A 100-mm range lens was used to detect particles between 0.5 μm and 175 μm calculated diameter. The presentation code corresponded to water (refractive index of 1.333) dispersed in air (refractive index of 1.000). To ensure consistent delivery of mist across the laser beam for all systems, an inhaler attachment was used that provided an enclosed system within which the mist from the nebulizer could be analyzed. Air flow rate was controlled by the software (Sympatec, Lawrenceville, New Jersey). The aerosol that passed across the laser beam was withdrawn by a vacuum extraction system to avoid data error arising from the recirculation of droplets.[15]

The first minute of data collection was selected to provide a satisfactory method of comparing the droplet size from the various brands of nebulizers. The laser diffraction analysis was performed in duplicate, using 3 different nebulizer/compressor systems per brand. The average volume median diameter (D50) in μm and the average percent of droplets < 5 μm were reported. The ambient humidity was recorded and ranged from 19% to 23% relative humidity, with an average and standard deviation of 22 $\pm$ 1.8% relative humidity.

Compressor Flow Rate

Flow rate measurements were evaluated at 20°C for each compressor by placing a rotameter in line with each nebulizer/compressor system. A Yokogawa Rota rotameter was used (Yokogawa, Atlanta, Georgia). These experiments were performed once on 3 separate nebulizer/compressor systems per brand. After an initial 3-minute equilibration period, measurements were taken at 1-min and 6-min intervals.

Results

The nebulizer/compressor systems differed from one another in the amount of arformoterol delivered. The Pari LC Star and the Sidestream had the greatest drug output of arformoterol (31% and 35%, respectively, of the nominal dose [the amount of drug in the marketed vial: 15 μg in 2 mL], Table 1). The other 3 systems had similar drug output (between 23% and 25% of the nominal dose). For all 5 nebulizer/compressor systems, the majority of the 15-μg dose remained in the nebulizer bowl (ranging from 7.8 μg to 9.5 μg). The mass balance was 97% to 103% for all systems. The weight of the emitted nebule solution ranged from 0.73 g to 1.14 g, with the Updraft II Opti-Neb delivering the lowest nebule solution weight relative to the other systems.

The droplet-size distribution profiles of all 5 systems are shown in Figure 1. The different nebulizer/compressor systems differed in the fraction of the amount delivered as

Table 1. Delivered Amount of Arformoterol (15 μg) for Each Nebulizer/Compressor System*

Nebulizer	Delivered Amount in μg (mean ± SD)	Delivered Amount in % of Nominal Dose (15 μg)	Retained Amount in μg (mean ± SD)	Mass Balance in % (mean ± SD)	Emitted Nebule Solution Weight in g (mean ± SD)
NebuTech	3.5 ± 0.34	23	9.2 ± 0.37	99 ± 1	0.99 ± 0.05
Updraft II Opti-Neb	3.6 ± 0.76	24	9.5 ± 0.94	99 ± 1	0.73 ± 0.11
Pari LC Plus	3.7 ± 0.40	25	8.9 ± 0.56	98 ± 0	0.93 ± 0.09
Pari LC Star	4.6 ± 1.39	31	8.0 ± 1.32	103 ± 6	0.92 ± 0.29
Sidestream	5.2 ± 0.45	35	7.8 ± 0.37	97 ± 1	1.14 ± 0.06

* $n = 6$

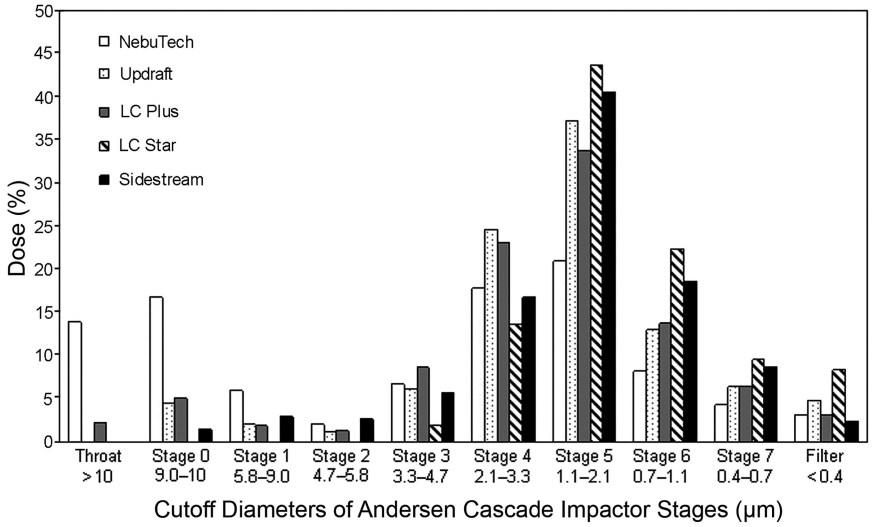

Fig. 1. Andersen cascade impactor profile for all nebulizer/compressor systems.

Table 2. Cascade Impaction Measurement of Fine-Droplet Fraction for Each Nebulizer/Compressor System* and Volume Median Diameter and Mean Percentage of Droplets < 5 μm for Each Nebulizer/Compressor System†

	Andersen Cascade Impaction		Laser Diffraction	
Nebulizer	Fine-Droplet Fraction in % (< 4.7 μm) (mean ± SD)	Fine-Droplet Dose in % of Nominal Dose (delivered dose × fine-droplet fraction/100)	Volume Median Diameter (D50) in μm (mean ± SD)	Percent < 5 μm (mean ± SD)
NebuTech	61 ± 5.4	14	6.8 ± 0.38	40 ± 2.1
Updraft II Opti-Neb	93 ± 0.9	22	3.4 ± 0.32	67 ± 3.4
Pari LC Plus	89 ± 1.7	22	3.4 ± 0.19	67 ± 3.4
Pari LC Star	100 ± 0	31	2.5 ± 0.12	84 ± 1.7
Sidestream	93 ± 2.5	32	2.4 ± 0.05	88 ± 1.9

* $n = 4$
† $n = 6$

fine droplets (< 4.7 μm) as measured via cascade impaction (Table 2). The NebuTech delivered the lowest fraction (about 61%, 14% of the nominal dose), and the Pari LC Star delivered the highest fine-droplet fraction (about 100%, 31% of the nominal dose) (see Table 2). The other 3 nebulizer systems delivered comparable percentages of the dose as fine droplets.

Consistent with the NebuTech having the lowest percent of the dose delivered as fine droplets, it also had the largest droplet-size distribution, as determined via laser

Table 3. Flow Rates of All Compressor/Nebulizer Systems*

Nebulizer	Flow Rate at 1 min (L/min)	Flow Rate at 6 min (L/min)
NebuTech	5.4	5.4
Updraft II Opti-Neb	4.8	4.8
Pari LC Plus	3.2	3.1
Pari LC Star	3.7	3.7
Sidestream	4.9	4.9

* $n = 3$

diffraction, in comparison with the 4 other nebulizer systems (see Table 2). The mean ± SD volume median diameter for the NebuTech was 6.8 ± 0.38 μm, compared with about 2.5 ± 0.12 μm for the Pari LC Star and 2.4 ± 0.05 μm for the Sidestream and approximately 3.4 μm for the Updraft II Opti-Neb and Pari LC Plus. Similarly, the NebuTech had the lowest percent of droplets that were < 5 μm (40 ± 2.1%), compared with the other nebulizer/compressor systems. The Pari LC Star and the Sidestream systems had the highest proportion (84 ± 1.7% and 88 ± 1.9%, respectively) of droplets < 5 μm.

The compressor flow rates ranged from 3.1 L/min (Pari LC Plus) to 5.4 L/min (NebuTech), and were stable over 6 min for all nebulizer/compressor systems (Table 3). There was no correlation between compressor flow rates and the fraction of fine droplets or size of droplets delivered by a nebulizer/compressor system.

Discussion

The deposition of inhaled medication into the lung and airways is influenced by multiple factors, including the characteristics of the nebulizer device, the formulation properties of the aerosol, the patient's breathing pattern, airway geometry, and potential differences in regional airway ventilation. Differences among nebulizer systems can impact by several-fold the efficiency of drug delivery to the lung.[3,6] Patient treatment with the marketed dose of an aerosolized drug using different nebulizer devices without consideration of the amount of drug delivered by a given nebulizer may result in variability in treatment efficacy and drug-related adverse effects.

The amount of drug in small droplets (< 5 μm), commonly described as the fine-droplet fraction, is the portion of an aerosolized drug most efficiently delivered to the distal airways.[3] This study found differences in the drug output and droplet size of the nebulized long-acting bronchodilator arformoterol by 5 nebulizer-compressor systems. The Pari LC Star and Sidestream systems emitted a higher average amount of arformoterol than the Pari LC Plus, Updraft II Opti-Neb, and NebuTech systems, which were similar in their drug output. The ranking of nebulizer/compressor systems with respect to the fine-droplet fraction via cascade impaction was consistent with the ranking based on droplet size via laser diffraction. Four of the 5 systems had a fine-droplet fraction in excess of 89%; only the NebuTech system was lower (61%). Laser diffraction analyses were likewise consistent with the above ranking, with both the volume median diameter and percent of droplets < 5 μm being lower for the NebuTech than for the other 4 systems.

The percent of the drug output by a given nebulizer correlated with the in vitro droplet size. The Sidestream and Pari LC Star showed the greatest drug output of arformoterol and had the highest fraction of the nominal dose emitted as small droplets. A similar correlation between drug output and droplet size was observed in previous studies.[8] In the current study there was no relationship between the compressor flow rate and the drug output or droplet size of arformoterol.

The results of these experiments imply that the NebuTech system may be less efficient than the Pari LC Plus, which was used in clinical trials in delivering arformoterol to the distal airways of subjects with COPD. Conversely, the Pari LC Star and the Sidestream systems may be somewhat more efficient than the Pari LC Plus in effecting distal airway delivery.

Although prior investigations have supported a relationship between in vitro analyses, airway deposition, and clinical effects,[12,13] such methods have some limitations. These results estimate the drug output of the 5 different nebulizer/compressor systems in an experimental system, and not that deposited in the lung or airways of COPD patients. Only the Pari LC Plus has been analyzed in vivo with regard to arformoterol delivered dose and clinical outcomes.[4,5] Different breathing patterns are known to affect drug output of a drug by a nebulizer.[7,10,16] Studies that utilize breath simulation that represents the range of tidal breathing patterns observed in COPD patients are required to determine how COPD may alter the aerosol properties of arformoterol from these different nebulizers. The performance of the different nebulizers driven by hospital wall gas systems (typically 50 psig air and oxygen flow meters) was not studied, and the present data should not be extrapolated to operation within the hospital setting.

Clinical inferences made from in vitro comparisons of the 4 nebulizer/compressor systems to the Pari LC Plus must be made with caution, as delivery of the biological dose to airway and lungs is complex and is influenced by patient-related factors, including breathing patterns,[12,16,17] and the individual nature and severity of airway obstruction.

Findings of other studies[8,18-20] have suggested that the selection of nebulizer/compressor systems could influence drug delivery. In particular, the aerosol properties of the

medication and the resultant biological delivered dose could be affected by such a selection. Clinical efficacy of arformoterol used in 4 of the 5 nebulizer/compressor systems has not been evaluated. However, the results of this study and prior clinical trials of arformoterol[4,5] suggest that efficacy is unlikely to be compromised for any of the systems studied. Clinical rather than in vitro studies, however, are required to determine the clinical efficacy and safety of arformoterol used with these other nebulizer/compressor systems.

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