

Delivery of Iloprost Inhalation Solution With the HaloLite, Prodose, and I-neb Adaptive Aerosol Delivery Systems: An In Vitro Study

Robert E Van Dyke MSc and Kurt Nikander

BACKGROUND: Iloprost (Ventavis) inhalation solution is approved in doses of 2.5 μg and 5.0 μg for treatment of pulmonary arterial hypertension (World Health Organization group I) in patients with New York Heart Association class III or IV symptoms, delivered with 2 Adaptive Aerosol Delivery (AAD) systems: Prodose and I-neb. The HaloLite device was the first-generation AAD system used in the clinical delivery of inhaled iloprost, and I-neb is the third-generation system. **OBJECTIVE:** Study the in vitro performance of the HaloLite, Prodose, I-neb, in terms of mass median aerodynamic diameter (MMAD), fine-particle fraction (FPF, percent of aerosol droplets < 4.7 μm), and inhaled mass of iloprost. **METHODS:** To analyze the MMAD and FPF, we collected the aerosol from each device with a cascade impactor. Because the devices are breath-actuated, airflow was regulated with flow-control valves to create inhalation and exhalation. To measure the inhaled mass of iloprost we used a breathing simulator with a filter system between the simulator and the device, and quantified the captured aerosol with iloprost-specific chromatography. **RESULTS:** With the HaloLite, Prodose, and I-neb, respectively: the MMADs were 1.4 μm , 1.7 μm , and 2.1 μm ; the FPFs were 91%, 82%, and 82%. The inhaled mass with the 2.5- μg dose ranged from 2.8 μg to 2.9 μg . The inhaled mass with the 5.0- μg dose ranged from 4.8 μg to 5.2 μg . **CONCLUSION:** The HaloLite, Prodose, and I-neb AAD systems have comparable MMADs, FPFs, and inhaled mass with iloprost. *Key words: pulmonary arterial hypertension, inhaled iloprost, Adaptive Aerosol Delivery, inhaled mass, mass median aerodynamic diameter, fine-particle fraction.* [Respir Care 2007;52(2):184–190. © 2007 Daedalus Enterprises]

Introduction

Pulmonary arterial hypertension is an incurable, chronic disease in which patients experience an increase in pul-

monary artery pressure, resulting in dyspnea, angina, palpitations, and syncope.¹ The current goals of therapy are to relieve symptoms by reducing pulmonary vascular resistance, to increase cardiac output, and to improve oxygenation. Intravenous infusion of prostanoids decreases mean pulmonary arterial pressure and pulmonary vascular resistance, and increases cardiac output, which increases exercise tolerance and improves survival.¹ Intravenous prostanoids have drawbacks, however, including the requirement for central venous access, the need for a continuous infusion, and adverse effects related to systemic availability of the drug.^{1,2}

Inhalation therapy with iloprost solution in pulmonary arterial hypertension aims at preferential pulmonary delivery to the lung vasculature to reduce systemic adverse effects. In the pivotal placebo controlled study of inhaled iloprost in patients with severe pulmonary arterial hypertension, initiated in the late 1990s, the HaloLite Adaptive Aerosol Delivery (AAD) system (Respironics Respiratory Drug Delivery, Cedar Grove, New Jersey) was selected to

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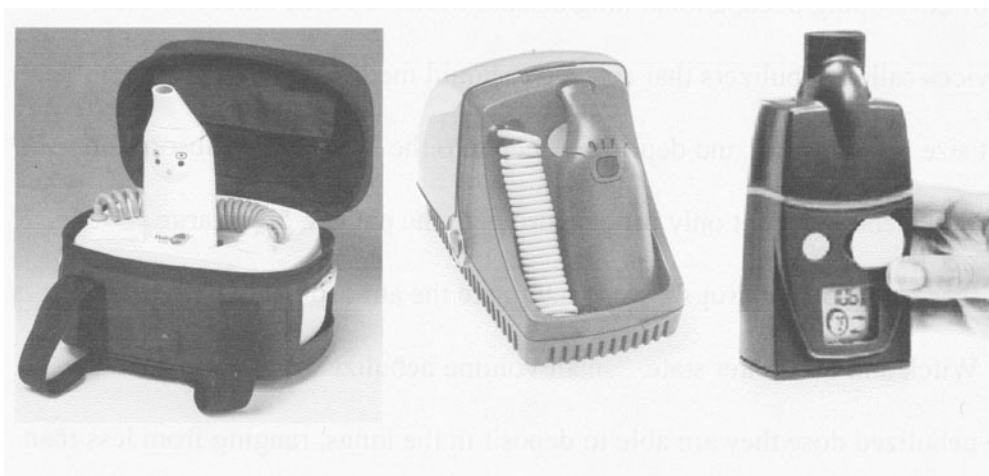


Fig. 1. Three Adaptive Aerosol Delivery systems: HaloLite (left), Prodose (center), I-neb (right).

deliver doses of 2.5 μg and 5.0 μg , 6–9 times daily.^{2–5} In the United States, inhaled iloprost was approved in December 2004, in doses of 2.5 μg and 5.0 μg , for the treatment of pulmonary arterial hypertension (World Health Organization group I) in patients with New York Heart Association class III or IV symptoms, delivered with the Prodose AAD system (Respironics Respiratory Drug Delivery, Cedar Grove, New Jersey). The labeling has since been extended to include the I-neb AAD system (Respironics Respiratory Drug Delivery, Cedar Grove, New Jersey), which is the third-generation AAD system from Respironics.

The AAD technology was developed to reduce the variability of the delivered dose, reduce the waste of aerosol to the environment during exhalation, and improve patient adherence to treatment and use of the device.^{3–5} HaloLite, Prodose, and I-neb analyze the patient's breathing pattern, which determines the timing of the aerosol pulse during inhalation. The systems analyze the pressure changes of the airflow of the first 3 breaths to ascertain the correct starting point for aerosol delivery during inhalation. The monitoring of the preceding 3 breaths continues throughout the treatment, and the device continually adapts to the patient's breathing pattern. The adaptation to the patient's breathing pattern eliminates the greatest source of variability in drug delivery associated with conventional nebulizers, because losses of aerosol during exhalation are reduced.⁵ The systems also provide the patient with feedback on how to effectively use the devices during treatment. When the preset dose has been delivered, the device switches off and a buzzer indicates completion of treatment.

Because of the progressive improvement of the AAD systems, from HaloLite to Prodose to I-neb, it is essential to determine whether the devices' aerosol characteristics and inhaled mass of iloprost are comparable. We designed

an *in vitro* study to test whether the delivery of iloprost was comparable between the 3 AAD systems, in terms of aerosol characteristics (particle size, fine-particle fraction, and particle distribution) and inhaled mass.

Methods

Study Design

The study was designed to evaluate *in vitro* the HaloLite, Prodose, and I-neb devices (Fig. 1), in terms of aerosol characteristics and inhaled mass of iloprost. Iloprost inhalation solution (Ventavis, CoTherix, Brisbane, California) (10 $\mu\text{g}/\text{mL}$, 2-mL ampule) was used throughout the study. The entire contents of one ampule were dispensed into the device's medication chamber for each delivered dose (2.5 μg or 5.0 μg). Three of each device (HaloLite, Prodose and I-neb) were tested for aerosol characteristics (mass median aerodynamic diameter [MMAD], fine-particle fraction, and particle-size distribution) and inhaled mass.

HaloLite

HaloLite was the first-generation AAD system and was made commercially available in Europe in 1997.^{3–5} The HaloLite system was designed based on active venturi jet nebulizer technology, and the system consists of a hand-piece, a mouthpiece, a medication chamber, and an electronic control unit, powered by a battery.^{4,5} The compressor is powered from a standard wall outlet. The aerosol pulse time is set to 50% of each inspiration, based on a rolling average of the last 3 breaths. The amount of drug delivered during each pulse is calculated by the software in the device, and summed over the course of the treatment. Upon attainment of the preset dose, the device gives

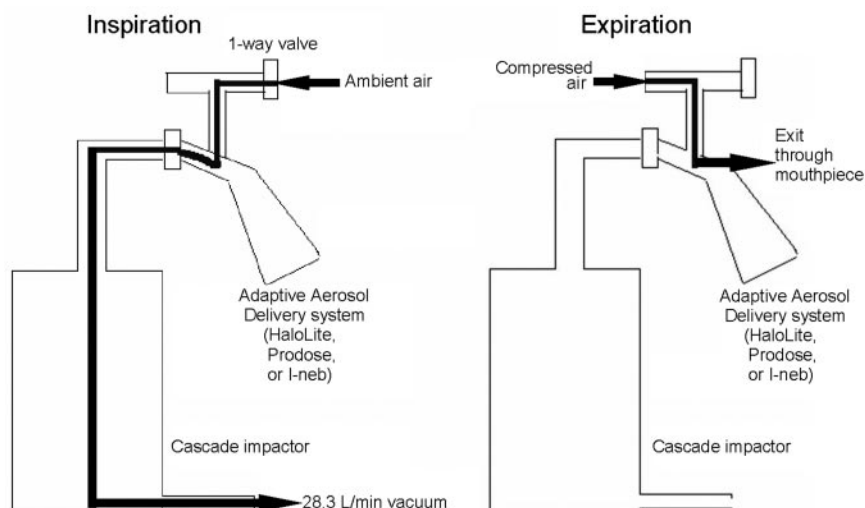


Fig. 2. Inspiratory flow (left) and expiratory flow (right) of air and aerosol through the Adaptive Aerosol Delivery system (HaloLite, Prodose, or I-neb) and the cascade impactor.

the patient both audible and visual feedback to indicate successful treatment. Since production of HaloLite has been discontinued, the HaloLite devices we used in this study were recalibrated units preset to deliver a dose of 2.5 μg iloprost. This setting was used in the large pivotal clinical study in which they delivered the 2.5- μg dose or two sequential 2.5- μg doses for the 5.0- μg dose.²

Prodose

Prodose, the second-generation AAD system, succeeded the HaloLite. The Prodose has better convenience and flexibility than HaloLite, including a self-powered hand-piece fitted with a liquid-crystal display,⁵ an improved software algorithm, and a more rugged compressor (again, powered from a standard wall outlet). One of the major design differences in Prodose is that it includes the “AAD Disc,” which is a plastic disc that contains an antenna and a microchip that controls the dosage. The 2 AAD Discs designed for iloprost are programmed to deliver 2.5 μg or 5.0 μg .

I-neb

I-neb is the third-generation AAD system, which succeeded the Prodose. I-neb is small, battery-powered, lightweight, virtually silent, substantially reduces the inconvenience of conventional nebulizer/compressor therapy, and delivers a precise, reproducible dose.⁵ The aerosol is created through a mesh technology, and the dose is controlled by the AAD Disc and specific medication chambers, which have a residual solution volume of about 0.1 mL.⁵ The medication chamber consists of a central “metered” section and an overflow section. Iloprost solution is trans-

ferred from the ampule into the metered section of the chamber until it is completely filled, and the remainder of the ampule contents flows into the overflow section. The volume in the metered section defines the delivered dose. The mesh has a variable power range to optimize the aerosol output. The AAD Disc in the I-neb uses the same algorithm used in Prodose. The I-neb devices used in this study were pre-production units that had 2 separate medication chambers: one for the 2.5- μg dose and one for the 5.0- μg dose.

Aerosol Characterization

The aerosol characteristics (particle size, fine-particle fraction, and particle distribution) were measured with a cascade impactor and iloprost-specific high-performance liquid chromatography. The cascade impactor sample-collection method we used was closely modeled after the United States Pharmacopoeia (USP) guidelines for particle-size determination of aerosol from powder inhalers, as required for regulatory submission.⁶ The effective cut-off diameters for the cascade impactor stages were: stage 0 = 9.00 μm , stage 1 = 5.80 μm , stage 2 = 4.70 μm , stage 3 = 3.30 μm , stage 4 = 2.10 μm , stage 5 = 1.10 μm , stage 6 = 0.65 μm , stage 7 = 0.43 μm , and the glass fiber filter captures particles < 0.43 μm . The aerosol passed through a USP throat before entering the cascade impactor.

The HaloLite, Prodose, and I-neb AAD systems are breath-actuated, and they sense pressure changes when the patient inhales through the mouthpiece. Aerosol is generated only during inhalation. Therefore, we designed a customized system to operate the devices with the cascade impactor (Fig. 2). A T-piece fitting was attached to the exhalation port of the mouthpiece. One arm of the T-fitting

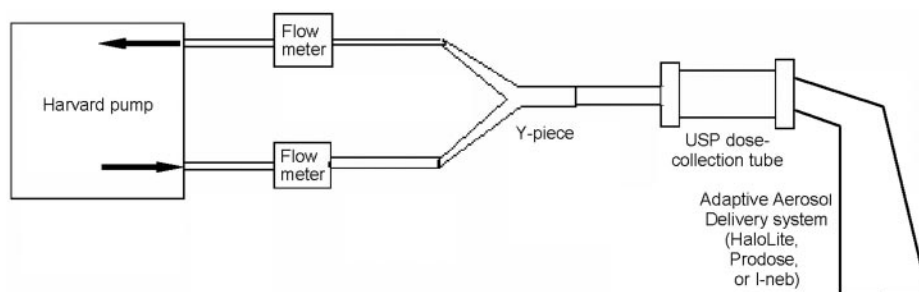


Fig. 3. In vitro setup for determining the inhaled mass of iloprost delivered by HaloLite, Prodose, and I-neb, including dose-collection tube, filter, and Harvard pump.

was connected to a compressed-air source to serve as the exhalation. A one-way valve was attached to the other arm of the T-fitting, which allowed ambient air into the device on inhalation. An air-tight adapter was fitted to the mouthpiece, which connected the device to the cascade impactor. The exhaust port at the base of the cascade impactor was connected to a vacuum pump, set to a flow of 28.3 L/min. The airflow was regulated with flow-control valves that provided vacuum flow (negative pressure) for the inspiration and compressed airflow (positive pressure) for the expiration. The one-way valve opened to allow ambient air (pulled by the vacuum pump) to flow into the nebulizer mouthpiece and carry the aerosol into the USP throat and through the impactor plates. Each inspiration consisted of approximately 4 L (8–9 s) of air (at ambient relative humidity and controlled room temperature), to allow complete deposition of the aerosol to all the cascade impactor stages. The one-way valve closed when the airflow was diverted, to allow compressed air into the mouthpiece, creating the exhalation. The compressed exhaled air was vented through holes in the mouthpiece, bypassing the cascade impactor (see Fig. 2).

Preliminary experiments indicated that a cumulative dose of 20 μg of iloprost was required to capture a sufficient amount of iloprost on all the cascade impactor stages and filter to permit reliable quantitation via chromatography. This was achieved by collecting 4 consecutive 5.0- μg doses of iloprost. Between each 5.0- μg dose, the medication chambers were emptied and rinsed to mimic patient use. With the HaloLite, this was achieved by collecting 2 sequential preset treatments of 2.5 μg for each dose, without rinsing. With the Prodose, 5.0- μg doses were collected using the 5.0- μg AAD Disc. With the I-neb, 5.0- μg doses were obtained from a single delivery from the 5.0- μg medication chamber and using the 5.0- μg AAD Disc. Each stage and filter from the impactor was extracted with 33% acetonitrile, and the samples were analyzed with the iloprost-specific chromatography method. Three of each device (HaloLite, Prodose and I-neb) were tested once each.

Inhaled Mass

The inhaled mass of iloprost was determined with a setup that included a Harvard pump (Harvard Apparatus, South Natick, Massachusetts), a standard USP sample-collection tube for metered-dose inhalers (USP 601 Apparatus A), filters (Filtrete, 3M, St Paul, Minnesota), and iloprost-specific chromatography (Fig. 3). The inhaled mass was defined as the amount of iloprost deposited in the collection tube and on the filter.⁷ Because the HaloLite, Prodose, and I-neb are breath-actuated, a Harvard pump was used to simulate an adult breathing pattern, with a 700 mL tidal volume, a breathing frequency of 20 breaths/min, and a duty cycle of 0.5.⁸ The sample-collection tube contained a 67-mm glass fiber filter, with a 25-mm backup glass fiber filter (type A/E, Pall, East Hills, New York). The sample-collection tube was connected to the Harvard pump and to the aerosol device with an airtight mouthpiece adapter, such that the mouthpiece orifice exited directly into the interior of the sample-collection tube. The contents of one ampule of iloprost inhalation solution (2 mL, 10 μg iloprost per mL) were dispensed into the device's clean medication chamber prior to each dose-collection run.

The iloprost on the surfaces of the sample-collection tube and the filters was extracted with 33% methanol and analyzed via iloprost-specific chromatography. The tests were run in triplicate (ie, 3 runs with each nebulizer), so at least 9 samples were collected for each of the 2 dose levels.

Statistics

The data on the particle-size distribution represent the mean of four 5.0- μg doses of iloprost. Iloprost deposition on the cascade impactor stages with the known effective cut-off diameters was used to calculate the MMAD and geometric standard deviation with the percent relative standard deviation. The data from the inhaled mass experiments are reported as mean \pm SD.

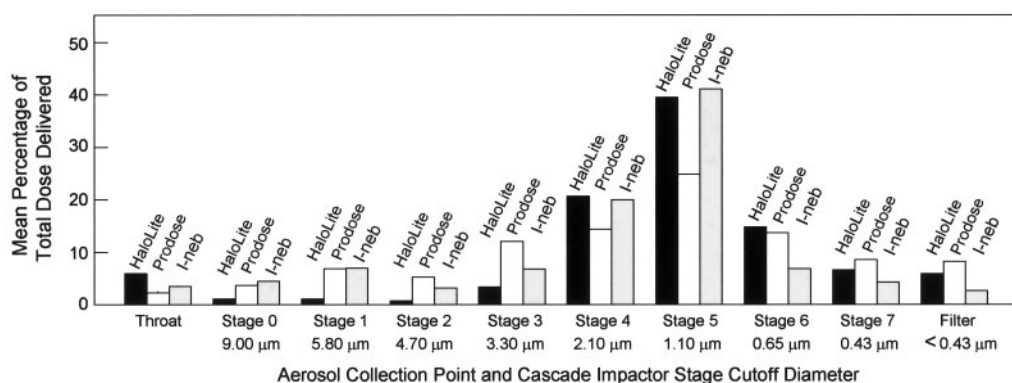


Fig. 4. Particle-size distributions of iloprost aerosol with the HaloLite, Prodose, and I-neb Adaptive Aerosol Delivery systems.

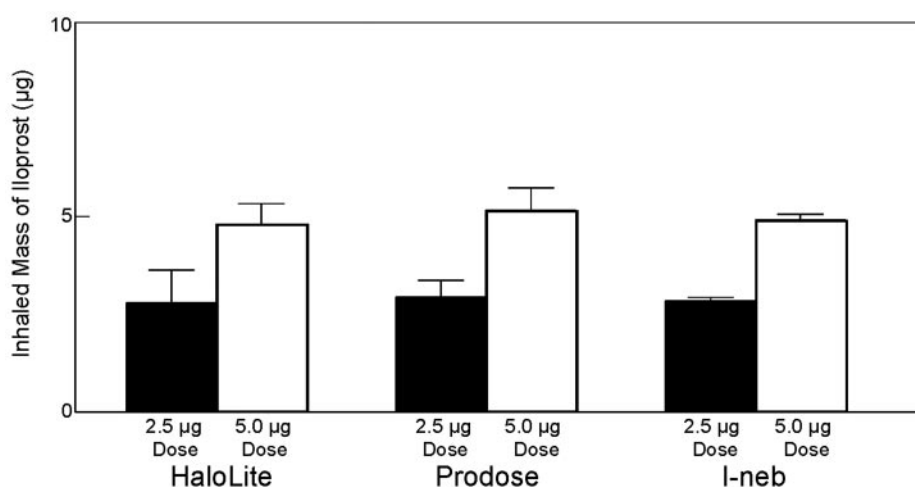


Fig. 5. Inhaled mass of iloprost with the HaloLite, Prodose, and I-neb, with preset doses of 2.5 μg and 5.0 μg.

Results

A pre-study validation of the test setup showed that the extraction efficiency of iloprost from the USP sample-collection tube with filters ranged from 97.5% to 98.7%. A mass-balance study of the test setup (emptied ampule, dose-collection tube, filter, mouthpiece, baffle or mesh, medication chamber, residual solution) for the inhaled mass experiments showed recovery of 97–104.4%.

Aerosol Characterization

For the HaloLite, Prodose, and I-neb, respectively: the MMAD values (with percent relative standard deviation) were 1.4 μm (1.5%), 1.7 μm (3.5%), and 2.1 μm (4.8%); the geometric standard deviations (with percent relative standard deviation) of the MMADs were 2.1 (4.5%), 2.7 (2.8%), and 2.2 (2.6%); and the fine-particle fractions (percent of aerosol droplets < 4.7 μm) (with percent relative standard deviation) were 91% (5.8%), 82% (3.4%), and 82% (2.5%).

Figure 4 shows the mean particle-size distribution in the USP throat, impactor stages, and filter. Most of the particles were deposited on stages 4, 5, and 6 (effective cut-off diameters 2.10 μm, 1.10 μm, and 0.65 μm, respectively). The particle-size distributions for the 3 devices were comparable, but with a slightly more monodisperse distribution for HaloLite and I-neb.

Inhaled Mass

Figure 5 shows the mean inhaled mass of iloprost for the 2 dose levels with each aerosol device. The inhaled mass with the 2.5-μg dose ranged from 2.8 μg to 2.9 μg. The inhaled mass with the 5.0-μg dose ranged from 4.8 μg to 5.2 μg. The standard deviation was smallest for I-neb and largest for HaloLite.

The fine-particle dose, as a function of the fine-particle fraction times the inhaled mass, ranged from 2.3 μg to 2.7 μg with the 2.5-μg dose, and from 3.9 μg to 4.8 μg with the 5.0-μg dose.

Discussion

The objective of this study was to test *in vitro* whether the HaloLite, Prodose, and I-neb AAD systems deliver a comparable dose of iloprost, in terms of aerosol characteristics and inhaled mass. These 3 AAD systems have been or are used in the clinic for delivering inhaled iloprost. These devices are breath-actuated, which means that a relevant *in vitro* study had to mimic patient use for both the aerosol characterization and the measurement of inhaled mass. The 3 systems performed comparably with iloprost, in terms of aerosol characteristics and inhaled mass.

The aerosol characterization was, however, a challenge, because the devices are breath-actuated and therefore could not simply be connected to an impactor and run in a continuous mode. The *in vitro* test setup was designed to mimic a patient's breathing pattern, and this required a setup that triggered the aerosol device to deliver aerosol during inspiration. The results of the pre-study validations of the iloprost-extraction efficiency from the USP sample-collection tube with filters and the results of the mass-balance tests indicated that the *in vitro* test setup gave reproducible performance. Because there are no USP guidelines for *in vitro* tests of nebulizers, we selected the *in vitro* setup described in the USP guidelines for particle-size determination with powder inhalers (required for regulatory approval).⁶

Are the particle sizes we measured for these 3 systems with this specific *in vitro* setup then clinically relevant? Recent publications highlight the requirement to run impactors with a more clinically relevant 15 L/min continuous flow through the impactor.^{9,10} Those studies did not, however, address how to test an AAD system with a low-flow impactor. In a recent study by Smaldone and Nikander, the aerosol particle size from the I-neb was measured *in vitro* with a low-flow impactor.¹¹ In that study a breathing simulator was used to mimic an adult breathing pattern, and albuterol aerosol labeled with technetium sulfur colloid was drawn through the low-flow impactor at 2 L/min, from the tubing connecting the I-neb to the breathing simulator. The MMAD from 3 runs with the prototype I-neb devices was 1.6 μm , which is reasonably similar to our result of 2.1 μm . Thus, the similarity of the measured particle sizes indicates that the high flow through the impactor in our *in vitro* test setup did not distort the results.

The *in vitro* inhaled mass test was designed to mimic patient breathing in an actual clinical situation.⁷ Because patients' breathing differs, the HaloLite, Prodose, and I-neb systems were engineered and tested *in vitro* to accommodate various breathing patterns recorded in both healthy subjects and patients.^{5,8} The inhaled mass tests showed that all 3 AAD systems accurately deliver doses close to the preset doses of 2.5 μg and 5.0 μg of iloprost, and that

82–91% of the aerosol was delivered in the fine-particle range ($< 4.7 \mu\text{m}$). The fine-particle dose ranged from 2.3 μg to 2.7 μg with the 2.5- μg dose, and from 3.9 μg to 4.8 μg with the 5.0- μg dose. This was achieved with different aerosol delivery technologies, as HaloLite and Prodose are based on an active Venturi jet nebulizer technology, whereas I-neb uses a mesh technology.⁵ The dosing algorithm used in HaloLite and Prodose was based on a predicted linear drug output, so the preset dose to deliver was a function of the cumulative inspiratory time (ie, the sum of the pulses).^{3–5} With the I-neb, the preset dose to be delivered was a function of the size of the metering section of the medication chamber.⁵

Previous results of *in vitro* tests with simulated breathing showed that the HaloLite, Prodose, and I-neb deliver preset doses of albuterol with a high degree of accuracy: with the HaloLite, 92% of the doses were within $\pm 25\%$ of the preset dose; with the Prodose 98% of the doses were within $\pm 25\%$ of the preset dose; and with the I-neb, 100% of the doses were within $\pm 25\%$ of the preset dose.^{5,12} This level of control cannot be achieved with conventional nebulizers, because with those devices the dose delivered depends on factors such as the patient's breathing pattern and the output characteristics of the specific nebulizer.^{3,5} As adverse effects limit the escalation of dosage of drugs that have a rather narrow therapeutic index, such as inhaled iloprost, the use of inhalation systems capable of precise dosing is important.¹³

Conclusions

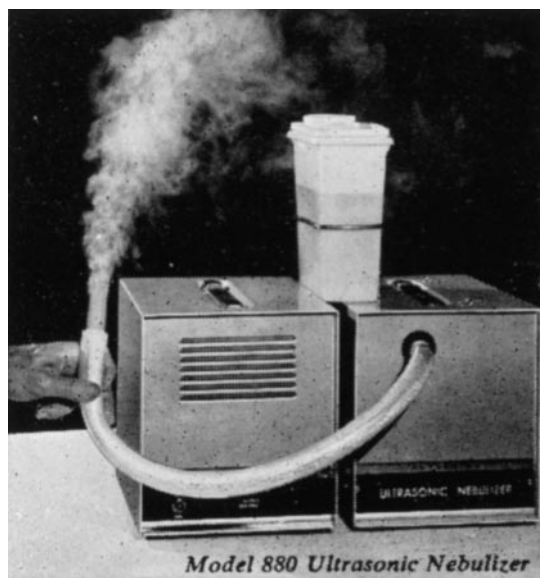
The present study bridged, through *in vitro* tests, the performance of 3 generations of AAD systems. HaloLite was used in the placebo controlled pivotal study of inhaled iloprost in patients with pulmonary arterial hypertension and thus was the comparator device for Prodose and I-neb for delivery of inhaled iloprost.² The results of the present *in vitro* tests indicate that Prodose and I-neb are comparable to HaloLite in terms of particle-size distribution, fine-particle fraction, and inhaled mass.

REFERENCES

- Farber HW, Loscalzo J. Pulmonary arterial hypertension. *N Engl J Med* 2004;351(16):1655–1665.
- Olschewski H, Simonneau G, Galie N, Higenbottam T, Naeije R, Rubin LJ, et al; Aerosolized Iloprost Randomized Study Group. Inhaled iloprost for severe pulmonary hypertension. *N Engl J Med* 2002;347(5):322–329.
- Nikander K. Adaptive aerosol delivery: the principles. *Eur Respir Rev* 1997;7:385–387.
- Denyer J. Adaptive aerosol delivery in practice. *Eur Respir Rev* 1997;7:388–389.

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- Denyer J, Nikander K, Smith NJ. Adaptive Aerosol Delivery (AAD) technology. *Expert Opin Drug Deliv* 2004;1(1):165–176. *Erratum in: Expert Opin Drug Deliv* 2005;2(1):199.
- US Pharmacopeia <601>, Aerosols, metered-dose inhalers, and dry powder inhalers. In: *US Pharmacopeia 25/National Formulary 20*, US Pharmacopeial Convention Inc, Rockville, Maryland, 1964–1980.
- Smaldone GC. Drug delivery via aerosol systems: concept of “aerosol inhaled.” *J Aerosol Med* 1991;4(3):229–235.
- Nikander K, Denyer J. Breathing patterns. *Eur Respir Rev* 2000;10(76): 576–579.
- Dennis JH, Pieron CA, Nerbrink O. Standards in assessing in vitro nebulizer performance. *Eur Respir Rev* 2000;10(72):178–182.
- Marple VA, Olson BA, Santhanakrishnan K, Roberts DL, Mitchell JP, Hudson-Curtis BL. Next generation pharmaceutical impactor: a new impactor for pharmaceutical inhaler testing. Part III. Extension of archival calibration to 15 L/min. *J Aerosol Med* 2004;17(4):335–343.
- Smaldone GC, Nikander K. Bench performance and in vivo deposition efficiency of the I-neb adaptive aerosol delivery system (AAD) during tidal versus slow and deep breathing. *Proceedings of the Aerosol Society* 2004; DDL 15:17–20.
- Young J, Dyche T. Precise dose delivery of salbutamol delivered using the I-neb AAD System. In: *Proc Drug Delivery to the Lungs XVI*. Aerosol Society, Edinburgh, Scotland, December 8–9, 2005: 274–277.
- Olschewski H, Walmrath D, Schermuly R, Ghofrani A, Grimminger F, Seeger W. Aerosolized prostacyclin and iloprost in severe pulmonary hypertension. *Ann Intern Med* 1996;124(9):820–824.



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