

Decreased treatment times with aerosolized iloprost following increase in power levels for the I-neb Adaptive Aerosol Delivery (AAD) System

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Summary

The I-neb AAD System (I-neb) is the 3rd generation AAD System following HaloLite and Prodose. We compared *in vitro* iloprost output rates, treatment times, MMADs for the three generations of AAD Systems (I-neb, power levels 6, 10 and 15). A breathing simulator was used to measure output rates, treatment times; an impactor setup for determination of MMADs. Mean output rates for HaloLite and Prodose were 0.63µg/min and 0.76 µg/min; for I-neb 0.71µg/min, 0.88µg/min 1.43µg/min, respectively. Mean treatment times for HaloLite and Prodose were 8min 15s and 6min 33s; for I-neb 7min 5s, 5min 41s, and 3min 30s. MMADs ranged from 1.4µm (HaloLite) to 2.5µm (I-neb power level 15). The results indicate that patient treatment times with I-neb could be shortened through a change of power level.

Introduction

Pulmonary arterial hypertension (PAH) is defined by a mean pulmonary arterial pressure greater than 25 mmHg at rest or 30 mmHg following exercise.¹ Symptoms like dyspnea, angina, palpitations and syncope follow the increase in pulmonary artery pressure. A vascular remodeling characterized by medial hypertrophy leads to endothelial dysfunction with a lack of vasodilators such as nitric oxide and prostacyclins. Iloprost, a chemically stable analogue of prostacyclin, is available as an inhalation solution (Ventavis; Actelion Pharmaceuticals US, Inc., South San Francisco, CA).² Inhaled iloprost was originally developed and approved in the EU based on clinical studies using the first generation AAD System as the predicate device (HaloLite; Respironics, Inc., Parsippany, NJ). Following this, inhaled iloprost was approved by the FDA in December 2004 in delivered doses of either 2.5 µg or 5.0 µg for the treatment of PAH (WHO Group I) in patients with NYHA Class III or IV symptoms. The only nebulizer originally approved by the FDA for delivery of iloprost was the second generation AAD System (Prodose; Respironics). The FDA approved labeling has since been extended to also include the third generation AAD System (I-neb; Respironics) with a power level 6 AAD Disc (Respironics). Inhaled iloprost is usually prescribed 6 to 9 times per day during waking hours.²⁻³

I-neb is a small, portable, hand-held, and battery operated device with aerosol delivery based on vibrating mesh technology.⁴⁻⁵ The configuration of I-neb to a specific power level setting ranging from 1 to 15 is facilitated through an AAD Disc. Each power level corresponds to a specific voltage that is applied to the piezo element which drives the horn and thereby the mesh. Higher power levels equate to higher applied voltages which creates higher aerosol output rates, and thereby potentially shorter treatment times.⁶ We report results from an *in vitro* comparison of the aerosol output rates, treatment times, and aerosol characteristics of iloprost delivered with the first and second generation AAD Systems (HaloLite, and Prodose) and the currently available I-neb AAD System using AAD Disc power levels 6, 10 and 15.

Materials and Methods

Iloprost inhalation solution (10 µg/mL, 2 mL vial; Ventavis; Actelion Pharmaceuticals US) was used throughout the *in vitro* study. The content of one ampule of the iloprost inhalation solution was dispensed into a clean medication chamber (HaloLite and Prodose) or into a 5 µg metering chamber (I-neb) prior to each test. An iloprost-specific HPLC assay was used throughout.

Iloprost output rates were determined using a study setup including three AAD devices of each brand (HaloLite, Prodose and I-neb), AAD Discs for the three different I-neb power levels (6, 10 and 15), a Harvard respirator (Harvard Apparatus, South Natick, MA), and a standard USP sample collection tube (USP 601 Apparatus A for metered dose inhalers) with 67 mm glass fiber filters (Filtrete, 3M, St Paul, Minnesota). Aerosol was collected at one minute intervals until a complete 5 µg dose was delivered. HaloLite and Prodose were run at their fixed output rates, whereas I-neb was run at power levels 6, 10 and 15. The tests were run in triplicate for each time-point.

The treatment times for the different AAD Systems were evaluated using the Harvard respirator to simulate an adult breathing pattern (tidal volume 700 mL, 20 BPM, and a duty cycle of 0.5). Aerosol delivered with each AAD System was collected in a standard USP sample collection tube containing a filter. The sample collection tube was connected at one end to the Harvard respirator and the device was connected to the other end of the tube with an airtight mouthpiece adaptor in such a way that the orifice of the mouthpiece exited directly into the interior of the sample collection tube.

The MMAD of the iloprost aerosol was determined using an Andersen Cascade Impactor (ACI). As all three AAD System brands were breath-activated and designed to sense pressure changes when the patient inhaled through the mouthpiece, the aerosol bolus was generated during the negative pressure created during inhalation, whereas no aerosol was generated during the positive pressure created during exhalation.³ The results of a previous study indicated that a cumulative dose of 20 µg of iloprost would be required to capture sufficient amounts of aerosolized iloprost on all ACI stages and filters to permit reliable quantification by HPLC.³ This was achieved by collecting 4 consecutive 5.0 µg doses of iloprost. Three HaloLite and three Prodose devices were tested once each, and three I-neb devices at each of power levels 6, 10 and 15.

Results

The mean output rates (Figure 1) of iloprost were with HaloLite 0.63 µg/min and with Prodose 0.76 µg/min. With I-neb and the three different power levels the mean output rates of iloprost were 0.71 µg/min (power level 6), 0.88 µg/min (power level 10) and 1.43 µg/min (power level 15).

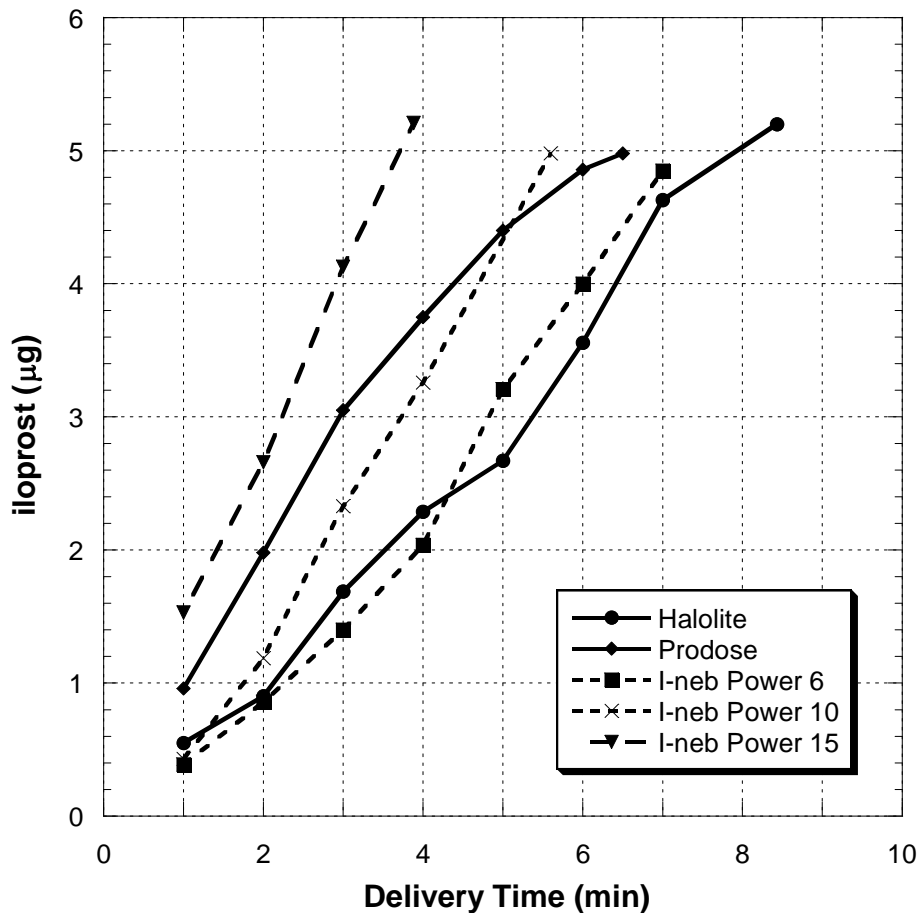


Figure 1. *In vitro* iloprost output rates for HaloLite, Prodose and I-neb Adaptive Aerosol Delivery (AAD) Systems. I-neb was tested using AAD Discs for power levels 6, 10, and 15.

The mean treatment times (Figure 1) were for Halolite 8 min 15 s, and for Prodose 6 min 33 s. With I-neb and the three different power levels the mean treatment times were 7 min 5 s (power level 6), 5 min 41 s (power level 10), and 3 min 30 s (power level 15).

The MMAD values were for Halolite 1.4 μm and for Prodose 1.7 μm . With I-neb and the three different power levels the MMAD values were 1.9 μm (power levels 6 and 10), and 2.5 μm (power level 15).

Discussion and conclusions

This is the first study to compare the *in vitro* aerosol output rates of the iloprost inhalation solution for the currently available I-neb AAD System using AAD Disc power levels 6, 10 and 15 with those of the first and second generation AAD Systems (Halolite, and Prodose). The results demonstrated a power level dependent increase in output rates of iloprost for I-neb, and a higher iloprost output rate with Prodose than with Halolite. The output rate of iloprost for I-neb at power level 6 closely matched that of Halolite, the device used to deliver iloprost aerosol in the original pivotal Phase 3 clinical study. The output rates of iloprost for I-neb at power levels 10 and 15 approximated the output rate for Prodose, the device that first gained approval in the EU and the US for delivery of the iloprost inhalation solution. The treatment times ranged from 3 min 30 s (I-neb at power level 15) to 8 min 15 s (Halolite). For I-neb the mean iloprost output rates and mean treatment times were power level dependent. Treatment times were shortened with increasing power levels.

References

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