Inspiratory Flow Profiles of PAH Patients with AOS™ Device Intended to Administer Inhaled Vardenafil

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Background

The use of inhaled therapies in PAH has been limited by technical and adherence difficulties, which may be overcome with dry powder inhaler (DPI) therapies. However, little is known about how inspiratory flow profiles (IFP) are affected in PAH patients, and whether they will be able to generate the inspiratory pressures and inhaled volumes needed to achieve therapeutic drug levels with DPI devices. It is important that subjects exceed the minimum ΔP needed to provide effective dose delivery of drug to the lungs. Relative to healthy subjects, many subjects with PAH have decreased muscle strength[1] . Decreased muscle strength may also negatively impact their ability to use a DPI. The objective of this study was to assess the impact of inhaler resistance and patient instruction on the inspiratory flow profiles of subjects with PAH when using breath-actuated DPIs.

Study Design

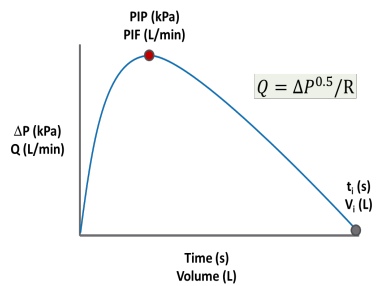
This was a noninterventional, observational study conducted at Houston Methodist Lung Center, Houston Methodist Hospital, Houston, Texas, USA. No active drug or placebo was administered to subjects. The study was approved by the local IRB. Informed consent was obtained from each participating subject.

Study design. Inspiratory flow profiles of PAH subjects were assessed in two randomized crossover studies: Subjects in Group A (N=18) were tested with three variants of the RS01 DPI (Plastiape S.p.A.,Italy), that differed in their resistance to airflow. The RS01 DPI is available in low resistance (R = 0.019 $kPa^{0.5}$ L^{-1} min) and medium resistance (R = 0.031 $kPa^{0.5}$ L^{-1} min) designs. The AOS™ DPI, a variant designed by Respira, has a high resistance (R = 0.050 $kPa^{0.5}$ L^{-1} min). Each device was loaded with an empty capsule that was pierced prior to the inhalation maneuver. Subjects were instructed to exhale to empty their lungs, then inhale with maximal effort until their lungs are full. Subjects in Group B (N=17) were tested with the AOS DPI and three different sets of inhalation instructions, viz:
1. Exhale to empty lungs, then inhale with maximal effort through inhaler until your lungs are full; 2. Exhale to empty lungs, then inhale comfortably through the inhaler until your lungs are full; 3. Inhale with maximal effort through inhaler until your lungs are full (no exhalation step before inhalation).

Methods

Patient inspiratory flow profiles were recorded with a calibrated custom data acquisition device designed by iPharma Limited (Union City, CA). Profiles were analyzed with a LabView software program (iPharma).

Figure 1: Parameters used to define the inspiratory flow profiles



Metric	Parameter
PIP	Maximum pressure drop
PIF	Peak inspiratory flow rate
V_i	Inhalation volume
t_i	Inhalation time
Q	Flow rate
ΔP	Pressure drop
R	Device resistance

Results

The study enrolled 35 subjects with a confirmed diagnosis of PAH. Consistent with the PAH patient population, a large percentage of the subjects (92%) were female. Mean age was 50 years, with 63% functional class (FC) II and 31% FC III.

The reduced muscle strength leads to decreased peak inspiratory pressures (PIP) when using portable DPIs. PIPs can be maximized by using a DPI with a higher resistance, and instructions that ask subjects to inhale with maximal effort until their lungs are full. The measured PIP and V_i observed were significantly dependent on the subject's lung function. While patients with asthma, COPD and CF typically have reductions in PIP by about 20% with decreasing lung function, the decrease in PIP in patients with PAH is >50%.

Conclusion

Despite having reduced muscle strength, PAH patients can effectively use a breath-actuated DPI. The probability of achieving effective dose delivery is increased by using DPIs with higher device resistance, particularly when patients do not follow prescribed inhalation instructions and inhale comfortably.

Table 1: Inspiratory flow profile parameters for subjects with PAH when using DPIs

	PIP (kPa)	PIF (L/min)	V_i (L)	t_i (s)
Device Resistance (N=18)				
Low	3.7 ± 1.6 **	100.2 ± 24.2 **	1.9 ± 0.5	1.7 ± 0.4 **
Medium	5.3 ± 2.3	71.4 ± 17.8 **	1.8 ± 0.4	2.4 ± 0.5 **
High	6.5 ± 2.9	49.4 ± 12.2	1.7 ± 0.5	3.3 ± 1.3
Instruction (N=17)				
Comfortable	2.1 ± 1.1 **	27.9 ± 8.4 **	1.4 ± 0.5	4.4 ± 1.1 **
Max effort (no exh)	5.8 ± 1.7	47.5 ± 7.5	1.5 ± 0.3	3.0 ± 0.6
Max effort	6.0 ± 1.8	48.2 ± 8.3	1.6 ± 0.5	3.0 ± 0.8
Lung function (N=35)				
FEV_1 < 50%	3.3 ± 1.4 **	35.4 ± 7.8 **	1.2 ± 0.2 *	3.3 ± 0.5
50% < FEV_1 < 60%	5.7 ± 2.7	46.2 ± 11.9	1.6 ± 0.4	3.5 ± 1.4
FEV_1 > 60%	7.2 ± 1.8	53.1 ± 6.7	1.8 ± 0.5	3.0 ± 1.0

*p<0.05; **p<0.01

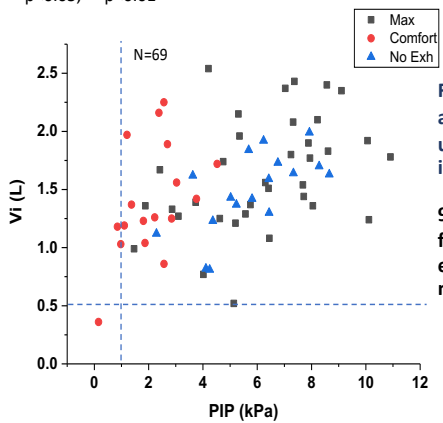


Figure 2: Plot of the V_i versus PIP achieved by PAH patients when using the AOS DPI with different inhalation instructions

97% of PAH patient inspiratory flow profiles with the AOS DPI exceed V_i > 0.5 L and PIP >1 kPa needed for effective drug delivery.

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