

Device Output is not a Predictor of Lung Dose

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Summary

For successful inhalation therapy the inhalation device is as important as the drug component itself. The objective of this characterization study was to quantify the delivery efficiency of the Akita JET inhalation system nebulizing inhaled corticosteroids and compare it to a conventional nebulizer and a dry powder inhaler. Particle size distribution was measured by cascade impaction. The Fluticasone dose delivered to the mouthpiece was assessed by analysis of filter samples by HPLC. Lung deposition was determined by lung deposition modeling (ICRP). The lung deposition of Fluticasone achieved with controlled inhalation was 3.5 times higher compared to a conventional nebulizer by filling the same amount into the nebulizer. The dry powder inhaler achieved 26% lung deposition of delivered dose compared to 74% for controlled inhalation and 38% for conventional nebulizer. Treatment time was calculated to achieve a lung dose of 100µg in all devices. Treatment time was 1.99min for the AKITA JET, 3.86min for the conventional nebulizer and 0.5min for the dry powder inhaler. The maximum lung dose that could be achieved within one filling dose was 497µg for the AKITA JET, 142µg for the conventional nebulizer and 55µg for the dry powder inhaler.

Introduction

Many pulmonary device companies report high output data but the crucial data to consider is total lung dose when comparing inhalation devices. The goal of a pulmonary drug delivery device is to optimize aerosol deposition and target the aerosol to a certain region of the human lungs. This can be accomplished using a controlled flow rate and inhalation volume coupled with the timed release of aerosol during inspiration.

Efficient drug targeting to the right airway regions is determined by the following factors:

- Particle size distribution
- Efficiency of aerosolization technology
- Timing of the aerosol bolus during inspiration
- Inhalation flow rate
- Inhalation volume
- Adherence monitoring

The AKITA JET nebulizer system guides the patient through the inhalation treatment and triggers a jet nebulizer (PARI LC SPRINT[®] Junior) once the patient starts to inhale. With a controlled inhalation flow and volume and the timing of the aerosol bolus during the inspiration manoeuvre, it is possible to optimize aerosol deposition and target the aerosol to a certain region of the lungs. The air and aerosol flow rate and volume delivered from the device can be individualized for each patient.

In different lung deposition studies, (Brand et al. 2000, Bennett et al. 2005) it has been shown that a lung deposition of 80 - 85% of the delivered dose and more than 70% of a nebulizer filled dose can be achieved, even in the lungs of patient with severe lung diseases.

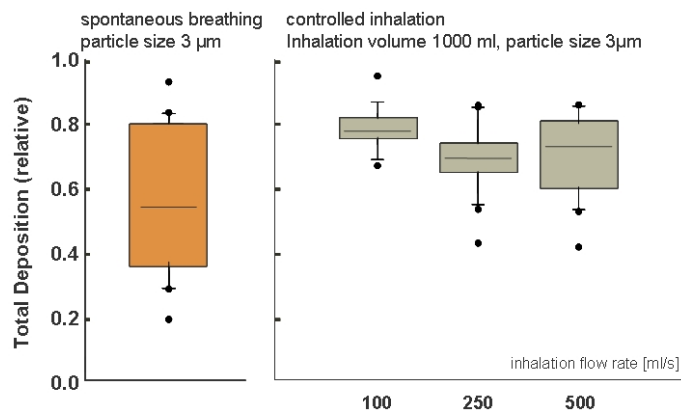


Figure 1: Total deposition in 18 patients with different lung diseases, particle size 3 µm monodispers, Total deposition = lung deposition + throat deposition (Brand, P. et. al. J Pharm Sci 6/2000)

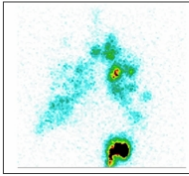
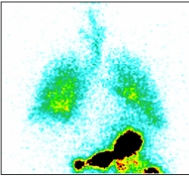
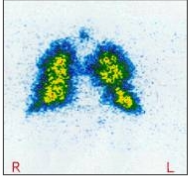
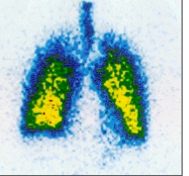
	Patients	Healthy	Deposition
Spontaneous breathing			15%: exhaled 15%: lung 70%: throat
Controlled breathing			3%: exhaled >80%: lung 4%: throat

Figure 2: Comparison of regional deposition of spontaneous and controlled inhalation

Objectives

The objective of this study was the evaluation of inhalation devices for delivery of high amounts of corticosteroids to the lungs for treatment of severe asthma. Therefore commonly used inhalation devices were characterized in regards to the available amount of Fluticasone at the mouthpiece. Additionally lung deposition was calculated by deposition modeling.

Materials and Methods

Three inhalation devices (Seretide 250µg Fluticasone/50µg Salmeterol), Pari Boy N with PARI LC SPRINT nebulizer, AKITA JET) were characterized in regards to particle size and dose delivered to the mouthpiece. Nebulizers were filled with a corticoid suspension containing 2000µg Fluticasone. Particle size was measured using cascade impaction. The cascade impactor tests were performed in an air-conditioned laboratory at a temperature range of 19.5 +/-1.5°C and a relative humidity (RH) of 50+/-5%. For the cascade impaction measurements, a Next Generation Impactor (NGI) with induction port was used (NGI Model 170, Copley Scientific Ltd, UK). The impactor was enclosed in a cooling cabinet and cooled to 15°C to avoid particle evaporation within the impactor. A constant airflow was adjusted to 15 L/min (\pm 10%) at nebulizer mouthpiece. Cascade impaction data was evaluated by the dedicated software (C.I.T.D.A.S. V 2.0, Copley Ltd, UK). Lung deposition was assessed by lung deposition modeling.

Delivered dose was assessed by analysis of filter samples by HPLC. To assess the dose delivered to the mouthpiece filter samples were taken while patient's breathing was simulated with a breathing simulator (Hans Rudolph, USA). An optimized breathing pattern was used during output tests controlled by the AKITA JET. For the dry powder inhaler a constant flow of 60 L/min was used and for the Pari Boy N a sinus breathing pattern was used to simulate patients breathing. Lung deposition of loaded dose was calculated using deposition modeling (ICRP). (3-5)



Figure 3: AKITA JET nebulizer system

Results

Table 1: Particle size (MMAD) measured by cascade impaction

Inhaler / Nebulizer	Particle Size MMAD by Cascade Impaction (NGI)	GSD
Dry Powder inhaler (250µg Fluticason, 50µg Salmeterol)	4.1 µm	1.97
Conventional Nebulizer Pari Boy Turbo N and LC Sprint (Fluticason 2mg/2ml)	4.26 µm	1.97
AKITA JET with PARI LC SPRINT JUNIOR (Fluticason 2mg/2ml)	3.76 µm	1.99

Results from output characterization and deposition calculation are shown in the following figure.

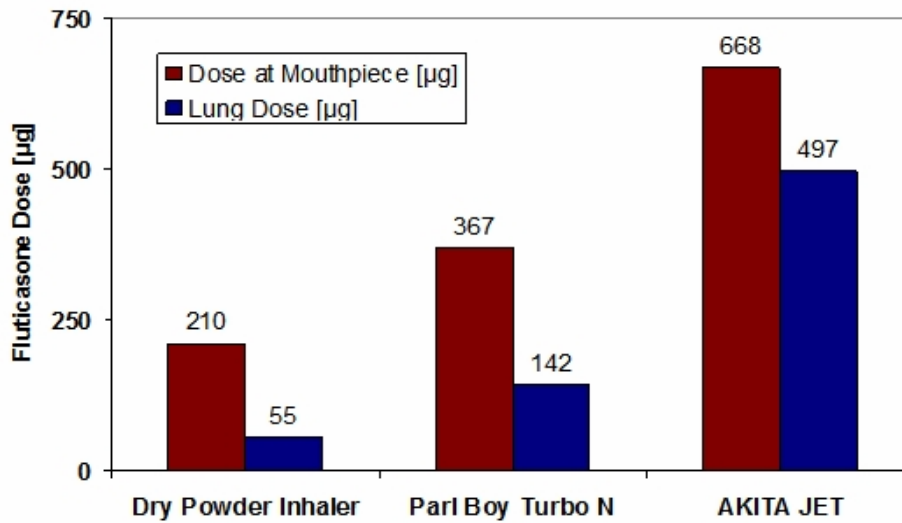


Figure 4: Comparison of delivery efficiency and lung deposition

Table 2: Comparison of treatment time according to lung dose

Inhaler / Nebulizer	Fluticasone Lung Dose	Treatment Time for 100 µg Lung Deposition
Dry Powder Inhaler (250µg Fluticason, 50µg Salmeterol)	55 µg	~ 30 sec
Conventional Nebulizer Pari Boy Turbo N and LC Sprint (Fluticason 2mg/2ml)	142 µg	3.86 min
AKITA JET with PARI LC SPRINT JUNIOR (Fluticason 2mg/2ml)	497 µg	1.99 min

Discussion and Conclusion

Controlled breathing reduces inhalation treatment time since lung deposition of inspired particles is higher if compared to conventional devices. In the dry powder inhaler a high percentage of filling dose could be delivered to the mouthpiece. However, lung deposition was rather low due to high extrathoracic deposition. This phenomenon is typical for dry powder inhalers and it causes side effects (e.g. oral fungal infections, hoarseness). These side effects can be reduced using nebulizer systems that ensure a slow inspiratory flow rate by controlled inhalation and therefore reduce the extrathoracic deposition. In order to ensure a time efficient and reproducible drug delivery to the lungs a nebulizer system should be used that controls the breathing pattern during inspiration phase.

Literature

1. Brand, P., Friemel, I., Meyer, T., Schulz, H., Heyder, J., Häußinger, K. (2000), "Total deposition of therapeutic particles during spontaneous and controlled inhalations", J Pharmaceut Sci, 2000, 89: 724-731.
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