Efficient Inhalation – High Dose Therapy of Colistin CF 1 Mio. IE and AKITA JET®

J Gleske (a), M Hartmann (a), T Werner (b), P Kroneberg (a), J Stegemann (a), B Müllinger (a)
(a) Activaero GmbH, Wohraerstr. 37, 35285 Gemuenden/Wohra, Germany; (b) Forest Laboratories Deutschland GmbH, Friedrichstr. 191, 10117 Berlin

Introduction

Colistin solution, available in two different concentrations, administered by aerosol is an established treatment of cystic fibrosis. Conventional nebulizers require either a large filling amount or a high concentration of the compound. Due to poor efficiency of these nebulizers only a small fraction is deposited in the targeted lung region.
The AKITA JET® nebulizer system guides the patient through the inhalation treatment using a controlled flow rate and inhalation volume. A jet nebulizer (based on PARI LC SPRINT® Sinus) is triggered by the device at a pre-selected period of time once the patient starts to inhale. In order to both individualize breathing pattern as well as assure correct dosage and reproducible drug delivery, a Smart Card is incorporated into the AKITA JET® inhalation system.
The objective of this study was to demonstrate an equivalent lung dose of Colistin CF 1Mio. IE/3ml (Forest GmbH,) applied with the AKITA JET® nebulizer system compared either to the standard inhalation therapy with Colifin 1Mio. IE/3ml (Pari Pharma GmbH) or to a high dose therapy with Colifin 2Mio. IE/4ml (Pari Pharma GmbH) both inhaled with the Pari eFlow® rapid nebulizer. Therefore both nebulizer systems were investigated in terms of particle size distribution and delivered dose, respectively. Additionally lung dose was calculated using the ICRP lung deposition model.

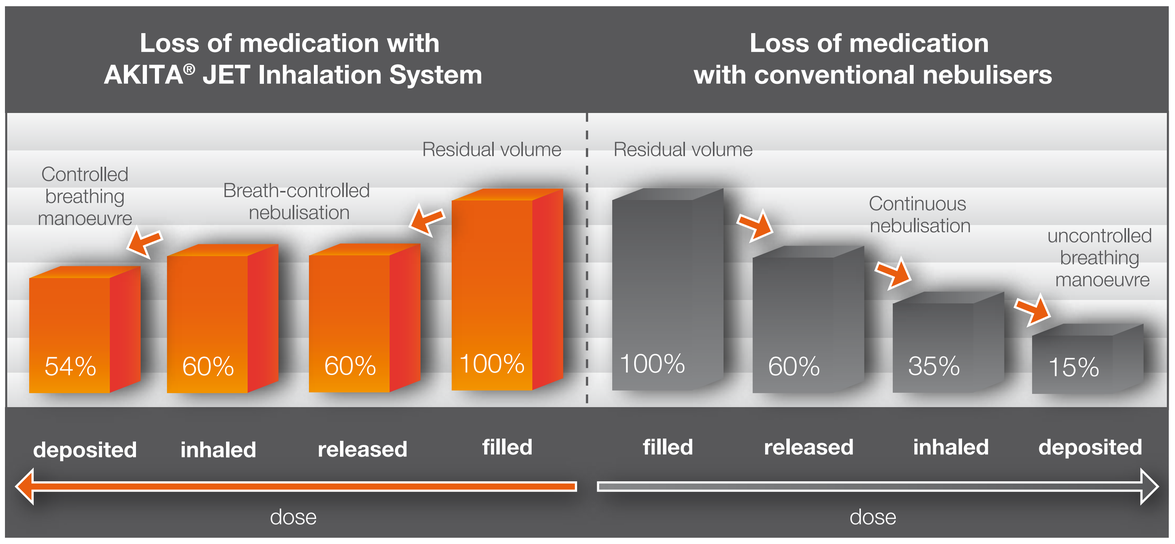

Figure 1: Quantitative losses of medication in nebulizer systems

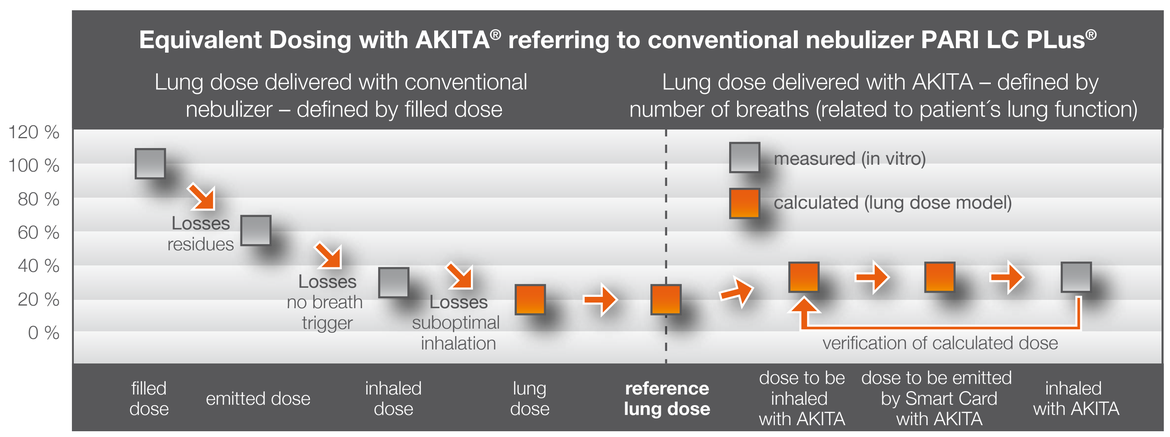

Figure 2: Calculation of emitted dose to achieve an equivalent lung dose using the AKITA JET®

Materials and Methods

While Colistin CF 1Mio. IE/3ml was aerosolized by a jet nebulizer with controlled breathing and aerosol pulse technology (AKITA JET®) as well as by a commonly used mesh nebulizer (Pari eFlow® rapid) the high dose (2Mio. IE/4ml) was aerosolized with the Pari eFlow® rapid only. Both devices were investigated in regards to particle size distribution and delivered dose (DD). All measurements were performed with one nebulizer handsets each fivefold. AKITA JET® nebulizer was filled with 3 ml Colistin CF inhalation solution containing 1 Mio. IE/3ml colistin. Pari eFlow® rapid was either filled with 3 ml of a 1 Mio. IE/3ml formulation or 4 ml 2Mio. IE/4ml formulation. Particle size distribution was determined using a laser diffraction particle sizer (Helos, Sympatec). Delivered dose was assessed by spectrophotometric analysis of filter samples. Therefore Colistin CF was nebulised and collected on a filter. The amount of colistin on the filter was determined by spectrophotometer. To determine the delivered dose filter samples were taken while patient's breathing was simulated (Hans Rudolph, USA). For the Pari eFlow® rapid a sinus breathing pattern was used to simulate patients breathing (0.5 l/breaths, 15 breaths/min). This breathing pattern is according to EN 13544 [7].
An optimized breathing pattern was used during output tests controlled by the AKITA JET® with 5.0 sec inhalation time per breath. This breathing pattern is typical for patients with cystic fibrosis using the AKITA JET® inhalation system.
Lung deposition of Colistin CF with both nebulizers and both concentrations was calculated using deposition modelling (ICRP).

Results

	MMD (µm)		GSD		FPF (%)	
	Mean	SD	Mean	SD	Mean	SD
AKITA JET 1 Mio. IE/3 ml	3.29	0.05	1.95	0.03	75.67	1.32
Pari eFlow rapid 1 Mio. IE/3 ml	4.05	0.07	1.61	0.03	68.31	2.01
Pari eFlow rapid 2 Mio. IE/4 ml	3.92	0.03	1.56	0.01	72.25	0.45

Table 1: Particle size (MMD) measured by laser diffraction

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

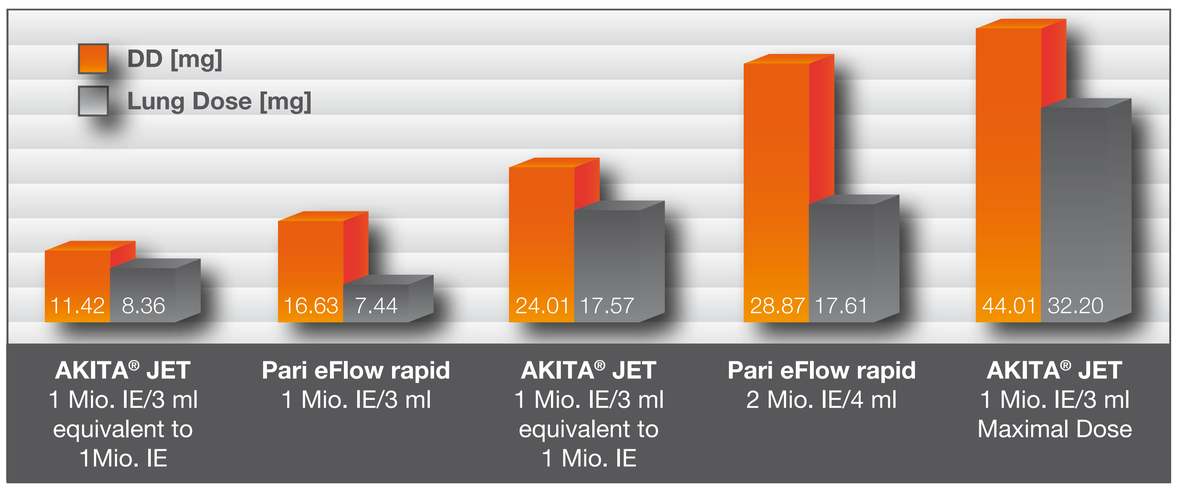

Figure 3: Comparison of delivered dose (DD) and lung dose

Conclusion

In this aerosol characterization study it could be demonstrated that the AKITA JET® can be adjusted to deliver an equivalent lung dose using 1 Mio. IE Colistin filling amount compared to 2 Mio. IE filled into the Pari eFlow® rapid system. However, a lower delivered dose (defined as drug dose that is available at the mouthpiece and would be inspired by the patient, not including losses into the ambient air and nebulization during the exhalation phase) is required using flow and volume regulated breathing pattern by the AKITA JET®.
In summary, our study demonstrates the feasibility of the controlled-breathing method for Colistin CF inhalation in cystic fibrosis patients. Compared with conventional inhalation techniques this method allows a reduction of the delivered dose of 30-40 %, while having comparable lung dose of the medication. It has to be noticed as well that it is possible to achieve an equivalent lung dose with the standard therapy medication. The only thing that changes is the Smart Card setting and the number of breaths. If you run the AKITA JET system until the nebulizer is empty, it is possible to achieve a maximal lung dose which can double the drug amount in the lungs compared to the high dose therapy. However, this maximum-setting should not be used in patients on a routine basis as safety and tolerability have to be revaluated for increasing the lung dose. Other two aspects to consider when treating patients frequently with inhaled antibiotics are side effects due to dispersion of the drug into the environment and the extrathoracic deposition. These may be reduced by using the AKITA JET® as a result of controlled-breathing method, aerosol pulse technology and a very low flow rate. Most of the aerosol is deposited within the lungs and not in the throat or being exhaled.

References

1. *Standaert, TA., Vandevanter, D., Ramsey, BW., Vasiljev, M., Nardella, P., Gmur, D., Bredl, C., Murphy, A., Montgomery, AB., "The choice of compressor effects the aerosol parameters and the delivery of tobramycin from a single model nebulizer", J Aerosol Med, 2000 Summer,13(2):147-53.*
2. *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.*
3. *Bennett, WD. (2005), "Controlled inhalation of aerosolised therapeutics", Expert Opin Drug Deliv, 2005 Jul, 2(4):763-7.*
4. *Fleming, JS., Epps, BP., Conway, JH., Martonen, TB. (2006), "Comparison of SPECT aerosol deposition data with a human respiratory tract model", J Aerosol Med, 2006, 19(3):268-78.*
5. *International Commission on Radiological Protection (1994), "Human respiratory model for radiological protection", (ICRP Publication 6), Ann ICRP, 1994, 24, 1-120.*
6. *Köbrich, R., Rudolf, G., Stahlhofen, W. (1994), "A mathematical model of mass deposition in man", Ann occup Hyg, 1994, 38, 15-23, I 469b.*
7. *EN 13544-1:2007 + A1:2009: Respiratory therapy equipment – Part 1 Nebulizer systems and their components.*

DDL, Edinburgh, Scottland, 07.-09. Dez. 2011 – Presentation ID 48

Activaero GmbH Headquarters & Logistics
Wohraer Straße 37 35285 Gemünden/Wohra Germany

ACTIVAERO®