Choice of Nebulizer for Inhaled Tobramycin Treatment in Cystic Fibrosis

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INTRODUCTION

The success of an anti-infective inhalation treatment is strongly dependent on the choice of the inhalation device (1). Generally, nebulizer systems are sold separately from solutions and suspensions containing active substances for nebulization. Therefore, these formulations are often inhaled via any available nebulizer rather than the system used during the development of the medicinal product. Most conventional nebulizers require a large filling amount of the compound, because only a small fraction is deposited in the targeted lung region. In contrast, techniques based on controlled inhalation allow a high and reproducible deposition of the drug in specific lung regions (2-4). The aim of this evaluation was to assess and compare in vitro performance of drug-device combination of standard jet, vibrating mesh, ultrasonic and intelligent controlled breathing nebulizers with a tobramycin solution for inhalation (Bramitob®, Chiesi Farmaceutici S.p.a).

A secondary objective was to assess the optimal setting for the controlled-breathing inhalation system to achieve an equivalent lung dose of tobramycin as compared to the reference PARI LC PLUS.

METHODS

Bramitob was aerosolized by a jet nebulizer with controlled breathing and aerosol pulse technology (AKITA JET® with PARI LC SPRINT® Sinus nebulizer) as well as by the jet nebulizer (PARI LC PLUS® with TurboBoy® N compressor) that was used in the phase III trials within EU for inhalation of Bramitob. The data for the vibrating mesh nebulizer (Pari eFlow®) and the ultrasonic nebulizer (Optineb-ir) was extracted from a previous aerosol characterization study (5).

The AKITA JET nebulizer system guides the patient through the inhalation treatment using a controlled flow rate and inhalation volume (Figure 1). The AKITA uses a jet nebulizer (PARI LC SPRINT Sinus) that is triggered by the AKITA at a pre-selected period of time once
the patient starts to inhale. In order to individualize the breathing pattern as well as assure correct
dosage and reproducible drug delivery, a smart card technology is incorporated into the AKITA
JET inhalation system.

Figure 1. AKITA JET® nebulizer system with PARI LC SPRINT® sinus nebulizer.

The devices were investigated in regards to particle size distribution and device output. All
measurements were performed with five different nebulizer handsets of each device. Nebulizers
were filled with 4 ml Bramitob inhalation solution containing 75 mg/ml Bramitob. Particle size
distribution was determined using a laser diffraction particle sizer (Helos, Sympatec).

Delivered dose was assessed by radioactive analysis of filter samples. Bramitob solution
was labelled with a radioactive tracer ($^{99m}$Tc), nebulized and collected on a filter. The radiolabelling
method and the filter method were validated for Tobramycin solutions at different drug concentra-
tions (7). The amount of radioactivity on the filter was determined by scintigraphy. To determine
the delivered dose, filter samples were taken while breathing was simulated (Hans Rudolph, USA).
A sinus breathing pattern was used to simulate breathing (0.5 l/breaths, 15 breaths/min) for devices
that did not provide active control of breathing pattern (PARI LC PLUS with BOY compressor).
For the AKITA JET, an optimized breathing pattern was used during output tests controlled by
the AKITA JET with 4.0 sec inhalation time per breaths and a fixed number of breaths to control
the delivered dose. This pre-set dose was calculated on the basis of the reference dose of the PARI
LC PLUS nebulizer (Figure 2?). The treatment time needed to achieve a lung dose of 38mg com-
pared to the reference nebulizer PARI LC PLUS was calculated by means of the actual measured
time. Lung dose was calculated using the deposition model that was developed by the International
Commission for Radiation Protection (ICRP). The ICRP deposition model is a semi-empirical
model that allows calculation of regional deposition within the respiratory tract based on the input
parameters such as particle size distribution, inhalation volume, inhalation flow rate for healthy
subjects at different age. (6-8)
RESULTS

Particle size (MMD) was smallest for AKITA JET (3.6µm) and largest for Optineb-ir (5.5µm). Geometric standard deviation was smallest for the PARI eFlow (1.6) (Table 1).

<table>
<thead>
<tr>
<th></th>
<th>MMD [µm]</th>
<th>GSD</th>
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<tbody>
<tr>
<td>AKITA JET with PARI LC SPRINT Sinus</td>
<td>3.6 0.3</td>
<td>2.0 0.0</td>
</tr>
<tr>
<td>PARI LC PLUS with BOY compressor</td>
<td>4.7 0.2</td>
<td>2.0 0.0</td>
</tr>
<tr>
<td>PARI eFlow</td>
<td>4.1 0.1</td>
<td>1.6 0.1</td>
</tr>
<tr>
<td>Optineb-ir</td>
<td>5.5 0.3</td>
<td>2.1 0.1</td>
</tr>
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In this aerosol characterization study of Bramitob, no significant differences in the lung dose could be noticed for the AKITA JET (p_{Wilcoxon}= 0.1046) and the PARI eFlow (p_{Wilcoxon}= 0.7868) compared to the PARI LC PLUS. But the Optineb-ir showed a significantly lower lung dose (p_{Wilcoxon}< 0.0001). Delivered dose and variability of dose was lowest for AKITA JET (Figure 3).

Calculated treatment time ranged between 5 and 12 min. Shortest treatment times were observed for the eFlow and AKITA JET (Figure 4).
DISCUSSION

In our study, it could be demonstrated, that compared with conventional inhalation devices, the AKITA JET allows for a reduction of the delivered dose of 44%, while having comparable lung dose of Bramitob. Because of the reduction of the required nebulized dose, there is a reduction of treatment time compared to the LC PLUS and Optineb systems, which may improve the compliance of the patients. The AKITA JET nebulizer system provides a time efficient and highly reproducible drug delivery to the lungs due to its controlled breathing and aerosol pulse technology.
REFERENCES


