Original Article

Disposable versus reusable jet nebulizers for cystic fibrosis treatment with tobramycin

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Abstract

Background: Jet nebulizers are commonly used to administer aerosolized tobramycin to CF patients. The aim of this study was to assess the performance of disposable jet nebulizers as an alternative to reusable nebulizers such as the Pari LC Plus.

Method: From a survey conducted in 49 CF centers in France, 18 disposable jet nebulizer systems were selected. An in vitro study was performed with 20 jet nebulizer/air source combinations (18 disposable and 2 reusable) to determine their performance with tobramycin solution (300 mg/5 mL). A scintigraphic deposition study in baboons was performed to validate the in vitro data.

Results: In vitro and in vivo results correlated. There was no overall relationship between the compressed air source and nebulizer performance, but the nebulizer interface was responsible for significantly different results.

Conclusions: None of the disposable nebulizers tested in this study can be recommended as an alternative to the Pari LC Plus nebulizer for tobramycin.

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Keywords: Tobramycin; Nebulizer; Aerosol

1. Background

Tobramycin is an aminoglycoside antibiotic commonly used to treat Pseudomonas aeruginosa bronchial colonization in cystic fibrosis (CF) patients. Aerosol delivery allows the respiratory tract to be targeted and limits the side effects associated with systemic treatment [1]. The efficacy of aerosolized antibiotics correlates with the amount of medication deposited in the patient’s lungs [2].

The amount of medication deposited in the lungs depends on three main parameters, namely airway anatomy, patient ventilation and aerosol characteristics [3]. Airway anatomy and ventilation depend on the patient and the practitioner has little control over them. The choice of nebulizer is therefore the only way the practitioner can optimize aerosol delivery. There are many nebulizers available on the market with significant differences in terms of performance. Following recommendations made by Novartis and in the European Cystic Fibrosis Society’s consensus document, the nebulizer currently recommended for administering tobramycin aerosols to CF patients is the Pari LC+ jet nebulizer with a suitable compressor operating at a flow rate of 4-6 l/min [4,5] because it is the only nebulizer used in the pivotal trials for determining safety and efficacy [5]. The Pari LC+ nebulizer is a reusable nebulizer which requires around 15 min of inhalation to deliver tobramycin into the lungs [6]. Like all reusable jet nebulizers, it needs to be washed, disinfected, assembled and prepared, which can be time-consuming for patients requiring daily and often lifelong treatment. The use of mesh nebulizers reduces nebulization time [7], but does not solve the problem of time-
2. Materials and methods

2.1. Nebulizer systems used in French CF centers

2.1.1. Disposable nebulizer systems

A survey of the nebulizer systems prescribed for either home or hospital care was carried out in 49 CF centers in France, using an e-mail questionnaire. A nebulizer system is defined as the association of a nebulizer reservoir, a compressor and an interface device (i.e., face mask, mouthpiece and tubes including valves) [2].

From this survey, 18 disposable nebulizer systems were identified, corresponding to nine different nebulizer reservoirs (Table 1). For example, the two Misty Neb nebulizer systems, Misty Neb 2050G and Misty Neb 2035G, have the same Misty Neb nebulizer reservoir but different interfaces (T piece and mouthpiece vs. T-piece, Y piece, tube, mouthpiece, filter and valves for the Misty Neb 2050G and Misty Neb 2035G, have the same Misty Neb nebulizer reservoir but different interfaces (T piece and mouthpiece vs. T-piece, Y piece, tube, mouthpiece, filter and valves for the Misty Neb 2050G) (Fig. 1).

A “one-day” jet nebulizer (Atomisor NLU) was also selected from the survey. It differs from the other disposable nebulizer systems considered as single-use devices in that it can be used several times during a single day.

2.1.2. Reusable nebulizer systems

Two reusable nebulizers recommended by the GRAM for both home use and care in CF centers were selected for the study. They were the Pari LC Plus nebulizer (Pari, Stanberg, Germany) associated with a Turboboy® compressor SX (Pari, Stanberg, Germany), and the Pari LC Sprint nebulizer (Pari, Stanberg, Germany) associated with a Turboboy® compressor SX.

2.2. In vitro measurement

2.2.1. Drug solution

The tested dose was 300 mg/5 ml of tobramycin (TOBI®, product No. 365723.2, Novartis, Rueil-Malmaison, France).

2.2.2. Pressure measurement

An analogue gauge (Aschcroft pressure gauge 100T5500, USA) was placed between the air source (compressor or wall air) and the nebulizer in order to measure the nebulizer operation pressure and to assess the influence of the operating pressure on the performance of the nebulizer systems.

2.2.3. Inhaled mass

The inhaled mass of tobramycin was measured using a respiratory pump (Harvard Apparatus, Ealing, UK) and by collecting the aerosol on a filter. The nebulizer was connected to its associated air source. An absolute filter (Pari Filter, Pulmomed, Nanterre, France) was positioned between the nebulizer and the respiratory pump operating at 15 breaths/min, 500 ml as inhalation volume and an inhalation/exhalation ratio (I/E) of 1:1 in accordance with the European Standard EN 13544-16 (CEN methodology). The total nebulization time, defined as the time elapsed between the beginning of nebulization and 1 min after the beginning of spluttering, was recorded. The tobramycin inhalable mass deposited on the filter was measured using the residual gravimetric method based on weighing the filters both before and after aerosol collection and by filter drying [10,11]. The output rate (ml/min) was calculated using the following equation:

\[
\text{Output rate (ml / min)} = \frac{\text{inhale mass (mg)}}{\text{Tobi concentration (60mg / mL)} \times \text{nebulization time (min)}}
\]

2.2.4. Aerodynamic particle size distribution of aerosols

Particle size distribution was measured using a laser diffraction method (Mastersizer-X, Malvern, UK) [12]. The aerosol was directed toward the laser beam. The dispersion code was “polydisperse” and the optical presentation was “2QAA”. Data inversion calculations were used to determine the Mass Median Aerodynamic diameter (MMAD) and the fine particle fraction (percentage of particles with a diameter of between 1 and 5 μm predicting the fraction of aerosol likely to be deposited in the lungs [4,13]).

2.2.5. Study design

The 20 nebulizer systems were tested six times in random order, with their corresponding interface, which was a mouthpiece in 14 cases and a facemask in six cases (Cirrus®, 1484, Hot Top Plus® 1464003, Kendall® 13962, Micromist® 41894, Misty-Neb® 2033 G, Respineb® RN211). Either a compressor or medical wall air at a flow rate of 8 L/min was used for all the nebulizers.

2.3. In vivo study

Three healthy baboons weighing 9 kg to 12 kg were studied. They were installed on a special chair under anesthesia administered via an intra-muscular injection of xylazine (1 mg/kg) and ketamine (5 mg/kg). They were then kept awake while aerosol was administered through a face mask. The face mask (Ref 93815028, Temsega, France), specifically designed for baboons, was tight-fitting, and a system of one-
<table>
<thead>
<tr>
<th>Nebulizer reservoir</th>
<th>Interface</th>
<th>Manufacturer</th>
<th>Nebulizer type</th>
<th>Air source</th>
<th>MMAD (μm)</th>
<th>Fine particle fraction (%1–5 μm)</th>
<th>Inhalable mass (mg)</th>
<th>Fine particle mass (mg)</th>
<th>Time (min)</th>
<th>Output rate (ml/min)</th>
<th>Pressure (bar)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrus®</td>
<td>2505 (T piece)</td>
<td>Intersurgical, Wokingham, UK</td>
<td>Disposable Wall air</td>
<td>3.5±0.4</td>
<td>61±7</td>
<td>74±4</td>
<td>46±6</td>
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<td>Disposable Wall air</td>
<td>4.4±1.6</td>
<td>55±16</td>
<td>67±5</td>
<td>37±13</td>
<td>20±2</td>
<td>0.06±0.01</td>
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<td>Cirrus®</td>
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<td>Intersurgical, Wokingham, UK</td>
<td>Disposable Wall air</td>
<td>4.0±1.2</td>
<td>62±13</td>
<td>67±2</td>
<td>41±9</td>
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<td>Cirrus®</td>
<td>1485 (mouthpiece)</td>
<td>Intersurgical, Wokingham, UK</td>
<td>Disposable Pulmoaid compressor Wall air</td>
<td>6.7±0.8</td>
<td>26±8</td>
<td>68±5</td>
<td>18±6</td>
<td>28±5</td>
<td>0.04±0.01</td>
<td>0.9±0.1</td>
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<td>Hot Top Plus®</td>
<td>1464003 (face mask)</td>
<td>Intersurgical, Wokingham, UK</td>
<td>Disposable Wall air</td>
<td>3.3±0.1</td>
<td>76±4</td>
<td>50±9</td>
<td>38±6</td>
<td>10±1</td>
<td>0.08±0.02</td>
<td>2.0±0.2</td>
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<td>Kendall®</td>
<td>13962 (face mask)</td>
<td>Tyco Healthcare, Germany</td>
<td>Disposable Wall air</td>
<td>5.6±1.3</td>
<td>39±11</td>
<td>53±4</td>
<td>20±5</td>
<td>8±1</td>
<td>0.11±0.02</td>
<td>1.8±0.1</td>
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<td>Micro mist®</td>
<td>41894 (face mask)</td>
<td>Hudson, Temecula, USA</td>
<td>Disposable Wall air</td>
<td>5.7±2.3</td>
<td>43±12</td>
<td>62±4</td>
<td>27±8</td>
<td>10±1</td>
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<tr>
<td>Misty-Neb®</td>
<td>002033G (face mask)</td>
<td>Cardinal Health, Châteauribert, France</td>
<td>Disposable Wall air</td>
<td>5.0±0.3</td>
<td>40±3</td>
<td>56±15</td>
<td>23±7</td>
<td>12±1</td>
<td>0.08±0.02</td>
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<td>Misty-Neb®</td>
<td>002050G (mouthpiece, tube, Y piece, T piece, valve and filter)</td>
<td>Cardinal Health, Châteauribert, France</td>
<td>Disposable Wall air</td>
<td>0.7±0.1</td>
<td>6±5</td>
<td>12±3</td>
<td>1±1</td>
<td>12±1</td>
<td>0.02±0.01</td>
<td>1.7±0.2</td>
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<td>Misty-Neb®</td>
<td>002035G (mouthpiece and T piece)</td>
<td>Cardinal Health, Châteauribert, France</td>
<td>Disposable Wall air</td>
<td>4.8±0.2</td>
<td>49±3</td>
<td>66±3</td>
<td>32±3</td>
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<td>Misty-Neb®</td>
<td>002035G (mouthpiece and T piece)</td>
<td>Cardinal Health, Châteauribert, France</td>
<td>Disposable Pulmoaid compressor Wall air</td>
<td>6.5±0.3</td>
<td>29±3</td>
<td>66±4</td>
<td>19±2</td>
<td>18±2</td>
<td>0.06±0.01</td>
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<td>Respinneb®</td>
<td>12NEB400 (T piece and valve)</td>
<td>Teleflex, Le Faget, France</td>
<td>Disposable Wall air</td>
<td>4.2±0.6</td>
<td>49±5</td>
<td>60±8</td>
<td>29±6</td>
<td>13±2</td>
<td>0.08±0.02</td>
<td>1.6±0.1</td>
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<tr>
<td>Sidestream®</td>
<td>4452SU (mouthpiece)</td>
<td>Respironics, Bognor Regis, UK</td>
<td>Disposable Wall air</td>
<td>0.9±0.2</td>
<td>29±23</td>
<td>27±4</td>
<td>8±7</td>
<td>9±1</td>
<td>0.03±0.01</td>
<td>1.5±0.1</td>
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<td>Sidestream®</td>
<td>4452SU (mouthpiece)</td>
<td>Respironics, Bognor Regis, UK</td>
<td>Disposable Wall air</td>
<td>2.7±0.7</td>
<td>83±2</td>
<td>50±4</td>
<td>42±3</td>
<td>9±1</td>
<td>0.09±0.01</td>
<td>1.6±0.2</td>
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<td>Sidestream®</td>
<td>4452SU (mouthpiece)</td>
<td>Respironics, Bognor Regis, UK</td>
<td>Disposable Portanbe compressor Wall air</td>
<td>3.4±0.1</td>
<td>78±3</td>
<td>62±6</td>
<td>49±6</td>
<td>11±1</td>
<td>0.09±0.01</td>
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<tr>
<td>UP-DRAFT II Optineb®</td>
<td>1734 (mouthpiece, T piece and tube)</td>
<td>Teleflex, Research Triangle Park, USA</td>
<td>Disposable Wall air</td>
<td>4.3±0.6</td>
<td>55±9</td>
<td>76±3</td>
<td>42±7</td>
<td>11±1</td>
<td>0.12±0.01</td>
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<tr>
<td>UP-DRAFT II Optineb®</td>
<td>1734 (mouthpiece, T piece and tube)</td>
<td>Teleflex, Research Triangle Park, USA</td>
<td>Disposable Pulmoaid compressor Abox + compressor</td>
<td>5.0±0.2</td>
<td>45±3</td>
<td>83±4</td>
<td>38±3</td>
<td>21±3</td>
<td>0.07±0.01</td>
<td>1.0±0.1</td>
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<tr>
<td>Atomisor NLU</td>
<td>mouthpiece</td>
<td>Diffusion Technique Française, France</td>
<td>One day</td>
<td>4.9±0.3</td>
<td>51±4</td>
<td>110±7</td>
<td>56±6</td>
<td>16±2</td>
<td>0.11±0.02</td>
<td>0.8±0.1</td>
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<tr>
<td>Pari LC Sprint</td>
<td>mouthpiece</td>
<td>Pari, Germany</td>
<td>Six months</td>
<td>3.9±0.2</td>
<td>62±4</td>
<td>134±9</td>
<td>84±8</td>
<td>13±3</td>
<td>0.17±0.03</td>
<td>1.5±0.1</td>
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<tr>
<td>Pari LC Plus</td>
<td>mouthpiece</td>
<td>Pari, Germany</td>
<td>Six months</td>
<td>3.4±0.2</td>
<td>64±8</td>
<td>116±10</td>
<td>74±6</td>
<td>14±1</td>
<td>0.14±0.01</td>
<td>1.7±0.1</td>
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</table>
way valves was used for the breath-enhanced device. Each baboon inhaled an aerosol produced by three different types of nebulizer selected from the in vitro data.

PariLC+ with turbo boy compressor was used as the reference nebulizer.

Mistyneb with the 2050G interface and Mistyneb with 2035G interface operating with wall air at 8 L/min were chosen as examples of medium and low efficacy nebulizers respectively.

The order of the nebulizers tested was randomized for each baboon, resulting in nine inhalations.

99mTc-DTPA was used to label the tobramycin solution and to perform the scintigraphic deposition study. It was prepared from a commercially available kit (Pentacis®, CIS Bio International, France) and mixed (74 MBq/0.2 mL) with Tobi (300 mg/5 mL) in the nebulizer reservoir. The nebulizer charge was controlled by counting the radioactivity in the syringe using a gamma counter (Capintec®, France) before and after charging. The nebulizer was then connected to the face mask and to an expiratory filter to avoid air contamination. It was operated until 1 min after the aerosol began to sputter. Immediately after aerosol delivery, the animals and the circuit components were scanned using a gamma camera (Ecam, Siemens). A 120-s posterior static view was acquired on a 128×128 matrix. The amount of 99mTc-DTPA deposited in the lungs was determined from the digitised images, taking into account attenuation coefficients derived from lung perfusion imaging of each baboon using pertechnetate-macroaggregated albumin. The total lung surface was determined from the pertechnetate-macroaggregated albumin scan. The amount of radioactivity remaining in the nebulizer reservoir, face mask and filter was determined with 120-s static acquisition imaging. The amount deposited in the extrathoracic region (stomach + mouth) was calculated by the activity balance method (difference between the initial radioactivity loaded in the nebulizer and the activity deposited in the lungs and circuit components). Corrections for physical decay of 99mTc were made on all measurements.

2.4. Data analysis

The fine particle mass, which is the amount of tobramycin that is expected to deposit in the lungs, was calculated by multiplying the inhalable mass by the fine particle fraction.

\[
\text{fine particle mass} = \text{Inhalable mass (mg)} \times \text{fine particle fraction(\%)}
\]

The extrathoracic dose was defined as the amount of tobramycin expected to deposit in the mouth or to be exhaled. It was calculated by the difference between the inhalable mass and the fine particle mass.

Results were presented as mean (SD) values.

A non-parametric test (Wilcoxon Mann Whitney) was used to compare the data generated from the in vitro study, including inhalable mass, nebulization time, operating pressure, MMAD, fine particle fraction and output rate under different conditions, using Statxact (Cytel Software Corporation, Version 3.0.2). \(p<0.05\) was considered statistically significant.

Comparison of nebulizer efficacy was based on the method used by Standaert [13], which considers that nebulizers are equivalent when fine particle mass is within 20% of the reference at a 97.6% confidence level.

A Pearson correlation test was used to compare in vivo and in vitro data in terms of fine particle mass, which corresponds to the tobramycin mass deposited in the lungs in the in vivo study.

3. Results

3.1. In vitro

3.1.1. Comparison of nebulizer systems

The Pari LC Plus/Turboboy SX had a significantly higher inhalable mass \((p<0.002)\) and output rate \((p<0.01)\) than all the single-use disposable jet nebulizers (Table 1 and Fig. 2). Comparison of the Pari LC plus and the Atomisor NLU in terms of inhalable mass revealed no significant difference \((p=0.4)\).
Based on Standaert’s comparison method, no single-use disposable nebulizer performed as well as the Pari LC Plus/Turboboy SX. The only nebulizer achieving the same performance as the Pari LC Plus/Turboboy SX for fine particle mass and nebulization time was the Pari LC Sprint/Turboboy SX.

3.1.2. Influence of air source pressure

Compared to a wall air source operating at 8 L/min, a compressor produced lower operating pressure with Cirrus 1485, Mistyneb 2035G, Sidestream 4452 U and Up Draft II Optineb nebulizers \((p<0.002)\). Air source had no influence on inhalable mass for Cirrus 1485 and Mistyneb 2035G nebulizers \((p>0.84)\), but did have an influence on Sidestream 4452 U and Up Draft II Optineb nebulizers \((p<0.004)\). There was an increase in nebulization time \((p<0.004)\) and in MMAD \((p<0.04)\) for the four nebulizers when used with wall air, resulting in decreased fine particle mass for Cirrus 1485 and Mistyneb 2035G \((p<0.02)\) and increased fine particle mass for Sidestream 4452U \((p<0.015)\). There was no influence of air pressure on fine particle mass \((p=0.36)\) for Up Draft II Optineb but an increase in nebulization time \((p<0.001)\).

3.1.3. Influence of the interface

The use of different interfaces with the Cirrus nebulizer reservoir (producing different nebulizer systems: Cirrus 1485/ wall air, Cirrus 1484/ wall air and Cirrus 2505/ wall air) did not have a significant impact on fine particle mass \((p>0.25)\). However, there was a significant influence of interface with Mistyneb (Mistyneb 2035G/wall air vs. Mistyneb 2050G/wall air) and Sidestream (Sidestream 4452U/wall air vs. Sidestream 12NEB400/wall air) reservoir nebulizers in terms of fine particle mass \((p<0.001)\). The 2050G interface used with the Mistyneb reservoir produced a fine particle mass 32 times greater than that obtained with the 2035G interface.

3.2. In vivo results

Deposition in the baboons’ lungs differed significantly between nebulizers (Fig. 2), with lung deposition about ten times greater with Pari LC Plus/Turboboy SX than with Mistyneb® 2050G operating with wall air (5.2 mg vs. 0.5 mg) (Fig. 3). There was also a significant difference between the Mistyneb® 2035G and the Mistyneb® 2050G in terms of aerosol deposited in the lungs (2.1 mg vs. 0.5 mg), as shown in Table 2. The ratio between the lungs and the extrathoracic region reflects the aerosol amount of aerosol deposited in the baboons’ airways. There was a higher ratio for the Mistyneb 2050G than the Pari LC Plus/Turboboy SX and the Mistyneb 2035G, which can be explained by the low MMAD of the Mistyneb 2050G (0.7 \(\mu\)m vs. 4.8 \(\mu\)m and 3.4 \(\mu\)m). Comparison of fine particle mass and tobramycin mass deposited in the baboons’ lungs revealed a good correlation between in vivo and in vitro data \((r=0.91, n=9)\).

4. Discussion

This study investigated 20 nebulizer systems and air source combinations which are commercially available on the French market for the administration of tobramycin aerosol and which are used both in CF centers and for home care.

Results obtained from our in vivo data are consistent with the in vitro data \((r=0.91, \text{correlation test})\), with a higher mass of tobramycin deposited in the lungs by the Pari LC Plus/Turboboy SX than by the Mistyneb 2035G, and by the Mistyneb 2035G than the Mistyneb 2050G. Most MMADs of
the single-use disposable jet nebulizers tested were between 3 and 5 μm and were not significantly different from the reference nebulizer system (Pari LC Plus/Turboboy SX). However, the Pari LC Plus/Turboboy SX had a significantly ($p<0.001$) higher inhalable mass resulting in higher fine particle mass. Based on Standaert's comparison method [13], neither of the disposable jet nebulizers tested in this study performed as well as the Pari LC Plus/Turboboy SX in terms of fine particle mass. Only the Pari LC Sprint/Turboboy performed as well as the Pari LC Plus/Turboboy SX reference nebulizer, and there was no significant difference between these two nebulizers in terms of duration of tobramycin nebulization.

There was no general correlation between air source and nebulizer performance.

For some but not all nebulizers, compressor and wall air produced similar fine particle mass, even though the pressure was significantly different ($p<0.001$). These results confirm the need to match the nebulizer/air source combination carefully to achieve optimum performance [14].

Many nebulizer systems use the same reservoir and differ in interface. Changing the interface but keeping the same reservoir can result in different fine particle fraction, inhalable mass and fine particle mass. This was the case for the Mistyneb® and Sidestream® nebulizers when powered with wall air (Table 1). The difference in terms of fine particle mass attained a factor of 32 for the Mistyneb 2050G when compared with the Mistyneb 2035G. These large differences between nebulizers in terms of performance can be explained by residual mass remaining in the nebulizer at the end of nebulization and aerosol leakage during expiratory phases. The Pari LC+ nebulizer is a breath-enhanced jet nebulizer producing less aerosol leakage than standard continuous jet nebulizers such as Mistyneb. Furthermore, the residual mass is determined by the nebulizer geometry including reservoir and interface. Mistyneb 2050G differs from the 2035G in its interface which contains tubing and a valve, on which some aerosol droplets might impact, which could also explain the difference in terms of particle size (MMAD 0.7 μm vs. 5.0 μm).

These high differences obtained from in vitro measurements were confirmed by the scintigraphic study comparing Mistyneb 2050G and Mistyneb 2035G but with a lower range of difference (a factor of 4 instead of a factor of 32). This difference can be explained by the macaque model, which is consistent with a child’s breathing pattern and results in different ventilation parameters and anatomy of airways than the adult pattern which was modeled in the in vitro study, and also by the definition of fine particle fraction which does not take into account particle size less than 1 μm [2].

In conclusion, none of the single-use disposable nebulizers tested in this study can be considered as a suitable alternative to the Pari LC Plus® for administering tobramycin aerosols.

There was no general relationship between the compressed air source (compressor or wall air) and performance of the nebulizer system. The performance of some nebulizers did not change when using different air sources, while the performance of others did.

This study highlights the influence of the interface on the nebulizer reservoir. This parameter can have a significant impact on treatment efficacy.

The choice of a nebulizer/interface/air source combination must be made carefully, as any change in the air source or the interface of the nebulizer can have a dramatic impact on the efficacy of the aerosolized tobramycin treatment.
Author disclosure statement

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