Changes in Performance of the Pari eFlow® Rapid and Pari LC Plus™ during 6 Months Use by CF Patients

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Abstract

**Background:** Nebulized antibiotics are important in the treatment of cystic fibrosis. The Pari eFlow® rapid with vibrating mesh is often used off-label for the administration of tobramycin (TOBI®) because of a reduced nebulization time and easier handling compared to a classic nebulizer–compressor combination. Mesh technology may be vulnerable, however. Therefore, we investigated particle size distribution and output as well as changes in the performance of the eFlow before and after 6 months of use, in comparison with the Pari LC Plus™ nebulizer plus Turboboy™ compressor.

**Methods:** Size distributions in the aerosols and nebulization times for TOBI were measured with laser diffraction technique; delivered doses by weighing.

**Results:** New eFlows produce considerably larger droplets ($X_{50} = 3.5 \mu m$) from TOBI than new LC Plus nebulizers ($X_{50} = 2.8 \mu m$). After use, the $X_{50}$ increases for both systems (to 3.7 and 3.3 $\mu m$, respectively). The relative span of the size distribution ($(X_{90}-X_{10})/X_{50}$) changes from 1.26 to 1.28 $\mu m$ for eFlow and from 2.19 to 2.45 $\mu m$ for LC Plus. The total nebulization time doubles for LC Plus, whereas in 51% of all experiments the eFlow switched off after 10 min, resulting in incomplete dose delivery. For the eFlow, changes during use are related to clogging of orifices. Once being clogged, only replacement of the mesh restores the original performance.

**Conclusions:** New eFlows produce larger droplets and in a narrower size range compared to new LC Plus nebulizers for TOBI, and therefore both devices are not equivalent. Theoretically a larger portion of the aerosol from eFlow is likely to be deposited in the upper airways. The performance of both tested nebulizers decreases after 6 months of use. For the eFlow, timely replacement of the mesh is necessary. These *in vitro* results underscore the importance of registration studies of new drug–device combinations.

**Key words:** cystic fibrosis, nebulizers, tobramycin, TOBI, eFlow rapid, PariLC Plus

Introduction

In patients with cystic fibrosis (CF) inhaled tobramycin is widely used to suppress *Pseudomonas aeruginosa* with the aim to preserve lung function and to prevent pulmonary exacerbations.  

1\(^\text{st}\)–3\(^\text{rd}\) A special tobramycin solution for inhalation (TSL: TOBI) was developed for use with the Pari LC Plus™ (LC Plus) with an appropriate compressor.  

4\(^\text{th}\) Nearly a decade after the FDA approved TOBI with a DeVilbiss Pulmo-Aide® compressor (1997), the new Pari eFlow® (eFlow) with vibrating mesh technology\(^\text{6}\) was cleared for the U.S. (2004) and the European markets (2005). Immediately afterward, the registered eFlow was in use for the aerosolization of TOBI in many different countries, although the combination of drug and device has not officially been approved and registered. The manufacturer of both devices showed in an *in vitro* deposition study (with the Andersen impactor) that LC Plus and eFlow produce aerosols with different size distributions from this drug solution.  

5\(^\text{th}\) Reduced nebulization time and ease of handling, both increasing patient compliance, were important stimuli for this off-label use. The difference in median droplet size and size distri-
bution between LC Plus and eFlow may have consequences for the site of deposition and safety, however. Although no firm recommendation for the target area can be found in the literature, it has been shown that most adult CF patients have recurrent upper airway infection with *Pseudomonas aeruginosa* from which colonization of lower airways occurs up to (and including) the alveoli. In addition to the difference in droplet size distribution between the LC Plus and eFlow, concern has been raised about the durabil-

ity of the eFlow in daily practice due to expected vulnera-

bility of the mesh, particularly in relation to cleaning and sterilization procedures. Therefore, the aim of this study was to verify the difference in performance of new devices as pre-

sented by the manufacturer and to investigate whether changes occur in the performance of both devices in daily practice (6-month therapy) when being used for the admin-

istration of TOBI. Such changes could have relevant implications for lung deposition, and may further increase the difference between the aerosols from the eFlow and the LC Plus. Laser diffraction technique was chosen because laser dif-

crinction data are already available for the LC Plus from a previous study. To make the results more comparable, used eFlow and LC Plus nebulizers were collected from the same group of patients.

## Material and Methods

### Study design

Fifteen adult cystic fibrosis patients in The Netherlands using a nebulizer for the administration of TOBI were ad-

vised by their physician to change over to the eFlow for the administration of TOBI and asked to volunteer in the study. The costs for these new devices were refunded by Chiron (now Novartis, East Hanover, NJ). The 10 patients who used a LC Plus nebulizer until then handed it in for performance testing. They were given appropriate instructions on cleaning, and provided with a disinfection device. After 6 months of use (three cycles of 28 days TOBI treatment) they handed in their eFlow for performance testing with a questionnaire regarding experiences, cleaning procedures, and other drugs nebulized with the device.

On returning their used eFlow (series 1), all patients received a new (substitute) device, also financially provided by Novartis. Collected (used) eFlows were checked on proper cleaning of the devices before starting the performance testing. Because some meshes appeared to be visibly polluted, it was decided to extend the study: all patients were asked to hand in their substitute eFlows for performance testing again after another 6 months use, and 8 out of 15 patients agreed to do so (series 2). Before the patients started using their substitute devices, even more emphasis was put on correct cleaning and handling compared to the first se-

ries.

The patients participating in this study were advised by their physicians to change over to the eFlow for therapy (compliance) related reasons and not asked to change over for this performance testing study. Therefore, this study is considered an observational study without intervention, and approval from an ethical committee according to the (Dutch) Law on Medical Scientific Research involving Human Beings (WMO) was not necessary. The median pe-

riod of use for the collected LC Plus nebulizers was 6 months.

### Materials

TOBI ampoules, exposed to room temperature 15 min before use, were supplied by Red Swan pharma logistics (Utrecht, The Netherlands).

Nebulizers and Petra disinfection apparatus were supplied by Novartis. eFlows (both new and used) were tested with a Pari mouthpiece with an exhalation filter in agree-

ment with daily practice. Two used eFlows from the first se-

ries of 15 were returned without the vibrating mesh, and were therefore excluded from the testing program. One of the visibly polluted devices from the second series was also tested after the mesh was replaced by a new one. The 10 used LC Plus nebulizers were tested in combination with a Pari TurboBoy N compressor. This compressor from the same manufacturer complies with the specifications mentioned for the aerosolization of TOBI (jet flow is 4 L/min). Using the TurboBoy N also enables comparison with data presented previously for new LC Plus nebulizers. Actually, the same compressor device was used for the new and used nebuliz-

ers after it was checked so that the jet flow was still the same and meeting the specifications of the manufacturer.

### Measurement of particle size distribution in the aerosol

Particle size distributions in the aerosols were measured with a HELOS Compact/KA laser diffraction apparatus (Sympatec, Germany) at a constant flow rate of 30 L·min⁻¹ using a 100-mm lens (measuring range from 0.5 to 175 μm), an INHALER 2000 adapter, and the Fraunhofer theory for the calculations. All eFlows (new and used) were tested three times, using three different TOBI ampoules; used LC Plus nebulizers were tested in duplicate. The first test with used devices was as collected from the patients. Between the tests, the devices were cleaned according to the procedures prescribed to the patients. A series of measurements of 10 sec each was started from the beginning of the nebulization process with interval times of 20 sec. Data from the eFlows were collected until the devices stopped nebulization (on detection of a minimum liquid level, or after 10 min). Measurement of LC Plus was continued into the phase of sputter-

ing, but the data obtained during sputtering were omitted from processing. Cumulative volume distribution curves (as function of diameter) were averaged per ampoule first, and next, the mean of three ampoules per device was calculated in order to obtain an overall mean size distribution per device. Data are presented as cumulative volume distribution curves (Fig. 1), or as characteristic values (X₁₀; X₅₀; X₉₀) derived from these curves (Fig. 2 and Table 1). The variations given in Table 1 and spread bars in Figure 2 represent the highest and lowest X₅₀ values obtained within all individual series (10 sec measurements) per device. The spread bars in Figure 1 represent the standard deviation for the averaged values per time interval. Because the cumula-

tive volume distribution curves were not log-normal, geo-

metric standard deviations (GSD’s) could not be calculated. Instead, relative spans (RS) of the size distributions (RS = (X₉₀−X₁₀)/X₅₀) are presented (Table 1). The mouthpieces of the nebulizers were positioned less than 5 mm from the laser.
Nebulization times and delivered doses

Total nebulization times (until switching off for the eFlow and the start of sputtering for the LC Plus, respectively) were recorded for individual ampoules and averaged per device. Delivered doses (in mg drug solution) were calculated from differences in weight before and after nebulization. Delivered weight may overestimate delivered drug dose because of evaporation in the LC Plus nebulizer cup (not for the eFlow). Mean optical concentrations in the aerosol cloud were recorded to detect changes in the output rate, indicative for dry running of the LC Plus nebulizers and severity of clogging of the vibrating meshes in the eFlows.

Results

Particle size distributions in the aerosols

Figure 1 shows the volume median droplet diameters (VMD = X50) with standard deviations and optical concentrations (Copt) in the aerosols from new nebulizers as function of the nebulization time. The curves represent the mean of five devices. For both types of nebulizers, the droplet size distribution is constant except for the first 10 sec of nebulization and after the optical concentration starts to decrease significantly. Table 1 compares the overall mean data for new and used devices and shows that the volume median diameter for TOBI from a new eFlow is approximately 24% higher than that from a new LC Plus (p < 0.05). However, the RS of the size distribution is narrower for the eFlow than for the LC Plus (p < 0.05).

The interdevice variation before and after use is shown in Figures 2A (for eFlow) and B (for LC Plus). The spread bars in Figure 2A and B indicate the maximum and minimum values obtained within the three ampoules. The relative standard deviation (RSD in X50) was found to increase from 2.8% for new eFlows to 6.7% (series 1) and 8.4% (series 2) for used devices and from 2.9% (new) to 11.4% (used) for LC PLus, respectively (all p < 0.05). Table 1 shows that overall mean values for X50 and RS both increase for eFlow (as well as for LC Plus) during use and both increases are significant (p < 0.05).

Figure 3A shows the array of round orifices of an unused vibrating mesh. For polluted meshes (Fig. 3B and C), orifices were either still more or less completely open, or practically totally clogged (as in Fig. 3C). The fraction of more or less totally clogged orifices in a severely polluted mesh was over 50% (Fig. 3B).

Patient compliance

Although all patients in the study indicated to have cleaned their eFlow with great care and consistency (warm...
water detergent), most eFlows were returned with polluted meshes. The same was true for the devices of the second series, despite more emphasis on good cleaning procedures, particularly after the last use. The majority of patients (85% in series 1; 75% in series 2) also used their eFlow for the administration of other medicaments than TOBI. They nebulized salbutamol, ipratropium, terbutalin, colistin, DNase (Pulmozyme), acetylcistein and/or saline.

![Graph A](image1)

**FIG. 2.** Comparison of characteristic values ($X_{10}$, $X_{50}$, and $X_{90}$) from the cumulative volume distributions (as function of the diameter) for the aerosols from new and used eFlow (A) and LC Plus nebulizers (B). The spread bars ($X_{50}$) indicate maximum and minimum values obtained within individual series.

![Graph B](image2)

**TABLE 1.** Comparison of overall mean median diameters ($X_{50}$), relative spans of the size distributions ($(X_{90} - X_{10})/X_{50}$), delivered doses (g drug solution), total nebulization times (min), and output rates (g drug solution per minute) for new and used eFlows and LC Plus nebulizers

<table>
<thead>
<tr>
<th>Device</th>
<th>Volume median diameter ($X_{50}$) (micron)</th>
<th>Relative span of the size distribution ($(X_{90} - X_{10})/X_{50}$)</th>
<th>Delivered dose (g drug solution)</th>
<th>Total nebulization time$^a$ (min)</th>
<th>Average output rate (g/min)</th>
<th>Number of eFlows switched off prematurely$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>eFlow new</td>
<td>3.5 (3.3–3.7)</td>
<td>1.3</td>
<td>3.85 (3.67–4.02)</td>
<td>6.7 (5.5–8.0)</td>
<td>0.58</td>
<td>15/0/0</td>
</tr>
<tr>
<td>eFlow used, series 1</td>
<td>3.8 (3.3–4.3)</td>
<td>1.3</td>
<td>3.35 (1.65–4.21)</td>
<td>9.0 (5.5–10)</td>
<td>0.37</td>
<td>39/22/6</td>
</tr>
<tr>
<td>eFlow used, series 2</td>
<td>3.5 (2.8–4.0)</td>
<td>1.3</td>
<td>3.48 (1.15–4.09)</td>
<td>8.7 (6.5–10)</td>
<td>0.40</td>
<td>24/10/2</td>
</tr>
<tr>
<td>LC Plus new</td>
<td>2.8 (2.7–3.0)</td>
<td>2.2</td>
<td>3.44 (3.41–3.50)</td>
<td>6.9 (6.8–6.9)</td>
<td>0.50</td>
<td>—</td>
</tr>
<tr>
<td>LC Plus used</td>
<td>3.3 (2.8–4.2)</td>
<td>2.5</td>
<td>4.19 (3.61–4.44)</td>
<td>13.0 (8.0–20.5)</td>
<td>0.32</td>
<td>—</td>
</tr>
</tbody>
</table>

Results between brackets are the lowest and highest values observed.

$^a$For eFlow: time reduced due to devices switching off automatically after 10-min nebulization time.

$^b$The first figure indicates the total number of ampoules tested (three per device); the second figure indicates the total number of switchings off; the third figure indicates the number of devices for which none out of three ampoules was completely nebulized.
The objectives of this study were to verify differences in droplet size distribution between eFlow and LC Plus (for TOBI) and to investigate possible changes in the performance of the vibrating mesh technology applied in the eFlow during (6 months) use in daily life (CF patients). With respect to the latter, the outcome of the study is that particularly the interdevice variation increases during use. Surprisingly, the changes in performance for the eFlow are less extreme than those concluded for the LC Plus (based on comparison of previous data for new LC Plus nebulizers and new data for used devices in this study).

This study has also confirmed that the VMD’s in the aerosols from new eFlows (3.52 μm from laser diffraction analysis) and the new LC Plus nebulizers (2.84 μm) are not the same. Pari presented for TOBI a mass median aerodynamic diameter from the Andersen cascade impactor (at 28.3 L/min) of 3.95 μm for the eFlow and 3.5 μm for the LC Plus, while using the same compressor we used in this study. The differences between our study and data from PARI cannot be explained easily. Contributing factors are that different measurement principles have been used and that different conditions such as relative air humidity may have been different. However, the difference in median diameter between the eFlow and LC Plus is consistent for both studies. The difference in median diameters between eFlow and LC Plus (by 24% in this study) raises concern about the site of deposition in the human lung, and therefore, the therapeutic effect and safety. Based on the impaction parameter (IP = \( p \times x_a^2 \times U \), where \( p \) is the particle density and \( U \) is the particle velocity), the difference is even 54%. In terms of fine particle fraction, the fraction <3.1 micron is 25% lower from eFlow than from LC Plus. In daily life, this difference may be even greater, because the manufacturer of TOBI recommends to use a compressor with a jet flow within the range from 4 to 6 L/min. In the present study, a compressor with a jet flow of 4 L/min was used, and from previous investigations it is known that higher jet flows result in smaller droplets. Hence, based on in vitro deposition data, the eFlow does not seem to be equivalent to the LC Plus. The volume median diameters of used eFlows and LC Plus nebulizers differ less from each other (13%) than those of new devices (24%) because the increase in volume median diameter during use is higher for the LC Plus (15.5%) than that for the eFlow (5.1%).

For nebulized antibiotics a high drug concentration on the site of infection is required. As already mentioned in the introduction, Pseudomonas infection may involve the whole lung. Consequently, the whole lung has to be treated with the antibiotic drug. Based on the exponentially increasing inner surface area of the airways from the lobar bronchi to the alveoli, an increasing amount of drug is necessary toward the lower airways in order to obtain a more or less equal drug concentration throughout the entire lung. According to various lung models the conducting airways (generally 0–11) contribute only approximately 1% to the total airway surface area, versus 4% for the transitional airways (generally 12–16) and 95% for the respiratory airways (generally 17–23). Hence, on the basis of the surface area distribution and the desired equal drug concentration, the amount of drug to be deposited in the respiratory airways needs to be 24 times higher than that in the conducting and transitional airways combined (generally 0 to 16). However, when aiming at deposition in the respiratory airways, losses occur in the preceding conducting and transitional airways. According to lung deposition models, these losses exceed the approximately 5% that is needed in these regions. This sup-

**Discussion**

The objectives of this study were to verify differences in droplet size distribution between eFlow and LC Plus (for TOBI) and to investigate possible changes in the performance of the vibrating mesh technology applied in the eFlow dur-

**FIG. 3.** Scanning electron micrographs of a new (A) and a heavily polluted used mesh (B and C) from the eFlow.
ports the idea that antibiotics for equal distribution over the entire lung have to exhibit the appropriate particle size for deposition in the respiratory Airways, or the concentration in the deep lung will be much lower than that in the conducting and transitional Airways.

From both deposition modeling(18–20) and in vivo deposition studies,(21) it is known that the optimal particle size for peripheral lung deposition at moderate flow rates (30–60 L/min) is rather between 2 and 3 μm than between 3 and 4 micron. Peak inhalation flow rates during tidal breathing as measured with a pneumotachograph may be in the range of 30 to 90 L/min for CF patients.(22) Because it is known that mean flow rates are approx. 70% of peak flow rates,(23) this reduces the expected range of mean flow rates through the eFlow to 20–60 L/min. As an overall conclusion, it seems rational to expect that the ratio of aerosol deposition in the conducting and transitional Airways to that in the respiratory Airways is higher from the eFlow than from the LC Plus. Therefore, it is recommended that a comparative in vivo deposition study is conducted to verify this expectation.

The reasons for a change in median droplet size during use of the eFlows have not been investigated. It has been observed though, that the wetting of the mesh and the adherence of expelled gas bubbles to the mesh surface change during use. This could influence the droplet formation process and the influence could depend on the mesh pollution. The size distribution in a wet aerosol is also affected by droplet coalescence and evaporation, which depend on the droplet concentration in the aerosol. For the eFlow, this droplet concentration is related to the number of open orifices. Clogging (Fig. 3B) appeared to reduce the optical concentration (Copt) from 80% for new meshes to less than 20% for strongly polluted meshes. When clogging of an orifice occurred, it seemed to be more or less complete (Fig. 3B–C), although it is expected that also partially clogged orifices do not produce droplets because the resistance to flow through an orifice increases exponentially with its diameter. Above a certain threshold value for the resistance, no droplets will effectively be formed. This may explain why the effect of mesh pollution on output rate is much greater than that of particle size distribution in the aerosol.

Despite the emphasis put on good cleaning procedures in the instructions for use, mesh pollution was visible for nearly all collected eFlows, but the devices of series 2 showed less clogging than the devices of series 1 (with only one exception). Considering that more emphasis was put on correct cleaning at the start of series 2, it must be concluded that cleaning and maintenance have a great effect on mesh pollution. In this respect, the mesh technology is vulnerable. Pollution may also have been influenced by unintended nebulization of other drug solutions than TOBI with the same device. Cleaning of a polluted mesh during performance testing appeared hardly effective in regaining the original eFlow performance. Only in a few examples it was observed that the second and third experiment of used devices (after cleaning) yielded slightly better results than the first. However, replacement of a polluted mesh fully restored the particle size distribution and nebulization time to values for a new device. PARI has recently developed an “easy care cleaning aid” for this purpose, but data about use in daily practice and efficacy have not been published yet. Possible reasons for differences in performance between new and used LC Plus nebulizer cups have been explained and discussed before.(11)

For the eFlow, the increase in nebulization time eventually leads to automatic switching off after 10 min. This implies that part of the dose is not administered to the patient and this has resulted in extreme variation in delivered dose in this study (Table I). In a recent personal communication with Pari we were informed that the time for automatic switch-off will therefore be prolonged to 20 min. This change in technical specification may indeed decrease the variation in delivered dose, but it will also increase the necessity to measure the nebulization time because of the observed increase in inter device variation due to mesh pollution.

Nebulization of other drug solutions than TOBI with the eFlow should be strongly dissuaded. Although we could not find clear correlations between the degree of clogging and the type of drug solutions nebulized in this study, neither with the cleaning methods applied, it may well be that mesh pollution is influenced by these parameters. Apart from possible consequences for mesh pollution, the droplet size distribution may vary with the properties of the drug solution.(14) Moreover, not all drug solutions are supplied in the same large volume as TOBI. Considering the high residual volumes left in the medicament chamber after the eFlow is switched off (upon detection of minimal level), the delivered dose may vary quite substantially with the volume of the drug solution inserted in the medicament reservoir.

Conclusions

LC Plus nebulizers and eFlows produce aerosols with different droplet size distributions for TOBI: the median droplet diameter from a new eFlow is 24% larger (fine particle fraction <3.1 micron is 25% lower) and the difference between the devices becomes even greater when a compressor with a higher jet flow is used. In addition, the size distribution is narrower from the eFlow. This is likely to have consequences for the drug deposition in the respiratory tract and the finding underscores the importance of extensive in vitro (and in vivo) testing before selecting formulation–nebulizer combinations for clinical use.(24,25) During use, median droplet diameters appear to slightly increase for both devices, but the observed increase was somewhat higher for the LC Plus than for the eFlow. Therefore, the aerosols from used devices are more comparable than those produced by new devices.

During use the interdevice variation and nebulization time increased for the eFlow, which seems most likely to be the result of mesh pollution (clogging of orifices). This occurred despite good emphasis on the cleaning instructions, and there may have been an influence on clogging from nebulizing other drug solutions than TOBI with the same device, like Pulmozyme. Mesh pollution changed the output rate quite dramatically, and the decreased output rate in combination with automatic switch-off after 10-min nebulization time resulted in an unacceptable variation in delivered dose. Therefore, timely replacement of polluted meshes is mandatory.

These in vitro data suggest that the eFlow is not equivalent to the LC Plus for TOBI administration, but a clinical effectiveness study (including assessment of adherence) should be performed to confirm that conclusion.

Acknowledgments

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Author Disclosure Statement

No conflicts of interest exist.

Abbreviations and Symbols

$C_{opt}$ Optical concentration in the aerosol. $C_{opt}$ is a measure for the light extinction, which is influenced by the droplet density and the droplet size distribution in the aerosol

GSD Geometric standard deviation (for log-normal distributions)

MMAD Mass median aerodynamic diameter

RS Relative span of the size distribution; ratio of $(X_{90}-X_{10})$ to $X_{50}$ (alternative for geometric standard deviation for skewed distributions)

VMD Volume median diameter

$X_{10}$ Diameter derived from the cumulative volume distribution curve: 10% of the volume is in particles smaller than $X_{10}$ (micron)

$X_{50}$ Diameter derived from the cumulative volume distribution curve: 50% of the volume is in particles smaller than $X_{50}$ (micron)

$X_{90}$ Diameter derived from the cumulative volume distribution curve: 90% of the volume is in particles smaller than $X_{90}$ (micron)

References


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