Comparison of tobramycin serum plasma levels in 5 CF patients after inhalation via a PARI LC PLUS® nebuliser and via eFlow®, a novel electronic inhaler

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Objectives

Therapy of CF is very time consuming. Duration of the therapeutic treatment regime can range up to 4.5 h per day [1]. This is based on a major extent on long nebulisation times with conventional nebulisers. Shortening of nebulisation times may increase compliance and quality of life in CF-patients.  

eFlow® [2]: A novel electronic inhaler based on a vibrating membrane principle, is designed for a more rapid and effective nebulisation of medication due to a higher rate of delivered and respirable dose compared to jet nebulisers [2].  

The current clinical case study was undertaken to assess the possibility of shortening nebulisation time with the eFlow® in combination with marketed drug formulations of tobramycin and tobramycin based on in vitro equivalence data in order to evaluate the potential of the eFlow® for simplification of CF patient therapy.

Materials and Methods

In vitro aerosol characterisation was performed by breath simulation measurements utilising the PARI COMPASS® breath simulator mimicking an adult breathing pattern (15 bpm, tidal volume: 500 ml, inhaled ration 1:1), 5 ml of tobramycin (60 mg/ml) or 2.5 ml of tobramycin (1 mg/ml) were nebulised with either PARI LC PLUS® / PARI BOY® or the eFlow® (pilot version). The drug was sampled on inhalation and exhalation filters to determine the drug distribution with respect to delivered doses (DD). Resulting sample solutions were assayed by HPLC, as reported earlier [2, 3].  

Drop size distributions were characterised by laser diffraction (LD) using a Malvern Mastersizer X to allow calculation of the respirable dose (RD, aerosol droplets delivered < 5 pm). An excellent correlation with Andersen cascade impactor data was found (results not shown) as reported earlier [4].  

5 patients (11 – 29 years) with a FEV1 of 12.1 % to 35.9 % predicted value inhaled at visit one 2.5 ml of salbutamol (2.5 mg/ml) and 5 ml of tobramycin (100 mg/ml) via a PARI LC PLUS® powered by a PARI BOY® compressor and, at visit two (at least 1 week after visit 1), 1.1 ml of salbutamol (1 mg/ml) and 3.3 ml of tobramycin (200 mg/ml) via eFlow®. For the pilot version of eFlow® investigated in this study, such full volumes were found to deliver an equivalent respirable dose (RD) compared to the fill volumes used for the LC PLUS. Patients were allowed to continue their routine CF medication. Inhaled or i.v. antibiotics were prohibited within the previous 7 days.  

Nebulisation time was determined after each application. A patient questionnaire was filled in after each visit.

Results

Table 1 shows the effects of the nebuliser type on the aerosol performance regarding mass median diameter (MMD), Geometric Standard Deviation (GSD), respirable fraction (RF), delivered dose (DD) and respirable dose (RD) of different volumes of salbutamol and tobramycin solutions. Results are given as a Mean Standard Deviation, n = 6.  

Table 1: Comparison of in-vitro aerosol characteristics of the PARI LC PLUS® and eFlow®.  

<table>
<thead>
<tr>
<th>Product</th>
<th>Volume (ml)</th>
<th>Nebuliser</th>
<th>MMD (µm)</th>
<th>GSD</th>
<th>DD (%)</th>
<th>RD (%)</th>
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<tr>
<td>Salbutamol (1 mg/ml)</td>
<td>2.5</td>
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<td>2.0</td>
<td>62</td>
<td>0.65</td>
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Table 1: Comparison of in-vitro aerosol characteristics of the PARI LC PLUS® and eFlow®.  

With references to in-vitro tests and comparable respirable doses (RDs), volumes of 5.1 and 5.5 ml were calculated and selected for in-vitro tests. Similar RDs are assumed to be in vitro bioequivalent.

Summary and Conclusions

In comparison to the PARI LC PLUS® there were no clinically relevant changes in lung function (FEV1), heart rate and oxygen saturation after administration of adapted doses of salbutamol with eFlow®.  

Due to the higher drug delivery rate of the new eFlow® system time reductions by a factor of 2.7 to 3.9 could be achieved for equivalent respirable doses with both salbutamol and tobramycin. This shows that for clinical use close adoption of drug and device would be ideal.  

The smaller GSD of eFlow® is associated with a lower percentage of coarser and very fine droplets [4] which may reduce side effects, such as pharyngitis.  

In vitro data are useful to predict in vivo performance. To verify the clinical efficacy and safety of the eFlow® further investigations in a higher number of patients are necessary.  

Patients liked the eFlow® because of its compactness, mobility and faster drug administration. It is most likely that eFlow® will improve acceptance of nebuliser therapy and quality of life in CF patients.

References

Device Name
Common Name: Electronic Nebulizer
Proprietary Name: eFlow®
Classification Name: Nebulizer

Marketing Clearance
The eFlow Electronic Nebulizer was cleared by the Food and Drug Administration on May 5, 2004.

510(k) Number: K033833

Device Description
The PARI eFlow® is a small, single patient use, reusable electronic nebulizer for the inhalation treatment of aerosol medications. It is a hand-held device containing a capped medication cup that can be filled by the user. Power input is provided by either 4 AA batteries, a DC adapter or a AC adapter. Alternate power cords/plugs/adapters allow use in any country.

Non-Clinical Test Summary
The eFlow® Electronic Nebulizer was tested to compare performance to the predicate devices, including:

- MMAD: eFlow MMAD is comparable to or lower than predicate devices
- RF: eFlow RF is comparable to or greater than predicate devices
- TOR: eFlow TOR is comparable to or greater than predicate devices
- Safety EMC: eFlow meets the requirements of EN/IEC 60601-1, DIN EN 60601-2 and UL 1431

Clinical Performance Summary
Clinical testing was not completed/is not required to show substantial equivalence.

Conclusions from Testing
The eFlow meets performance requirements and raises no new issues of safety or effectiveness.

Intended Use
The eFlow is a handheld nebulizer that will be used with patients for whom doctors have prescribed medication for nebulization. The eFlow is intended for adult and pediatric patients.

The eFlow SCF has not undergone human clinical studies with any medication to establish safety or efficacy. The FDA has not approved any combination of a medication with the eFlow SCF device as a drug/device combination.