The eRapid® Nebulizer for the Delivery of Inhaled Therapies for CF
Information for CF Centers

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Background

Orally inhaled therapies are a cornerstone of lung health maintenance in CF. Topical application of drugs in the airways increases the efficacy and reduces the systemic exposure and toxicity of these agents. Most CF patients are treated with aerosolized therapies, and many take multiple inhaled drugs on a daily basis. Treatments for bronchodilation, inflammation, airway clearance and early or chronic infection create a significant time burden for patients, leading to nonadherence with therapies and poorer outcomes. Newer aerosol delivery systems have been developed to improve one or more of the perceived deficiencies of standard aerosol devices, including convenience, portability, and time burden.

The eFlow® Technology devices (eFlow®, PARI Pharma GmbH, Germany) represent a platform based on vibrating perforated membrane (a.k.a. “mesh”) technology. The aerosol generator is a dome-shaped, wafer-thin, stainless steel membrane with hundreds to thousands of uniform, laser-drilled holes or perforations. The holes have a tapered shape, being wider on the drug-solution side. Surrounding the perforated membrane is an annular piezoelectric element (driven by the electronics in the controller) that serves to vibrate the mesh rapidly (around 100 kHz), building up sound pressure (like the movement of a speaker woofer) around the membrane that pushes the liquid through the holes to create an aerosol. An eFlow® device consists of the controller unit that contains the batteries and electronics, the medication reservoir cup, the aerosol generator, and the aerosol chamber/mouthpiece assembly (Figure). The aerosol chamber has a one-way valve that allows for the conservation of aerosol during exhalation. Expired air is diverted away from the aerosol chamber by another one-way valve in the mouthpiece. The eFlow® performance characteristics can be customized by changing the size of the membrane holes (to change droplet size distribution), the configuration of the medication reservoir cup and membrane, and the size of the aerosol chamber.

The eRapid® (PARI Respiratory Equipment, Inc., USA) was introduced to the U.S. in November 2012 as a general-use nebulizer for delivering CF aerosol drugs. It has been available in other countries (a.k.a. eFlow® rapid; names used interchangeably in this paper) since about 2005. A few months before the eFlow® rapid was introduced in Europe, the eFlow® SCF (now known as the Trio™ Electronic Nebulizer) became available in the U.S. as a general-use nebulizer. Then the Altera® Nebulizer System was released in 2010, specifically for use with aztreonam solution for inhalation (Cayston®, Gilead Sciences) as a drug-device combination. Finally, many CF Centers involved with clinical research have had experience with investigational eFlow® devices to deliver various drugs still in development for CF, especially anti-infective agents. Predictably, between the nomenclature changes and the different device characteristics, there is
considerable confusion in the CF community regarding eRapid® and how it should be used. This communication will help demystify the topic for clinicians and caregivers.

Similarities and Differences between eFlow® Devices

All eFlow® devices share the many benefits of vibrating mesh technology. Compared to jet nebulizers, these devices are small, portable, and operate quietly. Batteries or alternating current electricity can power them. Most important for patient burden is that the eFlow® devices nebulize liquids much faster than jet nebulizers. One drawback is the tendency for the tiny holes of the mesh to clog over time, causing the nebulization time to gradually increase. These devices require thorough cleaning and disinfection, and the membrane (mesh) has to be handled carefully to avoid damage. Longevity of a membrane will depend on how often it is used and how it is cleaned and handled; periodic replacement of the aerosol generator containing the membrane is required to maintain optimal operation.

The Trio® and Altera® nebulizers are highly efficient delivery devices, and judging by in vitro data are capable of delivering 2 to 4 times more drug to the lungs than most jet nebulizers. These devices have an efficient medication reservoir design that leaves minimal residual drug after nebulization is finished. The Trio and Altera share the same size aerosol chamber (size “large”), to conserve more aerosol during exhalation. They also have similar membrane pore size (manufacturing specifications are different between these two devices, but specific information is not publicly available). The Altera® nebulizer is recommended to be used only with Cayston® but the functionally similar and efficient Trio® is a general-use device that can potentially be used for almost any aerosol drug. When it was first introduced, the high delivery efficiency of the Trio® compared to jet nebulizers sparked concerns about toxicity or side effects from some drugs. Based mostly on in vitro aerosol models, compounding pharmacies recommended half the usual nominal dose than that used for a jet nebulizer like the PARI LC PLUS for drugs like tobramycin inhalation solution (TIS) and colistin. While many physicians felt the bench data alone were convincing, others were not comfortable prescribing the Trio®, since there were no clinical trials to substantiate safety and efficacy.

To help reduce time burden and eliminate uncertainty about dosing (including compounding and dose-splitting issues), PARI designed the eRapid® to match the pulmonary delivery of the LC® PLUS jet nebulizer (the on-label nebulizer for TIS and also on-label for dornase alfa), but with much faster delivery times. The differences between eRapid® and the other eFlow® devices are more subtle, at least by visual inspection. The eRapid was designed to have a less-efficient medication reservoir cup that retains about 1 mL of drug. Also, the aerosol chamber is smaller, conserving less of the aerosol during exhalation. The end result is that eRapid® has about half the in vitro delivered dose of the Trio® (just like the LC® PLUS).

In vitro tests show that the median aerosol diameter is similar for the eRapid® and the LC® PLUS for albuterol, TIS, and dornase alfa (about 4 microns). However, the aerosol droplets are more uniform in size with the eRapid® so there are fewer large particles that
may impact in the throat, and fewer tiny particles that may be exhaled. Similar results were seen with colistin delivered by the eRapid® compared to the LC® Sprint. *Based on these bench studies using standard unit-dose medications, the expectation is that one can expect similar lung deposition without having to decrease the loading dose.* The clear advantage of the eRapid® is that it nebulizes the drugs in half the time or less compared to the LC® PLUS.

**Clinical Studies: Pharmacokinetics (PK) and Scintigraphy**

The published reports of drug deposition in humans with the eRapid® used TIS as the PK marker. Hubert, *et al,* studied 25 CF patients with chronic *Pseudomonas* in an open-label cross-over study of TIS (300 mg in 5 mL, TOBI®, Novartis Pharmaceuticals). Study subjects received TIS twice daily for 15 days with either the eRapid® or an LC® PLUS nebulizer, and after washout they switched to the alternate device. Sputum and serum levels were measured after dosing on Days 1 and 15 of each cycle. Maximal serum concentrations were similar but slightly lower on day 1 (0.7±0.6 vs. 0.9±0.5 µg/ml) and day 15 (1.2±1.0 vs. 1.3±0.7 µg/ml) with the eRapid® vs. the LC® PLUS, respectively. On the other hand, sputum levels were much higher with the eRapid®, such that by Day 15 the geometric mean ratio vs. the LC® PLUS was about 1.8 for both Cmax and area under the curve (x 8 hours). Sputum levels are notoriously difficult to evaluate due to high variability and sampling issues, but some believe that the higher sputum tobramycin levels with the eRapid® were due to higher deposition in the central airways due to the more uniform particle size distribution. There were no safety issues between nebulizers, and the nebulization time was much shorter with eRapid® (10.5 minutes faster on Day 1, and 7.7 minutes faster on Day 15). A similarly designed study by Govoni, *et al,* using a more concentrated TIS solution (300 mg in 4 mL, Bramitob® [EU] or Bethkis® [US], Chiesi Pharmaceuticals) and 28-day cycles, demonstrated similar ratios for plasma levels to Hubert but only a 1.4 geometric mean ratio for sputum at Day 28. Again, delivery time was cut in half with the eRapid®. Clinical efficacy outcomes were not reported in these studies.

Lenney *et al* evaluated lung deposition of TIS in 7 CF patients and 6 healthy controls with both PK analysis and gamma scintigraphic imaging. In the healthy subjects, TIS serum levels and total lung deposition were comparable between devices. However, in the CF subjects the serum Cmax was 60% less and total lung deposition by scintigraphy was 40% less with the eRapid®. The small number of subjects and the high variability make these data difficult to interpret. But once again, delivery times were markedly decreased in the CF group with the eRapid® (7.0 vs. 20.0 minutes). Larger studies would have to be performed to determine the true comparability of *in vivo* delivery to the lungs, but it is the clinical relevance that is most important. In the Hubert and Govoni studies, high sputum levels (the site of action), and lower serum levels were seen, suggesting there should be no increase in systemic toxicity risk with the eRapid®. The dose-response to TIS is unknown, so if lung dose was truly lower with the eRapid® (as the Lenney study would suggest) it may or may not make a difference clinically. On the other hand, if faster dose delivery improves adherence significantly in an individual patient, then using...
the eRapid® for TIS would be expected to help that person significantly compared to not taking the drug at all.

Clinical “Real Life” Studies

Despite a paucity of clinical data, about 75% of European CF patients who receive nebulized drugs are now using the eRapid®. Naehrig’s group in Munich recently reported on their experience with adult CF patients who switched from conventional jet nebulizers to the eRapid® for delivery of their aerosol medications. Lung function tests were obtained at intervals for a year after switching, and results were compared to the results from the previous year. Of the 70 enrolled patients, complete data on lung function were available for 59 individuals. After 1 year of using the eRapid® the mean decrease in FEV1% was -1.4% compared to -3.1% for the control period (NS). Forced vital capacity improved by +2.9% over the year, compared to +1.1% in the control period (NS). The estimated mean daily nebulization time was 31.3 minutes for the conventional nebulizer and only 10.2 minutes for the eRapid®, a 2/3 reduction in time. Importantly, switching from a conventional nebulizer to the eRapid® did not lead to clinical deterioration in these patients, and the time savings was indeed significant.

Individual Drugs

Questions may remain about the safety and usefulness of the eRapid® for certain CF drugs. For example, dornase alfa is a protein and as a biologic agent, may be subject to degradation during nebulization. Scherer reported on the work of three independent labs that studied the delivery aspects of dornase alfa with eFlow®, including aerosol characteristics, delivery time, stability of the drug after nebulization, and reproducibility of results after repeated use. The eFlow® devices delivered dornase alfa more rapidly and efficiently than jet nebulizers, and did not affect the physicochemical properties of the drug. After 60 uses (including washing and disinfection procedures), the duration of nebulization rose modestly. The eFlow® technology works quite well to deliver dornase alfa. The technology has also been used to deliver other complex formulations (including liposomal products and oligonucleotides) currently in development.

Hypertonic saline (HS) is commonly used in CF as an adjunct for airway clearance, yet it can be very irritating to the airways. Is it possible that using a faster nebulizer could make HS intolerable? Elkins, et al, reported findings from their study of 40 adult CF patients treated with 4 mL of 6% HS via the eRapid® for 2 weeks. Only 3 individuals had FEV1 drops of >15% acutely with the first dose, and all recovered to above baseline within 15 minutes. Overall, HS was tolerated by all individuals in the twice-daily group, and 80% of those in the 4-times daily group (the 4 intolerant subjects switched to twice daily and were fine). Lung function improved over the 2 weeks, and the delivery time averaged less than 4 minutes for each treatment.
How Long Does the Aerosol-Generating Unit Last?

Like anything else, the longevity of a device depends on how often it is used and how well it is cared for. The PARI lab has extensive experience examining eFlow membranes after clinical use. Scanning electron microscopy has shown clogging of the membrane pores, but confocal Raman microscopy demonstrated that the material clogging the pores was not drug residue, but rather a variety of inorganic and organic debris that may come from the environment (ex: hard water, particles in the air; data at PARI). Rottier et al reported that after 6 months of use with inhaled tobramycin twice daily, many eRapid® membranes were fouled or did not nebulize as fast as when they were new. However, despite being instructed to the contrary, most of the patients in the study were nebulizing several drugs with the same device. The exact cleaning and disinfection procedures were not delineated, but clearly the function of any device depends on how well it is cared for. To exemplify this point, Bakuridze et al. put eFlow® rapid nebulizers through 60 cycles of nebulization with tobramycin or colistin, followed by cleaning with soapy water and rinse, followed by disinfection with a steam sterilizer. They found almost no change in nebulization time using this rigorous cleaning regimen.

PARI recognized that the longevity of the perforated membrane was an issue, and that clogging of the tiny holes was the main reason for device failure. In response, they developed a cleaning device called Easycare® which will “refresh the mesh.” In short, the holes in the membrane are tapered, so debris stuck in the holes must be pushed out the wider end. The Easycare® device holds the mesh backwards so saline can be nebulized and push debris out of the holes, restoring its function and efficiency (see CF Services website). The Easycare® can be operated with the eBase controller (eRapid® or Altera®) but not with Trio® controller.

Summary

- The eRapid® is a general-use nebulizer that has similar droplet size and total drug output to the PARI LC® PLUS, and was designed to accept full unit doses of most CF drugs. However, it should NEVER be used for aztreonam (Cayston™), which should be delivered by the drug-specific Altera® nebulizer.

- The eRapid® does not have regulatory approval for delivery of TIS and lacks clinical-outcome studies for that drug. Small PK studies did not show any safety concerns, though larger and longer studies would be ideal to fully explore the safety of using this device with TIS. Therefore, the decision to prescribe eRapid® for TIS has to be based upon in vitro aerosol data, small deposition studies, and substantial real-world experience in other countries for both the 4 mL and 5 mL formulations (300 mg each).

- The eRapid® is not approved for dornase alfa yet, but the drug has little dose-dependence and no safety concerns. Dornase alfa retains its function after nebulization. There is currently an ongoing clinical trial of dornase alfa delivered by eRapid®.
• The eRapid® has been widely used by the CF community in markets where it has been available for years, with no evidence of harm. In the U.S. prescribers now have two “general use” eFlow® devices to choose from (eRapid® and Trio®), and must be aware of the performance differences between the devices to ensure safety (Trio® has twice the predicted lung delivery as eRapid®).

• All nebulizers require cleaning and disinfection, including the eFlow® devices. The Easycare® cleaning device is available to extend the life of the membrane, reducing overall costs.

• The most important feature of the eRapid® is the reduction in nebulization time by 50-65% reducing time burden significantly for patients. There is the potential to translate lower burden to improved adherence; this can be explored with individual patients.
Figure: eRapid® Components

- Medication reservoir with cap
- Aerosol chamber & inspiratory 1-way valve
- Mouthpiece & Expiratory 1-way valve
- Perforated Membrane (not seen) between the med reservoir & aerosol chamber
- eBase Electronic Controller
References


Keller M, Hug M, Bitterle E, Bucholski A. Reduced treatment time for colistimethate sodium solutions (Colistin CF) aerosolized by eFlow® Rapid, a novel electronic nebulizer. 29th ECFC. Copenhagen, Denmark, June 2006.


CF Services website for eRapid® and Easycare® information (accessed 1/5/13): [https://www.cfservicespharmacy.com/ProductsandPrices/PARieRapidExclusivelybyCFServicesPharmacy](https://www.cfservicespharmacy.com/ProductsandPrices/PARieRapidExclusivelybyCFServicesPharmacy)