AEROSOL DRUG DELIVERY FOR INFANTS

Ryan Lacy, Tim Corcoran (PhD)
Division of Bioengineering, Division of Pulmonary, Allergy, and Critical Care Medicine, University of Pittsburgh

INTRODUCTION

Every year, approximately 2,500 children are admitted to the pediatric intensive care unit (PICU) at the Children’s Hospital of Pittsburgh at the University of Pittsburgh Medical Center alone [1]. Respiratory illnesses are one of the leading causes of admission [1]. For children with acute respiratory illnesses, inhaled medications are a common method of treatment, as this allows physicians to deliver drugs directly to the patients’ lungs. These treatments are typically delivered via a nebulizer using a face mask or mouthpiece [2]. Once a child is admitted to the PICU, humidified high-flow nasal cannulas are often used to deliver oxygen to the patient or provide airway support, if necessary [3-10]. Since nasal cannulas are regularly used in this setting, they may also provide a logical means of delivering inhaled medications to these patients. Additionally, as infants under the age of 4 months are obligate nose-breathers, delivering aerosols through nasal cannulas is a potential means to improving drug delivery in this cohort compared to the current standard method of delivery (masks) [11].

Despite the potential advantages of this method, using nasal cannulas to deliver inhaled medications in infants provides a variety of challenges. In vivo, the nose is a potential site of significant aerosol deposition, thereby decreasing the amount of drug being delivered to the lungs. Previous studies have shown significant deposition of aerosols in the noses of adults, and we expect this would be even worse for infants due to their smaller airways [12]. Additionally, the small-diameter tubes of a nasal cannula have the potential for significant internal aerosol deposition [13]. Lastly, there are issues with quantifying the dose delivered to the infant’s lungs using nasal cannula devices. In adults, gamma scintigraphy deposition studies have been utilized for determining the percentage of inhaled dose delivered to a patient’s lungs. Until recently, there have been no such studies in infants, due to IRB concerns of using radioisotopes in studies involving infants. Because of this restriction, it has not been possible to validate benchtop models simulating inhaled drug delivery to infants.

OBJECTIVE

Recently, our lab group has performed nuclear imaging lung clearance studies in infants with congenital heart defects (CHD). As part of this study, a respiratory therapist developed a nasal cannula device for delivering inhaled medications. This device has potential utility as a drug delivery device for patients throughout the PICU setting. Additionally, our clinical deposition images afford us a rare chance to validate a benchtop method of inhaled drug delivery to infants.

The purpose of this study is to assess the dose, as a percentage of loaded dose, of drug delivered to an infant’s lungs with this nasal cannula delivery device. Additionally, we aim to use the clinical image data from our associated study of infants with CHD to validate a bench-top model for simulating drug delivery to infants.

HYPOTHESIS/SUCCESS CRITERIA

Regarding dose delivered to the patient, we hypothesize less than 10% of loaded dose will be delivered to the lungs. Existing devices we have tested on adults have delivered ~10% of loaded dose to the lungs, and due to the challenges associated with drug delivery to infants, we expect our percentage to be less than that.

To establish a reliable bench top model for simulating drug delivery to infants, our success criteria is that our benchtop measurements must be validated by what we see in our clinical images (<5% difference in percentage of loaded dose delivered to the lungs between the two measurements).

METHODS

The nasal cannula delivery system utilized for both in vivo and in vitro testing is shown in Fig.1. An Aerogen Solo nebulizer (Aerogen/Nektar, Mountain View, CA) was utilized. Oxygen was delivered to the device at 2 LPM, as selected by a respiratory therapist.

Figure 1. Nasal cannula drug-delivery device.

Assessing the dose delivered to the patient is a multi-step process. First, we size the drug particles being produced by the device. Second, we perform output studies to determine the dose leaving the device and being inhaled by the patient. Third, we use an anatomical model to perform an output study which allows us to determine the dose being delivered to the patient’s lungs. Lastly, we analyze clinical images to evaluate regional deposition in vivo and compare it to our in vitro findings.

Aerosol size measurements were made using laser-diffraction techniques. A Malvern MasterSizer S (Malvern Instruments, Southborough, MA) was utilized to make open-air measurements of aerosol size as delivered from the cannula. The results are based on 30 individual size measurements with 3 identical versions of the device. Volume median diameter is reported.

For the first output study, evaluating dose delivered to the entire patient, dose quantification was performed using radioisotope techniques. Approximately 2 mCi of Technetium (Tc-99m) DTPA in 4 mL of isotonic saline (0.9%) was added to...
the nebulizer at the start of testing and nebulized until dry. Radioactivity was measured in the oxygen tubing, nebulizer, nasal cannula, and filter (which simulates dose delivered to patient). All measurements were made using a nuclear medicine dose calibrator (Radioisotope Calibrator CRC-4, Capintec Inc., Ramsey, NJ). All doses are presented as time-corrected percentage of the dose loaded into the nebulizer.

For the second output study, we will use the same setup, except instead of using a filter downstream of the cannula, we will insert the cannula into the nares of an anatomical model with another filter downstream of that, to simulate lung dose. Radioactivity will be quantified in the same manner as before, and regional percentage of loaded dose will be reported.

For in vivo image analysis, we delivered 2mCi Tc-99m DTPA in 4 mL of isotonic saline to five infants. We then used gamma scintigraphy techniques to capture images of the patient which quantify the amount of radioactivity delivered to different regions of their bodies. Once these images were collected, we utilized ImageJ image analysis software to draw regions of interest and quantify the percentage of loaded drug which deposited in each region of the body (Fig. 2).

Figure 2. Clinical images with ROIs drawn

RESULTS

Median particle size over 30 runs was found to be 2.5±0.2 μm. For our first output study, over 3 runs, the percent of loaded dose delivered to the patient was 58.9±2.5%, 20.8±3.5% deposited in the nasal cannula, and 20.7±0.6% left in the nebulizer. We are currently in the process of purchasing a Sophia Anatomical Infant Nose-Throat Model, so we have not yet completed our second output study. Once we have the model, we will execute and report the results of our second in vitro output study.

For our in vivo clinical image validation, we analyzed 5 subjects. The mean dose delivered to the patients’ lungs was 7.2±4.7% of total dose delivered to the patient, while the mean dose delivered to the patients’ upper airways was 88.2±4.4% of total dose delivered to the patient. Based on the results of our first output study, this translates to 4.2% of loaded dose delivered to the lungs and 52.0% of loaded dose delivered to the upper airways.

DISCUSSION

The results of our particle sizing tests indicate this nasal cannula device generates aerosol particles roughly 2.5 microns in diameter. Aerosol particle size is an important indicator of where in the body the particle will deposit, so in the case of delivery to infants (who possess small airways), we want the particles to be as small as possible [13]. 2.5 microns is considered to be small for aerosols, but if at all possible we would prefer this to be even smaller.

The results of our first output study of the nasal cannula device was promising. We measured the aerosol output dose, i.e. the dose that is delivered to the patient, to be approximately 58.9% of the loaded dose. This is an extremely high percentage compared to previous studies we performed using other nasal cannula devices, which saw them output between 8.4 and 18.6% of loaded dose [13]. This indicates that this specific device setup is highly efficient and minimizes losses in the system, which will naturally increase dose to the patient. We attribute this improvement to the design intuition of the respiratory therapist who designed this device.

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REFERENCES


