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REVIEW

Breathing easier: Addressing the challenges of aerosolizing medications to infants and preschoolers

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Summary
An increasing number of patients are dependent on aerosolized therapy to manage pulmonary diseases, including asthma, cystic fibrosis, and pulmonary arterial hypertension. An aerosol therapy is only useful if it can be appropriately and consistently delivered in the desired dose to the lower respiratory tract. Many factors affect this deposition in young children, including anatomical and physiologic differences between adults and children, patient–mask interface issues, the challenge of administering medication to uncooperative children, and behavioral adherence. Moreover, the techniques used to assess aerosol delivery to pediatric patients need to be carefully evaluated as new therapies and drug–device combinations are tested. In this review, we will address some of the challenges of delivering aerosolized medications to pediatric patients.

Contents

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Introduction

With its large surface area of conducting airways and thin epithelial lining, the lung represents an important delivery site for an increasing number of inhaled medications. Scientists have capitalized on this route of administration, and now inhaled therapies are routine in diseases like asthma and cystic fibrosis, and are being explored in arenas such as gene therapy for cancer [1]. Aerosolized delivery of medications has several advantages over systemic delivery. First, limiting systemic absorption often leads to fewer side effects. For example, intravenous administration of tobramycin can result in oto- and nephrotoxicity, while the occurrence of these side effects is much less frequent for inhaled tobramycin [2]. Additionally, delivery of therapeutics directly to the site of action within the airways allows for minimizing the dose needed for efficacy. Finally, medications may have a faster onset of action when administered via nebulizer versus intravenous or subcutaneous delivery.

We now know that structural and functional manifestations of genetic lung diseases begin within the first year of life, as evidenced by computed tomography scans of the chest, bronchoscopy, and infant pulmonary function testing (iPFT's) [3—7]. Diseases such as asthma and bronchiolitis are more common in infants and preschoolers than in older children or adults. These findings emphasize the need to be able to safely, accurately and efficiently deliver aerosolized medication to infants and preschoolers. Most clinical studies of drug delivery systems enroll older children and adults, leaving health care providers and parents to infer safety and efficacy in the younger patients [8]. Additionally, the anatomy, physiology, and developmental stage of the child need to be considered when prescribing a therapy. In this article, we will review the challenges and limitations of aerosolized delivery of medications to infants and preschoolers.

Aerosolization of medications

It has long been established that size of aerosol particles, as measured by mass median aerodynamic diameter (MMAD), greatly influences the depth of inhalation and deposition into the airways [9,10]. In general, inhaled particles with an MMAD of less than 0.8 μm are not deposited, but directly exhaled. Particles with an MMAD of 0.8—2 μm are deposited into the alveoli, and particles with an MMAD of 2—5 μm deposit within the lower airways. A particle with a size of >5 μm generally does not reach the lower airway but deposits within the oropharynx. The proportion of particles within an aerosol that are <5 μm is often called the fine particle fraction (FPF). The FPF reflects the number of particles that are available for true deposition into the airways. In diseases with bronchoconstriction, such as asthma, particles may not be able to deposit into the peripheral airways due to the narrow diameter of the airways. Diseases such as cystic fibrosis, hallmarked by bronchiectasis and mucus plugging, may show marked heterogeneity in aerosol deposition as particles are unable to move beyond the impacted airways. The optimal aerosol particle size for lower airway deposition in young children is unknown, although new animal models involving radiolabeled isotope are poised to begin to answer this question [11]. Given that airway diameter is more narrow than the adult airway, ideal particle size is likely smaller than that needed in adults; aerosol particle size may also be affected by age, height, and disease state.

Types of devices

Several different aerosol delivery devices are currently used to administer therapeutics to children. Drugs and delivery devices are often paired for joint use, and pharmaceutical companies intentionally design certain delivery devices to maximize delivery of specific therapeutics. A nebulizer, which employs the use of jet airflow, ultrasound, or a vibrating mesh membrane to aerosolize liquid medication, is a commonly used device for aerosol therapy. The advantage of this approach is that a nebulizer may be paired with either a facemask or a mouthpiece, which allows for medication administration in a very young child, particularly those who are uncooperative or in acute distress. Nebulizers can deliver drug even to those patients who demonstrate low inspiratory flow or volume, and a breath hold is not necessary for effective drug delivery. There is also a theoretical advantage to mixing two drugs in the nebulizer, although clinical testing for each medication combination needs to be tested before this can be routinely recommended. Disadvantages of the nebulizer include an increased treatment time compared with other devices and the added effort of cleaning nebulizers after each use. Additionally, unlike a pressurized metered dose inhaler (pMDI), a compressed air source is required for a nebulizer to function, making this a less convenient and less portable