Respiratory Medicine (2014) 108, 1069–1074

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

REVIEW

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

Jennifer L. Goralski [a,b,*], Stephanie D. Davis [c]

[a] Division of Pulmonary and Critical Care Medicine, The University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
[b] Division of Pediatric Pulmonology, The University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
[c] James Whitcomb Riley Hospital for Children, Section of Pediatric Pulmonology, Allergy and Sleep Medicine, Indiana University School of Medicine, Indianapolis, IN, USA

Received 1 April 2014; accepted 16 June 2014
Available online 25 June 2014

KEYWORDS
Nebulizer;
MDI;
Medication;
Adherence;
Infants;
Preschoolers

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

* Corresponding author.The University of North Carolina at Chapel Hill, Thurston-Bowles 5101, 104 Manning Dr. Chapel Hill, NC, USA. Tel.: +1 919 966 4350; fax: +1 919 966 7013.
E-mail address: Jennifer_goralski@med.unc.edu (J.L. Goralski).

http://dx.doi.org/10.1016/j.rmed.2014.06.004
0954-6111/

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

method of aerosolizing medication. Each of these small volume nebulizer types individually carry additional limitations. A jet nebulizer is appropriate for use with a wide variety of medications, but the overall duration of treatments may be prolonged because larger particles may fall back into the reservoir and be re-aerosolized [8]. Ultrasonic nebulizers are electrically powered to create high frequency vibrations in a piezoelectric crystal, which then creates a sound wave to aerosolize particles. While an ultrasonic nebulizer generally aerosolizes faster than a jet nebulizer, not all liquids can be aerosolized by this manner, including dornase alpha, which is inactivated by this process. The vibrating mesh nebulizer pumps liquid through a mesh containing thousands of tiny apertures to create an aerosol. These meshes need to be meticulously cleaned to prevent clogging of the tiny pores and subsequent diminished efficacy of the nebulizer.

A wide variety of inhalers also exist to administer aerosolized treatments. A pressurized metered dose inhaler (pMDI) is the most common device used worldwide for the administration of bronchodilators and inhaled corticosteroids. Once actuated, the inhaler emits a plume of aerosol with a range of particle sizes. Most pMDIs are used with a spacer device that attaches to the actuator and increases the distance between the actuator and patient, allowing for larger particles to deposit on the sides of the chamber and minimizing inertial impact on the upper respiratory tract; thereby allowing smaller particles to be inspired to the lower airways [12]. Due to issues with coordinating the actuation of a pMDI, and the need to inspire slowly to avoid proximal impaction, a valved holding chamber (VHC) is recommended to be used in concert to provide a reservoir for the medication from which a patient can breathe. Breath-actuated pMDIs (BA-pMDI) do not start delivering medication until inspiratory flow is detected, which may help to improve deposition. Finally, a dry powdered inhaler (DPI) requires a forceful inspiratory flow to deaggregrate the powder and generate aerosol. Inhaled steroid/long acting beta agonist combinations and novel antibiotic preparations are administered via this type of inhaler.

Meta-analyses suggest that when inhalers are used appropriately and per manufacturer instruction, all devices can be effective. [13] However, DPIs and BA-pMDI's require a threshold inspiratory flow rate to deliver drug, and thus are not appropriate for young children; pMDI's with a VHC or nebulizers are generally preferred for children under the age of 4 years. Additionally, many patients are not taught the correct technique when the medication is prescribed, or over time they modify the steps needed to appropriately deliver the medication [9]. In a study of several hundred children recruited at primary care practices, only 8.1% of children were able to complete all the steps needed for appropriate use of a pMDI despite having a pMDI prescribed for outpatient therapy [14]. This emphasizes the need for ongoing education regarding appropriate use of inhalers, even for patients who have been prescribed inhalers for years.

Patient—device interface

When nebulizing medication to children, the patient—device interface plays a large role in medication delivery [15—17]. Aerosols can be delivered either using a facemask or mouthpiece, and in general, a mouthpiece is preferred due to improved drug delivery to the lungs [18,19]. However, developmentally, children cannot maintain a seal around a mouthpiece until about age 4, thus necessitating the use of a facemask for the youngest patients. A large leak in a facemask will lead to ambient air being inspired, rather than medication from the VHC [20]; thereby diminishing the effective inhaled dose. A good seal is therefore essential to assure administration of the correct dose of aerosol to a patient. During clinical studies of aerosol deposition, facemasks are often tightly held against an infant's face, but in regular use at home, masks may be more leaky when they are held less forcefully against the face of a squirming infant [15]. This "real life scenario" will diminish the overall effectiveness of any drug that is nebulized.

Since there are minimal clinical studies to guide use of aerosols in children, researchers have turned to *in vitro* models of the upper airway, combined with representative breathing patterns culled from studies of children [8]. Development of models that are age specific and anatomically precise, based on 3D computed tomography images, is an ongoing science and crucial to understanding delivery of drug with different patient—device interfaces.

Anatomic and physiologic differences

The delivery of aerosolized medication to infants and young children is complicated as anatomic and physiologic differences exist when comparing children to adults, which limits the extrapolation that can be made about nebulizer efficiency or drug deposition from adult-focused studies. The nose is known to have the highest resistance to flow in the respiratory system [21], and nasal resistance in the pediatric airway exceeds that of adults [22]. Infants are obligate nose breathers until about 18 months of age, and the lung deposition that is accomplished when aerosolizing to an infant breathing almost exclusively through the nasal passages is minimal, at best [19]. As the nose is an efficient filter for particles, application of a facemask that also covers the nose can result in a large percentage of medication that is filtered and deposited in the nasal airway. A study using radiolabeled particles to compare inhalation through the nose versus the mouth demonstrated a reduction in lung deposition by 37% when the aerosol was inhaled nasally compared to mouth breathing using nose clips [23]. While it is known that the nasal passages of children differ substantially from adults, it is only recently that a model [24] has been developed to estimate nasal deposition across all age groups. This model suggests that nasal deposition depends mostly on particle size and pressure drop across the airway.

Within the pediatric airway, the larynx is located much more caudal, the epiglottis is typically more floppy, and the pharynx and supraglottic tissues have less innate tone, all of which contributes to a higher deposition of particles via impaction in the upper airway [17]. Because of the smaller diameter of the lower airways, airflow reduction in the setting of bronchospasm, mucus impaction, or airway

edema may be heightened when comparing children to adults.

Due to the rapid respiratory rate, lower respiratory flow velocity, more narrow airways, and lower tidal volumes, infants and young children can have a lower deposition of droplets into the peripheral airways and alveoli. The innate rapid respiratory rate of children decreases the time for sedimentation and deposition of particles in the smaller airways. Infants and young children have a relatively low tidal volume compared to older children and adults, and need to breathe rapidly to compensate for the additional fixed dead space that makes up the VHC and facemask. As the face size grows with age and facemask dead space is minimized, aerosol delivery becomes more efficient [15]. Infants also cannot be instructed to breath hold when using a pMDI, which limits the dwelling time of particles in the airways; thus a higher proportion of particles will be exhaled with each breath.

Challenges with patient/family cooperation with treatment

Aerosol therapy works best when administered to a calm patient who is breathing quietly; this allows for maximal deposition of smaller particles into the lower generation airways and larger particles into the trachea and mainstem bronchi. Multiple studies have evaluated the effect of crying on aerosol administration. A prevailing thought among pediatricians and parents is that some aerosol must be deposited in the airway of a crying infant, especially since there is often a deep inspiration at the end of the cry. In fact, crying actually consists of a fairly long expiration followed by several rapid, high flow inhalations, which is suboptimal for deposition of aerosol in the lower airways. Additionally, studies have shown that crying reduces the fit of the facemask seal, thus diminishing aerosol delivery [25—27]. Lung deposition in a crying infant is substantially less than an awake, calm infant, and may even be negligible [25,28,29]. Crying also increases the aerosol deposition in the upper respiratory tract and GI tract [17].

For many parents, the "blow-by technique", where the mask is held several centimeters away from the face, is frequently used to diminish the distress of the child. However, data strongly indicate that this is a suboptimal method of administering an aerosol. A study of albuterol administered via pediatric facemasks revealed that when the mask is moved 1 cm from the face, 50% of the inspired dose is lost. This loss increases to 80% when the mask is moved 2 cm from the face [30]. This effect has been challenged in a recent study comparing three different nebulizer/compressor systems. While each system individually performed most optimally when positioned directly against the face, the authors also noted that there were substantial differences between nebulizing devices, such that one system placed 4 cm from the face outperformed another mask placed directly against the face [31]. As noted above, infants must breath more rapidly to compensate for facemask dead space; dead space can also be minimized by caregivers applying relatively higher degrees of pressure to the facemask seal, although the innate rigidity of the mask plays a role in how effective this can be [32].

Parents who attempt nebulizing medication while a child sleeps fare no better. Research has suggested that because of the different breathing patterns in a sleeping child compared to an awake one, there is nearly doubling of the dose that is delivered to the trachea rather than the lower airways when aerosols are administered to the sleeping child [33]. Additionally, placement of a facemask often awakens the child and leads to difficulty with cooperation [34]. One might suspect that attempting to place a facemask over the mouth and nose of a sleeping child could terrify the child with a feeling of suffocation; thereby making future attempts at delivery more troublesome. Some companies have attempted to create devices that are more tolerable to a young child, such as a hood placed over a child's head [35] or a facemask that contains a pacifier [36]. Interestingly, the insertion of a pacifier into the facemask did not adversely affect lung deposition of aerosol, presumably because of the fact that the infants in both groups were obligate nasal breathers and the soothing nature of the pacifier eliminated crying and allowed for a better facemask seal.

Education and adherence

Patient (and parental) acceptance of an inhaled therapy is paramount to ensuring good technique and compliance, two features often implicated when an aerosol therapy is not resulting in the expected response. Poor understanding of the need for the drug may lead to poor compliance despite physician recommendations. A single center study of underserved children with asthma who received prescriptions for a controller medication by a specialist revealed that only 50% of ICS or ICS/LABA prescriptions were ever filled during an 18 month period, and the mean time to initial fill was 30 days from the date of the prescription [37]. Despite this, SABAs continued to be filled, likely reflecting an underlying lack of understanding of the importance of a maintenance therapy. A similar study of the Medicaid database [38] showed that of almost 9000 prescriptions for an asthma controller medication given to a patient aged $<$16 years old, 56% were never filled again after an initial fill. Another study [39] using electronic data capture to measure adherence with a prescribed inhaled antibiotic reported a mean adherence of 67% over 6 months, with significant improvement in the evening dose compared to the morning dose; these findings may be related to parental time constraints in the morning hours.

Even when doses are administered as prescribed, several other behavioral factors may limit the actual drug delivery. Poor coordination of drug actuation and inhalation in younger children, and in older children who have been improperly instructed, may lead to inhalation of a suboptimal dose. Cleaning of some of the drug delivery devices can be complicated; failure to clean appropriately can lead to clogging of the device and diminished nebulizer output. With nebulizer use, patients often fail to recognize that an increase in overall treatment time may reflect a compressor that is no longer functioning optimally.

Facilitating adherence and technique to improve medication delivery in children

Physicians are confident in their patients' ability to use inhalers appropriately, despite evidence to the contrary [40]. Physicians who prescribe inhaled therapies should be comfortable explaining inhaler technique and observing patient use. Indeed, guidelines suggest that prior to switching prescribed medications due to treatment failure, physicians need to review inhaler technique as many cases will uncover that treatment failure is actually attributable to technique failure [9,41]. In one study of 170 adolescents with asthma, all of whom had been hospitalized in the preceding year, only 5% were able to correctly demonstrate all the proper steps required for controller medication administration [42]. Review of the device (including demonstration with placebo devices [8]) and written instructions on appropriate use should be mandatory for all prescribers. Simply questioning a caregiver about difficulties with the device may uncover unexpected problems. Often, failure of a medication administered via pMDI is related to the patient not performing a breath hold at the end of inspiration, which leads to decreased residence time in the airway and diminishes time for deposition in the peripheral airways. Ideally, patients should use only one type of device so not to be confused by multiple delivery systems [43]. Utilizing inbuilt device electronic data recordings can provide a physician with important information about difficulties with adherence, and may even lead to changes in prescribed therapy [39]. In the near future, this may be accomplished in a busy outpatient setting [44], and can be used to help strategize for optimal ways to enhance adherence.

Immediate patient feedback about inhalation technique may be useful to improve drug deposition to the lung. Typically, nebulizers emit aerosols constantly, and tidal breathing delivers the aerosol particles to the lungs. Breath-activated nebulizers can sense inspiratory flow and limit delivery to inspiration only, which may increase treatment time but decrease the dead volume of medication wasted [43]. Novel "smart nebs" [45] have the technology to analyze the patient's first three breaths and synchronize a timed pulse of aerosol during the mid-phase of the fourth inspiration. This analysis of the preceding three breaths continues for the duration of nebulization, and visual and audio feedback is given to the patient when the target dose is reached [43]. Using a target inhalation mode (TIM) [46–48], the mouthpiece provides a vibratory sensation to the lips to signal when exhalation should begin. This method is designed to encourage patients to gradually lengthen inhalation time until maximal inspiratory time is reached and allow for maximal patient comfort. TIM has been shown to statistically shorten treatment times by nearly half in school-aged children and adolescents with cystic fibrosis [46]. However, since the device will only deliver during the optimal inhalation point, the device may actually lead to longer treatment times if the breathing pattern is erratic [43].

Conclusions

With an increasing number of diseases treated with aerosolized therapy, it is paramount that attention be paid to factors that limit the effective use of these medications and devices in infants and young children. Patient specific factors, such as increased nasal resistance, behavioral factors, such as crying during nebulization, and device specific factors, such as the ability to use a spacer with a pMDI, can all limit deposition in young patients. Moving forward, the availability of *in vitro* models of pediatric face–mask interface and modeling systems of the lower airways may help overcome the disparity in knowledge; thereby leading to improved aerosol delivery for the youngest patients.

Authors disclosure statement

The authors declare that no conflicts of interest exist.

References

[1] Zarogoulidis P, Darwiche K, Hohenforst-Schmidt W, Huang H, Li Q, Freitag L, et al. Inhaled gene therapy in lung cancer: proof-of-concept for nano-oncology and nanobiotechnology in the management of lung cancer. Future Oncol 2013;9(8):1171–94.

[2] Pai VB, Nahata MC. Efficacy and safety of aerosolized tobramycin in cystic fibrosis. Pediatr Pulmonol 2001;32(4):314–27.

[3] Davis SD, Fordham LA, Brody AS, Noah TL, Retsch-Bogart GZ, Qaqish BF, et al. Computed tomography reflects lower airway inflammation and tracks changes in early cystic fibrosis. Am J Respir Crit Care Med 2007;175(9):943–50.

[4] Davis SD, Rosenfeld M, Kerby GS, Brumback L, Kloster MH, Acton JD, et al. Multicenter evaluation of infant lung function tests as cystic fibrosis clinical trial endpoints. Am J Respir Crit Care Med 2010;182(11):1387–97.

[5] Stick SM, Brennan S, Murray C, Douglas T, von Ungern-Sternberg BS, Garratt LW, et al. Bronchiectasis in infants and preschool children diagnosed with cystic fibrosis after newborn screening. J Pediatr 2009;155(5):623–8. e1.

[6] Brown DE, Pittman JE, Leigh MW, Fordham L, Davis SD. Early lung disease in young children with primary ciliary dyskinesia. Pediatr Pulmonol 2008;43(5):514–6.

[7] Ramsey BW, Banks-Schlegel S, Accurso FJ, Boucher RC, Cutting GR, Engelhardt JF, et al. Future directions in early cystic fibrosis lung disease research: an NHLBI workshop report. Am J Respir Crit Care Med 2012;185(8):887–92.

[8] Fink JB. Delivery of inhaled drugs for infants and small children: a commentary on present and future needs. Clin Ther 2012;34(11):S36–45.

[9] Laube BL, Janssens HM, de Jongh FH, Devadason SG, Dhand R, Diot P, et al. What the pulmonary specialist should know about the new inhalation therapies. Eur Respir J 2011;37(6):1308–31.

[10] Brain JD, Valberg PA. Deposition of aerosol in the respiratory tract. Am Rev Respir Dis 1979;120(6):1325–73.

[11] Albuquerque-Silva I, Vecellio L, Durand M, Avet J, Le Pennec D, de Monte M, et al. Particle deposition in a child respiratory tract model: in vivo regional deposition of fine and ultrafine aerosols in baboons. PloS One 2014;9(4):e95456.

[12] Dalby RN, Somaraju S, Chavan VS, Jarvis D. Evaluation of aerosol drug output from the OptiChamber and AeroChamber spacers in a model system. J Asthma Off J Assoc Care Asthma 1998;35(2):173–7.

[13] Dolovich MB, Ahrens RC, Hess DR, Anderson P, Dhand R, Rau JL, et al. Device selection and outcomes of aerosol therapy: evidence-based guidelines: American College of

Chest Physicians/American College of Asthma, Allergy, and Immunology. Chest 2005;127(1):335—71.
[14] Sleath B, Ayala GX, Gillette C, Williams D, Davis S, Tudor G, et al. Provider demonstration and assessment of child device technique during pediatric asthma visits. Pediatrics 2011; 127(4):642—8.
[15] Amirav I, Newhouse MT. Review of optimal characteristics of face-masks for valved-holding chambers (VHCs). Pediatr Pulmonol 2008;43(3):268—74.
[16] Smaldone GC, Berg E, Nikander K. Variation in pediatric aerosol delivery: importance of facemask. J Aerosol Med Off J Int Soc Aerosols Med 2005;18(3):354—63.
[17] Amirav I, Newhouse MT. Deposition of small particles in the developing lung. Paediatr Respir Rev 2012;13(2):73—8.
[18] Chavez A, McCracken A, Berlinski A. Effect of face mask dead volume, respiratory rate, and tidal volume on inhaled albuterol delivery. Pediatr Pulmonol 2010;45(3):224—9.
[19] Chua HL, Collis GG, Newbury AM, Chan K, Bower GD, Sly PD, et al. The influence of age on aerosol deposition in children with cystic fibrosis. Eur Respir J 1994;7(12):2185—91.
[20] Amirav I, Newhouse MT. Aerosol therapy with valved holding chambers in young children: importance of the facemask seal. Pediatrics 2001;108(2):389—94.
[21] Cockcroft DW, MacCormack DW, Tarlo SM, Hargreave FE, Pengelly LD. Nasal airway inspiratory resistance. Am Rev Respir Dis 1979;119(6):921—6.
[22] Becquemin MH, Swift DL, Bouchikhi A, Roy M, Teillac A. Particle deposition and resistance in the noses of adults and children. Eur Respir J 1991;4(6):694—702.
[23] Everard ML, Hardy JG, Milner AD. Comparison of nebulised aerosol deposition in the lungs of healthy adults following oral and nasal inhalation. Thorax 1993;48(10):1045—6.
[24] Zhou Y, Guo M, Xi J, Irshad H, Cheng YS. Nasal deposition in infants and children. J Aerosol Med Pulm Drug Deliv 2013; 86(0):1—7.
[25] Iles R, Lister P, Edmunds AT. Crying significantly reduces absorption of aerosolised drug in infants. Arch Dis Child 1999; 81(2):163—5.
[26] Everard ML. Trying to deliver aerosols to upset children is a thankless task. Arch Dis Child 2000;82(5):428.
[27] Lin HL, Wan GH, Chen YH, Fink JB, Liu WQ, Liu KY. Influence of nebulizer type with different pediatric aerosol masks on drug deposition in a model of a spontaneously breathing small child. Respir Care 2012;57(11):1894—900.
[28] Murakami G, Igarashi T, Adachi Y, Matsuno M, Adachi Y, Sawai M, et al. Measurement of bronchial hyperreactivity in infants and preschool children using a new method. Ann Allergy 1990;64(4):383—7.
[29] Tal A, Golan H, Grauer N, Aviram M, Albin D, Quastel MR. Deposition pattern of radiolabeled salbutamol inhaled from a metered-dose inhaler by means of a spacer with mask in young children with airway obstruction. J Pediatr 1996;128(4): 479—84.
[30] Lin HL, Restrepo RD, Gardenhire DS, Rau JL. Effect of face mask design on inhaled mass of nebulized albuterol, using a pediatric breathing model. Respir Care 2007;52(8):1021—6.
[31] Mansour MM, Smaldone GC. Blow-by as potential therapy for uncooperative children: an in-vitro study. Respir Care 2012; 57(12):2004—11.
[32] Shah SA, Berlinski AB, Rubin BK. Force-dependent static dead space of face masks used with holding chambers. Respir Care 2006;51(2):140—4.
[33] Janssens HM, van der Wiel EC, Verbraak AF, de Jongste JC, Merkus PJ, Tiddens HA. Aerosol therapy and the fighting toddler: is administration during sleep an alternative? J Aerosol Med Off J Int Soc Aerosols Med 2003;16(4):395—400.
[34] Esposito-Festen J, Ijsselstijn H, Hop W, van Vliet F, de Jongste J, Tiddens H. Aerosol therapy by pressured metered-dose inhaler-spacer in sleeping young children: to do or not to do? Chest 2006;130(2):487—92.
[35] Amirav I, Balanov I, Gorenberg M, Groshar D, Luder AS. Nebuliser hood compared to mask in wheezy infants: aerosol therapy without tears! Arch Dis Child 2003;88(8):719—23.
[36] Amirav I, Luder A, Chleechel A, Newhouse MT, Gorenberg M. Lung aerosol deposition in suckling infants. Arch Dis Child 2012;97(6):497—501.
[37] Bollinger ME, Mudd KE, Boldt A, Hsu VD, Tsoukleris MG, Butz AM. Prescription fill patterns in underserved children with asthma receiving subspecialty care. Ann Allergy Asthma Immunol Off Publ Am Coll Allergy Asthma Immunol 2013; 111(3):185—9.
[38] Vaidya V, Gupte R, Balkrishnan R. Failure to refill essential prescription medications for asthma among pediatric medicaid beneficiaries with persistent asthma. Patient Prefer adherence 2013;7:21—6.
[39] McNamara PS, McCormack P, McDonald AJ, Heaf L, Southern KW. Open adherence monitoring using routine data download from an adaptive aerosol delivery nebuliser in children with cystic fibrosis. J Cyst Fibros Off J Eur Cyst Fibros Soc 2009;8(4):258—63.
[40] Molimard M, Raherison C, Lignot S, Depont F, Abouelfath A, Moore N. Assessment of handling of inhaler devices in real life: an observational study in 3811 patients in primary care. J Aerosol Med Off J Int Soc Aerosols Med 2003;16(3):249—54.
[41] British Thoracic Society Scottish Intercollegiate Guidelines N. British guideline on the management of asthma. Thorax 2008; 63(Suppl. 4):iv1—121.
[42] Naar-King S, Lam P, Ellis D, Bruzzese JM, Secord E. Asthma medication device skills in high-risk African American adolescents. J Asthma Off J Assoc Care Asthma 2013;50(6): 579—82.
[43] Rubin BK. Pediatric aerosol therapy: new devices and new drugs. Respir care 2011;56(9):1411—21. discussion 21—3.
[44] McCormack P, Southern KW, McNamara PS. New nebulizer technology to monitor adherence and nebulizer performance in cystic fibrosis. J Aerosol Med Pulm Drug Deliv 2012;25(6): 307—9.
[45] Kesser KC, Geller DE. New aerosol delivery devices for cystic fibrosis. Respir care 2009;54(6):754—67. discussion 67—8.
[46] McCormack P, McNamara PS, Southern KW. A randomised controlled trial of breathing modes for adaptive aerosol delivery in children with cystic fibrosis. J Cyst Fibros Off J Eur Cyst Fibros Soc 2011;10(5):343—9.
[47] Denyer J, Prince I, Dixon E, Agent P, Pryor J, Hodson M. Evaluation of the Target Inhalation Mode (TIM) breathing maneuver in simulated nebulizer therapy in patients with cystic fibrosis. J Aerosol Med Pulm Drug Deliv 2010;23(Suppl. 1):S29—36.
[48] Denyer J, Black A, Nikander K, Dyche T, Prince I. Domiciliary experience of the Target Inhalation Mode (TIM) breathing maneuver in patients with cystic fibrosis. J Aerosol Med Pulm Drug Deliv 2010;23(Suppl. 1):S45—54.