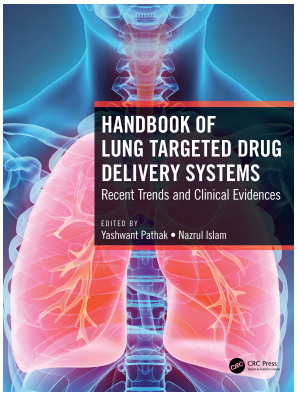

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Yashwant Pathak, Nazrul Islam

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Surovi Saikia, Aparoop Das, Yashwant Pathak
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Drug Delivery Using Aerosols: Challenges and Advances in Neonatal Pediatric Subgroup

Surovi Saikia[1], Aparoop Das[2], and Yashwant Pathak[3,4]
[1]Natural Products Chemistry Division, CSIR North East Institute of Science & Technology, Assam, India
[2]Department of Pharmaceutical Sciences, Dibrugarh University, Dibrugarh, India
[3]USF Health Taneja College of Pharmacy, University of South Florida, Tampa, Florida, USA
[4]Adjunct Professor, faculty of Pharmacy, Airlangga University, Tampa, Surabaya, Indonesia

45.1 Introduction

Frequent administration of aerosolized drugs to pediatric patients is often for facilitating mucus clearance, preventing and treating infections, enhancing pulmonary blood flow, etc., to lessen airway inflammation, and increases bronchospasm etc. Generally, off-label aerosolized drugs are used, which include those that have not been passed to be used as aerosols in neonatals, but in adults, and are being cleared by the US Food and Drug Administration (FDA) for use in different delivery devices. Efficacy and dose ranging studies are seldom performed by drug manufacturers and the overall proposition shows that drug delivery to patients seems rather safe and easy as the patient keeps inhaling the plume produced by the nebulizer. But it is likely that very small amounts of drug reaches the targeted sites and ways to measure this amount are highly challenging and confusing. In younger children, this estimation of efficacy is tedious for clinicians due to a lack of objective measurement techniques (1). Also, the challenges and difficulties associated with infants for aerosol delivery are huge as compared to adults.

A successful aerosolization procedure depends on the aerosol system used, which includes the drug, the target site, aerosol device, and respiratory system of the patient (for mechanically ventilated patients, the ventilator is also added to this list). The performance evaluation of the aerosol system is estimated using the overall emitted dose from the device (ED), the delivered dose to the lungs (the fine particulate factor, or FPF), and bioavailability of the lungs (2,3). ED and FPF are determined in vitro and mostly depend on the design of the device and particulate properties, and patient factors such as anatomy of lung and airway, membrane permeability to drugs, drug metabolism, and clearance of lungs (phagocytic) including FPF (3).

45.2 Issues with Neonates: Different in Many Ways

Neonates can neither be classified as small children nor small adults when viewed from a drug development perspective which encompasses term, preterm, and post-term babies. Adding 27 days to the day of birth defines the neonatal period for term and post-term babies, and for preterm babies this period is 27 days plus the expected day of birth (4). They have small intestinal transit time and surface area, slow gastric emptying and immaturity in transporting, lack of well-formed skin barrier, poor respiratory function, etc., which are critical for oral drug delivery. Other physiological factors, such as surface-to-body volume ratio, pH of of the gastrointestinal tract (GI), ratio of body fat to lean tissue, etc., are also dynamic with time (5).

With a relatively large tongue size in a small oral volume, infants are categorized as obligate nasal breathers. Also, the larynx and epiglottis are in close proximity to the base of the tongue. Added to these, babies have a shorter turbinate region, small nostrils, narrow pharynx–larynx and nasopharynx, and a large anatomical dead space (4). During early development, the fetus has a fully performing airway which changes significantly in the first few years of life. Growth and development lead to changes in breathing patterns. As tidal volume (V_T) and minute ventilation increases with age, resting respiratory rate decreases, wherein V_T increases by 300% from 7 ml/kg as during the initial year of life. A short residence time is accounted for aerosol particles, which disturbs the intended pulmonary deposition due to low vital capacity, low V_T, short respiratory cycle, low capacity for residual function, etc. (6).

45.3 Considerations for Neonatal Aerosol Therapy: What Do We Need to Know?

Various issues regarding neonatal therapy needs to be accounted for in aerosol therapy, otherwise infants may receive a considerably greater amount of aerosolized drug per kilogram of body weight. Factors discussed below make clinicians avoid giving aerosol therapy to infants.

During the first few years of life, the size of the airways changes dramatically, and with growth and development the volumes, flows, and breathing patterns change. With age, the

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resting respiratory rate decreases as there is an increase in tidal volume (V_T) and minute ventilation. V_T is around 7 ml/kg during the first year of life and increases to 300% along with increase in inspiratory flow. Pulmonary deposition is hampered in infants as a short residence time is exhibited by aerosol particles due to lower factors like V_T, functional residual capacity, vital capacity, short respiratory cycle, etc. Variable breathing frequencies, lower V_T, and high resistance to small cross sectional airway diameter also lead to poor drug delivery.

Infants have a proportionally larger tongue as compared to a small oral volume, along with the proximity of larynx and epiglottis to the base of the tongue, making them obligate nasal breathers. Further, small nostrils, short turbinate region, narrow nasopharynx and pharynx–larynx, and a large anatomical dead space also need to be taken into consideration for aerosol delivery (7), as do crying and screaming, since in babies they add to these considerations.

45.4 Challenges in Using Aerosol Medicines for Babies: In Baby Size

A report by the European Medicines Agency (EMA) to the European Commission shows that neonates represent a neglected pediatric subpopulation in medicine development (8). Due to lack of medicine specifically developed for pediatric patients, many off-label medicines are used and this remains to be a greater problem for neonatal population due to difficulties of conducting clinical trials owing to lesser number of patients. Also the low incentives provided to pharmaceutical companies for formulating medicines for neonatal populations is another factor.

Mixed outcomes were observed from the use of inhaled pharmaceutical aerosols in infants and neonates receiving mechanical ventilation. Reduced need for improved oxygenation, systematic glucocorticoids, and increased fluid resorption were observed in clinical trials of in ventilated infants (9–11). Delivery efficiency of aerosol to infant lungs is usually low and variable which occurs due to interface device, aerosol generator, and ventilation circuit, including endotracheal tube of around 3 mm internal diameter (in ventilated infants). Additional factors that add to this complexity include an increase in inertial short inhalation period due to low volumes of tidal air and short inhalation periods with an added increase in frequencies of high and small ratios of inspiratoion–expiration (6,12). Another challenge to delivery efficiency is the delivery of around 1% drugs to lungs by conventional metered-dose inhalers and jet nebulizers, which has remained consistent throughout in vitro studies, animal studies, and in humans (13). Some of the major clinical choices that have to be made in order to meet the existing challenges for neonatal aerosol therapies are discussed below.

45.4.1 Unique Cognitive Challenges

Behavioral and emotional development of infants is one of the largest challenges which are unique to pediatric patient population. They are devoid of the physical capabilities to produce coordinate breathing. In many cases, a mouthpiece or a tight-fitting aerosol mask is tolerated poorly by infants, resulting in thrashing, crying, and squirming. There exist fewer choices for children when it comes to ways to promote drug delivery and pulmonary conditions. During the time of hospital stay for a critically ill child, it is quite obvious for the patient to receive multiple drugs (inhaled) with varying delivery options. Thus, many clinical and age-related factors need to be considered in choosing the best strategy for therapy.

45.4.2 Challenges during Aerosol Device Selection

The present situation does not offer any clinical information that can be used as a guide for device selection. Nebulizers used for adults are also used in infants, however, caution has to be maintained for aerosol devices producing particle sizes >5 μm as this can promote tachycardia (1). The effect of jet nebulizers and pressurized metered-dose inhalers (MDIs) were as low as 0.33% and 0.13% in infants (14). The most common delivery devices used for infants include inhalers (dry powder), nebulizers (powered with gas or jet, ultrasonic, breath-actuated, vibrating mesh), valve holding chambers (VHCs) containing pMDIs, and aerosol generators producing small particles. Among them pMDI/VHC and vibrating-mesh nebulizers are the two most preferred devices for infants due to ease of handling, ability to integrate with ventilator systems, and above all, acceptance rate by patients, although they can be categorized a- high cost devices.

45.4.3 Challenges in Face Mask Design for Interface Selection

A mouthpiece is capable of delivering two times the drug amount compared to a simple face mask (aerosol), which also remains to be demonstrated effective in pediatric patients (15,16). The challenge that lies here is that most infants are not able, on command, to open and close their mouths to adequately seal the nebulizer mouthpiece. Further, another challenge is have the infant breathe deeply and subsequently hold their breath. Hence, the face mask design remains a critical challenge for small children in drug delivery as proper sealing of mask is a must to maximize aerosol delivery. Also, any leakage leads to the drug to entering the surrounding air resulting in lung deposition and prevents irritation in patients due to getting the drug to spread into eyes and face (17).

The design for face masks remains to a major challenge in smaller children regardless of the kind of nebulizer used (18). An important aspect to be considered in design is that the design should be warm, soft, flexible, and small, as small masks are required by small patients (19). As with lesser dead space, the probability of more dosage from the device is very likely to reach the lungs, which is true when pMDIs/VHCs or vibrating-mesh nebulizers are used, or another type which does not supply gas (20). In vitro studies done on this front show that a greater aerosol mass-to-lung ratio is provided by a front-loaded mask with low facial and eye deposition when compared to a bottom-loaded mask (21–24). However, contradictory results were obtained for the lung model in a pediatric population where greater drug delivery was observed using a bottom-loaded mask design compared to a front-loaded one (25). As a common nebulizer equipped with a face mask was not utilized for each study, a

general conclusion cannot be assumed, but a front-loaded mask directs the aerosol to the oronasal area, while a bottom-loaded mask directs the same toward the upper portion of the mask.

45.4.4 Challenges in Dealing with Patient Preferences

The preference of patients and caregivers in device selection remains to be the major challenge for effective aerosol therapies. Generally, devices that are regularly used are more preferred by patients as compared to devices they rarely use (26,27). Also, the variable impact of nasal breathing by infants and the small caliber of airway should also be considered while implementing preferences. Regular use of a device when device treatment options are many, continues to be a deciding factor in patient preference. Many factors drive these preferences, which also determine the preferences of parents toward their child's treatment.

Preference for a certain type of aerosol device encompasses aspects such as ease of use, portability, time taken for treatment, maintenance etc. Another point considered by patients for preference is the shape and size of the device. One or two time therapy could be easily given by battery operated nebulizers while small battery operated ones requires cleaning between treatments (27). Further treatment time is also another factor for preference as infant rejects each time the treatment is given the therapy is abandoned gradually by the care giver or parents unless and until the child has acute symptoms.

Infants show a poor adherence to aerosol therapy due to their inability to use the device, which remains a major challenge for patient preference. This has to be explained by the therapists to parents regarding dosage and device uses (26).

45.4.5 Challenges in Neonates for Device Synchronizing

A significant reduction of drug loss during exhalation can be achieved by synchronizing the aerosol device to the breathing pattern of the patient (28). This adjustment poses a significant challenge for infants (preterm) due to high respiratory rates and short inspiratory times (29). Aerosols can be damaged by the flow, and pressure-based sensors and their positioning within the vicinity of the aerosol and patient is not advisable. But technologies like the Graseby pneumatic capsule, neurally adjusted ventilators, etc., are used for synchronization of breath which does not require sensors to be placed within the ventilator tubes without causing risks related to aerosol impaction (30,31). These types of breath dependent synchronization methods improve drug delivery but much more data (in vivo) is required from ventilated infants (32).

45.5 Considerations for Neonatal Aerosol Applications

In the last decade, medication requirements for neonates has been largely neglected including various considerations in the areas of formulation, dosage, regulatory challenges, etc. Neonates admitted to Neonatal Intensive Care Units (NICU) require specialized incubators and overall environment care (33). The various influences on the efficiency of aerosol delivery by physical, anatomical, and physiological factors in neonates can be modeled using 3D technologies such as PrINT (34). Even though aerosol delivery has the highest degree of concern with respect to the route of administration, with high likelihood of interaction from packaging component. The dosage criteria still requires the critical aspects to be considered for using aerosol in neonates which needs monitoring in the following factors.

45.5.1 Air Flow Parameters

The aerosol in jet nebulizers is generated by airflow, and commercial nebulizers come with a variety of air-flow parameters for optimal performance, while mesh or ultrasonic vibrating nebulizers require gas flow to supply aerosol particles (35). Lung model studies on a 4 kg infant setting showed that airflow is indirectly related to lung delivery. The study has also showed that smashing of aerosol particles results in higher aerosol deposition within the ventilator circuit in the inspiratory arm (36,37). Similar results were also observed using a nose and throat model of a premature infant (34). However, these model studies have considered a continuous flow of air from the upper respiratory tract rather than considering a patient's breathing pattern. Thus, airflow remains a major factor which needs monitoring in neonatal applications.

45.5.2 Formulation

An aerosol generator with synchronized nebulizer, when placed close to the endotracheal tube (ET) in the inspiratory arm, causes a significant increase in dose emission at the ET as compared to continuous nebulization within the neonatal ventilator circuit. Emitted dose comparisons showed that terbutaline solution, as compared to budesonide suspension, was better, irrespective of synchronized nebulizer or placement (38). Also, improved pulmonary distribution was observed for aerosolized surfactants as compared to a standard liquid instillation (intra-tracheal). Animal model studies showed that large aerosolized surfactant particles, when moved through the vocal chords, form a film at the air–liquid interface, which then spreads to alveoli with better distribution (39). Surfactants have the ability to spread over mucosal surfaces, indicating they are potential carriers for aerosolized agents leading to uniform drug distribution and improved lung deposition. However, some other studies show just the opposite picture of suboptimal emission of dosage due to the highly viscous nature of the surfactant (40).

45.5.3 Aerosol Particle Size

Studies on aerosol lung deposition in both term and preterm infants showed that a marker compound called sodium cromoglycate measured in urine is used heavily. Comparison studies for drug delivery in non-intubated breathing infants (spontaneous) in three different nebulizers [Projet®; Artsana, Grandate, Italy (ultrasonic), LC Star®; Pari, Starnberg, Germany

(jet nebulizer) and LS 290®; Systam, Villeneuve sur Lot, France (ultrasonic)] showed that sleeping infants during aerosol delivery carried out breathing through a mask covering both nose and mouth, and the highest lung deposition was observed in the case of a jet nebulizer as compared to ultrasonic nebulizers (41). However, the jet nebulizer exhibited the highest rate of flow and the highest mass for droplets below 2 μm. The amount of retained sodium cromoglycate was tested for each nebulizer, of which the ultrasonic nebulizer was found to be higher as compared to others. Hence, this study concluded that aerosol particles (<2 μm) are more likely to find ways toward the lower airways in spontaneously breathing infants, and the higher deposition rate of the jet nebulizers may be due to the low residual volume of the nebulizer and is not related to particle size. This study has also rejected the concept of using sodium cromoglycate as marker for lung deposition (41).

Even though the jet nebulizers had the highest lung deposition, only around 0.89% of dosage was deposited after inhalation in the lungs. This study was at par with other studies suggesting that for both spontaneous breathing and mechanically ventilated infants, a nominal deposition of <1% is achieved (42). These studies indicate that effective delivery can be expected for ventilated patients thorugh those fine particles that can pass through artificial airways and upper airway tracts, and deposition rates can be achieved by the residual volume differences between nebulizers when expressed as a percentage of nominal dose. It has been observed that particle size between 2 and 6 μm is accumulated in central airways, and those of 6 μm are deposited in the oropharynx (43). However, there are limited studies dealing with particle size evaluation of the upper airways for preterm infants.

The majority of deposition occurs during the exhalation process during the breathing cycle in the tracheostomy tube, indicating that a significant amount of inhaled aerosol is lost during exhalation. Another study carried out on ventilated adults showed that around 53% of the total inhaled dose was found deposited in the lungs and the remaining part was deposited in the expiratory arm (44). The results of this study were of high importance for infants due to their short inspiratory times, which increases the extent of losses in exhalation. Around 20–30% of the aerosol passing via the mainstream bronchi was actually stored in the lungs (45).

The most critical aspect is particle size, which influences patient interface for intubated and non-intubated infants. The particles should be small enough to cross the interface with minimal impact, but at the same time the size should not be so small that they are lost in exhalation. Hence, particle size remains a major factor influencing pulmonary deposition of drugs in infants.

45.5.4 Gastric Deposition and Impact on Upper Airways

Deposition of aerosol in the upper respiratory tract remains a continuous challenge for clinical practitioners. Conventional treatment of infants using a nebulizer with a face mask is as good as hood nebulization with respect to lung deposition fraction, distribution of aerosol, clinical response toward hood nebulizers, etc. Salbutamol, a radiolabeled aerosol, was studied on wheezing infants of 1–19 months and spontaneously breathing infants with an MMAD (mass median aerodynamic diameter) of 4.2 μm. Lung deposition values of around 2.4–2.6% were observed and an improved saturation of oxygen with reduction in respiratory rate was also observed. In addition to local deposition of aerosol around the oropharyngeal region, around 7.6–8.4% was deposited in the gastrointestinal tract due to swallowing (46).

More aerosol deposition occurs in the upper respiratory tract in more distressed infants, which is due to the prolonged expiration on screaming or crying. This is followed by velocity gasps of high inspiratory flow, short in nature, which leads to aerosol impaction inside the throat and swallowing. Clinical impact for this kind of deposition does not hold true for asthmatic infants, but this may create concerns during nebulizer treatments with corticosteroids due to increased side effects and absorption (47).

45.6 Aerosol Therapies Side Effects

Inhaled corticosteroids during aerosol therapy have both systematic and local side effects, while, local effects include ocular and cutaneous effects, oral thrush, hoarseness etc., while systematic ones include absorption in gut via lung absorption, swallowing from deposits in oro- and hypopharynx (48,49). Around 80% of the emitted drugs deposited in the pharynx are due to DPIs and mDPIs, however using a VHC in combination with mDPIs may reduce the local effects of the inhaled aerosols like oral thrush, hoarseness, and dysphonia (48,49). Bruising and skin thinning may result when corticosteroids are administered through a face mask, and caution is needed to avoid eye and face deposition (50).

Decreased growth rate was observed in infants during the first year of inhaled corticosteroid therapy, but in budesonide treatment children did not showed significant changes in growth for a time period of 10 years (51,52). Delayed reduction in growth has been observed (>1 cm) due to poor asthma control. As growth suppression is drug and dose dependent, it is advisable that use of corticosteroids in young children be kept to a minimum. Further, post corticosteroid treatment, the face should be washed to prevent facial deposition. Also, fewer side effects are observed in pMDIs with VHCs, which are just as efficient as jet nebulizers with the same output and wider acceptance rate (1). Higher systematic side effects are observed in oral administration of anti-asthma medicines as compared to topical administration of drugs.

45.7 Improvements in Aerosol Therapies for Infants

A systematic approach to optimize aerosol delivery in infants and children involves the identification of specific determinants and challenges. Inherent limitations are related to pathophysiologic, anatomical, physiologic, and technical aspects of aerosol delivery in infants and young children. Aerosol efficiency can be enhanced by applying sound principles of aerosol delivery and

using control over factors which are changeable to intervention. Enhancing factors such as formulation and delivery system increases the efficiency of aerosol delivery with reduced risk, waste, and cost. Other factors, such as close attention to aerosol particle size (1–3 μm aerodynamic diameter and <2 μm geometric standard deviation) and the concentration of this particle produced by an aerosol system may increase the delivery via endotracheal tubes reaching the lower respiratory tracts in infants. Choice of delivery and proper MDI techniques such as priming, shaking prior to inhalation, avoiding multiple actuations and immediate actuations, choice of patient interface (mouthpiece, face mask type, endotracheal) and aerosol spacer, cleaning the spacer, and the medicine considered for aerosol (viscosity, suspension, solution) also contribute to optimal aerosol delivery (52).

Delivery efficacy and therapeutic response can also be improved by considering patient-related, system-related, and operator-dependent issues combined together. Further, motivation for and education to caregivers, parents, and medical professionals also influences efficiency and prioritizing the teaching of proper techniques improves delivery of aerosol therapy. Clear understanding of differences and efficiencies of drugs and devices makes the use of aerosol therapy well suited to infants and children (53). This has been substantially maintained by aerosol scientists and clinicians during the last decade, and must be the first priority for device and drug manufacturers and also regulatory agencies.

The choice of drug dose is determined empirically and the variability in lung doses between inter- and intra-subject is considerable (54). However, this does not have much to contribute toward therapeutic failures in conditions such as asthma because of the use of high doses to fulfill the variability of a wide therapeutic index. Thus, the therapeutic index determines the choice of dose. The delivered dose to an infant can be calculated from the drug deposited on the filter placed between the infant and delivery system as shown by many studies. It is considered to be proportional to lung dose, and doubling this will eventually double the lung dose only if other parameters remain unchanged. Any distressing element, however, may change the breathing pattern, leading to a different lung dose than the inhaled dose. Thus, these studies using filters are essential in product development — but more is required to obtain the lung dose (55).

45.8 Limitations and Advances for Aerosol Delivery

A systematic approach for better aerosol delivery to infants requires the identification of determining factors and challenges associated with it, which include anatomical, technical limitations, pathophysiologic, and physiologic related to infants and young children. Aerosol delivery can be enhanced through sound principles and by executing control over amendable factors. One critical factor on this line is the impact of the particle size (1–3 μm mass median diameter and standard deviation (geometric) < 2 μm) whose concentration enhances the delivery via endotracheal tubes with low V_T and inspiration in children. All issues related to patient, system, and operator-dependent factors greatly influences the aerosol delivery and efficacy improving therapeutic responses. A better understanding of the functional differences and efficiencies of the various drugs and devices will make aerosol delivery well suited for infants and children (53).

Limited factors are available in infants for choosing the right aerosol device. While pulmonary deposition of aerosol in neonates and infants is reduced as compared to toddlers or teenagers, and studies have shown that a similar lung dose/kg body weight was observed in children <3 years, this remains unclear in infants. Thus, due to the uncertainties associated with dire lack of clinical trials, inhaled doses for neonates etc., a careful and cautious approach toward the product used is important, including the therapeutic effects and associated toxicities (56,57).

Recent development of aerosolized vaccine has many advantages, but its clinical feasibility is still in its early stages of discovery. Further work is required for use of such vaccines to ascertain their effects on infants and children for mass use. Infants are highly vulnerable to inhalable medications, even though the aerosol deposition percentage is quite low. This is due to the fact that they receive more drug/kg body weight as compared to their adult counterparts (58). Also, the upper airway deposition in infants is more than in the geriatric population due to the nasal breathing pattern which determines the therapeutic index of drugs (26).

45.9 Conclusions

Thus we have seen that the pediatric population differs on many frontiers as compared to adult populations. Also, development of a drug itself is quite challenging and time consuming, and that, too, for neonates and preterm infants alone is even more difficult due to their rapidly changing physiology and biopharmaceutical conditions. They still fall under the category of therapeutic orphans owing to their access to drugs and formulations backed by studies with regulatory approvals. Certain factors, such as development, physiological studies, care environment, etc., determine the path of formulation preparation for neonates. Also, they constitute a small number of the population for specific formulations, so development remains to be limited in this regard.

A jet nebulizer is a better option for infants as compared to blow-by therapy, which is ineffective. Vibrating-mesh nebulizers can be used together with a total face mask in pediatric NIV (non-invasive ventilation). Hence, a lot of studies in this field are currently needed for aerosol therapy issues relating to neonates.

Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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