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Delivery of inhalation drugs to children for asthma and other respiratory diseases ☆

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ABSTRACT

Infants and children constitute a patient group that has unique requirements in pulmonary drug delivery. Since their lungs develop continuously until they reach adulthood, the airways undergo changes in dimensions and number. Computational models have been devised on the growth dynamics of the airways during childhood, as well as the particle deposition mechanisms in these growing lungs. The models indicate that total aerosol deposition in the body decreases with age, while deposition in the lungs increases with age. This has been observed on paediatric subjects in in vivo studies. Issues unique to children in pulmonary drug delivery include their lower tidal volume, highly variable breathing patterns, air leaks from facemasks, and the off-label or unlicensed use of pharmaceutical products due to lack of clinical data for this age group. The aerosol devices used are essentially those developed for adult patients that have been adapted to paediatric use. Facemasks should be used with nebulisers and spacers for infants and young children. An idealised throat that mimic the average particle deposition in paediatric throats has been designed to obtain more clinically relevant aerosol dispersion data in vitro. More effort should be spent on studying particle deposition in the paediatric lung and developing products specific for this subpopulation to meet their needs.

Contents

1. Introduction

'Children are not just small adults' is a popular cliché [1]. Indeed, much of their anatomy and physiology undergo development before adulthood so paediatric patients have unique requirements in drug

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delivery that differ from those of adults. For pulmonary drug delivery, these are mainly due to the smaller geometry of the respiratory tract and the lower inhalation flow rates. These fundamental characteristics consequently affect particle deposition in the airways and the performance of pharmaceutical inhalers. This review explores these aspects of paediatric inhaled drug delivery.

2. Age classification of paediatric patients

The upper age limit of paediatric patients differs depending on the regulatory authority. Since growth is a major trait of childhood, this patient group is heterogeneous and may be subdivided according to age or physiological maturity. Table 1 shows the age classifications from the United States of America Food and Drug Administration (FDA) [2], the European Agency for the Evaluation of Medicinal Products (EMEA) [3], the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) [4], and the World Health Organisation (WHO) [5]. Although the naming and age bands of the categories between the regulatory authorities are slightly different, the broad divisions are similar, namely, (a) 0–1 month, (b) 1 month–2 years, (c) 2–12 years, and (d) 12–16 to 21 years. The WHO classification is more comprehensive as it distinguishes between the young child (2–6 years) from the child (6–12 years) as well as including categories for premature and term newborns. Since its upper age limit of 18 years old is covered by the other regulatory classifications and is the most common minimum voting age throughout the world [6], the WHO classification will be followed in this review article.

3. Particle deposition in the respiratory tract

3.1. Theory of particle deposition in the airways

The major particle deposition mechanisms in the respiratory tract are inertial impaction, sedimentation, and diffusion [7]. These are governed by the following relationships [8]:

$$\text{Deposition by impaction} \propto \frac{\rho d^2 Q}{D^3} \quad (1)$$

$$\text{Deposition by sedimentation} \propto \frac{\rho d^2 D L}{Q} \quad (2)$$

Table 1
Age classifications of paediatric patients from the FDA [2], EMA [3], ICH [4], and WHO [5].

FDA	
Neonates	0–28 days
Infants	29 days–less than 2 years
Children	2 years–less than 12 years
Adolescents	12 years–21 years (up to, but not including the 22nd birthday)
EMA and ICH	
Preterm newborn infants	
Term newborn infants	0–27 days
Infants and toddlers	28 days–23 months
Children	2–11 years
Adolescents	12–16 to 18 years depending on the region
WHO	
Premature newborns	<38 weeks gestational age
Term newborns	>38 weeks gestational age
Neonate	0–30 days
Infant	1 month–2 years
Young child	2–6 years
Child	6–12 years
Adolescent	12–18 years

$$\text{Deposition by difussion} \propto \frac{L}{Qd} \quad (3)$$

where ρ is the particle density, d is the particle diameter, D is the airway diameter, L is the length of the airway section, and Q is the airflow rate. The equations above show that deposition is affected by dimensions of the airway, besides particle size and density. This is of particular significance for paediatric patients because firstly, their airways are smaller than those of adults. Therefore, particle deposition in the lungs in children is different from that in adults. Secondly, since paediatric airways undergo substantial growth before adulthood, particle deposition changes with age during this period [8]. From the equations, airway dimensions (D and L) affect impaction, sedimentation, and diffusion in decreasing order of influence. This is because D is a cubic variable in Eq. (1) so its effect is the greatest. On the other hand, the product DL in Eq. (2) can be considered as a quadratic variable of airway dimensions and L is a linear variable in Eq. (3) so their power is less stepwise. It can be deduced that particle deposition by impaction is higher in children than in adults due to the smaller D. Besides having smaller airways, children also have lower respiratory flow rates [8]. The equations show that airflow rate (Q) has the opposite effect to airway dimensions on deposition. However, since Q is a linear variable, its effect is less than that of D and L in Eqs. (1) and (2). Therefore, the overall influence of the smaller airways in children overpowers that of the lower airflow rate [8]. This is reflected in the increase in total particle deposition with a decrease in age (see below).

3.2. Computational deposition models

Knowledge on the theoretical particle deposition in children was primarily derived from mathematical modelling in the 1980s and 1990s [9–13]. With the advancement of computer technology in later decades, computational fluid dynamics (CFD) was employed to examine the airflow pattern inside the airways [14–17]. However, research on deposition modelling in paediatric airways is less than that in adults overall.

Hofmann [9] proposed a mathematical model for delineating the growth of the lung as a function of age. The calculation was based on the Weibel dichotomous airway model A fitted with morphometric data of various airway parameters at different ages. The pulmonary parameters included the dimensions of the trachea, main bronchi, terminal bronchioles, and alveoli; the number of respiratory airways and alveoli; and the total lung volume [9]. In accordance to morphometric observations, the lungs undergo two phases of growth in this model. From birth to about eight years old, new respiratory airways and the linings of these with the alveoli form. Beyond eight years, the pulmonary structure is completed and further growth results from increases in the linear dimensions of the airways [9].

Xu and Yu [10] investigated the total and regional deposition of orally inhaled particles (0.01–10 μm) in their lung model for 0 to 30-year olds with tidal breathing. Regional deposition was deposition in the head, tracheobronchi, and alveoli. It was found that the trend of total and regional deposition with respect to particle size was similar across the ages [10]. However, the total deposition in children was higher than that in adults for all particle sizes. Deposition in the head was higher in children for particles 5 μm and larger in size. On the other hand, deposition in the tracheobronchial and alveolar regions showed no clear dependency with age or particle size [10]. The head region is essentially the oropharynx, where large particles (>5 μm) deposit by inertial impaction [7]. Since airway diameter is a cubic variable for impaction (Eq. (1)), deposition by this mechanism is expected to be significantly higher in children, whose throats are smaller [8]. This is supported by the finding from Xu and Yu [10].

An increase in the total deposition in children was also observed in another model [13]. This study utilised purely algebraic calculations rather than a branched airway model and only considered the inspiration

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