Aerosol Therapy in Young Children

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AËROSOLTHERAPIE BIJ JONGE KINDEREN

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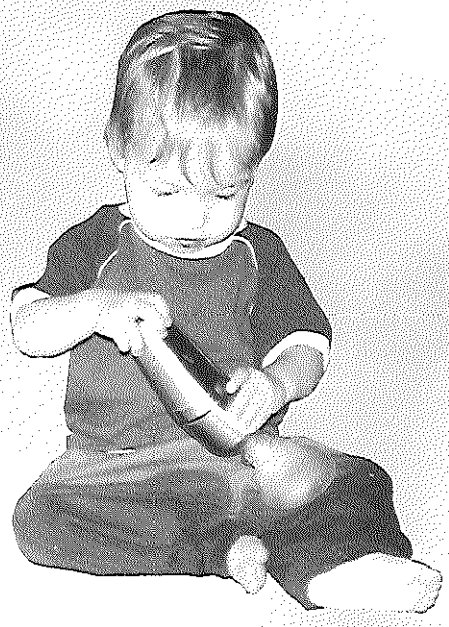
Contents

INTRODUCTION AND EXTENDED BACKGROUND



CHAPTER 1

Introduction and Aims of the studies

1.1 GENERAL INTRODUCTION

Inhalation of aerosolized drugs has become an established means for treatment of pulmonary diseases in the last fifty years [1-4]. The majority of aerosol therapy in childhood concerns inhaled corticosteroids and bronchodilators in the management of asthma [3,5]. Administration of drugs via the inhaled route has major advantages over the oral route. The drug is targeted directly to its site of action, which results in a more rapid effect and a lower dose needed with less systemic side effects [1,2,6-9]. However, to deliver the drug into the lungs reliably and reproducibly is difficult, especially in children [10,11]. It requires understanding of the mechanisms of aerosol deposition in the lungs and knowledge about the factors affecting delivery and deposition of aerosols. There are several ways to deliver therapeutic aerosols to the lungs. The current methods can be classified in three categories: nebulizers, pressurized metered dose inhales (pMDI's) with or without spacer, and dry powder inhalers (DPI's) [10-16]. Not all systems are suitable for use in young children [10,13,17,18]. Application of aerosol therapy in young children requires a different approach compared with adults and older children. Factors such as age, co-operation, breathing pattern, nose breathing and size of the airways should be taken into account as they can have substantial effect on the dose delivered to the lungs. Nebulizers have long been the mainstay of aerosol therapy in children [1,13]. Currently, the pMDI combined with spacer is recommended as the first choice for asthma therapy in young children [13,19-21]. However, the pMDI/spacer and most other aerosol delivery systems were primarily designed for use in adults, and subsequently adapted for use in children. Furthermore, studying efficiency of aerosol delivery systems in young children is difficult and has ethical limitations. This explains why there is extended information available on the performance of aerosol delivery systems in adults, but only limited data in children. The use of drugs with potential side effects, such as corticosteroids [22-28], requires precise dosing with the administration of the lowest effective dose. Therefore, knowledge about the dose inhaled and factors affecting this dose for each particular drug, device and patient is necessary for optimal application of aerosol therapy. Better understanding of aerosol therapy in children is urgently needed.

1.2 OUTLINES AND AIMS OF THE STUDIES

The aim of our studies was to improve the quality of aerosol therapy in clinical pediatric practice. Our studies mainly focussed on the performance of pMDI/spacers to deliver inhaled corticosteroids in young children with recurrent wheeze or asthma, since asthma or recurrent wheeze is the most common diagnosis in children in whom aerosol therapy is used. Furthermore, the pMDI/spacer combination is the most convenient and most widely used device for maintenance asthma therapy in children.

Knowledge about aerosol delivery efficiency is particularly important for inhaled corticosteroids, because of their potential side effects.

Extensive background information on aerosol therapy and delivery systems in children is presented in **chapter 2**.

REPRODUCIBILITY OF DOSE

Predictable and reproducible dosing is important to balance the lowest dose with maximal therapeutic effect and minimal risk of side effects. Surprisingly, dose-to-dose or within-subject variability of delivery from pMDI/spacers is not known for young children. It is known that many factors in a spacer can affect its dose delivery [29-34]. An important factor is electrostatic charge, which can be present on the inner surface of a plastic spacer and hence reduce the delivered dose substantially [32,35,36]. The introduction of a metal spacer eliminated the problem of electrostatic charge and was shown to deliver aerosol to children effectively [37,38]. All studies measuring dose delivery from pMDI/spacers in children have been performed in a laboratory setting in which the administration was performed under well-defined controlled conditions. Clearly, this does not reflect the daily life situation. In the first study described in **chapter 3** we aimed to assess and compare dose variability within children from 1-8 years from plastic and metal pMDI/spacers in a daily life setting.

In a second study we investigated within-subject dose variability in children aged 0-2 years old in daily life. We thereby aimed to investigate the effect of electrostatic charge on dose delivery and dose variability by comparing a metal spacer, a detergent coated and non-detergent coated plastic spacer. Additionally, we investigated how factors such as co-operation during the administration and inhalation technique affect the dose delivery and dose variability by using diary cards and video recordings. This study is described in **chapter 4**.

In both studies aerosol from the spacer was collected by means of filters, interposed between pMDI/spacer and child.

LUNG DEPOSITION

Filter studies measure the total dose inhaled by the patient. This is the dose that is delivered to the mouth, but this does not necessarily reflect the amount of drug deposited in the lung. Therefore we aimed to study lung deposition from pMDI/spacers in children using radiolabelled aerosol. The aim of the study described in **chapter 5** was to determine the lung deposition in asthmatic children of different ages inhaling through a plastic spacer with minimal electrostatic charge.

BREATHING PATTERN AND DEPOSITION

To study in detail how breathing patterns affect aerosol deposition in young children we aimed to develop an upper airway model of an infant. The making of this model is described in **chapter 6**. The model is called the SAINT-model, which is an

acronym of Sophia Anatomical Infant Nose Throat model. The SAINT-model can be used in an experimental set-up using simulated infant breathing patterns.

We aimed to study the influence of tidal volume and respiratory rate on aerosol deposition from 4 pMDI/spacer combinations, using the SAINT-model and a breathing simulator. Spacer-output, upper airway deposition, dose delivered to the lungs and particle size distribution were studied for different tidal volumes and respiratory rates. This study is described in **chapter 7**.

Poor co-operation during the administration procedure is a major problem in young children. Crying has been shown to reduce lung deposition to almost zero [39,40]. Therefore, it has been suggested that aerosol adminstration during sleep might be more effective for toddlers. However, the efficiency of administration during sleep is not known. We aimed to study in vitro the dose reaching the lungs from a pMDI/spacer using in vivo recorded breathing patterns of awake and sleeping children in the SAINT model. This study is described in **chapter 8**.

PARTICLE SIZE AND DEPOSITION

The banning of pMDI's containing chlorofluorocarbon (CFC) propellants to prevent further damage to the ozone-layer lead to the development of new inhaler devices. A recently introduced pMDI with hydrofluoroalkane (HFA)-134a propellant containing beclomethasone dipropionate (BDP) has a large proportion of small particles considerably below the particle size of currently available pMDI's. Smaller particles are more likely to bypass the upper airways of young children [41-44]. In the study described in **chapter 9** we aimed to compare the dose delivered to the lungs and the particle size distribution of HFA-BDP and CFC-BDP at different breathing patterns in the SAINT-model.

Chapter 10 gives a summary of the studies in this thesis, a general discussion with recommendation for aerosol therapy in young children and directions for future reseach.

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CHAPTER 2

Aerosol therapy and delivery systems In young children: *Science and practice*

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2.1 INTRODUCTION

Aerosol therapy in the management of pediatric respiratory disorders has gained importance over the last decades. Aerosol therapy is now the mainstay of asthma management in children, and is increasingly used for other respiratory disorders such as cystic fibrosis and bronchopulmonary dysplasia. Therefore, aerosol therapy in pediatrics has a wide field of application, and is relevant to a wide variety of patients, including prematures and adult-sized teenagers [1]. Aerosol therapy should be effective and efficient in these different patients.

Aerosol therapy is considerably more complex than oral therapy, since drugs must be delivered to an organ that is specialized in excluding foreign material. To deliver drugs to the lungs efficiently and reproducibly is extremely difficult, especially in young children. Effective aerosol delivery in the young child requires specific knowledge by the prescribing clinician. Success or failure of aerosol therapy depends on numerous factors. Despite the complexity of the method, treatment of pulmonary disease via inhalation of aerosols has major advantages compared with oral therapy. The medication is directly targeted to the site of action. Therefore there is a more rapid therapeutic effect and relatively low doses are required, compared with systemically delivered drugs. As a consequence, aerosol therapy has a favorable efficacy/toxicity ratio. Furthermore, inhalation of drugs is a non-invasive alternative to deliver drugs with poor gastrointestinal absorption or a high first-pass effect by the liver.

Delivery of aerosolized agents to the lungs for therapeutic purposes has been used for many centuries [2]. Inhalation of smoke of burning plants has been used since ancient times. In recent centuries, the "asthma cigarette" was used as the first portable aerosol delivery system, in which anticholinergic agents were inhaled during smoking [2]. Since the late nineteenth century, devices specifically designed to aerosolize therapeutic products were developed, like the steam driven atomizer and the hand-bulb nebulizer [2] (figure 1). The latter was the only available option for a portable hand-held aerosol delivery system before the introduction of the pressurized metered dose inhaler (pMDI) in 1956 [3]. Since the last fifty years, aerosol technology has developed rapidly, resulting in a great number of different aerosol delivery devices. However, most aerosol delivery systems were primarily designed for use in adults and subsequently adapted for use in children. As a consequence, there is extended information available on the performance of aerosol delivery systems in adults, but only limited data for children and for those of pre-school age in particular.

In the following section we will discuss the indications for aerosol therapy in children. Next, the basic principles underlying aerosol delivery and deposition and the methods to study the efficiency of aerosol delivery are discussed. Next, the requirements for aerosol delivery systems in children are discussed. Finally, currently available aerosol delivery systems are discussed with respect to their use in children.

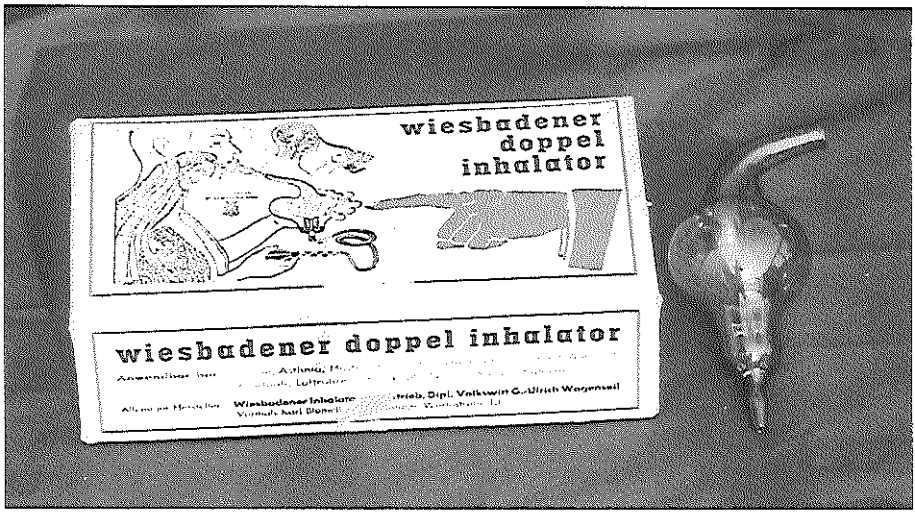

FIGURE 1. Hand bulb nebulizer

2.2 INDICATIONS FOR AEROSOL THERAPY

In children, aerosol therapy is used for diseases such as asthma, bronchopulmonary dysplasia (BPD), cystic fibrosis (CF), and croup. The main indication for aerosol therapy in childhood is management of asthma symptoms [4,5]. Therefore this review is focussed on aerosol therapy in asthma. The remaining indications will only be discussed briefly.

2.2.1 ASTHMA AND RECURRENT WHEEZE

The prevalence of asthma in the Netherlands is about 10% and epidemiological studies show an increase especially in the young age group [6,7]. In other countries prevalences of even 20-30% in children have been reported [7-11]. This implicates that worldwide many millions of children are in need for treatment of asthma symptoms. It is difficult to diagnose asthma in young children with the currently available diagnostic tests [12,13]. Therefore, asthma-like symptoms in young children are often described as recurrent wheeze. When we use the term asthma in this review we refer to both asthma and recurrent wheeze. Asthma is a chronic inflammatory disorder of the airways [4,14], which results in airway narrowing by airway wall thickening, bronchospasm and increased mucous production [15,16] In adults it has been shown that the inflammation extends from the central to the peripheral airways [17-19]. For effective treatment of both central and peripheral inflamed airways it is important that anti-inflammatory drugs penetrate into the periphery of the lungs. In a limited number of studies, it has been shown that asthma-like inflammation is present even at a very early age [20,21]. Elevated inflammatory cells and thickening of the lung basement membrane have been described in infants and

young children [20-22]. Asthma-like symptoms in young children have been associated with lung function abnormalities [20]. Lung function tests in children with persistent wheezing showed significantly lower dynamic flows by 6 years of age compared with children who had no wheezing episodes during the same period [20]. Differences between groups were not apparent at 6 months of age. Therefore, early treatment with anti-inflammatory agents may prevent long-term, irreversible impairment of lung function [13,23,24]. Furthermore, asthma treatment in young children is indicated to reduce symptoms and to improve quality of life of the children and their parents.

The most important class of anti-inflammatory drugs to treat asthma at present are inhaled corticosteroids, such as beclomethasone, budesonide and fluticasone [25,26]. Long term treatment with inhaled corticosteroids has been shown to reduce symptoms, exacerbations and hospital admissions in both adults and children [23,27-33]. Furthermore, early intervention with inhaled steroids in young children with persistent wheeze resulted in improved lung function at later age compared with later intervention [23]. Therefore, guidelines in the management of asthma stress the importance of inhaled corticosteroids in the treatment of young children with asthma [34]. A disadvantage of corticosteroids is that long term use in high dosages can cause adverse effects as growth retardation, adrenal suppression and bone density reduction [35-41]. Long-term use of inhaled corticosteroids in low to moderate doses has been shown to have no effect on growth rate [42,43]. This favours the use of the lowest effective dose [26].

Other inhaled anti-inflammatory drugs used in asthma treatment are cromones, such as disodium cromoglycate and nedocromil sodium [5,44]. These cromones are considered far less potent compared with inhaled corticosteroids to treat asthma and therefore no longer recommended in the latest Dutch guidelines for asthma therapy in children [45,46].

Other important drugs used in asthma treatment are the bronchodilators. These include β2-agonists and anticholinergics, which dilate the airways by relaxation of the bronchial smooth muscle [4]. Acute symptoms of dyspnea can be quickly relieved by inhaled bronchodilators [4,47]. Beta-2 agonists are available as short-acting agents, such as salbutamol and terbutaline [5,27,45,48,49], and the long-acting agents salmeterol and formoterol [50,51]. Beta-2-agonists have a relatively wide therapeutic index and can be used safely even in high doses, without the risk of serious adverse effects [48,52-55].

2.2.2 OTHER INDICATIONS FOR AEROSOL THERAPY

Inhaled corticosteroids have also been shown to be effective in croup in infants [56-61]. Both inhaled corticosteroids and bronchodilators are used for infants with BPD [1,62] and for children with cystic fibrosis [63,64]. There are several other aerosolized drugs used to treat other lung diseases in children. Inhaled antibiotics, such as tobramycine, are used to treat infectious lung disease in cystic fibrosis [65-71]. Recombinant human DNase is a mucolytic that is effective to reduce sputum viscosity in cystic fibrosis [72-77], primary ciliar dyskinesia [78] and to treat atelectasis [79,80].

A variety of new aerosolized drugs are in development, using the lungs as an alternative route to treat non-pulmonary disease. Inhaled insuline has been shown to be effective in the treatment of type I and II diabetes [81-87]. Drugs like morphine [88,89], prostaglandins for treatment of pulmonary hypertension [90-94], and vaccines [95-98] are being developed for inhalation. The use of aerosol therapy for new, often expensive and potent drugs requires efficient systems that deliver the aerosol to the patient reproducibly.

2.3 BASIC PRINCIPLES OF AEROSOL DELIVERY AND DEPOSITION.

The probability for inhaled particles to deposit and their distribution pattern in the respiratory tract depend on particle characteristics, such as size, density and shape, the anatomy of the respiratory tract and the breathing pattern [2,99-106]. These factors determine whether a particle will deposit by impaction, sedimentation or diffusion, which are the main physical mechanisms of particle deposition [99,106,107] (figure 2).

2.3.1 DESCRIPTION OF AEROSOL

An aerosol is defined as a suspension of solid and/or liquid particles in a gaseous phase. Therapeutic aerosols may consist of 'dry' solid or liquid particles [2]. An aerosolized particle may vary in shape, size and density. To define the aerodynamic behaviour of an aerosol, a particle is assigned a single value: the aerodynamic diameter [2]. Particles with a certain aerodynamic diameter have the same aerodynamic behaviour as a sphere of unit density with that diameter. In medical literature the term particle size is often used instead of aerodynamic diameter, but meaning the same. Medical aerosols usually

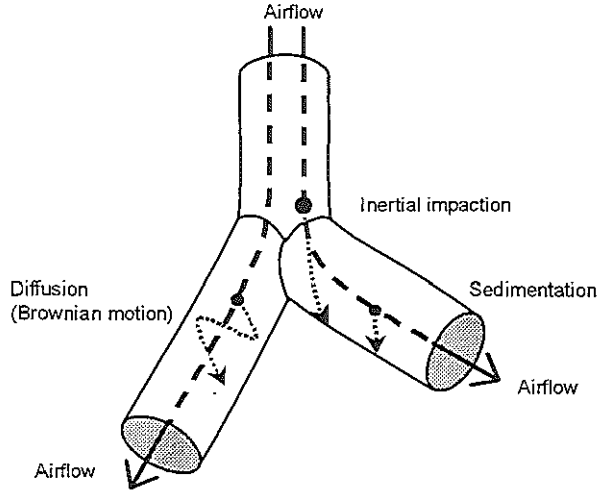

FIGURE 2. Mechanisms of particle deposition in the respiratory tract [269].

consist of particles with a wide range of aerodynamic diameters. Therefore aerosols are generally described in terms of their *median mass aerodynamic diameter* (MMAD) and *geometric standard deviation* (GSD) [2,99,108]. The MMAD is defined as the aerodynamic diameter of an aerosol of which 50% of particle mass is smaller and 50% larger. The GSD describes the distribution of particle diameters and is defined as the ratio of the diameter of the particle on the 84.2th percentile and the MMAD [2]. For a monodispersed aerosol, in which all the particles are the same shape and size, the GSD is 1. Medical aerosols are usually polydisperse.

2.3.2 MECHANISMS OF AEROSOL DEPOSITION

Impaction

Impaction is the collision of a particle on a surface, which occurs when a particle's momentum prevents it from changing course in a change in airflow direction. Impaction is determined by inertia. The larger the particle and the higher its velocity, the more likely it is to impact. Impaction is the main deposition mechanism in the upper and central airways and at bronchial bifurcations [109].

Sedimentation

Sedimentation is deposition of a particle by gravitational forces. Breath-holding after inhalation of an aerosol allows particles to settle and deposit by sedimentation. This is an important deposition mechanism in small airways where the air velocity is low [110,111].

Diffusion

Diffusion is determined by the Brownian motions of a particle [109]. The probability of particles smaller than 0.5 µm to deposit by Brownian motion is inversely related to particle size [2,112]. Diffusion is an important deposition mechanism in the bronchioles and alveoli [109].

2.3.3 FACTORS AFFECTING AEROSOL DEPOSITION IN THE RESPIRATORY TRACT

Particle size

Particle size is the most important factor to determine by which mechanism a particle will deposit in the respiratory tract [106,109,113] (figure 3). The relation between particle size and deposition has been studied in numerous theoretical and practical studies [101,113-116]. Based on these studies particles between 1 µm and 5 µm are considered to be within the 'respirable range' [117,118]. These particles are likely to bypass the upper airways and to be deposited in the lower airways [100,101,119] In general, smaller particles will deposit more peripherally in the lungs than larger particles [100,101,113,120]. Particles in the range of 0.1-1 µm are believed to have a higher probability to be exhaled [2]. Below

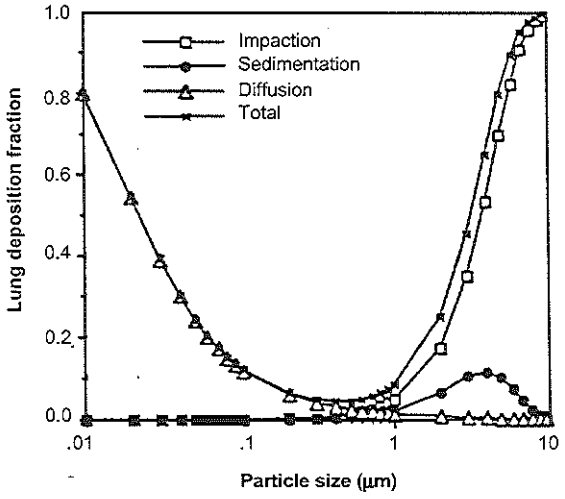

FIGURE 3. Efficiencies of the particle deposition mechanisms of inertial impaction, sedimentation, and diffusion in relation to particle size [113].

0.1 μm deposition is largely determined by Brownian diffusion [101]. However, these assumptions are mainly based on studies in adults and adult models. Mathematical models of infants and children exist, but these are based on the assumption that the airway geometry of children can be scaled down from adult dimensions. [100,120-122]. Validated deposition models using the airway geometry of children of different ages do not exist to date. Therefore, the 'respirable range' in particle size for infants and children is unknown.

Breathing pattern

The breathing pattern used to inhale an aerosol is another important determinant for the deposition of particles in the respiratory tract [2,123]. High inspiratory flow rates will enhance impaction of particles. Several studies in adults showed that slow inhalation increased lung deposition compared with fast inhalation [111,124-126]. Deep inspiratory breaths are more likely to enhance peripheral deposition. Inhalation of salbutamol from residual volume rather than from functional residual capacity resulted in higher relative bioavailability to the lung [124]. However, several other studies suggested that there is no advantage in inhaling from residual volume rather than from functional residual capacity [111,127]. Children inhale with deep inspiratory volumes when crying. It is a general misunderstanding that the deep inspiratory volumes during crying would enhance aerosol deposition. In fact, it has been shown that crying results in almost no aerosol being deposited in the lungs [128,129].

Children from the age of 8 years and older are able to inhale aerosols in one breath followed by a 10 seconds breath hold. This is the recommended inhalation technique

for pMDI's and dry powder inhalers (DPI's) [104,111,130]. Below the age of 8 years children are not able to perform such a complicated inhalation procedure reproducibly [131]. These children should therefore inhale via tidal breathing. Tidal breathing results in a larger proportion of the inhaled aerosol being exhaled [132,133] and shortens residence time of the aerosol in the lungs. Tidal breathing at a low respiratory rate was shown to increase lung deposition and decrease upper airway deposition in adults compared with a high respiratory rate [134]. It is largely unknown how breathing patterns relate to lung deposition for young children.

Airway geometry and deposition

The geometry of the respiratory tract determines aerosol deposition in several ways. Airway dimensions, the inhalational route and disease-related changes of the airway geometry affect the dose delivered and the deposition pattern of aerosol particles in the lungs. The airways can be seen as a trumpet shaped tube, meaning that the total cross-sectional diameter increases from the central to the peripheral airways [110]. Therefore, flow velocity is higher in central airways and lower in peripheral airways. This means that particles will mainly deposit by impaction in the central airways and by sedimentation and diffusion in the peripheral airways. In young children the airway diameters may be up to 4 fold smaller compared with adults [135]. Furthermore, it has been calculated that there are relatively high flows in the central airways in young children [135], which cause increased deposition of particles by impaction. Therefore, it is unlikely that aerosol deposition predictions derived from adult airway diameters will apply for the airway diameters in children. Inhalation via the nose instead of the mouth will negatively affect the dose delivered to the lungs in young children [136]. It has been shown that nasal inhalation of aerosol increases deposition in the upper airways by turbulent flows in the nose [119,137-139]. Disease related changes of the airways in patients with diseases like asthma, CF and BPD can lead to dramatically different geometry of airways compared with the geometry in healthy subjects [17;140-142]. Chronic airway inflammation leads to thickening of the airway wall, which is more severe in peripheral than in central airways [17,140-142] These changes in airway geometry can have a considerable effect on the deposition patterns in the lungs [106,143]. In adults with severe asthma or CF, lung deposition showed a more centrally localized and heterogeneous pattern compared with healthy volunteers [144,145].

2.4 METHODS TO STUDY EFFICIENCY OF AEROSOL DELIVERY DEVICES

There are numerous methods, in vitro and in vivo, to study the efficiency of aerosol delivery devices. In vitro systems are used to define particle size distribution of an aerosol. These characteristics can be used to predict the lung deposition [146]. In vivo methods include lung deposition studies using radiolabelled aerosols, pharmacokinetic studies, pharmacodynamic studies and studies showing the clinical

efficacy of a therapeutic aerosol device. Each method provides different aspects of the performance of the device. Both in vitro and in vitro data are required to adequately predict the performance of aerosol delivery devices in patients. It should be noted that each device/drug combination can behave differently [147]. Therefore, the effectiveness of a certain inhaler device with one drug does not predict the effectiveness of the same device with another drug.

2.4.1 IN VITRO METHODS

Measurement of particle size

In vitro, measurements of the particle size distribution of an aerosol play a key role in the development of new aerosol delivery devices and in quality control. There are many methods to characterize particle size distribution of an aerosol [148]. The most commonly used methods to characterize aerosols are laser diffraction and inertial impaction [148]. A laser diffraction system measures particle size distribution by passing a laser beam through an aerosol. The beam is scattered by opaque aerosol particles, or refracted by non-opaque particles. The scattered light is recorded by a series of detectors, and the resultant signals are converted into information relating to the volume distribution of particles within the aerosol. From this information the mass distribution of the aerosol can be derived [2]. Laser systems are expensive but are very convenient, producing results rapidly. It is an advantage that particle size distribution can be measured as the aerosol leaves the device without secondary artifacts resulting from drying. Laser diffraction is convenient to study wet aerosols from nebulizers [2,149].

Inertial impaction devices include liquid impingers and cascade impactors. Particle size distribution in impaction devices is determined by drawing the aerosol through the device at a constant flow. This can vary between 5 and 60 L/min depending on the device. The airflow passes through a series of stages before it passes through an absolute filter. The velocity of the airflow increases between the successive stages as the connecting jets narrow (figure 4). Particles from an aerosol introduced in this airflow impact on plates contained in each stage. The stage at which a particle impacts is determined by its aerodynamic diameter. Large particles impact on upper stages, whereas small particles impact on the lower stages. Each stage has a known cut-off value for a aerodynamic diameter. Next, the particle size distribution is derived from an assay that quantifies the mass of medication on each stage, e.g. by means of high performance liquid chromatography (HPLC) [2]. The most important advantage of the inertial impaction method is that it provides information on the distribution of medication in droplets of different sizes. The medication may not be evenly distributed amongst droplets from an aerosol delivery device. Some droplets may have no medication and others, particularly larger ones, carrying the bulk of the aerosolized medication. The impaction method is recommended for pMDI's and DPI's [2,118]. A disadvantage of this method is that it is very time consuming.

FIGURE 4. Picture of 8-stage Anderson cascade impactor showing the separate stages with progressively smaller orifices.

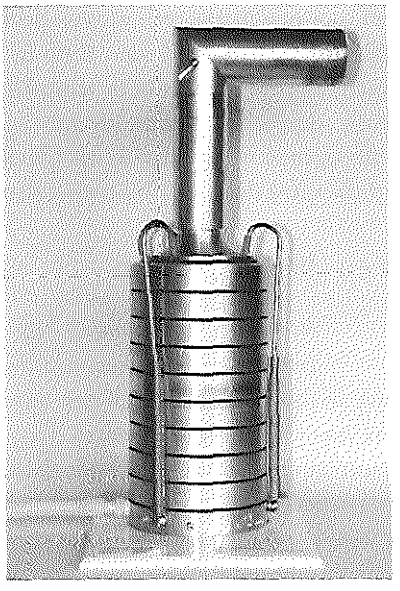

FIGURE 5. 8-stage Anderson cascade impactor with USP-throat.

Upper airway models

An impactor or impinger is usually used with an extension on top of the stages, to which the aerosol device is attached. This is often referred to as the 'throat'. The standard 'throat' used on impacting devices is the United States Pharmacopoeia (USP)-throat, which is a round tube with a 90° bend (figure 5) [150]. Obviously, this is a poor surrogate of the real anatomy of the oropharynx. For a more realistic estimate of the upper airway deposition, anatomical models of the oropharyngeal pathway were developed. Several models have been made, with different techniques. There are models made with the wax-waste method in cadavers [151,152], or made with help of CT-scans from the upper airways in combination with a stereolithographic technique [153]. A recently presented artificial throat is a geometric model using the dimensions derived from CT-scans, MRI-scans and direct observations of living subjects [154]. This latter model seems physiologically realistic. There are only a few models available of the nasal airways. All the models described above are adult models. There are no realistic models available for children.

Breathing simulation

To test the performance of aerosol devices for use in children, simulation of the breathing pattern is used for adequate prediction of the dose inhaled. There are several studies showing that the dose delivered from a pMDI/spacer with simulated tidal

breathing is lower compared with constant inhalation flow [133,155,156]. However, most studies using simulated breathing measure the total dose delivered from the device by filters [132,133,155-157]. These studies give information on the total dose delivered with a certain breathing pattern. However, this method does not give details about the distribution pattern of the aerosol in the respiratory tract. Additional information can be obtained by measurement of particle size during simulated breathing. This is a complicated technique because impacting devices are calibrated for use with a constant inhalation flow. Several experimental set-ups have been described to measure particle size distribution during simulated breathing [158-160].

The relevance of in vitro testing of aerosol devices increases when testing conditions mimic the in vivo situation as closely as possible. This may be achieved with anatomical models of the upper airways and realistic flow profiles in combination with impactors [118,161].

2.4.2 IN VIVO METHODS

Radiolabelled aerosol studies

Gamma scintigraphy is used to assess the lung deposition of inhaled drugs in vivo. By inhalation of radiolabelled aerosol the total amount of drug deposited in the lung can be estimated and the regional deposition pattern within the lung can be quantified [162]. The radiolabelling is done by adding a radionuclide, mostly ^{99m}Tc, to the aerosol formulation so that it forms a physical association with the drug particles or is incorporated into the drug molecule. For most formulations the label is only loosely associated with the drug [163]. Validation experiments should be carried out to establish whether the association between drug and radiolabel is consistent across all particle sizes and to show that the in vitro performance of the product has not been altered by the labeling process [162]. Following inhalation of the radiolabelled formulation, planar 2-dimensional images of the head and chest are made by a gamma-camera. To convert gamma counts into deposition of drug mass, data must be corrected for the attenuation of the gamma ray signal as it passes from the body to the gamma camera [162]. The 2D-image of the lung is subdivided in the peripheral zone and the central zone. The ratio (P:C ratio) between the two zones is used as a parameter to describe the regional lung deposition pattern. The problem using this P:C ratio is that the discrimination between the peripheral and central regions is not precise, and is therefore only an estimation. A more detailed regional deposition pattern may be obtained by using single photon emission computed tomography (SPECT), which provides 3-dimensional images of the lung [118,164]. However, this is a very expensive, complex method that requires higher radiation exposure. Furthermore, this method is less well validated than the conventional 2-dimensional gamma scintigraphy [118].

The use of radio-active aerosols in children raises ethical questions, since the long term risk for children per unit radiation dose is believed to be higher compared

with adults [165]. The total radiation dose of an inhaled radiolabelled dose is in the range of the dose received from natural background sources during a few weeks [163]. Therefore the risks are probably small. However, the risk of high local deposition of radiolabelled particles, which may occur on airway bifurcations, is not known. The localized radioactive dose of these 'hotspots' may be 20-100 times higher than the average radioactive exposure [166]. Therefore, radiolabelled aerosol studies in children should be limited to those studies of which the potential benefit justifies the unknown risks. Clearly, such studies should only be done when appropriate and validated techniques and study designs are used [163]. Furthermore, the exposure should be kept minimal. Finally, dose limits specified by the International Commission on Radiological Protection should not be exceeded [167].

Pharmacokinetic studies

A non-radioactive method to determine lung deposition is to measure the systemic availability of an inhaled drug after it has been absorbed from the lungs. The pulmonary availability equals the systemic availability in case the drug is not absorbed from the gastro-intestinal tract, or when it is completely eliminated by first-pass metabolism [168]. However, most inhaled drugs, such as steroids and bronchodilators, are significantly absorbed from the gut. Activated charcoal can be used to block the gastro-intestinal absorption [168]. The systemic availability can be determined by the pharmocokinetic technique in which area under the curve (AUC) of the plasma concentration of the inhaled drug versus time is compared with the AUC of a reference dose, which is generally given intravenously [169-171].

It has been shown that lung deposition measured with gamma scintigraphy is a few percent higher compared with the charcoal block method [168]. This is explained by the fact that gamma scintigraphy measures the amount of drug deposited on the lung surface, including drug which may subsequently be removed from the lungs by mucociliary action. The charcoal-block method measures only the amount of drug absorbed via the lung. These differences should be kept in mind when data obtained by the two methods are compared. The most important advantages of the bioavailability method are that it does not require a radioactive substance and that the intact drug formulation is used. However, it does not give information on the regional distribution of a drug within the lung, as is the case in the scintigraphic method [118].

Clinical efficacy

The most important method to test the efficiency of aerosol delivery devices is to measure the clinical efficacy and safety. The design of clinical efficacy studies is determined by the type of drug used. In general, to avoid bias, trials should be of a randomized, double-blind, and placebo controlled design [25]. Pharmacodynamic studies, which measure one clinical parameter, are often designed as a simplification,

but can not be considered as substitutes, for clinical efficacy studies. Bronchodilators are tested with lung function tests before and after inhalation. A rapid effect can be assessed with relatively small groups. Testing efficacy of inhaled steroids requires long-term studies, a large number of patients, frequent lung function tests, and registration of symptoms, hospital admissions, exacerbations and concomitant use of other drugs. In young children this type of clinical efficacy studies for anti-asthma inhaler devices are difficult to perform [172]. Firstly because of the difficulty in diagnosing asthma in this age group [173]. Secondly, because of the lack of reproducible endpoints suitable to measure a large number of infants [13]. For example, reproducible lung function testing is possible from age 6, but infant lung function testing is only available in a limited number of centers. Furthermore, infant lung function testing is extremely time consuming. An alternative for lung function tests is the use of symptom scores. Symptom scores have the disadvantage of high variability. Therefore there are only few studies showing clinical effect of inhaled steroids in pre-school children, and these are mostly based on symptom scores and recording of hospital admissions [28,29,33]. The development of non-invasive tests to measure inflammation and airway resistance in young children may provide reproducible end-points for clinical studies in this age group in the future [174-177]. A promising example to measure airway inflammation in asthma is the assessment of nitric oxide (NO) in exhaled air [174,176]. Airway resistance can be measured in young children with the interrupter technique (Rint) during tidal breathing [177]. Validation and assessment of reference values are in development for these techniques.

2.4.3 EXPRESSION OF DOSE

One should be careful in directly comparing aerosol delivery data from different studies, for the doses and deposition values can be expressed in different ways. Dose delivery or lung deposition can be expressed as a percentage of the nominal dose or the metered dose. The nominal dose is the dose that is mentioned on the label, also referred to as the label claim. This is a fixed reference value. The metered dose is the total dose that has left the aerosol delivery device. For pMDI's the metered dose is sometimes called actuated dose or ex-valve dose, and for DPI's it is sometimes called emitted dose. The metered dose is generally lower than the nominal dose and can vary between and within devices [130]. For pMDI's the metered dose is usually only a few percent below the nominal dose. However, for DPI's the metered dose is substantially lower than the nominal dose and can vary from 30 to 80 % dependent on inhalation flow [130,178]. Therefore, reading the literature one should always pay attention on the way aerosol deposition is calculated. The method used should always be clearly defined in the methods section to enable proper interpretation of the data. Interpreting deposition data, which are mentioned as percentages of the metered dose, can give considerably higher results when compared with data in percentages of nominal dose.

2.5 REQUIREMENTS FOR AEROSOL DELIVERY DEVICES IN YOUNG CHILDREN

The high number of available aerosol delivery devices makes aerosol therapy confusing. The choice depends on the patient, the device, and the drug. Therefore, knowledge about each of these items is important to make the right choice for individual patients. Aerosol therapy in young children demands special requirements for the aerosol delivery device [179]. Firstly, the device should be simple to use, requiring a minimum of cooperation and coordination of the child. Young children are not able to perform special inhalation manoeuvres, and are only able to inhale via tidal breathing. Secondly, the device should target the drug effectively into the lungs, with a minimum of naso-oropharyngeal deposition, since high doses of steroids in the upper airways can give local side effects as dysphonia and candida infections [25]. Young children preferably breathe through the nose while inhaling aerosols [136]. As the nose is designed for filtering aerosol particles from inhaled air, it forms a barrier for effectively targeting aerosols into the lower airways. Thirdly, the device should deliver a predictable and reproducible dose [179]. This is especially important for drugs with potent side effects that require a precise dosage regimen and treatment with the lowest effective dose. Therefore, the prescriber must be able to rely on predictable dosing within and between individuals, regardless of age and cooperation.

2.6 METHODS TO DELIVER AEROSOLS TO YOUNG CHILDREN

The current methods to deliver therapeutic aerosols can be classified in three categories: nebulizers (jet or ultrasonic), pMDI's used with a press-and-breathe method or as breath actuated device or in combination with a spacer, and DPI's. It is important to keep in mind that these devices were primarily designed for use in adults and subsequently adapted for use in children. These adaptations might have changed the characteristics of the device considerably. However, only limited data are available on the efficiency of devices to deliver aerosols to the lungs of young children.

The nebulizer and the pMDI/spacer are the most suitable aerosol delivery systems for young children, for they only require tidal breathing to inhale the aerosol. For a long time jet nebulizers have been the mainstay of aerosol therapy in young children, since there were no other good alternatives available. The introduction of the pMDI combined with spacer revealed new possibilities for effective aerosol therapy in children. Currently, the pMDI/spacer is recommended as the first choice for aerosol delivery to treat asthma in young children [45,180]. Therefore, this thesis focuses on the use of pMDI/spacers. Nebulizers and DPI's are discussed briefly. The advantages and disadvantages of the different devices are summarized in table 1.

TABLE 1: Advantages and disadvantages of aerosol delivery devices for use in children

Device	Advantages	Disadvantages
Nebulizer	• all ages • tidal breathing • delivery of high doses over prolonged period • face mask can be used • only aerosol delivery device for liquids	• cumbersome • noisy • time consuming • easily contaminated • poor reproducibility in dose and particle size • maintenance required • large inter-device variability
pMDI	• small, handy • quick • low dose-to dose variability	• complicated hand-mouth coordination • high velocity of aerosol causing high oropharyngeal deposition • not suitable for children
pMDI breath-actuated	• small, handy • quick • no hand-mouth coordination required • low inspiratory flow rate required	• high aerosol velocity causing high oropharyngeal deposition • deep inspiration required • not suitable < 7-8 years
pMDI/spacer	• all ages • tidal breathing possible • face mask can be used • quick • reduction of oropharyngeal deposition, less local side effects	• electrostatic charge of plastic spacers • size • many mistakes can be made
DPI	• small, handy • quick • no hand-mouth coordination • propellant free	• high inspiratory flow required • effort dependent-efficiency • not suitable <7-8 years • between-device differences in handling and inhalation technique

2.6.1 PRESSURIZED METERED DOSE INHALERS AND SPACERS

Pressurized metered dose inhalers

The pMDI was first introduced in 1956 [3]. Since then it has become the most widely prescribed aerosol delivery device. The principle of a pMDI is based on a spray-can as used for hair spray [3]. It consist of a canister with an actuator-valve mechanism, which is filled with micronized drug, propellant and surfactant [181] (figure 6). The

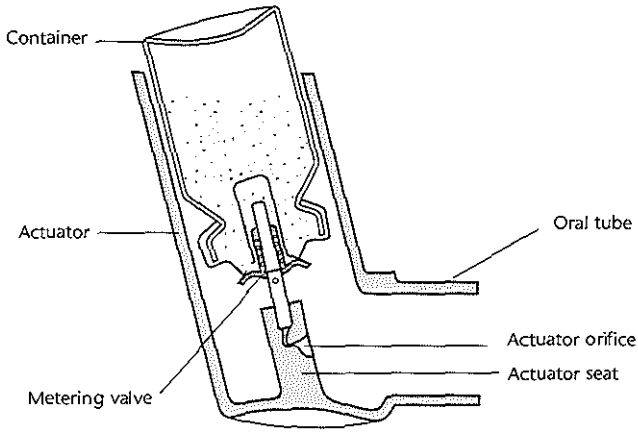

FIGURE 6. Schematic drawing of a pMDI.

medication is usually suspended rather than dissolved in the propellant-surfactant mixture. Surfactants reduce aggregation of the particles during actuation and lubricate the valve mechanism of the canister. The propellant serves as an energy source to expel the drug formulation from the canister in the air. Before use the pMDI must first be shaken vigorously, because the drug and propellant separate out very rapidly within the pMDI (figure 7)[2]. Failure to shake results in variations in dose up to 25% [182]. During actuation, a metered dose leaves the metering chamber that is closed to the canister and open to the atmosphere by the valve mechanism. An aerosol cloud containing droplets of drug particles, propellant and surfactant leaves the actuator with high velocity. The particles dry, as the propellant evaporates [2]. Other factors that can contribute to dose variability are: no priming of the pMDI by firing waste puffs before initial use, extreme temperatures, and tailing off when the pMDI is nearly empty [181,183].

Inhalation technique: The recommended technique for the patient to inhale an aerosol from a pMDI is: deep exhalation, coordination of actuation of the dose with the onset of inhalation, slow inhalation till total lung capacity and breath-holding for 10 seconds. [111,124,184]. This technique is known as the press-and-breathe technique and has proven to be complicated; only 9 - 48% of adults and older children can perform this correctly [185,186]. The pMDI is used directly in the mouth. This has the disadvantage that the majority of aerosol particles, leaving the actuator with high velocity, impact in the oropharynx [187]. With optimal inhaler technique a lung deposition of around 10% can be achieved by asthmatic adults, with an oropharyngeal deposition of around 80% [103,187].

Breath-actuated pMDI's: Breath-actuated pMDI's have a flow-triggered system to release a dose at the onset of an inhalation [188]. This system overcomes the difficulty

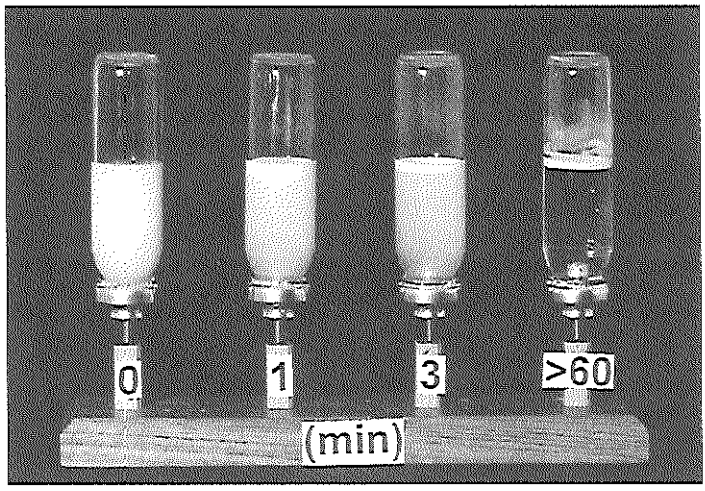

FIGURE 7. The behaviour of the contents of a pMDI as revealed in a special glass-walled container: Showing the suspension in the pMDI immediately after shaking at time 0 and the separation of the suspension within 1, 3 and > 60 minutes after [181].

of synchronizing the actuation of the dose with the inhalation [189,190], but does not eliminate the problem of high oropharyngeal deposition. The breath-actuated pMDI may be effective in children from 6 years of age and older [190,191]. However, one has to keep in mind that children in studies are optimally instructed and guided.

Recent developments: Since the introduction of the pMDI, its technology has been changed little. Until recently, chlorofluorocarbons (CFC's) were used as propellant in pMDI's. The need to ban CFC containing products, in accordance with the Montreal Protocol on Substances that Deplete the Ozone Layer in 1994 [192], created an opportunity to improve pMDI-technology. Hydrofluoroalkanes (HFA's) are now used as an alternative more environment-friendly propellant. The first HFA-pMDI containing salbutamol has improved valve design, resulting in a consistent dose from the first to the last actuation. Dose variability is further decreased because the dose does not change with extreme temperatures [193]. Furthermore, the aerosol cloud from the actuator travels with lower velocity and has a smaller volume compared with a CFC-pMDI [194].

Some major manufacturers opted for 'equivalence' when developing CFC-free pMDI's [161]. One manufacturer recognized the need to improve the delivering characteristics of inhaled steroids [195]. Therefore, a new HFA-pMDI was developed, containing beclomethasonedipropionate (BPD) in solution rather than in suspension. This resulted in an aerosol with a MMAD of 1.1 µm. Lung deposition of HFA-BDP in adults has been shown to be up to 10-fold higher compared with CFC-BDP. Furthermore, deposition in the peripheral regions is higher and oro-pharyngeal deposition lower compared with CFC-BDP [195]. In a dose-response study in adults

it was shown that the same clinical efficacy was achieved with 2.6 times lower doses using HFA-BDP compared with CFC-BDP [196]. The small particles of this HFA-BDP might be a particular advantage for aerosol delivery in young children.

Spacers

To overcome the co-ordination problems of the press-and-breath technique for the pMDI's, spacers were introduced [197-204]. Furthermore, spacers have the advantage that they reduce oropharyngeal deposition [187] since coarse particles impact on the walls of a spacer and the particles have a longer distance to decelerate and evaporate. Therefore, the dose available for inhalation from a spacer contains a large proportion of fine particles.

In adults, the use of a spacer with a pMDI has been shown to result in improved lung deposition, better clinical effect and less local side effects compared with the use of a pMDI with the press-and breathe method [201,202,204-209].

Lung depositions of 20-45 % of metered dose (approximately 19-43 % of nominal dose) have been achieved in adults using pMDI/spacer with an oropharyngeal deposition of 5-30% depending on type of spacer [187,210-212]. The pMDI/spacer has been proven to be a useful aerosol delivery system in children [213-219]. The use of inhalation and exhalation valves offers the opportunity to inhale with multiple breaths, which is an advantage in children [203,220]. An attached facemask, instead of a mouthpiece makes spacers also applicable in young children [29,132,219,220]. Although a clinical effect is shown with pMDI/spacers in young children [221-223], the dose delivered to the lungs is low. Radiolabelled aerosol studies in children < 5 years of age showed lung depositions of 0.67% to 5.4% of metered dose [128,224,225]. It can therefore be concluded that the efficiency of aerosol delivery from pMDI/spacers for young children can be substantially improved.

Types of spacers: In the Netherlands, there are four different spacers commercially available (figure 8); 1) The Aerochamber® (Boerhinger Ingelheim, Alkmaar, The Netherlands) is a small volume (150 ml) spacer made of plastic (Ektar®). It has a low resistance inspiratory valve. It is available with facemask or mouthpiece and all types of pMDI's fit in the spacer-inlet. 2) The plastic (polycarbonate) Babyhaler® (GlaxoSmithKline, Zeist, the Netherlands) has a volume of 350 ml. It has low resistance in-and expiratory valves. It is available with a face mask, but can also be used without. The inlet of the spacer is only compatible for Glaxo- pMDI's. The same is true for 3) The Volumatic® (GlaxoSmithKline), which has a large volume (750 ml) and is also made of polycarbonate plastic. It has a relatively high resistance valve integrated in the mouthpiece. It is only available with a mouthpiece. 4) The metal Nebuchamber® (AstraZeneca, Zoetermeer, The Netherlands) is a small volume (250 ml) spacer, which is only compatible with Astra pMDI's. The low resistance in and-expiratory valves are integrated in the mouthpiece. It can be used with or without a facemask.

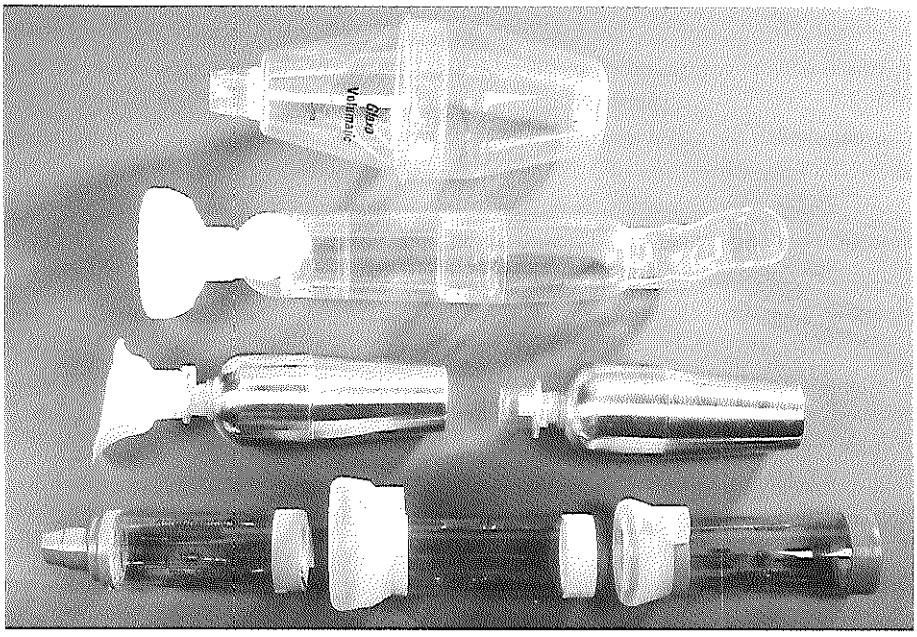

FIGURE 8. Commercially available spacers in the Netherlands. From top: Volumatic® (GlaxoSmithKline), Babyhaler® (GlaxoSmithKline), Nebuhaler® (AstraZeneca), Aerochamber® (Boehringer Ingelheim).

The growing number of available pMDI's and spacers makes comparative studies necessary. It has been shown that each pMDI/spacer combination behaves differently [147,226] and that numerous factors affect the dose delivered from pMDI/spacers.

Volume of a spacer: The volume of a spacer is critical for children with small tidal volumes. Actuation of a dose in a small volume spacer results in a highly concentrated aerosol. Therefore more drug can be inhaled in the first breaths. Furthermore, it takes less time to empty a small volume spacer for children with small tidal volumes. In large volume spacers there is more aerosol available for inhalation because less particles impact on the walls of the spacer, the dose delivered in children with small tidal volumes is higher from small volume spacers [132].

Electrostatic charge: Electrostatic charge can build up on the inner surface of plastic spacers, which attracts the aerosol and reduces the dose delivered from the spacer considerably. Electrostatic charge can be reduced by coating the spacer with an antistatic lining, such as household detergent [212,227,228] or by priming the spacer by several puffs from the pMDI [210,226]. In adults, lung deposition has been shown to increase from 11% of metered dose with a static untreated spacer to 45% with a detergent coated plastic spacer [212]. A metal spacer was introduced to overcome the negative effects

of electrostatic charge on the dose delivered [229]. The metal spacer delivered twice as much aerosol compared with several plastic spacers in children aged 0.5 to 6 years old [226]. However, a plastic spacer with detergent coating can deliver an equal dose compared with the metal spacer in young children [230]. A radiolabelled aerosol study showed a lung deposition of 34% of metered dose in adults, using the metal spacer.

Delay after actuation: A one or more seconds delay of inhalation following actuation has been shown to decrease dose delivery. This is especially seen in static spacers, because electrostatic charge shortens the half life of aerosol available for inhalation in the spacer. [227-229]

Dead space: A large dead space between the in- and exhalation valves or from a large face mask causes loss of aerosol with tidal breathing inhalation. Adding a dead space of 50 ml can reduce the dose delivered from the spacer by half when using a tidal volume of 50 ml [132].

Multiple actuations: It has been shown that the dose delivered per actuation decreases when more actuations are introduced in the spacer [132,227,228,231,232]. This is probably due to the relatively greater loss from impaction on the walls of the spacer when multiple actuations are fired into the spacer. Therefore, each single actuation should be followed by inhalation, and a single actuation can be repeated in case more than one actuation need to be administered.

Valves: In adults it has been shown that during acute asthma the expiratory flow of a patient may be too low to close the valve of a large volume plastic spacer, and hence aerosol is blown out of the device during expiration [233]. A partially open valve is likely to impair drug delivery significantly. In young children the valves of a spacer need to be of low resistance to function effectively even at low tidal volumes [132].

pMDI: Characteristics of the pMDI, such as formulation, particle size, and aerosol cloud characteristics, interact with the design and shape of the spacer and may therefore also affect the dose delivered [194]. For example, the aerosol cloud from the earlier discussed HFA-pMDI with salbutamol moves with lower velocity and has a smaller volume compared with a CFC-pMDI [194]. This results in a higher dose delivered to the patient when used with a spacer, since less aerosol is impacted on the spacer wall [158,194].

Inhalation technique: The recommended inhalation technique for pMDI/spacers is shown in table 1. The use of a pMDI/spacer is relatively simple compared with a nebulizer or a pMDI alone. However, several studies showed that patient still can make many mistakes [185,234] and that even pediatricians and nurses have lack of knowledge about the correct use of the prescribed inhalation devices [235,236].

Since many factors affect dose delivery, it is hard to predict the dose from a particular pMDI/spacer in a particular patient. Several studies showed high inter-subject variability in dose delivery in children [226,237,238]. Within-subject variability has not been studied yet. Therefore it is not known how a dose can vary from day to day, which makes optimal dosing difficult.

2.6.2 NEBULIZERS

The most frequently used method of nebulization is the jet nebulizer. The design of a jet nebulizer is based on the Bernoulli principle. A jet of air is forced through a narrow orifice, creating a vacuum as it expands beyond the orifice. Fluid is drawn up into the region of low pressure via the Venturi effect. The fluid becomes entrained into the airflow, creating long filaments of liquid that then break into droplets. The majority of these primary droplets are too large to inhale. To prevent wastage, modern small-volume therapeutic nebulizers use a baffle placed between the jet orifice and the patient. Smaller droplets can follow the airstream around the baffle as the majority of large droplets impact on the baffle and fall back into the nebulizer reservoir to be renebulized [2,239]. Another method of nebulization is the ultrasonic nebulizer which uses ultrasonic energy, produced by a piezoelectric crystal, to convert fluid into a fine mist [240,241]. The output of ultrasonic nebulizers is higher compared with jet-nebulizers, which is useful for admininstration of large volumes [242]. However, ultrasonic nebulizers are not suitable to nebulize suspensions such as steroids or viscous fluids such as antibiotics. Furthermore they are expensive and produce relatively large particles compared with jet-nebulizers [2].

The nebulizer can be used in combination with a mouth piece or a face mask. A face mask should be used only for children who are unable to inhale via a mouthpiece [157,243]. Lung deposition studies showed a deposition of 1.3% to 5.4% of nebulized dose in young children using a facemask [136,224,225] and 6.3% to 11.1 % in children from 5 years and older using a mouthpiece [136,225].

Nebulizers have the advantage that they can be used by patients of all ages since they only require tidal breathing. Another advantage is that high doses can be nebulized over a prolonged period [179]. The disadvantages of nebulizers are numerous. The equipment is expensive, cumbersome, noisy and it needs a power supply [179 165]. The administration time can be as long as 20 to 30 minutes several times a day. This is not beneficial for patient compliance [244]. Furthermore, it requires regular cleaning, with a high risk of contamination if the cleaning instructions are not followed correctly [245]. There are numerous technical factors that can affect aerosol output and particle size distribution of a nebulizer. These may result in highly variable doses and poor reproducibility of particle size [109,239,241]. These technical factors include the fill volume, driving gas flow [157,246], the viscosity, concentration and temperature of the solution or suspension [246], nebulizer design [156,239,246,247] and breathing pattern [156,157]. Unvented nebulizers, with continuous output of aerosol, are inefficient since there is loss of aerosol during exhalation [179]. More efficient systems have been developed, such as breath-enhanced and open vent nebulizers with in- and exhalation valves, and breath-actuated systems, which follow the patient's breathing pattern [123,248-252]. The use of breath actuated systems results in improved dose reproducibility and reduced loss by exhalation and residual volume.

The use of nebulizers in the maintenance therapy of asthma is limited, because of the improvements in other delivery systems which are more convenient in use, such

as the pMDI/spacer. Nebulizers in maintenance asthma therapy are still used for some unco-operative children, who only accept a nebulizer. Even for the treatment of acute asthma the pMDI/spacer may be a more attractive alternative. Numerous studies in both adults and children and several meta-analyses have shown that pMDI/spacers are at least equally effective compared with nebulizers to treat acute asthma [253-264]. The continued preference for nebulizers in acute asthma is because the advantage that high doses of bronchodilators can be given relatively easy in combination with oxygen [2]. Nebulizers are continued to be used for drugs which are only available as nebulizer fluids. Examples of such drugs are antibiotics, surfactants, rhDNase and pentamidine. Efficient and effective nebulizing is important for these often potent and expensive drugs.

2.6.3 DRY POWDER INHALERS

DPI's contain micronized particles of drug in aggregates, either alone or in combination with larger carrier particles, commonly lactose. The aggregates are disintegrated into small particles in the DPI by the energy created by the patient's inspiratory flow. All currently available DPI's are breath-actuated devices and hence no hand-mouth coordination as in pMDI's is required. Other advantages of DPI's are that they are compact and portable and therefore convenient in use. Furthermore, they do not contain gasses that are harmful for the environment like the CFC-pMDI's. Radiolabelled aerosol studies with a DPI in both adult and children from 6 years of age showed lung depositions of around 28% of the metered dose [265,266], which is approximately 20% of the nominal dose. DPI's have the major disadvantage that high inspiratory flows are required to deagglomerate the powder. Insufficient inspiratory flow results in a lower inhaled dose and larger particles [130]. The required high inspiratory flows are often not achieved by children below 8 years of age or by older children with severe dyspnea [131]. Two studies showed adequate lung deposition from a DPI in children from 6 years of age, below this age lung deposition was less reliable [266,267]. Therefore, DPI's are often recommended for children from 6 years of age. However, these recommendations are based on studies using optimally trained and instructed children in a laboratory setting. It is likely that below the age of 8 there is substantial day-to-day variability in the inhaler technique. Therefore DPI's should not be used in clinical practice for children below the age of 8 years, for whom the pMDI/spacer is a better flow-independent alternative. A prototype of a flow-independent DPI has been described [268]. However, it is questionable whether this device will become commercially available.

2.7 CONCLUSIONS

The majority of aerosol therapy in childhood is prescribed to control asthma symptoms. The most important classes of inhaled drugs are corticosteroids to treat inflammation and bronchodilators for dilation of obstructed airways. The potential

side effects of corticosteroids make it necessary to select an efficient aerosol delivery system to be able to administer the lowest effective dose. The delivery of aerosols to the respiratory tract is complex, and depends on numerous factors, like particle size of the aerosol, breathing patterns and the geometry of the airways. Aerosol therapy in young children requires special attention with respect to the aerosol delivery device. Problems like cooperation during the administration, inability to perform an inhalation manoeuvre, nasal breathing and small airways need to be considered. Currently there are three categories of delivery devices available, pMDI's with or without spacer, nebulizers and DPI's. Nebulizers and DPI's have numerous disadvantages for use in young children. The pMDI/spacer is the recommended aerosol delivery device for maintenance asthma therapy in young children. However, there is lack of knowledge about the efficiency of pMDI/spacers to deliver aerosols to young children. Knowledge of aerosol delivery devices in young children is needed to optimize aerosol therapy.

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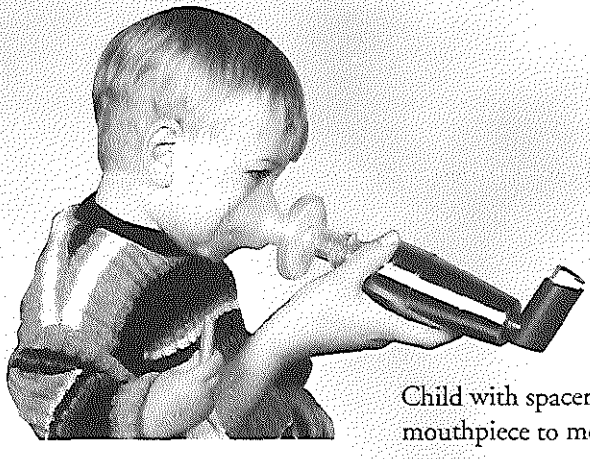
REPRODUCIBILITY OF DOSE



Child with spacer and filter between mask and mouthpiece to measure delivery from the spacer.

CHAPTER 3

Variability of aerosol delivery *via* spacer devices in young asthmatic children in daily life.

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ABSTRACT

Pressurized metered dose inhalers (pMDI) are widely used together with spacers for the treatment of asthma in children. However, the variability of daily medication dose for pMDI/spacer combinations is not known. Electrostatic charge is a potential source of dose variability. Metal spacers have no static charge. This study assessed and compared within-subject variability of aerosol delivery of metal and plastic spacers. This was a randomized, crossover study in children with stable asthma aged 1-4 (group I, n=17) and 5-8 (group II, n=16) yrs. In both groups the amount of drug delivered to the mouth by a metal spacer (Nebuchamber®) and one of two plastic (polycarbonate) spacers, *i.e.* Babyhaler® in group I and Volumatic® in group II was measured. The metal and plastic spacers were tested at home in a randomized order for 7 days each, using budesonide (200 µg *b.i.d.*). Aerosol was collected on a filter positioned between spacer and facemask or mouth. Budesonide on the filter was assessed by high performance liquid chromatography. The mean filter dose for each child (mean±SD) during the 7 days was expressed as a percentage of the nominal dose. Within-subject variability was expressed as coefficient of variation (CV).

Mean filter dose in group I was 41.7±10.1% for Nebuchamber and 26.0±4.0% for Babyhaler ($p<0.001$). Mean filter dose in group II was 50.2±9.2% for Nebuchamber and 19.4±7.2% for Volumatic ($p<0.001$). Mean CV in group I was 34% for Nebuchamber and 37% for Babyhaler ($p=0.44$). Mean CV in group II was 23% for Nebuchamber and 34% for Volumatic ($p=0.003$).

There was substantial within-subject dose variability in aerosol delivery in children usig a pMDI/spacer at home. This variability was lower for the metal than for the plastic spacer in children 5-8 yrs of age. The dose delivered to the mouth was about two-fold higher for the metal than the plastic spacer independent of age.

INTRODUCTION

Pressurized metered dose inhalers (pMDI) combined with spacers are widely used for the treatment of asthma in children. Although pMDI/spacers are convenient and relatively simple to use, the dose delivery from a spacer depends on a number of patient and device features [1-4]. Predictability and reproducibility of dosing are relevant for any drug therapy. This general pharmacological principle allows the clinician to select the proper dose and device for a given patient. Considerable between-subject variability in aerosol delivery from spacers has been described [1, 5]. These results were based on only one or two observations per child in a laboratory setting, recorded within a short interval. Though such studies may provide a good impression of the quality of the different devices, it may not adequately represent the situation in daily life, which is obviously important when prescribing inhaled drugs.

One of the factors that can contribute to variability in aerosol delivery is the material from which the spacer is made. Until recently, spacers were made of plastic. Various studies have shown that electrostatic charge on plastic spacers decreases drug delivery [6,7]. Recently, a metal spacer (Nebuchamber® (Astra Draco, Lund, Sweden)) has been developed that does not have this disadvantage [5]. The aim of this study was to assess within-subject variability of aerosol delivery from several spacers in asthmatic children 1-8 yrs old in a daily life setting in an open randomized, crossover study. Secondary aims were to compare the variability of aerosol delivery from metal and plastic spacers and to investigate whether within-subject variability was age dependent.

MATERIALS AND METHODS

STUDY POPULATION

Children aged 1-8 yrs with stable asthma and on daily inhalation therapy were recruited from the asthmatic population treated at the Princess Margaret Hospital for Children in Perth, Australia. Stable asthma was defined as having no exacerbations requiring additional oral corticosteroids or any change in asthma medication for at least one month prior to the onset of the study. None of the children suffered from any other disorder that could affect lung function. The children were divided into two age groups, 1-4 yrs (group I) and 5-8 yrs (group II), to distinguish between inhalation *via* a face mask or a mouthpiece. Written informed consent was obtained from all parents. The study was approved by the local ethics committee.

MATERIALS

Group I used the metal Nebuchamber® (250 mL; Astra) and the polycarbonate Babyhaler® [8] (350 mL; Glaxo Wellcome, Lodon, UK) both with face masks. Group II used the Nebuchamber® without face mask and the polycarbonate Volumatic® (750 mL;

Glaxo Wellcome). The inlet of the Babyhaler was slightly adapted to obtain a good fit and a straight plume of the Pulmicort® pMDI (Astra) into the spacer. For the Volumatic a small plastic connector (Astra) was used to fit the Pulmicort pMDI. The day before the spacers were allocated to the children, they were washed in water with normal household detergent, rinsed thoroughly with warm water and drip-dried according to the instructions for use from the manufacturers. Each week the subjects received a clean spacer. Budesonide pMDI 200μg·dose^{-1} (Pulmicort®) was used as the study medication. Each child received a new budesonide pMDI. The first 10 actuations of a new pMDI were wasted, to avoid variable doses in the first 10 actuations [9,10]. Aerosol from the spacers was collected on a filter (Vital Signs, Totowa, NJ, USA) inserted between the face mask or the patient's mouth and spacer. The filter has been shown to retain > 99% of the budesonide delivered from a spacer [5]. The filter added a dead space of 20 mL to the system. The pressure drop over the filter was 230 Pa at 60 L·min^{-1} [5], which is approximately one fifth of the airway resistance of a young child [11].

To evaluate asthma stability, all parents filled out a diary card on asthma symptoms twice a day during the study period. The symptoms cough, wheeze and shortness of breath, and co-operation during drug administration were each assigned a score of 0-3.

STUDY PROCEDURE

The study was designed as a randomized crossover study. During the 3 study weeks, the investigator visited the children 4-times at home. On the first visit the use of the pMDI/spacers with the filter was demonstrated and study materials provided. The study medication had to be administered twice daily, before regular maintenance therapy, which was continued during the study period using the patient's own medication and device. Before each administration the parents attached a new filter to the spacer. The spacer was held in a horizontal position, while ensuring a close fit of the face mask or lips sealed around the mouthpiece with the child in an upright position. The pMDI had to be shaken vigorously for 10 s just prior to actuation. One puff of budesonide was actuated into the spacer. The child had to inhale for 60 s with quiet tidal breathing. Subsequently, the filter was removed from the spacer and both sides of the filter holder were sealed with sticky tape. Each filter was labelled with a unique code. Finally, the filters were wrapped in aluminium foil to protect the budesonide from destabilisation by light. In the first study week, all children practised the use of both spacers with filters and a placebo. After this run-in period the children were randomized to start with budesonide *via* the metal or the plastic spacer. On the second visit any problems were discussed. The administration procedure was demonstrated by the child, corrected if necessary, and new spacers, filters and pMDI were provided. On the third visit the filters and the first spacer were collected and the second spacer and set of filters were issued. On the fourth visit the filters and the second spacer were collected. Thus, for each spacer 14 samples were obtained per child, *i.e.* two samples per day.

FILTER ANALYSIS

All filters were analysed in a blinded fashion. Filter and filter holder were washed in ethanol, containing an internal standard (fluocinolone acetonide). Budesonide was quantified by high-performance liquid chromatography (HPLC), using an ethanol-water (43:57) mobile phase and a Supercosil LC-18 column (5μm particles, 5 cm x 0.46 cm ID; Supelco, Bellafonte, PA, USA). Budesonide was detected by UV spectrophotometry at a wavelength of 254 nm.

STATISTICAL ANALYSIS

SPSS for Windows version 6.1 (SPSS, Chicago, IL, USA) was used for the statistical analysis. The filter dose, *i.e.,* the amount of budesonide deposited on the filter, was expressed as a percentage of the nominal dose. The mean ± SD of the filter dose of the 14 samples collected in 1 week was calculated for each child. Within-subject variability was expressed as coefficient of variation (CV). Paired t-tests were used to compare means, after verifying that there were no period or carry-over effects [12]. The presence of a priming effect was investigated by plotting all filter doses for each child against the 14 consecutive sample numbers and drawing individual regression lines through these data points. The mean slope of the individual regression lines per spacer was calculated for the two groups.

Relationships between age and filter doses, age and within-subject CV, between individual filter doses of both spacers and between within-subject CV of both spacers were calculated by means of regression analysis. Mean asthma scores, defined as the sum of asthma symptoms recorded on the diary card during one week, while using one of the two spacers were compared by paired t-test.

This analysis was repeated after excluding the samples where the child had not cooperated (score 2 and 3) during the procedure, as indicated in the diary. A p-value of ≤ 0.05 (two-sided) were considered significant.

RESULTS

Forty-one children were enrolled into the study. Eight dropped out after the run-in-period. The reasons for drop out were: noncooperative child (n=4), asthma exacerbation (n=1) and noncompliant parents (n=3). Seventeen children (12 male) in group I, and 16 (12 male) in group II completed the study. Mean age in group I was 40 months (range 17-59), mean age in group II was 83 months (range 65-104). All children had been using a pMDI/spacer for more than six months, except one who had been using a dry-powder device. The devices used before study entry were for group I: Breath-a-Tech® (Scott Dibben, New Castle, NSW, Australia) (n=8), Volumatic (n=2), Aerochamber® (Trudell Medicals, London, Ontario, Canada) (n=6), Babyhaler (n=1), and for group II: Breath-a-tech® (n=3), Volumatic (n=12), Turbuhaler® (n=1) (Astra).

TABLE 1. Mean filter dose and within-subject variability in aerosol delivery

	Group I (1 - 4 yrs)		Group II (5 – 8 yrs)	
	Nebuchamber	Babyhaler	Nebuchamber	Volumatic
Filter dose	41.7 ± 10.1	26.0 ± 4.0‡	50.3 ± 9.2	19.4 ± 7.2‡
within-subject CV†	34.1 ± 15.6	37.2 ± 5.0§	23.1 ± 9.1	34.0± 6.5§

Results are mean±SD in % of nominal dose. †: coëfficient of variation (CV) as measure of variability. ‡: p<0.0001 compared with Nebuchamber; §: p= 0.44 compared with Nebuchamber; §: p= 0.003 compared with Nebuchamber.

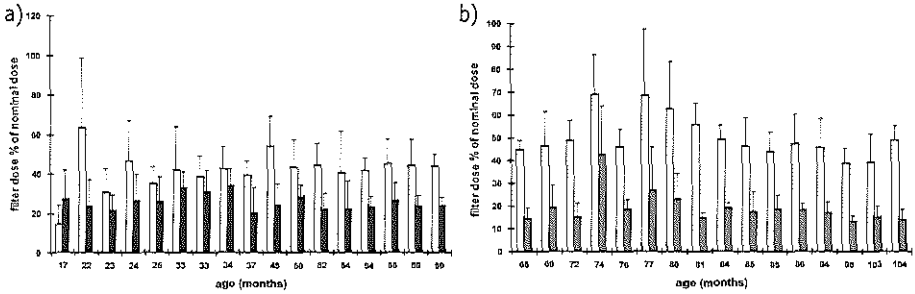

FIGURE 1. Aerosol dose delivered to the mouth for various spacer devices in relation to age. a) Group I (age 1-4 yrs, n=17) with mean (±SD) filter-dose of budesonide for each child for the Nebuchamber (□) and the Babyhaler (■) as a percentage of the nominal dose (200 µg). b) Group II (age 5-8 yrs, n=16) With mean (±SD) filter-dose of budesonide for each child for the Nebuchamber (□) and the Volumatic (▨) as a percentage of the nominal dose (200 µg). Each pair of columns represents one child in ascending order of age.

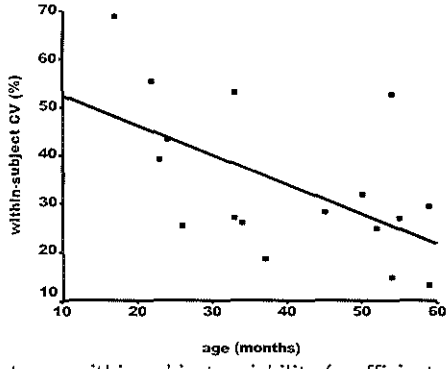

FIGURE 2. Correlation between within-subject variability (coefficient of variation (CV)) of dose and age for the Nebuchamber in group I. (r = -0.6, p = 0.02)

FILTER DOSE

Filter doses (mean± SD) for the spacers in group I and II are shown in figure 1 and in table 1. Filter doses were significantly higher ($p<0.0001$) in the Nebuchamber than in the plastic spacers. There was no significant correlation between age and filter dose in group I and II with both spacers. In group II there was a significant positive correlation between the filter dose for the Nebuchamber and the Volumatic ($r = 0.79$, $p = 0.0003$). In other words, children with higher filter doses for the Nebuchamber also tended to have higher filter doses for the Volumatic. This correlation was not found in group I.

In group I, a small but significant priming effect was found for the Babyhaler but not for the Nebuchamber ($p<0.05$). The filter dose in the Babyhaler increased 0.4% per consecutive sample, or 0.8% per day. In group II there was no correlation between filter dose and sample number for the Nebuchamber or for the Volumatic.

VARIABILITY

Within-subject variability of aerosol delivery in both groups (mean±SD) is shown in table 1. In group I the within-subject CV for the Nebuchamber and for the Babyhaler were similar ($p = 0.44$). In group II the within-subject CV for the Nebuchamber was significantly smaller than for the Volumatic ($p = 0.003$). The range of within-subject CV was large in both groups for all spacers. In group II, children with a higher within-subject CV for the Nebuchamber also had a higher within-subject CV for the Volumatic ($r = 0.7$, $p = 0.028$). This correlation was not found in group I. The within-subject CV decreased significantly with age in group I for the Nebuchamber (figure 2). For the Babyhaler, within-subject CV tended to decrease with age ($r = -0.5$, $p = 0.06$), but this was not the case for the spacers in group II.

DIARY CARDS

Mean asthma scores were similar during the use of the different spacers in both groups. The majority of children were cooperative during the procedure. Of the 476 assessments in group I score 2 or 3 were recorded 41 times (8.6%) and of the 448 assessments in group II, twice (0.4%). The analysis of the data was repeated after excluding the assessments where the cooperation was scored as 2 or 3. This did not change the outcomes.

DAILY LIFE OBSERVATIONS

Despite careful repeated instruction, mistakes were still made. Some were mentioned on the diary cards or could be concluded from the raw data, while others were observed. Recorded faults were not shaking pMDI before actuation, leaving the cap on the pMDI during actuation, the wrong number of actuations (6 samples of >100% and 15 samples of >80% of the nominal dose), and using the face mask of the Nebuchamber upside-down by a 17-month-old child, resulting in a very low filter dose.

DISCUSSION

This study assessed the within-subject variability in aerosol delivery from pMDI/spacer devices in asthmatic children aged 1-8 yrs old in a daily life situation. It was found that the within-subject variability in aerosol delivery was considerable. Former studies have already indicated large between-subject variability in aerosol delivery in children using plastic and metal spacers [1,5,13]. In clinical practice the performance of inhalation devices should be known in order to prescribe medication dosages correctly and consistently.

There are seveal sources of dose variability. Electrostatic charge which retains the drug in the spacer can build up on plastic (polycarbonate) [14,15]. Therefore, we hypothesized that electrostatic charge in plastic spacers is a potential source of dose variability. It was found that the within-subject variability in the metal and plastic spacers was the same in younger children, and significantly less in the metal spacer in older children. A small but significant priming effect was found in the Babyhaler but not in the Volumatic. Previously, it has been shown that several actuations from a pMDI reduce the negative effect of electrostatic charge on aerosol delivery [5]. The present results indicate that electrostatic charge probably plays a minor role as a cause of variability. The fact that no priming effect was shown in the Volumatic is difficult to interpret. It is possible that some priming was present but that other factors, such as valve design or volume, in the Volumatic were more important for aerosol delivery and therefore masked a possible small effect of priming. It is also possible that because of the larger volume, and therefore larger inner surface, the priming was not sufficient to show an increase of filter dose within a week of use.

It was found that within-subject variability of aerosol delivery was inversely related to age only in children <5 yrs old. This relation was stronger for the Nebuchamber than for the Babyhaler. A difference between age groups might be explained by the use of a face mask in group I. The effectiveness of a face mask depends on the fit and the cooperation of the child. A fitting problem with the facemask can lead to aerosol dilution by air entrained from the side of the facemask. The low mean filter dose of the17-month old child, who used the face mask of the Nebuchamber upside-down, illustrates this possibility. However, mask fit was not systematically investigated in this study, so its importance can only be speculated upon.

Other patient-related factors could have contributed to variability in aerosol delivery. Within-subject variability for Nebuchamber and Volumatic in group II were positively correlated. A likely explanation for this correlation is that consistent differences in inhalation technique or administration procedure between children occured. This is confirmed by the positive correlation between the mean filter dose for the Nebuchamber and the Volumatic, which indicates that children with a better technique are able to inhale more aerosol from each device. Mistakes were made despite repeated instruction: filter doses of 0% and >100% demonstrated that the instructions had not

been followed correctly by some children and parents. These data were not excluded from the analysis because mistakes in the administration procedure will always contribute to variability in aerosol delivery in daily life. In an *in vitro* study, it has been shown that the way in which the pMDI is handled before inhalation contributes to the variability of dose. For instance not shaking the pMDI reduced the dose delivered by 25.5% [16]. The present results and observations confirm that differences in inhalation technique and administration procedure are indeed important factors in the variability in aerosol delivery in daily life.

It can be argued that the plastic spacers were not designed for the use of a Pulmicort pMDI. Each formulation/spacer combination may behave differently, therefore it is not known how the results would have varied if a different drug had been used. However, the large within-subject variability appeared to be not only spacer-dependent and can therefore be considered as a general feature in the use of pMDI/spacers for inhalation therapy in young children. Further research to assess dose variability in other pMDI/spacer combinations is needed.

Within subject variability is expressed as CV which cannot be interpreted separately from the mean filter dose. There were large differences between the filter doses of the various spacers, whereas the variabilities expressed as CV were similar. This indicates that the plastic spacers with the lower dose also had the lowest absolute variability. It is encouraging that the average amount of aerosol a child received over a 1-week period appeared reasonable. The filter dose was significantly less with the two plastic spacers than with the metal Nebuchamber. It is likely that electrostatic charge on the plastic spacers contributed to this difference, as it has been shown that the Babyhaler performs as well as a Nebuchamber when electrostatic charge is minimized by detergent coating [17]. However, this was not the case in the present study, as the majority of plastic spacers are actually used without coating, in accord with the manufacturer's instructions.

In this study, filter dose was found to be independent of age in both groups. This is in agreement with previous studies.[1,13,17]. The difference in mean filter dose between group I and II is probably not an effect of age, but a result of the use of a face mask in group I. The face mask adds dead space and may cause air entrainment, thereby reducing the filter dose in group I selectively.

It is can be argued that filter studies only provide information about the amount of aerosol delivered to a patient and not about deposition in the respiratory tract. In the present study, the primary aim was to assess reproducibility of aerosol delivery from pMDI/spacer combinations in children and not to assess the efficiency of inhalation systems to deliver aerosol to the lungs. Therefore, the assessment of aerosol delivery by means of a filter is a valid method to obtain such information. Clearly, further research should focus on the therapeutic implications of the present findings.

In conclusion, there was a considerable within-subject variability in aerosol delivery from both metal and plastic spacers in asthmatic children 1-8 yrs old in daily life. This variation was age dependent below the age of 4 yrs. Only a small part of the

variability in aerosol delivery could be attributed to differences in spacers. The absence of electrostatic charge on the metal spacer did not result in more constant dose delivery in children aged 1-4 yrs. However, the relative within-subject variability was less for metal than for plastic spacers in children >5 yrs old. Factors such as spacer design, use of a face mask, age, inhalation technique and compliance with a correct administration procedure are possible causes of variability in aerosol delivery. Further research is required to investigate the causes and consequences of dose variability in aerosol treatment with pressurized metered dose inhalers/spacers in asthmatic children.

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CHAPTER 4

Aerosol delivery from spacers in wheezy infants: A daily life study

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ABSTRACT

The aims of this study were to assess and compare dose delivery and dose variability of pressurized metered dose inhalers (pMDI)/spacers in wheezy infants in daily life and to investigate factors influencing aerosol delivery.

In an open randomized cross-over study in 25 wheezy infants aged 5-26 months, a metal spacer (Nebuchamber®), a detergent coated (DC) and a non-detergent coated (nonDC) plastic spacer (Babyhaler®) were tested at home for 7 days each. Budesonide (200 µg *b.i.d.*) was administered *via* a Nebuchamber or fluticasone (125 µg *b.i.d.*) *via* a Babyhaler. Aerosol was trapped in filters, positioned between the spacer and facemask. Cooperation was scored on diary cards. Electrostatic charge (ESC) of the spacers was measured. Evaluations of administration technique were made from video recordings.

Median (range) dose delivery on the filters expressed as per cent (%) of nominal dose, was 34% (3 - 59), 23% (1 – 49), and 41% (12 – 55) for the Nebuchamber, nonDC-Babyhaler, and DC-Babyhaler respectively. Considerable dose variability was found, median (range) within-subject dose variability, expressed as coefficient of variation, for the Nebuchamber (49% (15-249)) was significantly higher compared with both nonDC- (36% (12-325)) and DC-Babyhalers (27% (10-122)), for which dose variabilities were similar.

Detergent coating was effective to reduce electrostatic charge, and to increase dose delivery, but had no effect on dose variability. Bad cooperation was an important cause for high dose variability for all spacers (R=0.5-0.6, p<0.02). Many mistakes were made during the administration procedure.

INTRODUCTION

Spacers were introduced to facilitate inhalation of therapeutic aerosols from pressurized metered dose inhalers (pMDI), being especially useful for the treatment of asthma in young children. Spacers are widely used, but little is known about their dose delivery, and dose variability in daily life use. This information is important, since it allows the clinician to select the proper dose and device for a patient. The dose delivered from a spacer can be unpredictable and depends on a number of patient and device-related factors [1-4]. Considerable between-subject variability in aerosol delivery from spacers has been found in a laboratory setting [1,5]. However, these previous studies did not adequately represent the situation in daily life.

In a previous study the authors showed that there is considerable dose-to-dose (or within-subject) variability from metal as well as plastic spacers when studied at the homes of children aged 17 months-8 years [6]. In children aged <4 yrs, dose variability was inversely related to age. However, this study resulted in a number of unanswered questions, which prompted further research. Firstly, the number of children aged <2 yrs was too small for the results to be conclusive for this age group. Young children of this age form a special treatment group, as factors such as cooperation, acceptance and the use of a face mask may determine the success or failure of inhalation therapy. The relevance of these factors on aerosol delivery from pMDI/spacers in daily life has not been studied previously. Additionally, many mistakes in the administration technique were observed or suspected but it was not systematically evaluated. Secondly, it was not clear whether the results of the metal and plastic spacers could be interpreted as differences in spacer design or due to the presence or absence of electrostatic charge (ESC). Various studies have shown that plastic spacers can get electrostatically charged, which decreases drug delivery [7,8]. ESC can be minimized by coating the plastic spacer with a household detergent [8,9]. ESC is absent in a metal spacer. Furthermore, the authors wanted to repeat the study using a different pMDI/spacer combination, for it has been shown that each pMDI/spacer combination behaves differently [2]. Thereforea study to assess and compare aerosol delivery for a metal spacer (Nebuchamber®, AstraZeneca, Lund, Sweden) [5] with budesonide pMDI (Pulmicort®, AstraZeneca) and for a DC and nonDC plastic spacer (Babyhaler®, Glaxo Wellcome, London, UK) [10] with fluticasone pMDI (Flixotide®, GlaxoWellcome), in wheezy infants aged 0-2 years in a daily life setting, was designed. Various factors, such as cooperation and administration technique, that might affect dose delivery and dose variability in daily life were studied.

MATERIALS AND METHODS

STUDY POPULATION

Twenty-six children aged 5-26 months with recurrent wheeze requiring daily inhalation therapy were recruited from the outpatient clinic of the Sophia Children's Hospital (Rotterdam, the Netherlands), the Merwede Hospital (Dordrecht, The Netherlands) and from a general practitioner population (Brielle, The Netherlands). None of the subjects suffered from other disorders that could affect cooperation or lung function. Written informed consent was obtained from all parents. The study was approved by the local ethics committee.

STUDY DESIGN

In a four-week randomized cross-over study, the children were visited on five occasions. At the first and second home visit standardized instructions were given on the use of the spacers. During the first week, the run-in week, the children had to practice with both types of spacers. Over the next three weeks a metal spacer, a nonDC and DC plastic spacer were tested in a randomized order, twice a day for 1 week each. Aerosol delivery was assessed by means of filters, placed between the face mask and spacer. The parents completed a diary card on symptom score and cooperation score during the administration procedure twice daily. ESC of the plastic spacers was measured before and after one week of use. The administration procedure was recorded on video twice, once at the end of the week of using the metal spacer and once after using one of the plastic spacers.

SPACERS AND PMDI'S

The spacers tested were the metal Nebuchamber® (250 mL) and the polycarbonate Babyhaler® (350 mL), both with their original face masks. The Babyhaler was used with and without detergent coating, to evaluate the influence of ESC. All spacers were washed the day before they were allocated to the children. The Nebuchamber and the nonDC Babyhaler were washed in soapy water with normal household detergent, rinsed thoroughly with warm water and drip dried according to the instructions for use provided by the manufacturers. The DC Babyhaler was also washed in soapy water but not rinsed with water, and left to drip-dry [9]. All subjects received a clean spacer each week.

Budesonide pMDI 200 $\mu g \cdot dose^{-1}$ (Pulmicort®, AstraZeneca, Lund, Sweden) was used as the study medication for the Nebuchamber. Fluticasone pMDI 125 $\mu g \cdot dose^{-1}$ (Flixotide®, GlaxoWellcome, London, UK) was used for the Babyhaler. Each child received new pMDI's. The first ten actuations of a new pMDI were wasted, to avoid variable doses [11,12].

At the end of each week, spacers were rinsed with ethanol to quantify the amount of drug retained in the spacer for evaluation of the effect of detergent coating.

FILTERS AND FILTER ANALYSIS

Aerosol delivery was measured by means of a filter (Vital Signs Inc, Totowa, USA), inserted between the face mask and spacer. The filter has been shown to retain >99% of the drug delivered from a spacer [5]. The filter added a dead space of 20 mL to the spacer. The pressure drop over the filter is 230 Pa at 60 $L \cdot min^{-1}$ [5], which is approximately one-fifth of the airway resistance of an infant [13]. A preliminary study showed that the filter did not significantly alter the tidal volume and respiratory rate in nine children aged 10-24 months (data not shown). For each spacer a maximum of 14 filters was obtained per child, (*i.e.* two filters per day). Budesonide and fluticasone on filters and spacers were quantified by a validated method with high-performance liquid chromatography (HPLC), using an ethanol:water (43:57) mobile phase and a Supelcosil LC-18 column (5 mm particles, 5 cm x 0.46 cm (inner diameter)). The coefficient of variation of the method was <3%.

DIARY CARD

To monitor symptoms and cooperation during the study period, parents filled out a diary card twice a day. The following items were scored; cough, wheeze, shortness of breath, and cooperation during the administration procedure. Each item was assigned a score of 0-3. Score 0 for no symptoms or good cooperation, score 3 for severe symptoms or for struggling against the procedure. Total symptom score, with a maximum of 9, was defined as the sum of scores for the 3 items: cough, wheeze and shortness of breath. This symptom score was used to assess whether the different spacers were tested under similar conditions.

ELECTROSTATIC CHARGE

To evaluate the effect of detergent coating, (ESC) on the inner surface of the nonDC-Babyhaler and DC-Babyhaler was measured during the home-visits immediately before and after 1 week of use with a custom made electrometer (Central Instrumentation Dept, Erasmus University Rotterdam, The Netherlands). The electrometer consisted of a metal probe with a length of 12 cm connected to a high impedance voltmeter. To measure ESC the probe was positioned exactly in the middle of one-half of the spacer, using a wooden disc at the bottom of the probe, which fitted as a lid on the spacer half. The variability of this method of measurement was 5%. Any ESC on the inner surface of the spacer induced a charge on the probe, which was shown on the display of the electrometer. The electrometer had been calibrated on a foil-coated Babyhaler with applied voltages. The measurements were done in a standardized fashion. Both halves of the disconnected Babyhaler were measured separately. The measured voltage was used as a measure for ESC. The ESC of the entire spacer was calculated according to the formulas: $Q_1+Q_2 = Vtotal\ (C_1+C_2)$ and $Q_1+Q_2= C_1V_1+C_2V_2$ in which numbers 1 and 2 refer to the two separate spacer halves, Q is charge, C is capacitance of spacer, V is measured voltage and Vtotal is voltage of total spacer.

VIDEO

The administration technique was recorded on video during 2 of the 5 home visits, for the Nebuchamber and the nonDC-Babyhaler or DC-Babyhaler after they were used for one week. After completion of the study all recordings were scored on administration technique according to a checklist with 10 items (table 1) in a binomial scale, by five experienced observers. Observers were trained how to use the scoring system with an instruction video. The video recordings were scored in a randomized order. An item was considered correct if at least 3 observers had scored this item as correct.

Agreement between video observers was calculated as follows: for each child, all 10 items (table 1) were added by each observer per spacer to give a total score ranging from 0 (all items wrong) to 10 (all items correct). The agreement between each pair of observers regarding this score was assessed by calculation of the intra-class correlation coefficient. All pairwise coefficients were found to be >0.72 (mean: 0.84), indicating a good level of agreement between observers.

INSTRUCTION OF ADMINISTRATION TECHNIQUE

On the first visit the use of the pMDI/spacers with the filter was demonstrated. The study medication had to be administered twice daily, before regular maintenance therapy, which was continued during the study period. Before each administration a new filter was placed on the spacer by the parents. The face mask and the pMDI were attached to the spacer. Subsequently the pMDI/spacer was shaken for 10 s before placing the face mask on the child. The spacer was held in a horizontal position, while ensuring a close fit of the face mask, with the child in an upright position. Next, one puff of

TABLE 1. Checklist for the administration technique

Items		Number (%) scored correctly	
		Nebuchamber (n=22)	Babyhaler (n=24)
1.	Child sits upright	20 (91)	22 (92)
2.	PMDI is placed correctly into the spacer.	22 (100)	24 (100)
3.	PMDI/spacer is shaken for at least 5 seconds	15 (68)	16 (67)
4.	Time between shaking and actuating is < 5 seconds?	17 (77)	18 (75)
5.	Face mask is placed on face before actuation of the puff.	19 (86)	22 (92)
6.	There is a close fit of the face mask.	16 (73)	22 (92)
7.	One puff is actuated?	20 (91)	23 (96)
8.	Child breathes for 30 seconds through the spacer.	10 (46)	14 (58)
9.	Child breathes quietly through the spacer?	14 (64)	15 (63)
10.	Face mask is held on face during the 30 seconds?	11 (50)	13 (54)

pMDI: pressurized metered dose inhalers. Nebuchamber: n=22; Babyhaler: n=24

aerosol was actuated into the spacer. The child had to inhale for 30 s with quiet tidal breathing. Subsequently, the filter was removed from the spacer and both sides of the filter holder were sealed with tape. Each filter was labelled with a unique code. Finally, the filters were stored in a black plastic bag to protect the drug from destabilization by light. On the second visit the administration technique was demonstrated by the parent and child to the investigator and corrected where necessary.

STATISTICAL ANALYSIS

Filter dose was calculated as the amount of aerosol deposited on the filter as a percentage of nominal dose. Nominal dose for the budesonide pMDI was 200 μg and for the fluticasone pMDI 125 μg. Dose delivery, was calculated as the mean filter dose of the 14 samples collected in one week for each child. The within-subject dose variability, expressed as coefficient of variation (CV), was calculated for each child and spacer. Drug retained in the spacer after one week use was expressed as a percentage of the total amount of drug administered in 1 week. Mean symptom score was defined as the average of the total symptom score recorded on the diary card during one week. Mean cooperation score was calculated for each child per spacer.

Consecutive actuations into an electric spacer may reduce ESC and subsequently increase the dose delivered [5]. Whether this "priming effect" was present during 1 week use, was investigated by plotting all filter doses for each child against the 14 sample numbers and drawing individual regression lines through these data points. For each spacer the mean slope of the individual regression lines was calculated.

The Friedman test was used for overall comparisons between the various parameters investigated for the three spacers. If significance was present ($p<0.05$), pairwise comparisons were made with the Wilcoxon signed ranks test. The comparisons were carried out in triplicate: a) analysis of all available data, b) after excluding the samples where the child had not cooperated during the procedure (cooperation score 2 and 3), and c) after excluding the filters where filter dose was 0. Correlations were investigated between dose delivery and within-subject dose variability *versus* age, mean cooperation score, and video score using Spearman's correlation coefficient (r). Dose delivery and dose variability of children who were using a Nebuchamber for maintenance therapy before study entry were compared with the dose delivery and dose variability of children who were using another spacer. There were only five children who used a Babyhaler before study entry, a number that was too small to reliably compare this group with those who used other spacers. Results are given as median (range) unless otherwise indicated.

RESULTS

Of the 26 children included in the study, one child was excluded because the fluticasone pMDI had been used with the cap on, resulting in no drug on the filters. The remaining 25 children (21 male) form the study group of this report. Median age was 14 (5-26) months. The inhalation devices used before study entry were: Nebuchamber (n=12), Babyhaler (n=5), Aerochamber® (n=5) (Trudell Medicals, London, Ontario, Canada), nebulizer (n=2), nebulizer+Nebuchamber (n=1). A total of 319, 326 and 325 filters were collected for the Nebuchamber, the nonDC-Babyhaler and the DC-Babyhaler respectively. Symptom scores were low and similar during the use of the different spacers: median score was 0.2, 0.1, and 0.4 for the Nebuchamber, the nonDC-Babyhaler, and DC-Babyhaler respectively (p= 0.99).

DOSE DELIVERY

Dose delivery, expressed as a percentage of nominal dose, for all spacers is shown in figure 1. Median (range) dose delivery was 34% (3 – 59), 22% (1 – 49) and 41% (12 – 55) for the Nebuchamber, the nonDC-Babyhaler, and DC-Babyhaler respectively. Median dose delivery for the Nebuchamber was significantly higher than for the nonDC-Babyhaler (p= 0.03) but lower than for the DC-Babyhaler (p=0.005). The difference in dose delivery between nonDC-Babyhaler and DC-Babyhaler was highly significant (p<0.001). There was a positive correlation between the dose delivery of the Nebuchamber and the DC-Babyhaler (r=0.5, p= 0.01) and between the nonDC- and DC-Babyhaler (r=0.5, p=0.02). In other words, children with a low dose delivery in one spacer tended to have a low dose delivery in the other spacers too. This correlation was not significant between the Nebuchamber and the non-DC Babyhaler (r=0.3, p=0.1). No drug was found on the filter in n= 37 (12%), n=20 (6%) and n=11 (3%) filters of the Nebuchamber, the nonDC-Babyhaler and DC-Babyhaler respectively. The conclusions as described above did not change when the filters without drug were excluded from analysis. No significant priming effect was found for any of the three spacers. No significant correlation was found between age and dose delivery for any of the three spacers.

DOSE VARIABILITY

Dose variability, expressed as the within-subject coefficient of variation (CV), for each spacer is shown in figure 2. Median dose variability was 49% (15-249), 36% (12-325) and 27% (10-122) for the Nebuchamber, the nonDC-Babyhaler, and DC-Babyhaler respectively. The dose variability for the Nebuchamber was significantly higher than the dose variability for the nonDC-Babyhaler and DC-Babyhalers. The dose variability for the nonDC-Babyhaler and the DC-Babyhaler were not significantly different. There was a positive correlation between the dose variabilities of the Nebuchamber and the nonDC-Babyhaler (r=0.4, p= 0.03) and between the nonDC-

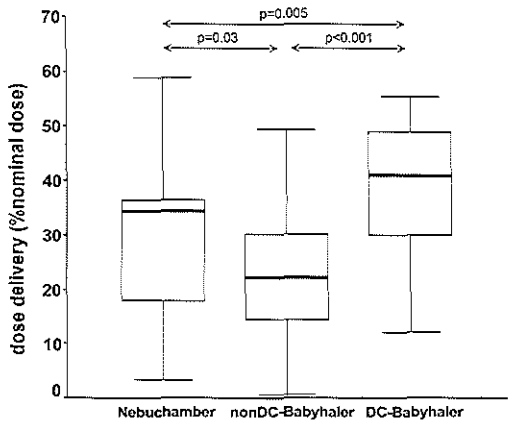

FIGURE 1. Boxplot of dose delivery, calculated from the mean dose on the filters as a percentage of nominal dose per child, for the Nebuchamber, non-detergent coated (nonDC) Babyhaler and the detergent coated (DC) Babyhaler. Whiskers represent largest and smallest observed value that is not outlier, box represents 25th and 75th percentiles, and bar represents median.

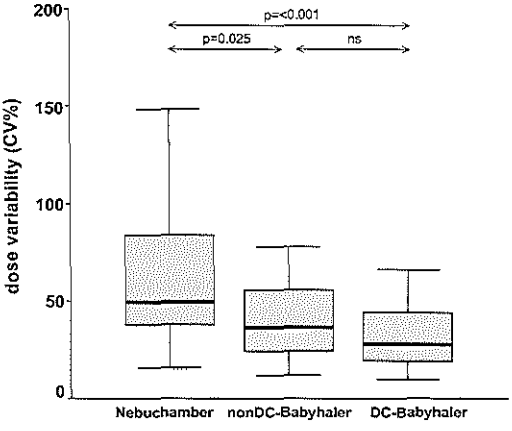

FIGURE 2. Boxplot of within-subject dose variability, expressed as coefficient of variation (CV%) for the Nebuchamber, non-detergent coated (nonDC) Babyhaler and the detergent coated (DC) Babyhaler.

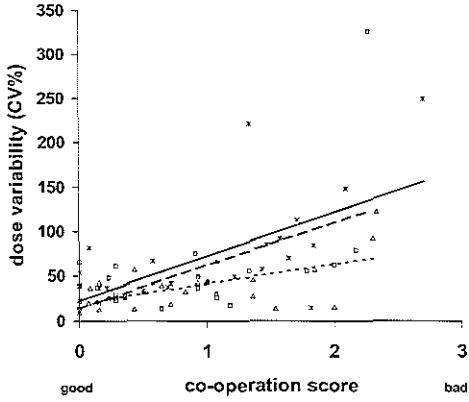

Figure 3. Scatterplot of within-subject dose variability (CV%) *versus* mean cooperation score for the Nebuchamber, non-detergent coated Babyhaler and detergent coated Babyhaler. —,*Nebuchamber (r=0.6, p=0.002);---,□:non-detergent coated Babyhaler (r=0.5, p=0.02); ·····, ▵ detergent coated babyhaler (r=0.5, p= 0.009). Cooperation score: 0=good, 3=bad.

and DC-Babyhaler (r=0.6, p=0.001): children with a high dose variability in one spacer, also tended to have a high dose variability in the other spacers. This correlation was not significant for the combination Nebuchamber *versus* DC-Babyhaler (r=0.3, p=0.1). There was no significant correlation between dose variability and age. Differences in dose delivery and dose variability between children who used a Nebuchamber before study entry and children who used another spacer were not significant.

COOPERATION SCORE

Mean cooperation scores, obtained from the completed diary cards, were not significantly different between the three different spacers: median (range) was 0.7 (0-2.7), 0.4 (0-2.3) and 0.6 (0-2.3) for the Nebuchamber, nonDC-Babyhaler and DC-Babyhaler, respectively. Bad cooperation during administration (score 2-3) was scored in 28%, 19% and 22% of all scores for the Nebuchamber, the nonDC-Babyhaler and the DC-Babyhaler respectively. The overall comparisons of the data were repeated after excluding the filter doses on which cooperation was scored 2 or 3 (bad cooperation). This did not affect the conclusions as described. A high (=bad) cooperation score led to a higher dose variability for all spacers (figure 3) and a lower dose delivery for the Nebuchamber only (R=0.5, p=0.009).

ELECTROSTATIC CHARGE

ESC_{before} and ESC_{after} one week use for each spacer is shown for the nonDC-Babyhaler and DC-Babyhaler in figure 4a and 4b respectively. In both the nonDC-Babyhaler and the DC-Babyhaler the ESC increased significantly during us for one week

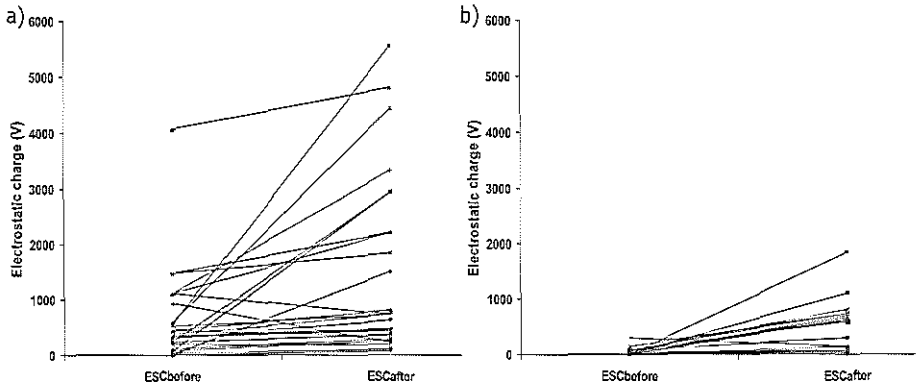

FIGURE 4. a) Electrostatic charge (V) for the non-detergent coated Babyhaler before (ESC_{before}) and after (ESC_{after}) one week use for each child ($p<0.001$). Median ESC_{before} = 370 V (range: 0-4071), median ESC_{after} = 740 V (range: 74-5550)
b) Electrostatic charge (V) for the detergent coated Babyhaler before (ESC_{before}) and after (ESC_{after}) one week use for each child ($p<0.001$). Median ESC_{before}: 0 V (range: 0-295), median ESC_{after}: 296 V (range: 0-1850). ESC_{before} and ESC_{after} for detergent coated Babyhaler compared with ESC_{before} and ESC_{after} for non-detergent coated Babyhaler respectively: $p<0.001$ for both.

($p<0.001$). ESC_{before} and ESC_{after} were significantly higher in the nonDC-Babyhaler compared with the DC-Babyhaler ($p<0.001$). ESC_{before} was 0 V in only one (4%) of the nonDC-Babyhalers, against 18 (72%) of the DC-Babyhalers. ESC_{after} was 0 V in none of the nonDC-Babyhalers and in three (12%) of the DC-Babyhalers.

Detergent coating significantly reduced the amount of drug retained in the spacer. This was 50% (32-78) and 29% (21-60) for the nonDC-Babyhaler and DC-Babyhaler respectively ($p<0.001$). Amount of drug retained in the Nebuchamber was 46% (23-93), which was not significantly different from the amount retained in the nonDC-Babyhaler but significantly higher than in the DC-Babyhaler ($p<0.001$).

ADMINISTRATION TECHNIQUE

Table 1 shows the number of children that performed the administration technique correctly for each item of the checklist for both spacers. In one-third of the cases the pMDI/spacer was not shaken correctly. A close fit of the face mask was observed in 73% of the cases for the Nebuchamber and in 92% for Babyhaler. Additional observations for the Nebuchamber mask were that substantial pressure was used (pressing the nose down and causing flattening of the nose and whitening of the skin) or that parents folded their fingers around the edges to keep the face mask in place. Furthermore, the seal between the Nebuchamber mask and the face was easily interrupted by movements of the child. The suboptimal fit was clearly visible especially around the

nose. Only half of the children managed to breath for 30 s or more through the spacer or managed to maintain the mask on the face. This showed that items requiring good cooperation (items 8, 9, and 10) during the administration procedure appeared to be difficult to achieve in this age group.

DISCUSSION

In this study dose delivery and within-subject dose variability from a metal and a plastic spacer in children aged 5-26 months were compared. Furthermore, several factors that could affect dose delivery and dose variability in daily life were studied. Dose delivery from the spacers was on average one-third of the nominal dose with a wide range between the children. Dose delivery was lowest in the nonDC-Babyhaler and highest in the DC-Babyhaler. The dose variability, in daily life, in all of the tested spacers was found to be considerable. Dose variability in the nonDC-Babyhaler and the DC-Babyhaler were not significantly different and were lower than in the Nebuchamber. These findings are in contrast with other studies, in which the Nebuchamber with face mask delivered a similar dose as a detergent coated Babyhaler [9], and a higher dose than other spacers [5,14,15]. However, these previous studies were performed in a laboratory setting, using controlled and standardized procedures, where one experienced person performed the administration. The present study was performed in a daily life setting where the administration was done by parents. In this set-up the influence of factors such as cooperation and administration technique on dose delivery and dose variability of spacers could be investigated.

For both the Nebuchamber and the Babyhaler, it was found that non-cooperation increased dose variability. For the Nebuchamber bad cooperation reduced dose delivery, but this correlation was not significantly present in the Babyhaler. It seems logical that the drug delivery of a spacer improves when a child is cooperative during the administration. However, the importance of cooperation for the administration of inhaled drugs in daily life has not been investigated previously. Tal *et al.* [4] found that lung deposition, in two infants, from a small volume plastic spacer was negligible when they were crying. Recently, it was shown that crying significantly reduces drug delivery to the lungs in infants [16]. The present study has clearly shown that cooperation is a major problem for aerosol therapy in young children in daily life. The video recordings showed that items requiring good cooperation during the administration procedure, *i.e.* quiet breathing, inhaling for 30 s and holding the face mask on the face for 30 s were achieved by only half of the children. It should be remarked that 30 s is quite a long period, which was obviously not achieved by many children. However, the optimal time in which for children to empty a spacer is not known. The authors chose 30 s inhalation time after taking into account the small tidal volumes and irregular breathing patterns of children of this age [17]. Bad cooperation was scored by the parents in more than one-fifth of

all assessments. Even though the cooperation score was a subjective measure, scored by the parents on the diary cards, dose variability was found to be significantly higher when children were less cooperative. The findings emphasise the importance of stimulating good cooperation for optimal aerosol delivery from pMDI/spacers in infants.

The seal of the face masks used might explain the discrepancies of our 'daily life' findings with previous 'laboratory' studies. The video-recordings showed that children were often struggling against the procedure, which is likely to affect the seal of the face mask. It seemed that in these young children the seal of the Nebuchamber face mask was more sensitive to movements than the Babyhaler face mask. The face mask of the Nebuchamber lost contact with the face more easily, which was visible on the video-recordings. However, the seal of the face mask was not objectively measured. The finding that dose delivery was correlated to the cooperation score for the Nebuchamber but not for the Babyhaler, supports the authors impression that cooperation plays a larger role in the dose delivery of the Nebuchamber. Additionally, it has been previously shown that the dose delivery for older and more cooperative children (17 months-4 yrs) was higher and also dose variability was equal for the Nebuchamber when compared to the Babyhaler [6]. The results may be explained by the difference in design of the Nebuchamber mask and the Babyhaler mask. The Nebuchamber mask is pre-shaped to the facial contours, but did not seem to fit on each face. This mask was designed to minimize the dead space of the inhalation system. The Babyhaler mask has a larger dead space, but is round and made of a more flexible material than the Nebuchamber. With this facemask it seemed easier to achieve a tight fit in these young (uncooperative) children. Recently, Amirav and Newhouse [18] found that the ventilation through a pneumotachograph was better and less variable with a Babyhaler face mask than with a Nebuchamber face mask, when tested in children <5 years of age. It has been shown before that holding a face mask 2 cm from the face substantially reduces the dose delivered [3]. Based on these arguments it is suspected that the relatively high dose variability of the Nebuchamber can be explained by a suboptimal fit of its face mask. The authors hypothesize that aerosol delivery of the Nebuchamber for infants can be improved by an improved design of the face mask.

The results of the checklist for administration technique showed that even when instructions were given repeatedly, many mistakes were still made. Similar findings were found in another study in older children where 14% to 26% of children, depending on the type of spacer used, failed to demonstrate critical skills for using a spacer efficiently [19]. Consistent differences between children in administration techniques, breathing patterns and cooperation can explain why children with a low dose delivery or high dose variability in one spacer tended to show this in the other spacers also. It has been shown that patient-dependent factors such as tidal volume [3] and inhalation flow [20] are determinants for drug delivery from spacers , which can vary the dose delivered remarkably. The results emphasize the need for regular evaluation of administration technique while a child is treated with inhaled drugs by pMDI/spacer.

Plastic spacers accumulate ESC, which decreases the dose delivered [7,8]. The present study showed that detergent coating of the spacer was effective in reducing ESC, although its effect diminished over a one week period of daily use. Reducing ESC resulted in a higher dose delivery and less drug retained in the spacer. Priming of the spacer, during one week use, did not decrease ESC. The effect of priming was probably too small to compensate for other, not studied, factors that increase ESC. The influence of ESC on dose variability was investigated. Dose variability in the nonDC-Babyhaler and the DC-Babyhaler were comparable, and the dose variability was higher in the Nebuchamber, in which ESC is absent. Furthermore, in an earlier study caried out by the authors, dose variability was the same in the Nebuchamber and in the non-DC Babyhaler in children 1-4 yrs of age [6]. In the present study, it was found that ESC is not a potential source for dose variability in the plastic Babyhaler. Whether this is applicable to all plastic spacers needs to be investigated further.

No correlation between age and dose delivery or dose variability was found. In previous studies dose delivery from a Nebuchamber and a Babyhaler were also age dependent [5,6,9]. Previously, it was shown that dose variability was inversely related to age in children <5 yrs of age [6]. The small range in age might explain why no age dependent dose variability was found in the present study. Also the fact that cooperation played a larger role in this age group than in the group of <5 yrs of age, could have masked a small age effect.

Caution must be taken when interpreting filter studies, as was the case with the present study, with regard to clinical efficacy and lung deposition. The doses found on the filters is the amount of aerosol delivered to the mouth. It does not give any information on where in the respiratory tract the drug will be delivered. However, the filter method was sufficient to answer the authors questions with regards to the reproducibility of aerosol delivery from pMDI/spacers of spacers in daily life. Further research is needed to study the therapeutic implications of the present findings.

To conclude, considerable within subject dose variability was found when spacers were used at home by infants aged 5-26 months. High dose variability means that the day-to-day dose delivered from spacers is unpredictable. Reducing electrostatic charge by detergent coating of a spacer was effective for increasing dose delivery but had no influence on dose variability. Hence, electrostatic charge appeared not to be important for dose variability in the spacers studied. Dose variability was highest in the Nebuchamber and it was speculated that this was caused by a suboptimal fit of the face mask in this age group. Children with good cooperation during the administration procedure had a lower dose variability in all the spacers. The results of the present study show the importance of performing studies in 'daily life' setting. Whether or not the training of parents and their children and the evaluation of cooperation during the administration of inhaled drugs leads to more effective aerosol treatment, remains to be shown.

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LUNG DEPOSITION

CHAPTER 5

High-Percentage Lung Delivery in Children From Detergent-Treated Spacers

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ABSTRACT

Pressurized metered-dose inhalers attached to spacers are now the most common form of delivery of anti-asthma medication in children. However, no reliable data are available of how drug reaches the lungs in children of different ages. This information is crucial, as it determines the efficacy of therapy. In this study, we present information on the amount of drug reaching the lungs in children from a pressurized metered-dose inhaler attached to a detergent-coated spacer to minimize electrostatic charge on the spacer wall. Lung deposition was much higher than expected when using detergent-coated spacers. Mean (SD) lung deposition, expressed as a percentage of the total actuated dose (five actuations), was 16.4% (5.5) in younger children inhaling through a small volume spacer, and 28.2% (6.7) and 41.8% (3.8) in older children inhaling with different breathing patterns through a large volume spacer. These findings have major implications for dosage regimens for inhaled anti-asthma medication in children. Lower doses may be sufficient for adequate drugs delivered through spacers treated for static to achieve a desired clinical response.

INTRODUCTION

Pressurized metered-dose inhalers (pMDIs) are widely used for the treatment of childhood asthma. Direct, local administration of the drug to its site of action in the airways is preferable to systemic administration. The amount of dose deposited in the airways determines the efficacy and side effects. Previous deposition studies assessed lung deposition from a p MDI/spacer in young children. Only a small proportion (<2%) of each individual drug dose released from a salbutamol pMDI through a spacer reached the airways.[1,2] The most important technical factor limiting drug delivery from a pMDI through a spacer in vitro is electrostatic charge on the surface of plastic spacers. [3] We have shown that this can be abolished by coating the spacers with detergent. [4] By this simple and practical method, in vitro drug delivery is increased by more than five times and hence, in vivo delivery to adult patients is significantly increased with less variability. [5] The current study was undertaken to determine how much of the total actuated dose of a drug released from a p MDI reaches the airways in children with asthma, using a spacer treated to minimize static.

MATERIAL AND METHODS

STUDY SUBJECTS

Eighteen children (14 males), mean age 68 months (range 12 to 146 months), were included and divided into three groups according to their age: A, <48 months; B, 49-96 months and C, >96 months. All patients had asthma in a stable state as judged by the absence of an exacerbation in the preceding 4 weeks and, when it was possible to measure, an FEV_1 >80% of predicted values. Patients underwent a prestudy evaluation which included clinical examination and instructions in the optimal use of the inhalation device and, where possible, measurements of pulmonary function. The parents were given information regarding the use and effects of radioactive aerosols in children. The radioactive dose to be used was explained to be less than the natural exposure to he radioactivity on a flight from Prth to Sydney. Written informed consent was obtained from all parents, and where appropriate, from the children. The study was approved by the local hospital ethics committee and the State Radiation Safety Officer.

STUDY DESIGN

All children inhaled five puffs from a radiolabelled salbutamol pMDI through a plastic spacer in which stati charges were reduced. The number of actuations to be given to each patient was assessed on each study day prior to the inhalation procedure, based on the actual amount of radiactivity per actuation measured by using a multistage liquid impinger (MSLI: Copley, Nottingham, UK), so that patients would not receive a dose exceeding 2 Megabecquerels (MBq) in total dose. Children <48 months (group A)

used a small volume spacer with face mask (Babyhaler®; Glaxo Welcome, Schoenbuehl, Switzerland). Children >48 months (groups B and C) used a large volume spacer (Volumatic®; Allen Hanburys, Sydney, Australia). Electrostatic charge on the internal surface of the spacers was reduced by detergent (Cetrimide 40%; Princess Margaret Hospital Pharmacy, Perth, WA, Australia) coating (the spacers were soaked in diluted detergent and subsequently drip-dried). Residual electrostatic charge was measured using a modified electrometer (Electronic Instruments, model 37C, Jacoby Mitchell, Sydney, Australia).[5] The pMDI was shaken between actuations. Patients from Groups A and B were allowed five tidal breaths between each actuation. Patients from Group C inhaled with a single, slow maximal inhalation following each actuation and held their breath for 10 sec after each inhalation. Following inhalation, subjects from group B and C exhaled slowly through a filter (Curity® Anesthesia Filter; Kendall, MA) and subsequently rinsed their mouths and gargled with water. Washings were collected. Activity in these washings was quantified using an ionisation chamber (Atomlab 200 dose calibrator; Gammasonics, Sydney, Australia). A filter (Curity® Anesthesia Filter) was inserted at the expiratory valve of the Babyhaler® to collect the expired aerosol in Group A.

Quantification of the distribution of radioactivity depositing in the patients' lungs was done in the following way. A flood source containing approximately 37 MBq of ^{99m}Tc was used to obtain values for attenuation of activity due to absorption by body tissues. [6,7] Since attenuation of activity is dependent on size and body mass, and since these parameters varied greatly between patients, an attenuation value was determined for each patient. After the inhalation procedure, anterior and posterior images of the chest and the abdomen were obtained together with lateral images of the upper airway, using a gamma camera (Dual Head GCA-7200A; Toshiba Corporation, Tochigi-Ken, Japan). Collection times were 2 min for each of the images. Areas of interest were defined for each of the images, and separate count rates were determined for the right and left lungs, stomach, oesophagus, throat and mouth. Each count rate was corrected for background counts and attenuation, and the geometric means of corresponding anterior and posterior count rates were calculated. The dose deposited in the lungs was then expressed as a percentage of the total actuated dose, defined as total body dose, dose retained in the actuator and spacer, dose exhaled, and, where obtained, dose from mouthwashing and dose from gargle. All these doses were measured using the same gamma camera and the same collection timeof 2 min. The total dose deposited in the mouth, throat, oesophagus, stomach and, where obtained, in the mouthwash and *gargle, was* defined as gastrointestinal deposition. Deposition within the lungs was then subdivided into two regions: peripheral and central. The peripheral to central deposition ratio (P:C ratio) was quantified using the method described by O'Doherty et al.,[8] in which deposition in the central region representing half the width of the lung and one third the height was compared with the remaining peripheral region. The distribution index was defined as the following ratio: lung deposition divided by gastrointestinal deposition.

LABELING OF SALBUTAMOL PMDI

Salbutamol pMDI (Ventolin®; Allen Hanburys, Sydney, Australia) was labeled using a modification of the method described by Köhler et al.[9] For the labeling of one canister, 500-600 MBq ^{99m}Tc (0.5-1.0ml) were eluted from a generator (Technetium 99m Generator, Australian Radioisotopes, Lucas Heights, Australia) and mixed with 2 mL of 20% NaCl. The 2 mL were then poured into a separating funnel and shaken together with 4mL of ethyl methyl ketone (butanone). The two phases were allowed to separate, and the top layer (^{99m}Tc in butanone) was collected in a new pMDI canister. The collected butanone containing the radioactivity was evaporated for 12 min in a nitrogen flow (9-13L.min^{-1}). The canister was placed into an oven for half an hour at a temperature between 73-85°C to evaporate the water content. The canister was then placed in dry ice to be cooled. A frozen (dry ice) commercial pMDI was opened with a pipecutter (TC 1000, Imperial Eastman), and the contents were poured into the cooled canister containing the radioactivity and immediately crimped (Crimper Type 555G, Pamasol; Willi Mäder AG; Pfäffikon, Switzerland).

The closed canister was subsequently shaken for half an hour in different positions. In vitro assessment of radiolabelling was done by measuring in vitro particle size distribution and total drug delivery using a multistage liquid impinger (MSLI) before and after testing the children. The sizes of particles deposited on stages 1, 2, 3 and 4 were >13µm, 6.8-13µm, 3.1-6.8µm and <3.1µm, respectively. Ten actuations of radiolabelled salbutamol from the pMDI were drawn through the MSLI at a continuous flow of 60 L min^{-1}. The actuator, the glass throat and the four stages of the MSLI were washed with 45 mL of methanol. Five milliliters of 0.1M NaOH were added to each wash. The absorbance of salbutamol (wavelength = 246 nm) was measured in each wash, using a spectrophotometric method. The concentration of salbutamol was calculated using the absorbance of a solution containing a known concentration of salbutamol. The standard curve for salbutamol was linear (r^2=1.00) for concentrations between 0 and 21µg.ml^{-1}. The distribution of radioactivity in the different washes was measured in an ionisation chamber (Atomlab 200 dose calibrator; Gammasonics, Sydney, Australia). The output and the particle size distribution of ^{99m}Tc labeled salbutamol from the study pMDIs (n = 6) were then compared to the particle size distribution of salbutamol from commercial Ventolin® pMDIs (n = 6). This was done to confirm that ^{99m}Tc acts as a suitable marker for salbutamol and to determine the amount of radioactivity and of drug per actuation by dividing the amount recovered in the MSLI by a factor of 10.

ANALYSIS

The Minitab statistical package, version 11.12 (Minitab Corporation), was used to perform the statistical analysis. Descriptive statistics were generated using the Excel program, version 5.0 (Microsoft Corporation). The following variables were calculated in Mbq as a percentage of total actuated dose: a) total lung deposition; b)

gastrointestinal deposition; c) dose exhaled; d) dose retained in the actuator and spacer; and e) ratio of peripheral to central lung deposition. Continuous variables were compared using the Pearson product moment correlation coefficient (r). The mean of continuous variables across two categories of a variable were compared using a two-sample *t*-test. The mean of a continuous variable across more than two categories of a variable were compared using ANOVA.

RESULTS

Figure 1 shows the drug particle size distributions from commercial and labeled salbutamol pMDIs, compared with the distribution of the radioactivity, assessed with the MSLI. A good correspondence was found. The mean (SD) amount of particles <3.1μm from stage 4, expressed as a percentage of the metered dose, was 37.5% (2.1), 37.4% (0.8) and 35.9% (1.6) for unlabeled drug (commercial Ventolin®), radiolabel (labeled salbutamol pMDI) and labeled drug (labeled salbutamol pMDI), respectively. The mean (SD) amount of radioactivity and salbutamol per actuation was 0.37 (0.02) MBq and 98.5 (2.8) μg, respectively.

Gender, age and height of the patients who completed the study (n = 18) are shown in Table 1, together with individual FEV_1 values, lung deposition, and gastrointestinal deposition.

Mean (SD) lung deposition expressed as a percentage of the metered dose was 16.4% (5.5), 28.2% (6.7), and 41.8% (3.8) in Groups A, B and C, respectively ($P < 0.001$) (see Table 2). There was a positive correlation between total lung deposition

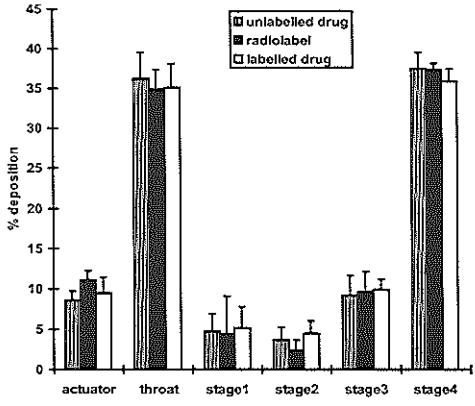

FIGURE 1. Drug (salbutamol) particle distribution from commercial and labelled pMDIs compared to the distribution of the radioactivity from labeled pMDI (n = 6).

TABLE 1. Demographic Data for the Patients (n = 18) Including Individual FEV_1 Values, Total Lung Deposition, and Gastrointestinal Deposition Expressed as Percentage of Total Metered Dose.

Gender	Age (months)	Height (cm)	FEV_1 (% predicted)	Total lung deposition (% of total delivered dose)	Gastrointestinal deposition (% of total delivered dose)
f	12	75		12.3	20.2
m	18	81		11.3	23.1
m	23	88		20.0	23.0
m	24	87		8.5	27.4
m	25	87		21.9	17.1
m	34	95		14.4	26.9
m	44	106		18.6	14.3
m	45	102		23.9	14.8
m	73	116	1.69 (138)	29.0	22.3
m	78	109	1.13 (120)	27.6	13.1
f	81	115	1.25 (113)	22.7	16.7
f	85	118	1.74 (111)	22.6	13.6
m	94	121	1.38 (99)	38.9	18.1
m	98	130	1.66 (101)	39.4	18.4
m	104	129	1.73 (103)	48.5	11.4
m	120	152	2.61 (106)	39.5	16.7
m	121	134	1.64 (89)	41.2	16.7
f	146	142	2.02 (98)	40.2	19.2
Mean (range) values				26.7(8.5 - 48.5)	18.5(11.4 - 27.4)

f, female; m, male

TABEL 2. Mean (SD) amount of lung and gastrointestinal deposition and Mean (SD) amount of dose retained in the actuator, filter, spacer, and face mask, expressed as percentage of total actuated dose in different age groups (Group A, B, and C)

	Group A	Group B	Group C
Actuator	12.3% (5.2)	12.4% (4.3)	8.5% (2.7)
Spacer	36.9% (2.6)	42.4% (10.3)	32.9% (2.7)
Filter	8.7% (3.9)	0.2% (0.1)	0.3% (0.2)
Mask	4.7% (2.8)		
Gastrointestinal deposition	20.9% (5.1)	16.8% (3.7)	16.5% (3.0)
Lung deposition	16.4% (5.5)	28.2 (6.7)	41.8% (3.8)

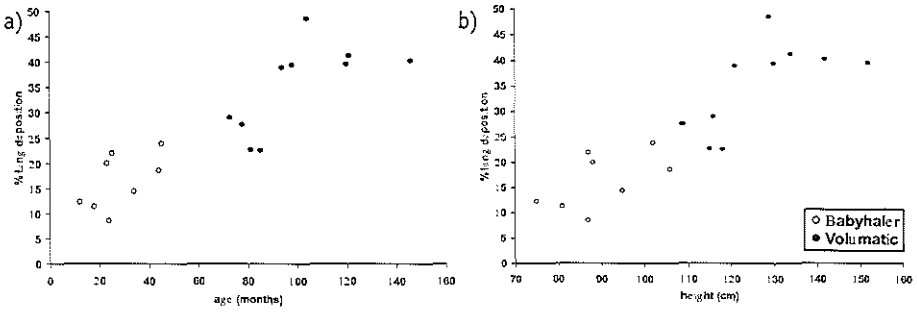

FIGURE 2. Scatter plots of total lung deposition expressed as a percentage of the total metered dose vs. (a) age (R^2 = 0.78, P <0.001) and (b) height (R^2 = 0.76, P <0.001).

and age (r = 0.88, P < 0.001) (Fig. 2a) and height (r = 0.88, P < 0.001) (Fig. 2b). When the amount deposited in the lungs was corrected for body weight (BW), there were no differences between the different age groups. Mean (SD) lung deposition corrected for BW was 1.1%/kg BW (0.4), 1.3%/kg BW (0.3), 1.3%/kg BW (0.3) and 1.3%/kg BW (0.4) in Groups A, B, and C, respectively (P = 0.49). The mean (SD) P:C ratio was 1.9 (0.3), 1.8 (0.3), 1.6 (0.5) and 1.7 (0.4) in Groups A, B, and C, respectively (P = 0.67). There was no significant correlation between P:C ratio and age (r = -0.26, P = 0.30) or height (r = -0.34, P = 0.17).

Mean (SD) gastrointestinal deposition (mouth, throat, oesophagus, stomach and, where obtained, mouthwash and gargle) was 20.9% (5.1), 16.8% (3.7), and 16.5% (3.0) in Groups A, B, and C, respectively (P = 0.08). There was a small, positive correlation between gastrointestinal deposition and age (r = -0.47, P = 0.05) or height (r = -0.47, P = 0.05).

The distribution index was 0.9, 1.7 and 2.5 in groups A, B, and C, respectively (P = 0.001).

DISCUSSION

Total lung deposition of ^{99m}technetium labeled salbutamol from a pMDI through a plastic spacer treated with detergent in asthmatic children was much higher than predicted. Several in vitro and filter studies using different plastic spacers have estimated the lung deposition in children to be less than 10%.[10-12] Our finding of a higher lung deposition is most likely explained by reducing electrostatic charge on the surface of the plastic spacer. O' Callaghan et al. [3] showed that electrostatic charge plays a major role in drug delivery through a plastic spacer. Static on the spacer surface attracts the small particles and hence, leads to a much lower delivery of particles available for deposition in the lungs. Reduced static leads to a higher and more consistent dose delivery in vitro and in vivo.[5]

A major improvement in the delivery efficiency of inhalation devices is likely to have considerable clinical and economic impact. By simply reducing electrostatic charge, the dose deposited in the lungs can be greatly increased with markedly reduced variability. This will allow for a lower prescribed dose in asthmatic children and results in the same clinical effect that a suboptimal device could achieve. Costs of therapy would be reduced. However, the treating physician must be aware of the increase in dose reaching the patient, as side effects may arise with a higher amount of drug being absorbed systemically. There has been an increasing trend to escalate the doses (relative to body size) of inhaled drugs given to children, despite there being no direct measure of the amount of drug that is actually delivered to the patient. This dose escalation has given rise to concerns regarding the safety of both inhaled bronchodilators and corticosteroids, particularly in children.[13,14] Anti-asthma drugs are widely used in the pediatric age group, often in similar dosages to those used in adults. This practice results in children receiving a much higher dose relative to their size than adults. Considering lung deposition obtained in our present study, each child received a dose independent of age when corrected for body weight.

There is ongoing discussion regarding the most efficient and suitable delivery device for aerosol therapy in children. The results from this study are comparable to the results obtained in a similar patient group inhaling from a dry powder inhaler (range of lung deposition, 15.6-47.2%).[15]

Our results show the importance of radiolabeled depostion studies for determination of the efficiency of delivery systems. These studies answer questions on termining dosage regimens in childhood therapy. However, ethical issues must be considered when radioactivity is used in young children. As a research group, we are aware of the ethical aspects of performing studies with radiolabeled medications in children. Studies such as this passed stringent examination by both our Ethics Committee and the State Radiation Safety Officer. The doses used in our studies were kept to the absolute minimum to allow an image to be obtained over background levels of radioactivity and are equal to the natural background doses over 2 weeks and much lower than the doses used in diagnostic imaging procedures.

In summary, using detergent-treated spacers, drug delivery to the airways was much greater than expected for nonstatic treated spacers. This raises important questions regarding the need to change current aerosol dosing practices in children. Improving delivery efficiency may greatly increase efficacy and reduce treatment costs. When using detergent-treated spacers, children should be monitored for potential side effects due to the delivery of larger amounts of medication per actuation of metered-dose inhalers.

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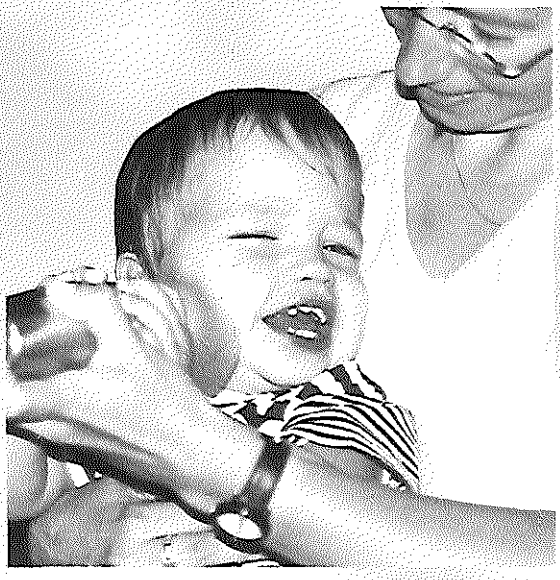
BREATHING PATTERN AND DEPOSITION



CHAPTER 6

The Sophia Anatomical Infant Nose-Throat (SAINT) model: A valuable tool to study aerosol deposition in infants

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ABSTRACT

Relatively little is known about the variables that influence lung deposition of inhaled aerosols in children. A model of the upper airways of an infant could be a useful tool to study these variables in-vitro. **Objective** To construct an anatomically correct model of the upper airways of a young child. **Methods** A routine 3D CT-scan of the skull and neck of a child was selected that included the airway from the nasal cavity down to the subglottic region. The CT-scan was edited to obtain an anatomically correct distinction between air and mucosa. Next, a model was constructed with a stereolithographic technique using a UV-sensitive resin. To validate the model a 3D-CT-scan of the model was made and compared to the anatomy of the original image. To study aerosol deposition the model was connected to a breathing simulator. Medical aerosols were delivered to the model by MDI/spacer during simulated breathing. **Results** An upper airway model was made of a 9-month-old child that needed reconstructive surgery for a skull deformity and with normal anatomy of the upper airways. The nasal airway of the model was open for air passage and the oral airway was closed. The CT-scan of the model matched the original in-vivo CT-scan closely. Aerosol deposition measurements showed that dose passing the model or 'lung dose' was comparable with in vivo lung deposition data. **Conclusions** We have constructed an anatomically correct model of the upper airways of a child, using a stereolithographic method for in-vitro studies of aerosol deposition in young children. This model will be used to obtain insight in aerosol treatment that cannot be obtained in vivo.

INTRODUCTION

Effective targeting of therapeutic inhaled aerosols into the lungs is crucial for effective treatment. Therefore aerosol delivery devices have to be extensively studied to determine their efficiency to deliver aerosol to the lungs. In children such studies are more difficult to perform than in adults for practical and ethical reasons. Therefore, relatively little is known about the variables that influence lung deposition of inhaled aerosols in children. In-vitro studies using models could be a useful alternative to study new aerosol delivery devices and aerosol deposition mechanisms in children. Several deposition models, both mathematical and anatomical, have been developed for adults.(1-4) These show that the upper airways of adults (nose, mouth pharynx down to the larynx) are an important trap for inhaled aerosols.(1,3,5-8) However, adult models are not suitable to study deposition mechanisms in children for the following reasons. Firstly, young children mainly breathe through their nose while inhaling aerosols (9), while adults predominantly inhale through their mouth. Therefore, a young child has to inhale through a face mask until it is old enough to inhale through a mouthpiece on demand. In practice this is not before the age of 4 years (10,11). Secondly, children inhale via tidal breathing, whereas in most deposition studies adults inhale via slow deep inhalations. Thirdly, the geometry of the upper airways of children is different compared to adults, and changes with age. For instance, with age the diameters of the upper and lower airways increase and the conchae progressively intrude into the nasal cavity.(12) Flow patterns are also known to be different, which will affect aerosol deposition.(7,8)

To our knowledge no suitable upper airway model of young children is available. Therefore, we aimed to develop a model of the upper airway of a child.

MATERIALS AND METHODS

The Sophia Anatomical Infant Nose-Throat (SAINT) was made as follows: Firstly, a three dimensional CT scan (3D CT-scan) of the upper airways of a child was made, the imaging phase. Secondly, the 3D CT-scan images were 'translated' into a hard-copy model, using stereolithography, the modeling phase. Thirdly, the model was tested for anatomical accuracy, the validation phase. Finally, in vitro aerosol deposition measurements were done, the experimental phase.

IMAGING

In our hospital 3D-CT scans of the head and neck of children with congenital skull malformations are made routinely prior to reconstructive surgery. A helical CT evaluation of the skull was performed with a GE Pro-Speed S Fast scanner (GE Medical Systems, Milwaukee, Wis. USA) under anesthesia with the child in a supine position. Technical parameters included: 3-mm collimation, 1.0 pitch, 120kV, 100mA and a

2 second rotation time. Slice orientation was parallel to the lower surface of the mandible. After data acquisition transverse 3 mm slices were recontructed with an overlap of 1 mm. These images were studied on a workstation with 3D and multiplanar reformations (Advantage Windows release 1.2, GE Medical systems, Milwaukee, Wis. USA). From these routinely made scans a 3D CT-scan was selected for the model by an otolaryngologist, radiologist, and the principal investigator, who were blinded to the patient's identification. The following criteria were evaluated:

- age < 1year,
- nasal airway open for air passage
- spontaneously breathing, no endotracheal or oropharyngeal tube used for anesthesia
- normal anatomy of upper airways
- scan minimally extends from the frontal bone to the subglottic region, including vocal cords

MODELING

The SAINT model (figure 1) was made from the 3D CT-scan of a 9-month-old Caucasian girl of 10 kilograms, who needed a pre-operative CT-scan for correction of an isolated skull deformation, which is not associated with abnormalities of the viscero-cranium. The 3D-scan showed that the nasal airway was open and the oral airway was closed for air passage. The CT-scan showed a normal viscero-cranium as judged by the radiologist and otolaryngologist. The upper airways were included in the CT-scan from the nasal bone to the subglottis, about 3 mm below the vocal cords. The selected CT-scan was stored on optical disk (DEC-702, Pioneer) and sent to for stereolithography imaging (Materialise, Leuven, Belgium). The images were edited for optimal 3D reconstruction with a special software package (Materialise's Interactive Medical Image Control System, MIMICS®, Leuven, Belgium). Optimal thresholds were chosen for each slice to get an anatomically correct distinction between air and mucosa. Subsequently, the edited scan was reconstructed to a 3D image. The software interpolated the cascades between the 2 mm slices during reconstruction, to obtain a smooth surface. Finally, the model was constructed using stereolithographic equipment, which consists of a computer controlled UV-laser beam radiating a liquid monomer resin (Stereocol®, Vantico, Cambridge, UK) in a basin. The laser radiation polymerizes the resin, which becomes solid. The model was built in layers of 0.25 mm.

VALIDATION

The model was scanned with 1-mm collimation and 130 mA, since radiation exposure was not an issue. Other settings were identical to the original CT-scan. Both the original CT-scan and the CT scan of the model underwent multiplanar reconstructions in transverse, sagittal and coronal directions and were compared using

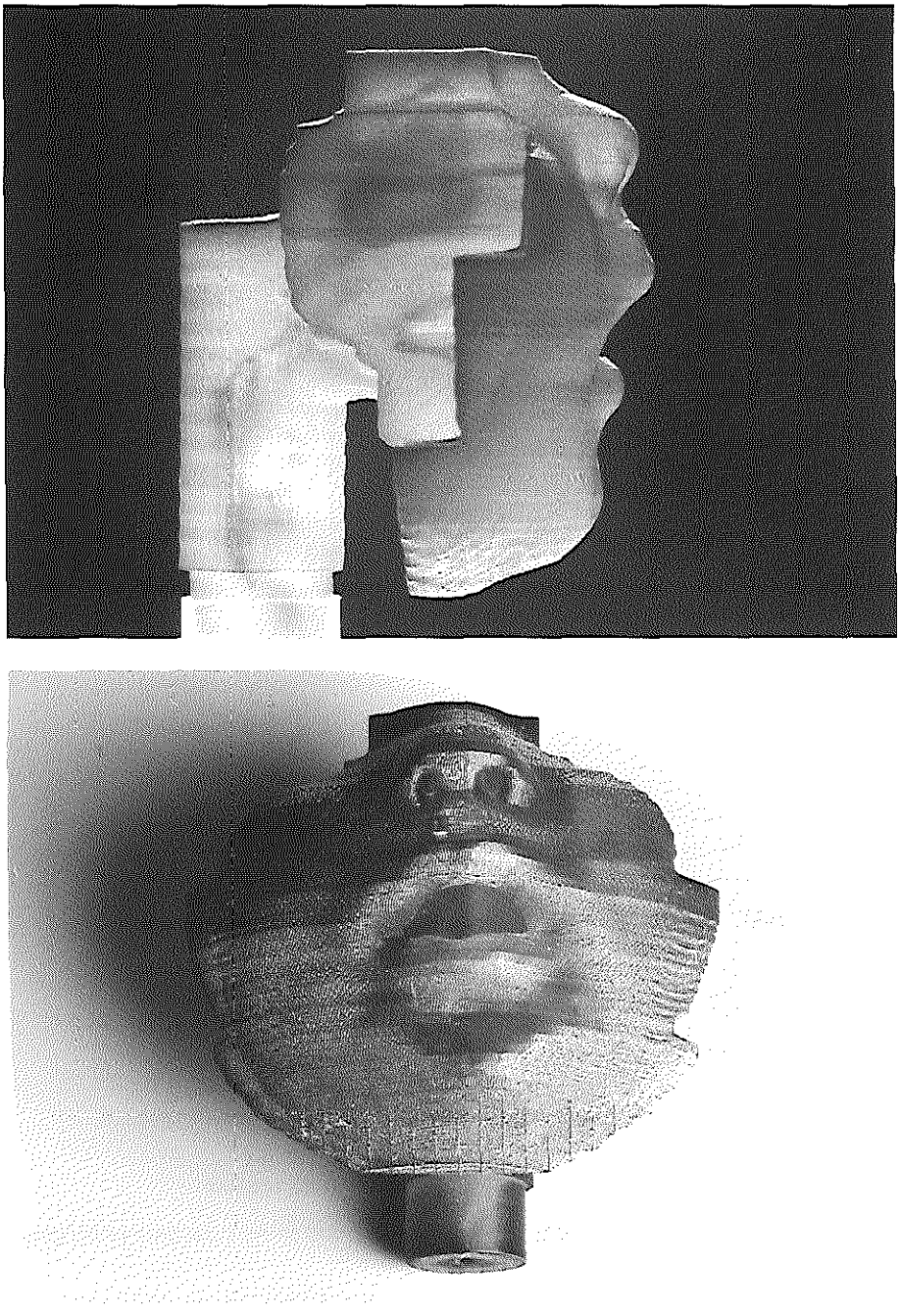

FIGURE 1. The Sophia Anatomical Infant Nose-Throat (SAINT) Model. Side view (top) and front view (bottom).

identical soft tissue windows. The airway images of both scans were compared at the level of several anatomical landmarks. The images were judged for similarity by the principal investigator, radiologist and otolaryngologist. The resistance profile of the model was tested by measuring pressure drop over the model during applied flows. A flow calibrator (Godart, Bilthoven, The Netherlands) generated flow rates of 0 to 20 L/min in a continious scale. These flow rates are within the physiological range of flows during tidal breathing in infants. Flows were measured with a Fleisch no. 0 pneumotachograph (Medical Electronic Construction, Brussels, Belgium) placed between the subglottis region of the model and the flow calibrator. Subsequently, the pressure drop over the model from the nose to the subglottis was measured using a differential pressure transducer (LCVR 0-100 cmH2O, Celesco, Canoga Park, CA, USA) , connected to the subglottic region of the model and the atmosphere.

AEROSOL DEPOSITION EXPERIMENTS

Budesonide aerosol was generated by pMDI (Pulmicort® 200 µg) and delivered into a spacer (Nebuchamber®, AstraZeneca, Lund, Sweden) with attached facemask. The total dose of budesonide that passed through the model was defined for this study as 'lung dose'. The particle size distribution of the lung dose was quantified during simulated tidal breathing using the experimental set-up as previously described and validated.(13) (figure 2). A similar set-up has been used by Finlay et.al. (14) The model

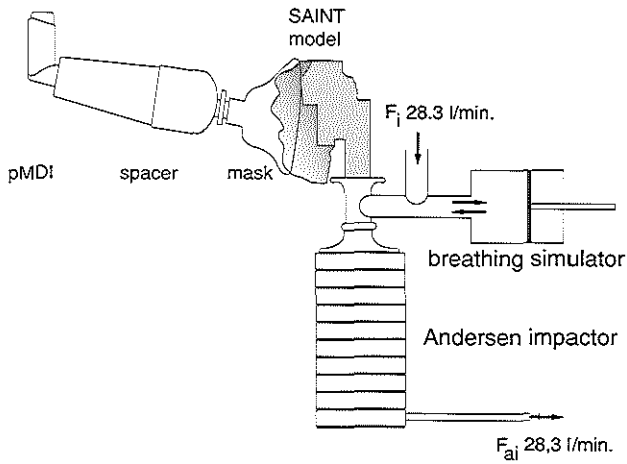

FIGURE 2. Experimental set-up used to measure lung dose and particle size from pMDI/spacer during simulated tidal breathing.

The breathing simulator supplied tidal breathing through the SAINT-model and pMDI/spacer while a constant flow F_{ai} of 28.3L/min flows to the Andersen impactor, balanced by an inflow F_i of 28.3 L/min. A three-way glass connection attached all the parts together.

was connected to a breathing simulator (Pari Sinus Breathing Simulator, Pari GmbH, Starnberg, Germany) and an Andersen 8-stage cascade impactor (Graseby Andersen, Smyrna, GA, USA) by means of a three-way glass connection. A constant flow of 28.3 L/min through the Andersen impactor (F_{ai}) was balanced with an inflow (F_i) of 28.3 L/min through the glass connection, resulting in a flow of zero through the model. When the breathing simulator was switched on, there was simulated tidal breathing through the model and a constant flow through the Andersen impactor. To test that no aerosol was drawn into the breathing simulator we placed a filter between breathing simulator and glass-connection. No drug was detected on this filter. The breathing simulator settings were as follows: 1) Sinusoidal pattern, 2) inspiration-expiration ratio of 1:1.3, 3) tidal volumes: 50, 100 and 200 ml, and 4) respiratory rate: 30 breaths/min. These settings are according to reference values appropriate for the age and weight of the subject used to construct the model.(15) Before deposition experiments the inner surface of the model was coated with a thin layer of glycerol/Brij-35 (polyoxyethylene 23 laurylether) mixture by pipetting 4 ml into the model and allowing the excess fluid to drip out. This coating was to mimic a sticky mucosa and to eliminate electrostatic charge. A dose of budesonide was delivered to the model as follows: 1) the facemask of the spacer was put on the face of the model using therapeutic putty (Carters, Westbury, Wilts, UK) to ensure an airtight fit. This was otherwise not possible because of the non flexible face of the model. 2) the pMDI/spacer was shaken and put on the model with facemask. 3) during simulated tidal breathing a puff of budesonide was actuated into the spacer at the end of an expiration, within 5 seconds after the pMDI was shaken. Tidal volume breathing was continued for 30 seconds before the next dose was given. Ten separate puffs were actuated for each measurement. Finally, the amount of budesonide deposited on the glass connection and impactor plates was assessed by high performance liquid chromatography (HPLC) as follows: Budesonide on the impactor plates and glass connection was dissolved in ethanol containing an internal standard (fluocinolone acetonide). Budesonide was quantified by a validated HPLC method, using an ethanol:water (43:57) mobile phase and a Supelcosil LC-18 column (5µm particles, 5 cm * 0.46 cm (i.d.)). The coefficient of variation of the method was below 3%.

The total dose passing the model or 'lung dose' was the sum of the amount of budesonide on the glass connection and all parts of the impactor. Lung dose of budesonide was expressed as a percentage of nominal dose. Measurements were done in triplicate, in a randomized fashion. Results shown are mean (SEM).

We intended to measure upper airway deposition by rinsing the model with ethanol, and assessing the amount of drug in the ethanol solution by HPLC. However, it appeared that the polymerized resin of the model disturbed the HPLC chromatogram. Hence, drug deposited in the model could not be assessed directly. However, we did clean the model with ethanol after use. Repeated cleanings of the model with ethanol over 2 years of intensive use did not change the internal geometry. This was tested by repeated CT-scans and resistance measurements.

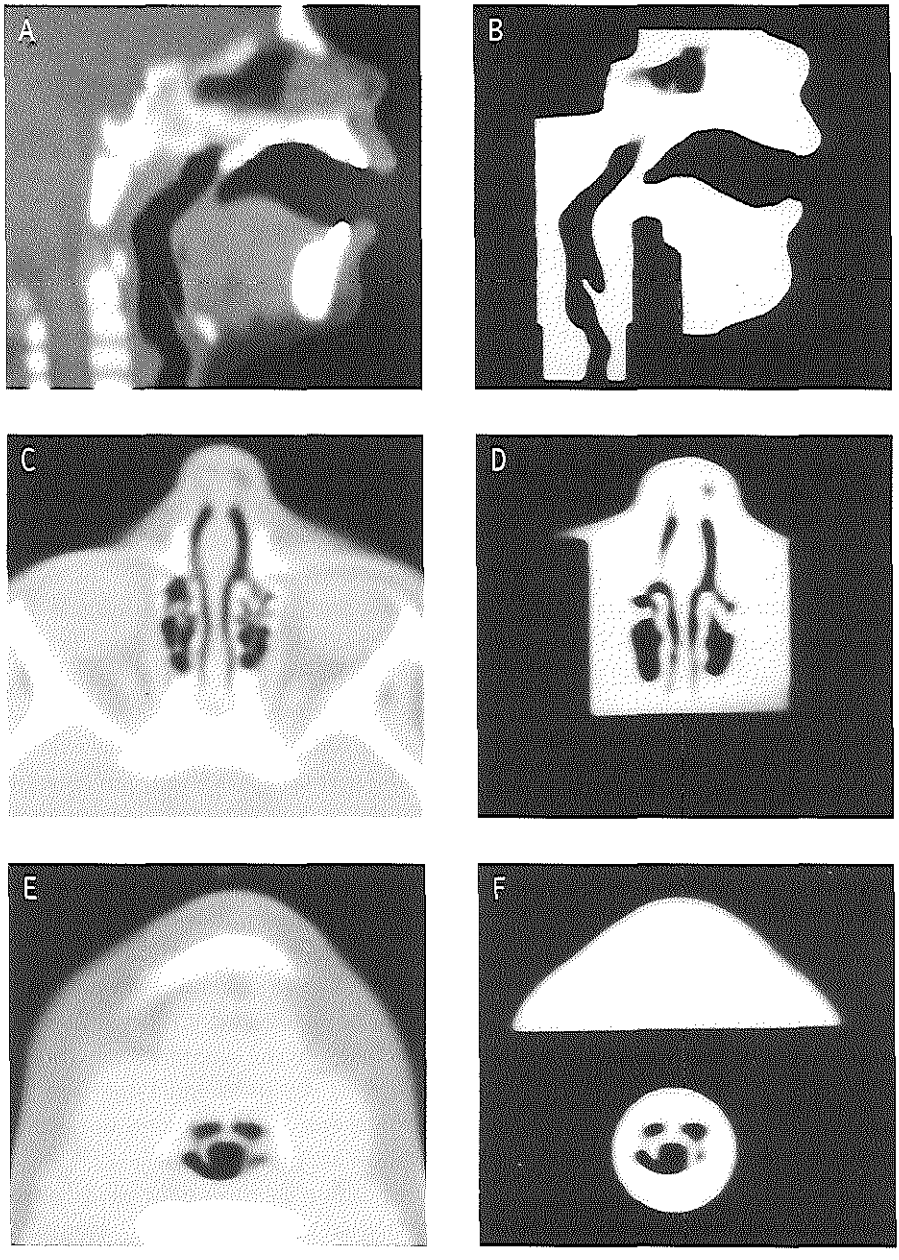

FIGURE 3. Comparison of original CT-scan with CT-scan of model
A, C and E: Multiplanar reconstructions of original CT-scan, with mid-sagital and transverse views through the nasal cavity region, and transverse view through the epiglottic region, respectively.
B, D and F: Corresponding images of SAINT-model.

RESULTS

The CT-scan of the SAINT model and the original CT-scan matched closely (figure 3).

RESISTANCE PROFILE

The resistance profile for inspiratory and expiratory flow is shown in figure 4. Upper airway resistance of the model was within the range of reported physiologic in-vivo data (mean 14 cm $H_2O \cdot l^{-1} \cdot sec$ (range: 3.7 - 23.9)) for Caucasian infants, weighing 1.5 - 10.2 kg.(16)

EXAMPLES OF AEROSOL DEPOSITION MEASUREMENTS:

Lung dose, dose in particles <4.7 µm and dose in particles <2.1 µm from a pMDI/spacer (Pulmicort® 200 µg/Nebuchamber®) measured during simulated breathing at different tidal volumes with the SAINT model are shown in figure 5. The 'lung dose' decreased with increasing tidal volume from 13.9 (0.9) %, 8.8 (0.3)% to 3.2 (0.1)% of nominal dose at 50, 100 and 200 ml tidal volume, respectively. The dose in particle <4.7 µm decreased from 11.8 (0.7)%, 8.1 (0.3) to 3.0% of nominal dose with increasing tidal volumes of 50, 100 and 200 ml, respectively. The dose in particles <2.1 µm showed no change with tidal volume, which was 1.6 (0.07)%, 1.8 (0.02)% and 1.3 (0.03)% of nominal dose for tidal volumes of 50, 100 and 200 ml, respectively. The MMAD of the lung dose was 3.3 (0.05), 2.8 (0.01) and 2.3 (0.01) µm and the geometric standard deviations (GSD) were 1.4 (0.01), 1.4 (0.01) and 1.5 (0.01) for tidal volumes of 50, 100 and 200 ml, respectively.

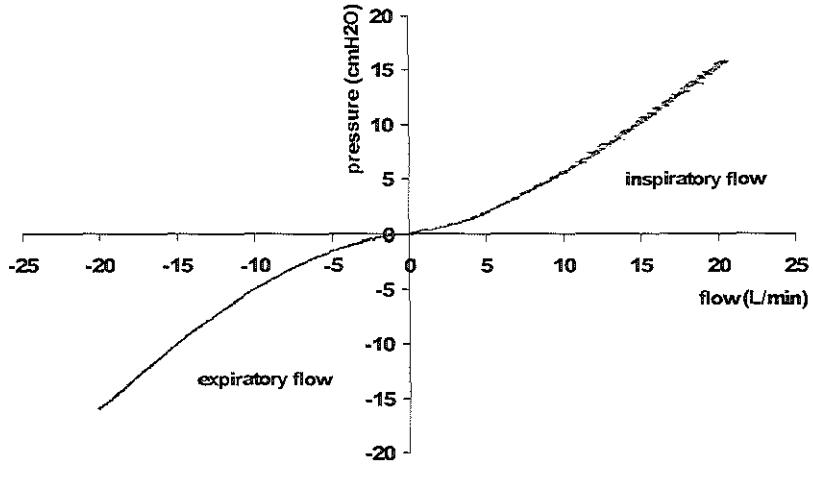

FIGURE 4. SAINT-model resistance profile for inspiratory and expiratory flows.

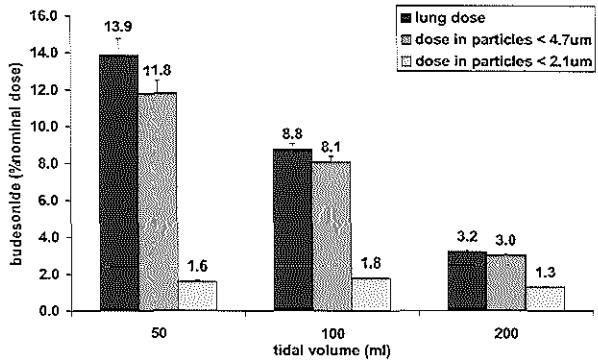

FIGURE 5. Aerosol deposition with pMDI/spacer for SAINT-model.
Lung dose, dose in particles < 4.7 µm and dose in particles < 2.1 µm for budesonide pMDI with Nebuchamber, expressed as a percentage of the nominal dose (200 µg). Results are mean (SEM).

DISCUSSION

There is a lack of knowledge about factors that determine aerosol deposition in infants. To study these factors it is desirable to have an in-vitro system that mimics the in-vivo situation as well as possible. Therefore, an anatomically correct model of the upper airways of a 9-month-old infant, the Sophia Anatomical Infant Nose-Throat (SAINT) model, was developed to study variables that influence aerosol deposition. The SAINT model has advantages in comparison to other currently available models.

Several human upper airway casts have been made to study aerosol deposition. Several adult casts of the oral airway (2-4,17), or the nasal airway (7,18,19) have been described. However, to our knowledge, only two infant casts are available. An infant nasal cavity model was described by Phalen et.al.(7) It consisted of two hollow silicone-rubber models, each representing the anterior region of one side of an infants nose. This model was geometrically similar to an adult model. The adult model was a simplification of reality and was constructed according to a number of dimensions of the adult nose, derived from other studies.(20) The infant model was extrapolated from the adult model by reducing adult airway dimensions by 50%. However, the nasal cavity of young children is not a proportionally smaller version of an adult nasal cavity.(12,21) The SAINT model has major advantages over the Phalen model since its airway dimensions are derived directly from a CT-scan of a living infant. Furthermore the SAINT model also contains the pharyngeal and laryngeal region, which are important locations for aerosol particles to deposite before entering the lower airways.(22)

Another model of a child is the anatomical throat of a 3.5-year-old child made by the late Prof. DL Swift, which has not been described in literature but has been used in previous studies.(13) This throat-model was made by the wax-waste method in a cadaver. It is not known how postmortem changes influence airway dimensions. The Swift model might therefore not adequately reflect in-vivo airway dimensions. Another limitation of the Swift model is that it consists of the oropharynx only. Therefore the Swift model is suitable for studying inhalation of aerosols through the oral passageway, which is applicable for children who are able to inhale orally (usually older than 3 years). However, most children of this age and younger preferably breathe through their nose while inhaling aerosols.(9) The SAINT model has advantages over the Swift model since it includes the nasopharynx and its dimensions are derived from a child breathing spontaneously through the nose. Aerosol deposition studies were done with the Swift model using the same experimental set-up as used for the SAINT model.(13) Breathing simulator settings for these tests were: inspiration-expiration ratio 1:2, tidal volume 200 ml, respiratory rate 25 breaths/min. Using the Swift model, 'lung dose' was 19.6% of nominal dose, dose in particles < 4.7 μm was 15%, dose in particles <2.1 μm was 1.4% and MMAD was 3.6 μm (E. Berg, Lund, personal communication). This is a substantially higher 'lung dose' than was found in our model, whereas the extra fine particle dose seems to be similar. The lower 'lung dose' for the SAINT model is probably caused by the nasal route of inhalation which is likely to decrease 'lung' deposition as the result of a more turbulent airflow pattern in the nose. Apparently, particles <2.1 μm deposite independently of the inhalation route.

Though the SAINT model is an improvement over other currently available models it is still a model and therefore a reduction of reality. Its anatomy is derived from a single anesthetized but spontaneously breathing child who was positioned on its back during the making of the CT-scan. The time needed to make the total CT-scan is about 2 minutes. As a consequence, the model represents an average configuration of the anatomy during breathing. Apparently, the geometry of the upper airways does not change significantly during a breathing cycle, for there were no large cascades between the several slices of the CT-scan images.

At best the SAINT model will predict adequately aerosol deposition of the infant from whom the CT-scan was taken. For ethical reasons we could not validate this assumption, by doing a lung deposition test in the child from which the model was made. There are reasons to believe that the SAINT model reflects the in vivo situation. Firstly, upper airway dimensions on the CT-scan of the SAINT model closely matched those on the CT-scan of the infant. Secondly, airway resistance of the upper airways of the model is within a the physiological range. Thirdly, lung dose (or total dose passing the modell) of budesonide delivered by pMDI/spacer in the model is within the range of in vivo lung deposition data.(23,24) In these studies a mean lung deposition of 1.7% of metered dose with

salbutamol/Aerochamber was found by Tal et.al, 13% of metered dose with salbutamol/Babyhaler (Glaxo Wellcome, Uxbridge, UK) by Wildhaber et.al for children under 2 years of age. The large differences between these studies can be explained by the use of different spacers and by the presence (Tal) or absence (Wildhaber) of static charge. Furthermore, the accuracy of the Tal study is not clear for there was no validation of the radiolabeling method. Our data are close to those of the Wildhaber. This can be explained by the fact that we also used a non-static spacer: the metal Nebuchamber. However, in comparing the data it should be noted that the in vivo values are expressed as percentage of metered dose and the SAINT-values as percentage of nominal dose. Furthermore, in comparing the lung dose obtained in vitro with the SAINT model to the lung deposition data obtained in vivo, one has to keep in mind that we were able to deliver the aerosol in the most optimal circumstances. The pMDI/spacer was handled in the most optimal way, the seal of the facemask to the face of the model was air-tight, and the aerosol was inhaled with a regular breathing pattern.

A disadvantage of the present SAINT-model is that ethanol can not be used as a solvent for measuring deposition in the model. The Stereocol[19] of which the model is made, interferes with the HPLC-signal. This means that upper airway deposition in the model cannot be measured directly for ethanol soluble products, but can be assessed indirectly by measuring the dose-ex-model and substracting this from the dose entering the model. Future efforts should focus on the development of new versions of the model using a more inert polymer.

In conclusion we made an anatomically correct upper airway model of a nasally breathing infant, which mimics the in-vivo situation for infants in in-vitro aerosol deposition studies better than the currently used "throats".The SAINT model enables us to obtain useful information which is either difficult or impossible to obtain in vivo. With the help of the model we are able to study the influence of variables like breathing patterns on lung deposition. Furthermore, the SAINT model might be useful to test new aerosol devices for infants or in the field of environmental medicine.

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CHAPTER 7

Influence of tidal volume and respiratory rate on aerosol deposition from 4 pMDI-spacer combinations used in infants

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Submitted

ABSTRACT

Aim The aim of this study was to measure the influence of tidal volume (Vt) and respiratory rate (RR) on aerosol deposition from 4 pMDI/spacer combinations, which are used for infants. **Methods** An anatomically correct upper airway model of a 9-month-old infant was connected to a breathing simulator. Sinusoidal breathing patterns were simulated with; duty cycle T_i/T_{tot}= 0.42, Vt: 25, 50, 75, 100, 150, 200 ml (RR: 30 breaths/min); and RR: 20, 30, 42, 60, 78 breaths/min (Vt: 100 ml). pMDI/Spacers tested were: budesonide 200 µg/Nebuchamber®, fluticasone 125 µg/Babyhaler®, and both budesonide and fluticasone with Aerochamber®. Plastic spacers were detergent coated to reduce electrostatic charge. Spacer-output and lung dose were measured by a filter positioned between spacer and facemask or between model and breathing simulator. Particle size distribution of lung dose was assessed with an impactor during simulated breathing. **Results** Spacer-output was significantly positively correlated with Vt for all pMDI/spacers (all R>0.77, p<0.001), but not correlated with RR. Lung doses initially increased from Vt= 25 to 50ml (Nebuchamber, Aerochamber) or to 100 ml (Babyhaler) and then decreased, with increasing Vt and RR (R:-0.98 to -0.82, p<0.001). Lung doses of fluticasone were 1.5 to 6 fold higher compared with budesonide, irrespective of spacer type (p< 0.001). MMAD decreased with increasing Vt and RR. Dose to the lungs of particles < 2.1 µm was independent of Vt and RR. **Conclusions** Lung dose decreases with increasing inspiratory flow (increasing Vt or RR) by increasing impaction of coarse particles in the upper airways. Deposition of particles <2.1 µm is relatively flow independent. When electrostatic charge of spacers is reduced, lung dose is pMDI dependent and spacer independent.

INTRODUCTION

A popular way to deliver aerosol therapy to infants is by a pressurized metered dose inhaler (pMDI) in combination with a holding chamber (spacer). However, most of the available pMDI/spacer combinations have not been thoroughly tested in young children. Only few deposition and efficacy studies have been done in this age group. This leaves us with lack of knowledge of the behaviour of aerosols and inhaler devices in the treatment of young children. Most *in vitro* data on spacers were obtained using inhalation flow rates typical for adults, who inhale in a single breath. These adult data cannot be extrapolated to pediatric flow rates, since young children inhale via tidal breathing. Recognizing this, several studies measured aerosol delivery from spacers during pediatric tidal breathing [1-5]. A limitation of these studies was that aerosol delivery was measured directly from the spacer with either a filter [1,2,4,5] or an impactor [3]. This gives us information on the amount of aerosol delivered to the mouth at tidal breathing, but not on the actual dose delivered to the lungs. Furthermore, it is known that young children have variable breathing patterns [6]. In addition, tidal volume and respiratory rates will vary according to the age and weight of the child. In vitro studies have shown that tidal volume affects the dose delivered from spacers. An increase of tidal volume results in an increased dose from the spacer [2,5,7]. Furthermore, it has been shown that each pMDI/spacer combination delivers a different dose [8]. However, it is not known how the dose from the spacer relates to the dose delivered to the lungs. This relation is difficult to investigate in young children. Therefore, it is unknown for young children how breathing patterns relate to lung deposition. To study the relation between breathing patterns and aerosol deposition in vitro we recently developed an anatomically correct model of the upper airways of an infant [9]. The aim of this study was to measure the influence of tidal volume and respiratory rate on the deposition of inhaled steroids from 4 pMDI/spacer combinations, which are used for infants.

MATERIALS AND METHODS

UPPER AIRWAY MODEL

A model of the upper airways of a 9-month-old infant was used for the aerosol deposition measurements. This model, known as the Sophia Anatomical Infant Nose-Throat (SAINT) model, was extensively described in detail elsewhere [9]. In short, it is a stereolithographically made, anatomically correct model of the upper airways. The model includes the face, nasal cavity and pharynx till the subglottic region. The nasal airway is open for air passage, the oral airway is closed. To mimic a sticky mucosa and to eliminate electrostatic charge on the inner surface of the model, the model was coated with a glycerol/Brij-35 (poly-oxyethelene 23 laurylether) mixture before use by pipetting 4 ml into the nose of the model and allowing the excess fluid to drip out.

PMDI/SPACERS

Two inhaled steroids available in pMDI formulation were tested in their respective spacer and in a general purpose spacer. Budesonide pMDI (Pulmicort® 200 µg, AstraZeneca, Zoetermeer, The Netherlands) was tested in the Nebuchamber® (AstraZeneca) (bud/Nebuchamber), which is a metal spacer with a volume of 250 ml. In addition budesonide was tested in an Aerochamber® (Trudell Medical, London, Canada) (bud/Aerochamber), a plastic (Ektar plastic) small volume spacer with a volume of 135 ml. Fluticasone pMDI in HFA-formulation (Flixotide® 125 µg, GlaxoWellcome, Zeist , The Netherlands) was tested in the Babyhaler® (Glaxo Wellcome) (flut/Babyhaler), which is a polycarbonate spacer with a volume of 350 ml, and in the Aerochamber (flut/Aerochamber). Before testing the pMDI's were primed by firing 10 waste puffs. All spacers were used with infant face-masks as provided by the manufacturers. Electrostatic charge can develop on the inner surface of a plastic spacer, which decreases drug delivery by retaining the drug in the spacer [10]. Therefore, electrostatic charge of the plastic spacers was reduced by coating it with household detergent several hours before use. Detergent coating was done by washing the spacer in diluted detergent and subsequently leaving it to drip-dry. Detergent coating has been shown to reduce electrostatic charge on the inner surface of the spacer effectively [11,12].

EXPERIMENTAL SET-UP

FILTER MEASUREMENTS

The SAINT model was connected to a custom made computer-controlled breathing simulator [13] which was adapted for simulating infant breathing patterns. Filters were used to collect drug from the pMDI/spacers at different positions in the breathing pathway. Spacer-output, defined as dose delivered from the spacer, was assessed by placing a filter (Vital Signs®, Totowa, NJ, USA) between facemask and spacer (figure 1A). Lung dose, defined as total dose passing the model, was assessed by placing a filter between model and breathing simulator (figure 1B). Drug deposited on the face mask was also measured and expressed as percentage of nominal dose. 'Upper airway deposition', defined as the dose deposited in the model, was calculated as follows: spacer output – (lung dose + dose-on-facemask).

PARTICLE SIZE MEASUREMENTS OF LUNG DOSE

Particle size distribution of the lungdose was measured during simulated breathing. The SAINT model was connected to a breathing simulator (Pari Infant) and an Andersen 8-stage cascade impactor (Graseby Andersen, Smyrna, GA, USA) using a three way glass connection (see figure 2). A balanced inflow made it possible that there was a constant flow of 28.3 L/min through the impactor and tidal breathing through the model and spacer. This set-up has been previously described by Berg et.al. [14]. A similar set-up

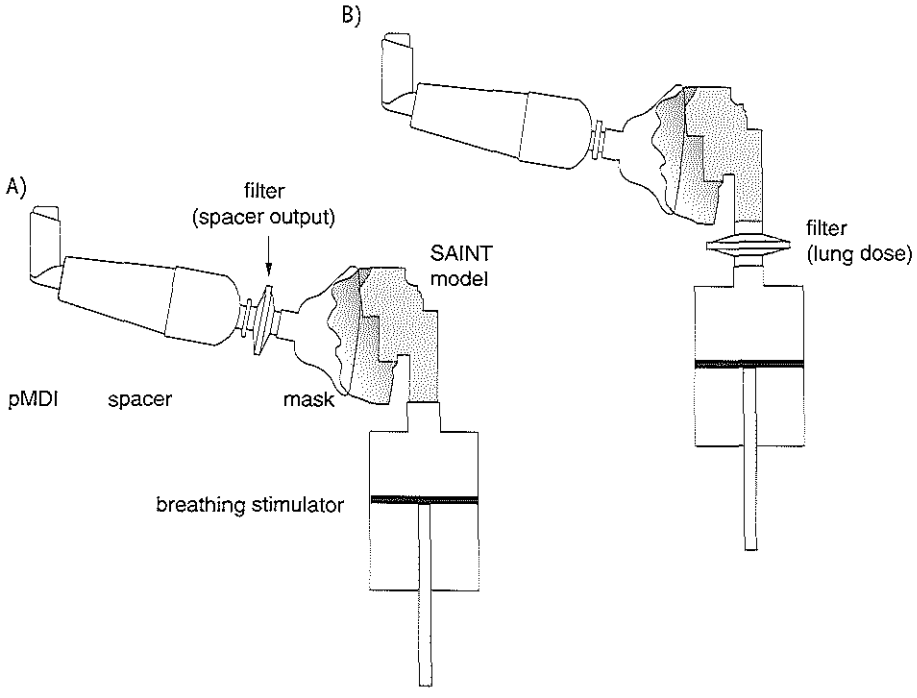

FIGURE 1. Experimental setup: A. To measure spacer-output, B. To measure lungdose

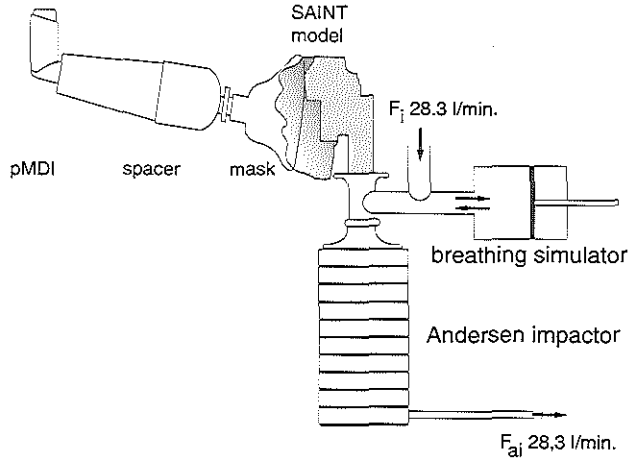

FIGURE 2. Experimental set-up: to measure particle size distribution of lung dose during simulated breathing.

for measuring particle size distribution from spacers with simulated tidal breathing was used by Finlay et.al. [3]. Fine particle dose (FPD) was defined as the mass of the lung dose in particles < 4.7 µm (impactor stage 3-8) expressed as a percentage of nominal dose. Extra fine particle dose (EFPD) was defined as the mass of the lung dose in particles < 2.1 µm (impactor stage 5-8) expressed as a percentage of nominal dose. Particle size distribution of lung dose was expressed as median mass aerodynamic diameter (MMAD).

BREATHING SIMULATION

Influence of tidal volume (Vt) and respiratory rate (RR) on aerosol delivery was investigated by using sinusoidal breathing patterns with the following settings for the breathing simulator:

1. Respiratory duty cycle (inspiratory time (T_i) / total respiratory cycle time (T_{tot})): 0.42.
2. Influence of Vt on spacer-output, lung dose and upper airway deposition was tested with Vt's of 25, 50, 75, 100, 150 and 200 ml with a fixed RR of 30 breaths/min. Influence of Vt on FPD, EFPD, and MMAD was tested with Vt's of 50, 100 and 200 ml with fixed RR of 30 breaths/min.
3. Influence of RR on spacer-output, lung dose and upper airway deposition was tested with RR's of 18, 30, 42, 60, 78 breaths/min with a fixed Vt of 100 ml. Influence of Vt on FPD, EFPD, and MMAD was tested with RR of 18, 30 and 42 with fixed Vt of 100 ml.

A respiratory duty cycle (T_i/T_{tot}) of 0.42, Vt of 100 ml and RR of 30 breaths/min are in accordance with reference values appropriate for the 9-month-old subject used to construct the SAINT model [15]. Measurements for the Vt and RR series were done in a randomized order and repeated three times for each Vt and RR.

STUDY PROCEDURE

A new filter or a clean impactor were placed in the appropiate position before each experiment. Next, the breathing simulator was set on the selected breathing pattern. The pMDI/spacer with attached facemask was shaken and placed on the face of the model ensuring an airtight fit using therapeutic putty (Carters, Westbury, Wilts, UK). Subsequently, one puff of budesonide or fluticasone was actuated into the spacer just before the start of an inspiration, within 5 seconds after the pMDI was shaken. Drug from the spacer was withdrawn during 30 seconds of simulated tidal breathing. For the impactor measurements, 10 separate puffs were actuated for each measurement to get detectable amounts of drug on the impactor plates. The experiments were performed in ambient conditions with 30-40% humidity.

DRUG ANALYSIS

Drug on the filters, masks and impactor plates was dissolved in ethanol containing an internal standard (fluocinolone acetonide). Budesonide and fluticasone were quantified by a validated high performance liquid chromatography (HPLC) method, using an

ethanol:water (43:57) mobile phase and a Supelcosil LC-18 column (5µm particles, 5 cm * 0.46 cm (i.d.)). The coefficient of variation of the method was below 3%.

STATISTICAL ANALYSIS

Amount of drug found on the filters and impactor plates is expressed as a percentage of nominal dose. Results shown are mean (± SEM). The correlation between Vt or RR and deposition variables were investigated using Spearman's correlation coefficients (R) and were tested for linearity. Tests using multiple regression analysis showed that the profiles of variables significantly differed from parallelism, therefore all spacers were compared at separate Vt's and RR's. Overall comparisons between spacer-output, upper airway deposition, lungdose, FPD, EFPD and MMAD between the 4 pMDI/spacer combinations were made using one-way analysis of variance (ANOVA) for each Vt and RR. Subsequently, if significance was present, comparisons were made for each pair of means. Bonferroni correction for multiple comparisons was made. Statistical significance was set at $p = 0.05$.

RESULTS

FILTER MEASUREMENTS

Spacer-output

The relation between spacer-output and Vt is shown in figure 3A. For all spacers a significant increase of spacer-output with increasing Vt was found (all $R>0.77$, $p<0.001$). For bud/Nebuchamber and flut/Babyhaler this was a non-linear relationship. Spacer-output was significantly higher for the bud/Nebuchamber and the flut/Babyhaler compared with the spacer-output from the bud/Aerochamber and flut/Aerochamber for all Vt's except at 25 ml. At Vt=25 ml spacer-output for the bud/Nebuchamber was significantly higher compared to the flut/Babyhaler. Additional observations were that at Vt=25ml the in- and expiratory valves of the Babyhaler did not open and close sufficiently. Spacer-outputs were significantly higher for flut/Aerochamber compared to bud/Aerochamber at Vt = 50, 100 and 150 ml.

The relation between spacer-output and RR is shown in figure 3B. The flat curves obtained for all spacers indicate that RR has no significant influence on spacer-output. Spacer-output from bud/Nebuchamber was significantly higher compared to bud/Aerochamber at all RR's. Both flut/Babyhaler and flut/Aerochamber had intermediate spacer-outputs in relation to bud/Nebuchamber and bud/Aerochamber.

Lung dose

The relation between lung dose and Vt is shown in figure 3C. All spacers showed a significant non-linear relationship with Vt, with an initial increase and a subsequent decrease in lung dose with increasing Vt. Bud/Nebuchamber, bud/Aerochamber, and

flut/Aerochamber showed maximum lung dose at about Vt= 50 ml, whereas flut/Babyhaler showed its maximum dose at Vt = 100 ml. Lung dose of fluticasone was significantly higher compared with budesonide irrespective of spacer used, except at a Vt of 25 ml where there were no significant differences between any pMDI/spacer. Maximum lung doses were at Vt= 50 ml 11%, 9% and 16% for respectively bud/Nebuchamber, bud/Aerochamber and flut/Aerochamber and at Vt =100 ml 19% for flut/Babyhaler.

The relation between lung dose and RR is shown in figure 3D. For all spacers, increasing RR generally resulted in decreasing lung dose (all R: between -0.98 and -0.82, $p<0.001$). Lung doses of fluticasone were significantly higher compared with budesonide irrespective of spacer used, except for lung doses at RR=18, where flut/Babyhaler was not significantly different from bud/Nebuchamber and bud/Aerochamber.

Upper airway deposition

For the calculation of upper airway deposition drug deposited on the facemask was measured. Dose-on-facemask showed no relationship with Vt or RR. Mean (SEM) dose (% of nominal dose) found on the facemask was 1.9 (0.1)% for bud/Nebuchamber, 8.3 (0.7)% for flut/Babyhaler, 3.5 (0.4)% for the bud/Aerochamber and 8.4 (0.5)% for the flut/Aerochamber.

The relation between upper airway deposition and Vt is shown in figure 3E. In general, it was shown that upper airway deposition increased with increasing Vt. Upper airway deposition was significantly higher for the bud/Nebuchamber compared with the bud/Aerochamber and flut/Aerochamber at all Vt's, and for the flut/Babyhaler at Vt=100 and 150 ml. There was no significant difference between Bud/Aerochamber, flut/Aerochamber and flut/Babyhaler.

The relation between upper airway deposition and RR is shown in figure 3F. There was no significant difference of upper airway deposition between any spacer at any RR.

PARTICLE SIZE MEASUREMENTS OF LUNG DOSE.

Fine particle dose

The relation between FPD and Vt is shown in figure 4A. A significant negative correlation was found for FPD and Vt for all spacers (R: between -0.95 to -0.84, $p< 0.005$) except flut/Babyhaler, which showed no significant correlation (R=0.053, p=0.9). FPD for fluticasone was significantly higher than for budesonide irrespective of spacer used, except for FPD at Vt= 50 ml where there were no significant differences between the 4 pMDI/spacer combinations.

The relation between FPD and RR is shown in figure 4B. There was a significant negative correlation between FPD and RR for bud/Nebuchamber and

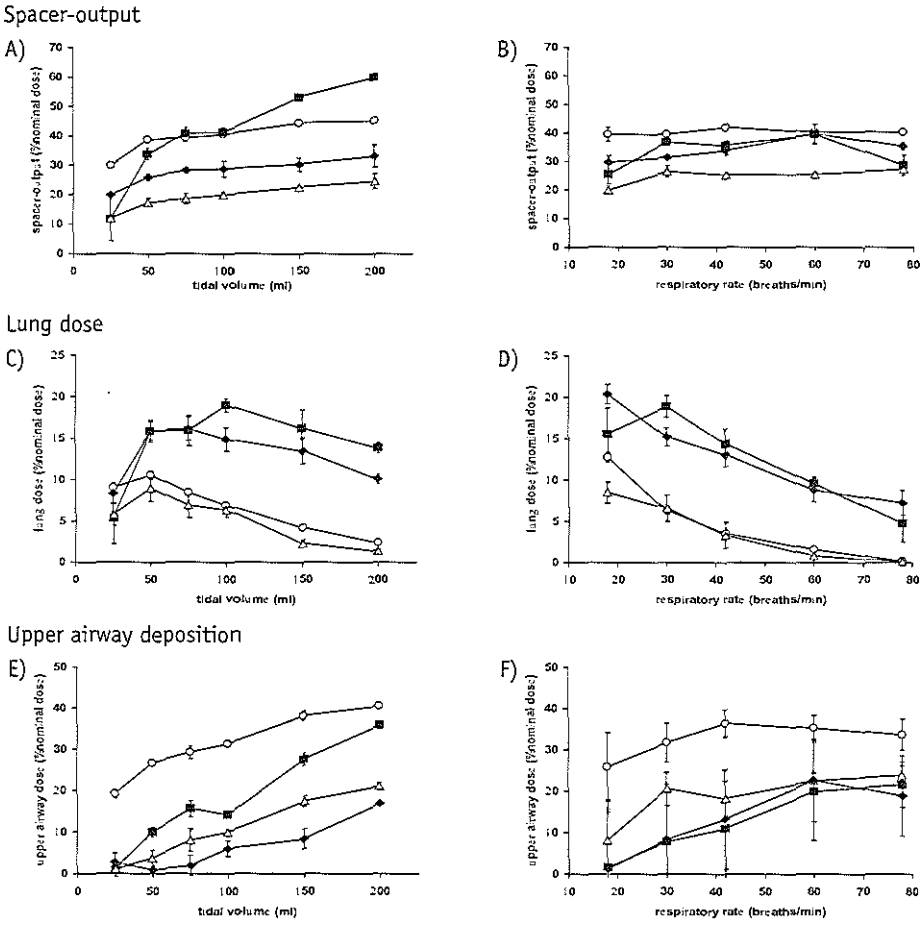

FIGURE 3. Filter measurements

Explanation of symbols: ○ = Bud/Nebuchamber (bN), △ =Bud/Aerochamber (bA), ■ = Flut/Babyhaler (fB), ◆ = Flut/Aerochamber (fA). Symbols represent mean values of three measurements, error bars are standard error of the mean. Vt series at fixed RR=30 breaths/min, and RR series at fixed Vt=100 ml. A: Spacer-output *versus* Vt: for all pMDI/spacers R>0.77, p<0.001; bN and *versus* bA and fA: p<0.05, at Vt =25 ml: bN *versus* fB (p<0.05). B: Spacer-output *versus* RR: for all pMDI/spacers R<0.2, p>0.5; bN *versus* bA:p<0.05. C: Lung dose *versus* Vt: Significant non-linear relationship for all pMDI/spacers; bN *versus* bA, and fB *versus* fA: not siginifant *(NS)*; bN and bA *versus* fB and fA: p<0.05, except at Vt=25 ml, *NS* differences between pMDI/spacers. D: Lung dose *versus* RR: for all pMDI/spacers R: -0.98 to -0.82, p<0.001; bN *versus* bA, and fB *versus* fA: *NS*; bN and bA *versus* fB and fA: p<0.05, except at RR =18 breaths/min: bN, bA and fB: *NS* difference. E: Upper airway deposition *versus* Vt: bN *versus* bA and fA: p<0.05 at all Vt's; at Vt=100 and 150 ml: bN *versus* fB: p<0.05. bA, fB, fA: *NS* difference. F: Upper airway deposition *versus* RR: *NS* differences between pMDI/spacers.

bud/Aerochamber (both R= -0.95, p<0.001), but not for flut/Babyhaler and flut/Aerochamber (R= -0.58 and –0.53 resp., p≥0.1). Again FPD for fluticasone was significantly higher than for budesonide irrespective of spacer used, except at RR= 18 breaths/min where none of the pMDI/spacers were significantly different from each other and at RR= 42 breaths/min where FPD of flut/Babyhaler was not significantly different from the other 3 pMDI/spacer combinations.

Extra fine particle dose

The relation between EFPD and Vt is shown in figure 4C. Vt did not influence the EFPD significantly for any of the pMDI/spacer combinations (p>0.1). The EFPD for fluticasone was significantly higher than for budesonide irrespective of spacer used, except at Vt = 50 ml where flut/Babyhaler was significantly different from flut/Aerochamber.

The relation between EFPD and RR is shown in figure 4D. There was no significant correlation between RR and EFPD for any of the pMDI/spacer combinations (p>0.1). Both bud/Nebuchamber and bud/Aerochamber had a significant lower EFPD compared with both flut/Babyhaler and flut/Aerochamber, except at RR=18 breaths/min, where flut/Babyhaler was not significantly different compared with bud/Nebuchamber and bud/Aerochamber.

Median mass aerodynamic diameter

The relation between the MMAD and Vt is shown in figure 4E. MMAD significantly decreased with increasing Vt for all spacers (all: R= -0.95, p<0.001). MMAD of fluticasone was significantly smaller than for budesonide irrespective of spacer used, except at Vt=200 ml where all 4 pMDI/spacers were significantly different from each other.

The relation between MMAD and RR's are shown in figure 4F. Increasing RR significantly reduced MMAD for all spacers (all R: between-0.95 and -0.80, p<0.01). The MMAD for fluticasone was significantly smaller than for budesonide, irrespective of the type of spacer used.

DISCUSSION

In this study we investigated the influence of Vt and RR on aerosol deposition from 4 pMDI/spacer combinations, using an anatomically correct upper airway model of a nose-breathing infant. We found that spacer-output increased with increasing Vt, but was not influenced by changing RR's. Lungdose decreased with increasing RR and Vt, from Vt = 50 ml or higher. Increase in Vt and RR lead to an increase in upper airway deposition. Furthermore, extra fine particle dose to the lungs was relatively independent of Vt and RR. Finally, lungdose appeared to be pMDI dependent, but independent of spacer.

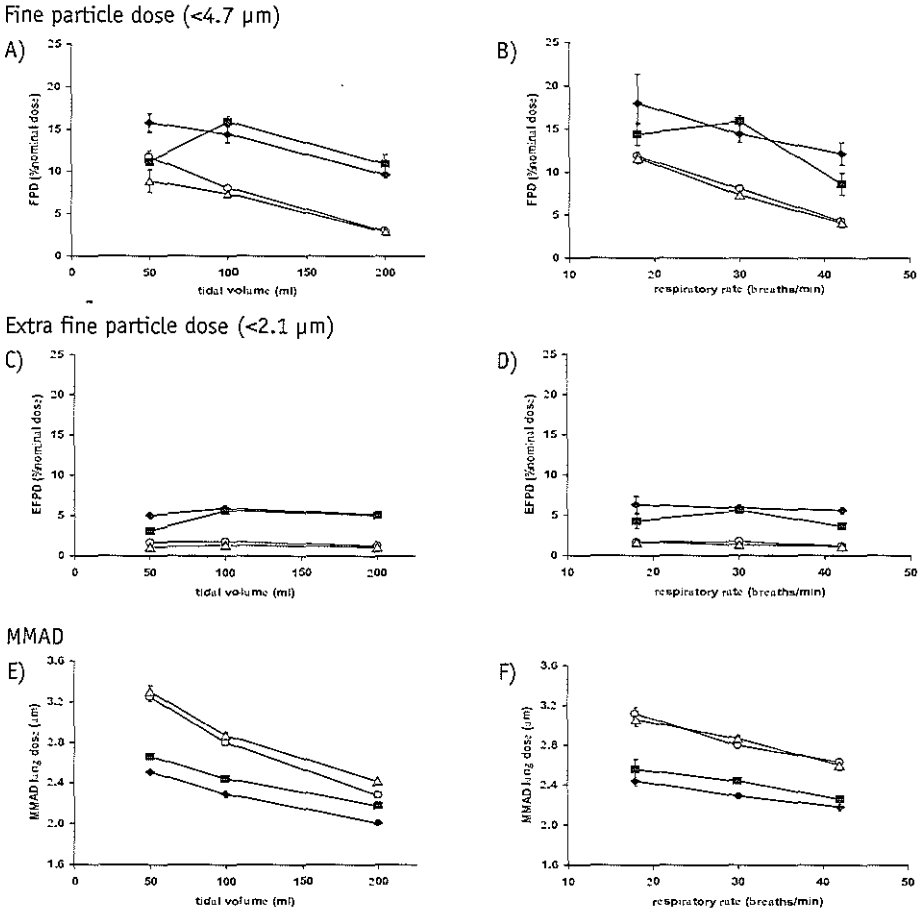

FIGURE 4. Particle size measurements (Explanation of symbols, see figure 3.)
A: Fine particle dose (FPD) *versus* Vt: for bN, bA and fA: R=-0.95 to -0.84, p<0.005, for fB *NS* correlation; bN *versus* bA, and fB *versus* fA: *NS*; bN and bA *versus* fB and fA: p<0.05, except at Vt =50 ml: *NS* differences between pMDI/spacers. B: Fine particle dose (FPD) *versus* RR: for bN and bA: R=-0.95, p<0.005; for fB and fA *NS* correlation (R= -0.5, p≥0.1); at RR = 18: *NS* difference between pMDI/spacers; at RR = 30: bN *versus* bA, and fB *versus* fA: *NS*; bN and bA *versus* fB and fA: *NS*; at RR = 42: fB *versus* bN and bA: *NS*. C: Extra fine particle dose (EFPD) *versus* Vt: no significant correlation for any spacer; bN *versus* bA, and fB *versus* fA: *NS*; bN and bA *versus* fB and fA: p<0.05, except at Vt =50 ml: fB *versus* fA:p<0.05. D: Extra fine particle dose (EFPD) *versus* RR: *NS* correlation for any spacer; bN *versus* bA, and fB *versus* fA: *NS*; bN and bA *versus* fB and fA: p<0.05, except at RR=18 ml: fB, bN and bA: *NS* difference. E: Median mass aerodynamic diameter (MMAD) *versus* Vt: for all pMDI/spacers R= -0.95, p<0.001; bN *versus* bA, and fB *versus* fA: *NS*; bN and bA *versus* fB and fA: p<0.05, except at Vt =200 ml: all pMDI/spacers significantly different from each other. F: Median mass aerodynamic diameter (MMAD) *versus* RR: for all pMDI/spacers R: -0.95 to -0.80, p<0.01. bN *versus* bA, and fB *versus* fA: *NS*; bN and bA *versus* fB and fA: p<0.05, at all RR's

Spacer-output In general the spacer-ouput increased with increasing Vt. This is in agreement with previous studies [2,3,5,7,16]. Compared to the 3 other pMDI/spacers, the Babyhaler showed the largest increase in spacer-output with increasing Vt. This can be explained by the larger volume of the Babyhaler compared with the Nebuchamber and Aerochamber (350 ml, 250 ml and 150 ml respectively). In a larger volume spacer aerosol concentration and particle impaction is less than in smaller volume spacers, which results in a lower inhaled doses at small tidal volumes but higher doses when the spacer can be emptied faster with larger tidal volumes [2]. Furthermore, the relatively large dead space in the Babyhaler (40 ml) and suboptimal functioning of the valves are additional factors that can explain the relatively low spacer-output at small tidal volumes [2]. The spacer-output values found for the different spacers in our study correspond with in vivo values found in wheezy infants [17,18], although different pMDI/spacer combinations were used. One needs to be cautious with directly comparing spacer-output of spacers with different pMDI's, for this study and previous studies have shown, that each pMDI/spacer combination delivers different doses [8].

Lungdose The initial increase of lungdose with increasing Vt can be explained by the fact that with low tidal volumes each breath mobilizes more aerosol from the spacer. The subsequent decrease in lungdose with increasing Vt and with increasing RR is explained by the higher inspiratory flow rates. With high flows, coarse particles are more likely to deposit by inertial impaction in the narrow upper airways resulting in decreased penetration of aerosols to the lower airways [19]. Our findings do not completely comply with the concept that lower tidal volume leads to reduced delivery of aerosol to the lungs [7]. This concept is based on studies where only spacer output was measured, without taking the route of inhalation into consideration [2,3,5,7,16]. Our results show that measuring spacer-output is not sufficient to predict the dose delivered to the lungs. The finding that lung dose decreases with increasing Vt and RR, i.e. inspiratory flow rate, fits in with studies in adults [20-22]. These studies showed that slow inspiratory flow rate gives higher lung deposition of therapeutic aerosols.

The lung doses with the SAINT model for the 4 pMDI/spacer combinations are close to values found in in-vivo lung deposition studies. A detergent coated Aerochamber or Babyhaler with radiolabeled salbutamol showed mean lung depositions of resp. 5.4% (range 2.5-9.7%) and 16.4% (range 8.5-23.9) in children under 4 years of age [23,24]. Although the lung doses found with our model reasonably correspond with these in vivo data, the data should still be considered as in vitro data. The aerosols were administered in optimal conditions, with idealized breathing patterns. Additionally, differences in upper airway geometry between children are likely to result in different lung deposition for a given pMDI/spacer combination. Furthermore, the lung doses found only show the measured dose at subglottic level of the model, but this does not give any information on the distribution of drug in the lower airways. For instance, large tidal volumes showed low lung doses, but deep inspiratory breaths

are likely to enhance peripheral deposition [25]. Measurements of particle size give an indication on where the aerosol will deposit. Small particles are more likely to deposit peripherally in the airways than larger particles [26-29].

Particle size Particle size measurements of lung dose, showed that the total lung dose measured with the filters mainly consisted of particles < 4.7 μm. Furthermore, it was found that with increasing inspiratory flow rate the MMAD of the lung dose decreased. This means that the larger particles impact in the upper airways of the model, while smaller particles still pass the model at higher inspiratory flow rates. In general, the FPD decreased with increasing Vt and RR, except for flut/Babyhaler and for the flut/Aerochamber with RR for which this relationship was not significant. The EFPD appeared relatively independent of Vt and RR. Apparently, extra fine particles (<2.1 μm) passed the upper airway model flow-independently. This probably explains why the relationship of FPD with Vt and/or RR was not significant for the spacers tested with fluticasone, for the FPD contains a larger percentage of extra fine particles, of which deposition is relatively flow independent. From these results it can be extrapolated that pMDI's containing extra fine particles will deliver drug to the lungs relatively independent of breathing pattern.

pMDI/spacer combinations. For the four pMDI/spacer combinations tested in this study, lungdose depended especially on the type of pMDI used and much less on the type of spacer used. In general, lung dose, FPD and EFPD were significantly higher and MMAD smaller for fluticasone than for budesonide irrespective of spacer used. Only at the small Vt's and low RR's there were some differences between the spacers. It should be noted that the fluticasone pMDI contains HFA-propellant and the budesonide pMDI CFC-propellant. The technical characteristics of the HFA-formulation of fluticasone, however, has been claimed to be identical to the old CFC-fluticasone [30]. Furthermore, it should be stressed that the spacers used in this study were used in optimal conditions, i.e. electrostatic charge of the plastic spacers was reduced by detergent coating and the face mask was put airtight on the model. A recent study in adults showed that coating a plastic spacer with detergent increased lung deposition 4 fold compared with non-detergent coated spacer [12]. We did one measurement in triplicate, at Vt=100 ml and RR 30 breaths/min, with the flut/Babyhaler when it was washed, water-rinsed and towel-dried and thus not detergent coated. Lung dose was 2.9%, FPD was 2.8% and EFPD was 1.2% (data not shown). The corresponding data for the detergent coated Babyhaler were: 19%, 15.9% and 5.7% respectively. This confirms that when electrostatic charge is present in a spacer, aerosol delivery to the lungs can be considerably reduced. Therefore, our finding that lung dose is dependent of pMDI but relatively independent of spacer used is only valid if the electrostatic charge of a spacer is minimized.

Upper airway deposition. Increased inertial impaction at higher inspiratory flow rates explains that upper airway deposition was found to increase with Vt and RR for all pMDI/spacer combinations. The deposition in the upper airways increased to almost 90% of the spacer-output at high Vt and RR for all studied spacers.

Clinical consquences The present findings suggest that the use of pMDI's delivering a high mass of particles smaller than 2.1 µm will increase the dose delivered to the lungs in infants and that the dose delivered will be less dependent on the breathing pattern. Especially, in crying children, when high inspiratory flows are present, the use of small particles can be an advantage. Crying during the administration reduces lung deposition substantially [31,32]. Furthermore, it should be taken into account that the dose to the lungs is also reduced in other cases when high inspiratory flow rates are present, such as in tachypnoea caused by an asthma attack or after physical exercise. Quiet breathing during inhalation of aerosols should be encouraged, when ever possible. The dose delivered to the lung is primarily determined by the pMDI and much less by the spacer (if optimally used). The choice for the spacer becomes important for children with a tidal volume below 50 ml. The Babyhaler is less suitable in these children due to a large dead volume and suboptimal functioning valves at small tidal volumes.

In conclusion In this study we tested 4 pMDI/spacer combinations using a upper airway model of a 9-month-old infant and a breathing simulator. We found that lungdose initially increased, but then decreased with increasing inspiratory flow rate (Vt and RR) by impaction of coarse particles in the upper airways. Furthermore, we found that the spacer-output, increased with increasing Vt, but was not influenced by changing RR's. The lungdose of particles < 2.1 µm was relatively independent of the breathing pattern. Furthermore, with the studied pMDI's and (detergent-coated) spacers, lungdose appeared to be pMDI dependent and spacer independent. We believe that the use of pMDI's delivering a high mass of particles smaller than 2.1 µm will increase dose delivered to the lungs and dose reproducibilty in infants.

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CHAPTER 8

Aerosol adminstration during sleep: An alternative for the fighting toddler?

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Submitted

ABSTRACT

Background Insufficient cooperation during administration of aerosols by metered dose inhaler (MDI)/spacers is a problem in nearly 50% of treated children younger than two years old. For these children administration during sleep might be more efficient. However, it is unknown how much aerosol reaches the lungs during sleep. **Aim** To determine in vitro the dose to the lungs in young children from a MDI/spacer during sleep and while being awake. **Methods** Breathing patterns were recorded by a pneumotachograph in 18 children (age 11 ± 5.1 months) during sleep and wakefulness. Next, breathing patterns were replayed by a computer-controlled breathing simulator to which an anatomically correct nose-throat model of a 9-month-old child (Sophia Anatomical Infant Nose-Throat (SAINT) –model) was attached. One puff of budesonide (Pulmicort® 200 µg) was administered to the model via a metal spacer (Nebuchamber®). Aerosol was trapped in a filter placed between model and breathing simulator. Finally, the amount of budesonide on the filter (= lung dose) was analyzed by HPLC. For each of the 36 breathing pattern lung dose was measured in triplicate. **Results** The sleep breathing patterns had significantly lower respiratory rate and peak inspiratory flows, and had smaller variability in respiratory rate, tidal volume and peak inspiratory flows. Lung dose (mean ± sd) was 6.5 ± 3.2 µg and 11.3 ± 3.9 µg (p=0.004) for the wake and sleep breathing pattern respectively. **Conclusions** This infant model-study shows that the lung dose of budesonide by MDI/spacer is significantly higher during sleep compared to inhalation while being awake. Administration of aerosols during sleep might, therefore, be an efficient alternative for uncooperative toddlers.

INTRODUCTION

Inhaled drugs are widely used for management of asthma in children. Several devices are available to deliver inhaled drugs to the lungs in young children. The pressurized metered dose inhaler (pMDI) combined with a spacer with attached face mask is considered the most convenient way to administer inhaled drugs to young children [1,2]. However, the efficiency of the pMDI/spacer system is relatively low in this group. Lung deposition studies showed that little of the administered dose is deposited in the lungs of young children [3-5]. When children are crying, lung deposition is even reduced to almost zero [3,6]. Furthermore, it was shown in a filter study that the dose delivered from a spacer decreased and the dose variabilty increased when a child was not co-operative during the administration procedure [7]. Therefore, anti-asthma therapy could fail in non co-operative children. To treat these children it has been suggested to administer the drugs by pMDI/spacer during sleep [3]. However, the efficiency of administration during sleep has not been investigated. Breathing patterns of young children have been shown to vary for the different behavioral states [8-10]. It is likely that this will affect the dose delivered from a pMDI/spacer, for it has been shown that tidal volume and inspiratory flow rate are important determinants for aerosol deposition [11,12]. We studied the dose reaching the lungs from a pMDI/spacer in vitro in an anatomically correct upper airway model of an infant and simulated breathing patterns of awake and sleeping children.

MATERIAL & METHODS

BREATHING PATTERNS

Breathing patterns were recorded from children under the age of two years who were referred for lung function tests to the out-patient clinic of the Department of Pediatric Pulmonology of the Sophia Children's Hospital in Rotterdam. Before routine lung function testing the wake breathing pattern was recorded during tidal breathing. The recording of the breathing pattern was done with a pneumotachograph (Jaeger, Germany) which was attached to a face mask (Babyhaler® face-mask, GlaxoWellcome, UK). The child was sitting in an upright position. The mask was put on the face, while an airtight fit was assured. The child needed to breathe through the facemask for 1 minute. Children who were not co-operative during the recording were excluded. Subsequently, chloralhydrate (7.5 mg/kg) was administered to the child according to the routine protocol for infant lung function testing in our hospital. It has been shown that chloralhydrate does not significantly alter the breathing pattern of a child [13]. After routine lung function tests were completed the breathing pattern was again recorded while the child was in a supine position and sleeping in quiet or non-REM sleep.

The breathing patterns were recorded digitally, using a multi channel recording program (MKR-system, custom made software development, Erasmus University Medical Center Rotterdam, the Netherlands). The sampling rate was 125 Hz. A representative 16 seconds part of the registration was selected for simulation, as the breathing simulator could simulate the breathing patterns in cycles of maximally 16 seconds.

The breathing patterns were analysed using an adapted computer programme based on existing software MATLAB® release 12 (The Maths Works, Natrich, Mass, US). The programme recognises breath-to-breath intervals in the digitised flow-signal, by detecting zero flow crossings. A single breath was defined as the distance from the onset of an inspiration to the next inspiration. Respiratory rate, tidal volume and peak inspiratory flow were calculated for each breath. The mean of these values was calculated for each breathing pattern. Variability of these values was expressed as coefficient of variation [14-16].

UPPER AIRWAY MODEL

A model of the upper airways of an infant was used for the aerosol deposition measurements. This model, the Sophia Anatomical Infant Nose-Throat (SAINT) model (Sophia Children's Hospital, Rotterdam, The Netherlands) was extensively described elsewhere [17] and has been shown to be a valuable tool to study aerosol deposition in vitro. In short, it is a CT-scan derived stereolithographically made, anatomically correct model of the upper airways of a 9-month-old infant. The model includes the face, nasal cavity and pharynx till the subglottic region. The nasal airway is open for air passage, the oral airway is closed. Before use, the inner surface of the model was coated with a thin layer of glycerol/Brij-35 (polyoxyethylene 23 laurylether) mixture by pipetting 4 ml into the model and allowing the excess fluid to drip out. This was to mimic a sticky mucosa and to eliminate any electrostatic charge present on the inner surface of the model.

EXPERIMENTAL SET-UP AND STUDY PROCEDURE

The SAINT-model was connected to a custom made computer-controlled breathing simulator [18], which was adapted for simulating infant breathing patterns (figure 1). The pMDI/spacer used for these experiments was the budesonide pMDI (Pulmicort® 200 µg, AstraZeneca, Lund, Sweden) and the metal Nebuchamber® (AstraZeneca) spacer with attached facemask. Filters (Vital Signs, Totowa, NJ, USA) were used to collect drug delivered from pMDI/spacer. A clean filter was placed before each experiment between model and breathing simulator (figure 1). The pMDI/spacer with attached facemask was shaken for 5 seconds and placed on the face of the model ensuring an airtight fit using therapeutic putty (Carters, Westbury, Wilts, UK). One puff of budesonide was actuated into the spacer just before the start of an inspiration, within 5 seconds after the pMDI was shaken. Drug from the spacer was withdrawn

during 30 seconds of simulated breathing. The amount of budesonide found on the filter was defined as lung dose, which equals the total dose passing the model. For each breathing pattern, lung dose was measured three times. Breathing patterns were selected in a randomized order.

DRUG ANALYSIS

Budesonide was washed from the filters with ethanol containing an internal standard (fluocinolone acetonide). Budesonide was quantified by a validated high performance liquid chromatography (HPLC) method, using an ethanol:water (43:57) mobile phase and a Supelcosil LC-18 column (5µm particles, 5 cm * 0.46 cm (i.d.)). The coefficient of variation of the method was <3%.

STATISTICAL ANALYSIS

The mean values for respiratory rate, tidal volume and peak inspiratory flow were analyzed for each breathing pattern. Variability, expressed as coefficient of variation, was calculated for these variables for each breathing pattern. Sleep and wake breathing patterns were compared using paired t-test test.

Lung dose is expressed in micrograms of budesonide. The mean lung dose of the three measurements of each breathing pattern was used for further statistical analysis. Paired t-test was used to compare lung doses of wake and sleep breathing patterns.

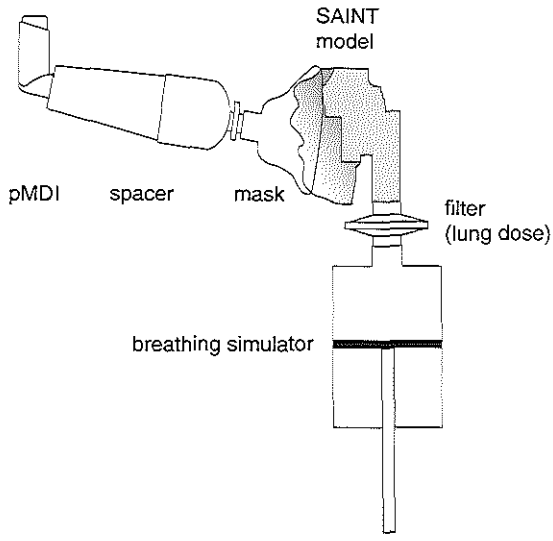

FIGURE 1. Experimental set-up to measure lung dose (filter) for a pMDI/spacer during simulated breathing using the Sophia Anatomical Infant Nose-Throat (SAINT) -model.

RESULTS

The breathing patterns of 18 children were recorded. The children had a mean age of 11 (SD 5.1) months. The reasons for lung function tests were suspicion asthma (n=7), bronchopulmonary disease (n=3), dyspnoea of unknown origin (n=3), frequent pneumonia (n=3), cystic fibrosis (n=1), sequestration (n=1). Table 1 shows the characteristics for the recorded breathing patterns. In general it was seen that wake breathing patterns were irregular and sleep breathing patterns were regular. A typical example of a wake and sleep breathing pattern of one child is shown in figure 2.

Results for lung doses are shown in figure 3. Mean (±SD) lung dose for sleep breathing patterns was 11.3 (3.9) µg and significantly (p=0.004) higher compared with lung doses for wake breathing patterns, which was 6.5 (3.5) µg. Only in three cases lung dose for sleep breathing pattern was lower than for the wake breathing pattern.

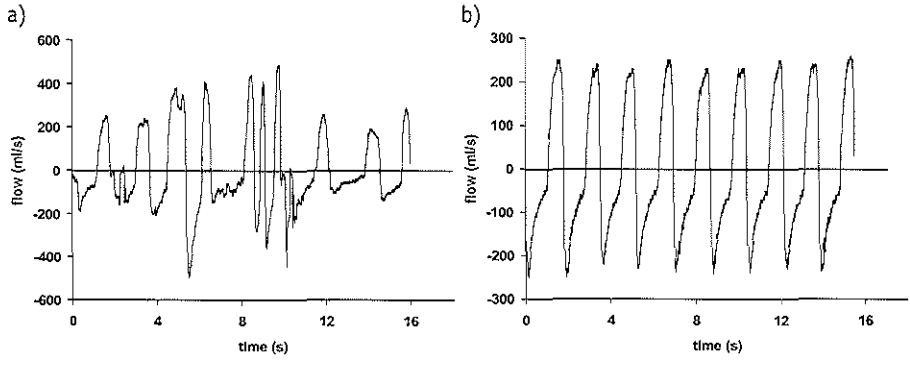

FIGURE 2. Example of typical breathing pattern of a 10 month-old child while awake (a) and asleep (b).

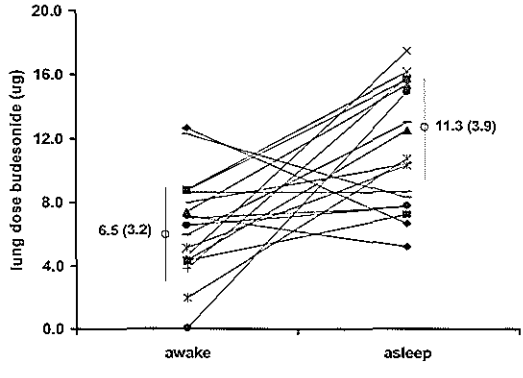

FIGURE 3. Comparison of lung dose for pMDI/spacer with wake and sleep breathing patterns of 18 children. Results are mean±SD. Difference between wake and sleep patterns: p=0.004

TABLE 1. Characteristics breathing patterns:
Descriptives are means of mean values.
Variability is expressed as coefficient of variation (CV)

n=18	Sleep mean (range)	Wake mean (range)	p-value
Descriptives			
• Respiratory rate (breaths/min)	32 (22-53)	49 (33-83)	<0.001
• Tidal volume (ml)	97 (39-138)	83 (20-141)	0.094
• Peak inspiratory flow (L/min)	10.2 (4.6-14.4)	13.8 (5.7-33.8)	0.039
Variability (CV)			
• Respiratory rate (%)	4.7 (0.8-12.1)	29.2 (6.0-89.3)	<0.001
• Tidal volume (%)	7.0 (2.1-33.5)	29.4 (4.4-58.2)	<0.001
• Peak inspiratory flow (%)	7.2 (1.9-18.6)	31.6 (6.5-60.4)	<0.001

DISCUSSION

In this study we compared the dose of budesonide delivered to the lungs from a pMDI/spacer during wakefulness and sleep using a anatomical infant upper airway model and in vivo recorded breathing patterns. The total dose passing the model, or lung dose, was significantly higher for the sleep breathing patterns than the wake breathing patterns.

The differences between the wake and sleep breathing patterns can be explained as follows. Firstly, the variability of respiratory rate, tidal volume and peak inspiratory flow of the wake breathing patterns were significantly higher compared with the sleep breathing pattern. This implies that in general wake breathing patterns were irregular, and sleep breathing pattern were more regular. Even though the children in our study were co-operative during the recording, the wake breathing patterns were very irregular. Our findings are in agreement with other studies in which higher values and higher variability was found for respiratory rate in young children while being awake compared with being asleep [9,10,19]. It should be noted that there is also difference in variability between the different sleep-states. Regular breathing patterns are particularly seen in quiet or non-REM sleep, whereas breathing becomes more irregular during REM-sleep [8]. The children in our study were all recorded during quiet sleep, which probably corresponds to non-REM sleep.

Secondly, mean respiratory rate and peak inspiratory flow were significantly higher for the wake breathing patterns compared with the sleep breathing patterns. It has been shown that lung deposition decreases with high respiratory rate [20] or high inspiratory flow rate in adults [12,21]. High inspiratory flow rate, especially with nose-breathing will lead to increased impaction of aerosol particles in the upper airways, resulting in a lower dose to the lungs.

Our results suggest that administration of inhaled drugs during sleep may be a good alternative for uncooperative toddlers. However, a number of questions need to be answered before it can be used in practice. In this study the total amount of drug reaching the lungs was measured, but not the distribution pattern within the lung. It is likely that the distribution pattern in the awake and upright position will be different from the pattern in the sleeping and supine position. In adults it has been shown that lung deposition in the supine position was more homogeneous through the lung compared with the upright position [22,23]. It is unknown whether this would be the same for infants. Furthermore, we do not know whether administration of aerosol during sleep is a feasible alternative since this was not studied in practice. Children might wake up and get up-set due to the handling. The next question to answer would be, whether administration during sleep is more effective than during wakefulness to reduce asthma symptoms in the fighting toddler. This can only by studied by clinical efficacy studies. Unfortunately such studies in this age group are difficult to perform. Firstly because of the difficulty in diagnosing asthma [24] and secondly due to the lack of reproducible endpoints suitable to measure a large number of infants [25].

In conclusion, we found a higher lung dose for sleep breathing patterns compared with wake breathing from a pMDI/spacer with attached face mask in an anatomically correct upper airway model of an infant. Administration of inhaled drugs during sleep seems therefore a good alternative for the fighting toddler. Feasibility in practice and clinical efficacy should be studied further.

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PARTICLE SIZE AND DEPOSITION

CHAPTER 9

Extra fine particles improve lung deposition of inhaled steroids in infants: a study in an upper airway model

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Submitted

ABSTRACT

The particles of a new hydrofluoroalkane–134a beclomethasone dipropionate (HFA-BDP)metered dose inhaler (Qvar™) are considerably smaller than those of chlorofluorocarbon (CFC)-BDP. This may improve lung deposition in infants, who inhale nasally, have irregular breathing patterns and small airways. Aim To compare the dose delivered to the lungs of HFA-BDP and CFC-BDP at different breathing patterns using an upper-airway model of an infant. Methods An anatomically correct upper-airway model of a 9-month-old child with an open nasal airway was connected to an Andersen impactor and breathing simulator. HFA-BDP 100µg and CFC-BDP 100 µg were delivered to the model through a detergent coated Aerochamber®. The total dose leaving the model (lung dose), its particle size distribution and median mass aerodynamic diameter (MMAD) were assessed during simulated tidal breathing with a tidal volume (Vt) of 50, 100 and 200 ml and 30 breaths/min. Dose was expressed as percentage of nominal dose. **Results** Lung dose for HFA-BDP was 25.4, 26.5 and 30.7% compared with 6.8, 4.8 and 2.1% for CFC-BDP at Vt= 50, 100 and 200 ml respectively. Dose of particles <2.1 µm to the lung for HFA-BDP was 23-28%, compared with 0.6-0.8% for CFC-BDP. Lung dose of CFC-BDP mainly consisted of particles between 2.1 and 4.7 µm. MMAD for HFA-BDP was 1.2 µm, and 2.6-3.3 µm for CFC-BDP depending on Vt. Lung dose for CFC-BDP decreased significantly with increasing Vt. HFA-BDP lung dose did not alter significantly with Vt. **Conclusions** In this infant model study, the use of HFA-BDP with a high dose of particles < 2.1 µm improves lung deposition substantially, and reduces variability related to breathing pattern compared with CFC-BDP.

INTRODUCTION

Inhaled steroids have been shown to reduce symptoms in wheezy infants [1]. A convenient way to administer inhaled steroids to the lungs of infants is by pressurized metered dose inhaler (pMDI) combined with spacer and attached face mask [2]. However, only a small proportion of the administered dose is deposited in the lungs of young children [3,4] and the inhaled dose is highly variable [5]. The replacement of chlorofluorocarbons (CFC's) byozone-friendly propellants, such as hydrofluoroalkane (HFA), has been an opportunity to revise the delivery properties of pMDI's [6]. The new HFA-beclomethasone dipropionate (BDP)(Qvar™) has a large proportion of small particles compared with conventional formulations. This has been shown to result in a higher and a more peripheral lung deposition in adults [7]. There are reasons to believe that these small particles may also be beneficial for treatment of infants. Firstly, infants inhale aerosols mainly nasally [8]. Small particles are more likely to bypass the nose and to be deposited in the lungs compared with larger particles [9]. Secondly, infants may not co-operate during the administration procedure, leading to crying or irregular and fast breathing while inhaling the aerosol. Crying and high inspiratory flow rates have been shown to result in decreased lung deposition [4,10], with only small particles reaching the lungs [11]. Thirdly, the narrow airways of infants are characterised by high velocity and turbulent airflow causing increased deposition of particles in the proximal airways [12,13]. Small particles are more likely to reach the peripheral airways [14]. Lung deposition of the new HFA-BDP has not yet been studied in infants. Lung deposition studies in infants using radiolabelled aerosols are difficult to perform and subject to ethical discussion [15]. Therefore, we studied the delivery of HFA-BDP via a spacer to an infant upper airway model. We hypothesized that HFA-BDP would deliver a substantially higher dose to the lungs with less dependence on breathing pattern or inspiratory flow rate, compared with CFC-BDP.

MATERIALS & METHODS

UPPER AIRWAY MODEL

A model of the upper airways of an infant was used for the aerosol deposition measurements. This model, the Sophia Anatomical Infant Nose-Throat (SAINT) model, was extensively described elsewhere [16]. In short, the SAINT-model is a CT-scan derived stereolithographically made, anatomically correct model of the upper airways of a 9-month-old infant. The model includes the face, nasal cavity and pharynx untill the subglottic region. The nasal airway is open for air passage; the oral airway is closed. To mimic a sticky mucosa and to eliminate any electrostatic charge present on the inner surface of the model, the inner surface of the model is coated with a thin layer of glycerol/Brij-35 (polyoxyethylene 23 laurylether) mixture by pipetting 4 ml into the model and allowing the excess fluid to drip out.

PMDI/SPACER

Two pMDI's containing beclomethasone dipropionate (BDP) were tested. HFA-BDP (Qvar™, 3M Pharmaceuticals, St. Paul, MN, USA) was compared with chlorofluorocarbon BDP (CFC-BDP)(Becotide®, GlaxoWellcome, Uxbridge, UK). Before testing, the pMDI's were primed by shaking and firing 10 waste puffs. The pMDI's were used in combination with a small volume plastic spacer, the Aerochamber® (Trudell Medical, London, Canada). The Aerochamber was used with the infant face-mask as provided by the manufacturer. Electrostatic charge can develop on the inner surface of a plastic spacer, which decreases drug delivery by retaining the drug in the spacer [17]. To reduce the electrostatic charge of the Aerochamber it was coated with household detergent. Several hours before use the spacer was washed in diluted detergent and subsequently left to drip-dry. Detergent coating has been shown to reduce electrostatic charge on the inner surface of the spacer [18,19].

EXPERIMENTAL SET-UP

The SAINT model was connected to a breathing simulator (Pari Sinus Breathing Simulator, Pari GmbH, Starnberg, Germany) and an Andersen 8-stage cascade impactor (Graseby Andersen, Smyrna, GA, USA) by means of a three-way glass connection (figure 1). A constant flow of 28.3 L/min through the Andersen impactor (F_{ai}) was balanced with an inflow (F_i) of 28.3 L/min through the glass connection, resulting in zero flow

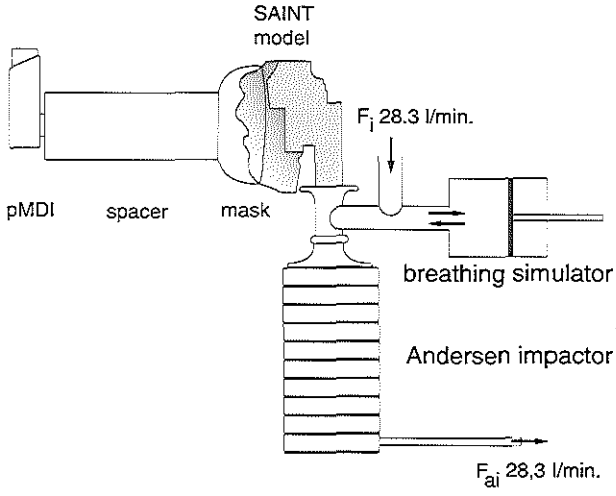

FIGURE 1. Experimental set-up used to measure lung dose and particle size from pMDI/spacer during simulated tidal breathing. The breathing simulator supplied tidal breathing through the SAINT-model and pMDI/spacer while a constant flow F_{ai} of 28.3L/min flows to the Andersen impactor, balanced by an inflow Fi of 28.3 L/min. A three-way glass connection attached all the parts together.

through the model. When the breathing simulator was switched on, there was simulated tidal breathing through the model and a constant flow through the Andersen impactor. This set-up has been previously described and validated. [20,21]. Lung dose was defined as the total dose leaving the SAINT-model, expressed as a percentage of nominal dose. Fine particle dose (FPD) was defined as the mass of the lung dose in particles < 4.7 µm (impactor stage 3-8) expressed as a percentage of nominal dose. Extra fine particle dose (EFPD) was defined as the mass of the lung dose in particles < 2.1 µm (impactor stage 5-8) expressed as a percentage of nominal dose. Particle size of lung dose was expressed as median mass aerodynamic diameter (MMAD).

BREATHING SIMULATION

Aerosol delivery was tested at various tidal volumes (Vt) using sinusoidal tidal breathing patterns with the following settings for the breathing simulator: Respiratory duty cycle (inspiratory time (T_i) / total respiratory cycle time (T_{tot})): 0.42 and Vt of 50, 100 and 200 ml with fixed respiratory rate (RR) of 30 breaths/min. A respiratory duty cycle (T_i/T_{tot}) of 0.42, Vt of 100 ml and RR of 30 breaths/min are in accordance with reference values appropriate for the age of the subject used to construct the model [22]. Measurements for each Vt were done 3 times in a randomized order.

STUDY PROCEDURE

The SAINT-model was attached to the clean impactor and the breathing simulator was started. The pMDI/spacer with facemask was shaken and placed on the face of the model ensuring an airtight fit using therapeutic putty (Carters, Westbury, UK). Within 5 seconds of being shaken, one puff of HFA-BDP or CFC-BDP was actuated into the spacer just before the start of an inspiration. Aerosol was drawn from the spacer during 30 seconds of simulated tidal breathing. Ten separate puffs were actuated for each impactor measurement to get detectable amounts of drug on the impactor plates. The experiments were performed in ambient conditions with 30-40% humidity.

DRUG ANALYSIS

Drug on the impactor plates and glass connection was dissolved in ethanol containing an internal standard (fluocinolone acetonide). Beclomethasone dipropionate was quantified using a validated high performance liquid chromatography (HPLC) method, comprising an ethanol:water (43:57) mobile phase and a Supelcosil LC-18 column (5µm particles, 5 cm * 0.46 cm (i.d.)). The coefficient of variation of the method was <3%.

STATISTICAL ANALYSIS

The amount of BDP found is expressed as a percentage of nominal dose. Results shown are means (± SEM). Comparisons between dose delivery from HFA-BDP and

CFC-BDP were tested using independent sample t-test for each Vt. The following variables were tested: lungdose, FPD, EFPD and MMAD. The correlation between Vt and these variables were investigated using Pearson correlation coefficients (R). Analysis of covariance (ANCOVA) was used to show differences between the relationships of HFA-BDP and CFC-BDP deposition variables with Vt. Statistical significance was set at $p \leq 0.05$.

RESULTS

Results for lung dose are shown in figure 2A. Lung doses for HFA-BDP were 25.4 (2.0)%, 26.5 (3.6)% and 30.7 (0.5)% compared with 6.8 (1.1)%, 4.8 (0.7)% and 2.1 (0.1)% for CFC-BDP at tidal volumes 50, 100 and 200 ml, respectively. The differences between HFA-BDP and CFC-BDP were highly significant ($p<0.001$) for all Vt's. Furthermore, lung dose of HFA-BDP did not significantly depend on tidal volume ($R=0.6$, $p=0.1$), whereas lung dose of CFC-BDP showed a significant decrease with increasing tidal volume ($R=-0.9$, $p=0.002$).

Results for FPD (particles <4.7 μm) are shown in figure 2B. FPD's for HFA-BDP lung dose were 24.1 (1.9)%, 24.5 (2.7)% and 28.7 (0.5)% compared with 5.8 (1.0)%, 4.4 (0.6)% and 1.9 (0.1)% for CFC-BDP at tidal volumes 50, 100 and 200 ml, respectively. The differences between HFA-BDP and CFC-BDP were highly significant for all Vt's ($p<0.001$). Furthermore, FPD of HFA-BDP did not significantly depend on tidal volume ($R=0.6$, $p=0.1$), whereas FPD of CFC-BDP showed a significant decrease with increasing tidal volume ($R=-0.9$, $p=0.003$).

Results for EFPD (particles <2.1 μm) are shown in figure 2C. EFPD's for HFA-BDP lung dosewere 23.6 (1.9)%, 23.5 (3.1)% and 28.3 (0.5)% compared with 0.8 (0.2)%, 0.6 (0.3)% and 0.6 (0.1)% of CFC-BDP at tidal volumes 50, 100 and 200 respectively. The differences between HFA-BDP and CFC-BDP were highly significant ($p<0.001$). EFPD of HFA-BDP and of CFC-BDP showed no significant correlation with tidal volume (resp. $R=0.6$, $p=0.1$ and $R=-0.3$, $p=0.5$).

Results for MMAD of lung dose are shown in figure 2D. MMAD's of HFA-BDP were 1.3 (0.03), 1.1 (0.1) and 1.1 (0.05) μm compared with 3.3 (0.01), 3.1 (0.05) and 2.6 (0.02) of CFC-BDP at Vt = 50, 100 and 200 respectively. The differences between HFA-BDP and CFC-BDP were highly significant ($p<0.001$). MMAD of CFC-BDP showed a significant decline with increasing Vt ($R=-0.9$, $p<0.001$), wheres this decline small and borderline significant for the HFA-BDP ($R=-0.6$, $p=0.052$)

Calculations of the separate regression lines for both HFA-BDP and CFC-BDP, showed that the slopes were significantly different ($p \leq 0.008$), for lung dose, FPD and MMAD, but not for EFPD. This means that the relationships with Vt significantly differed between HFA-BDP and CFC-BDP except for EFPD.

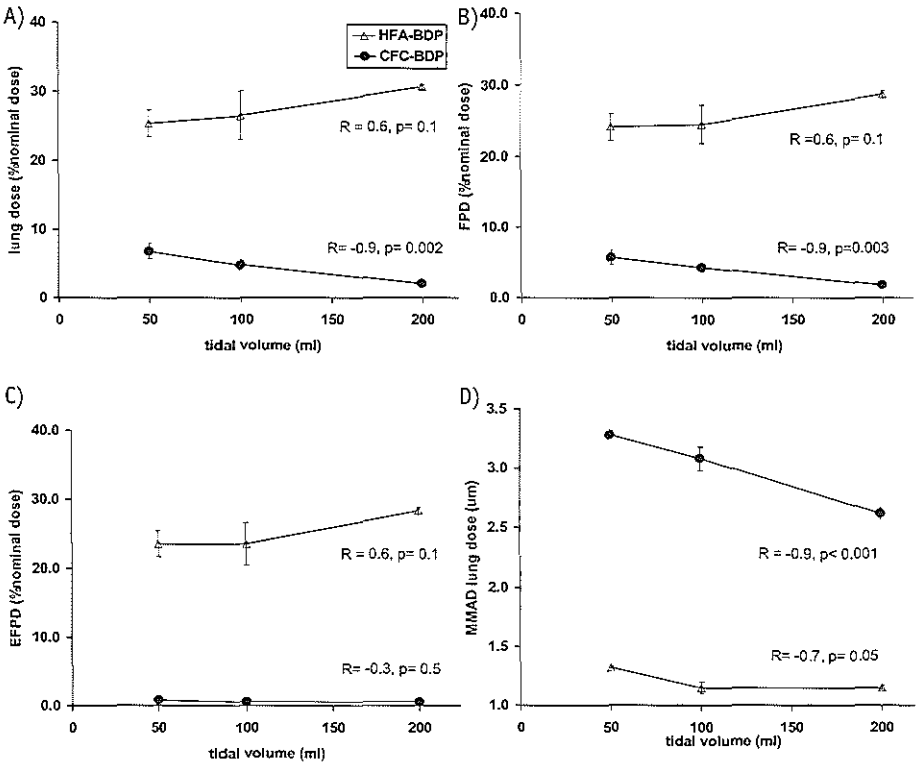

FIGURE 2. Comparison of aerosol deposition measurements in SAINT-model with HFA-BDP (△) and CFC-BDP (●) in relation to tidal volume. Results are mean (SEM) of 3 measurements. A. Lung dose: B. Fine (<4.7 μm) Particle Dose (FPD): C. Extra Fine (<2.1 μm) Particle Dose (EFPD) D. Median Mass Aerodynamic Diameter (MMAD). A, B, C, D: p<0.001 for differences between HFA-BDP and CFC-BDP at all Vt's.

DISCUSSION

We studied the relation between lung dose and particle size for HFA-BDP and CFC-BDP delivered by Aerochamber at different tidal volumes in an anatomically correct upper airway model of an infant. Lung dose of HFA-BDP was 3.5 to almost 15 fold higher compared with CFC-BDP for different tidal volumes. Furthermore, lung dose of HFA-BDP was independent of tidal volume, whereas lung dose of CFC-BDP showed a significant decrease with increasing tidal volume. Lung dose of HFA-BDP consisted mainly of particles smaller than 2.1 μm, whereas lung dose of CFC-BDP consisted mainly of particles between 4.7 μm and 2.1 μm.

Our study is in agreement with previous radiolabelled studies using radiolabelled aerosols in adults, where lung deposition was up to10 fold higher with HFA-BDP pMDI compared with CFC-BDP, when used without spacer [7]. The lung dose found using the SAINT-model of around 30% for HFA-BDP is in line with a recent study, measuring lung deposition of radiolabelled HFA-BDP in children. Lung deposition of 41%, 45%, and 54% of metered dose was found for children resp. 5-7 years, 8-10 years and 11-14 years old, respectively, when inhaling HFA-BDP via an Autohaler® (3M Pharmaceuticals) [23]. That we found a lower dose can be explained first by the fact that we used a spacer and second by the younger age of the child used for the model compared with the age of the children in the deposition study. The model inhaled through the nose during tidal breathing which is the usual situation for a 9-month-old child, whereas the older children inhaled with a single breath via the mouth. Inhalation through the nose reduces the amount of drug delivered to the lungs [8]. In addition, with tidal breathing some of the aerosol is lost with exhalation, as there is no breath-hold. Furthermore, the expression of lung deposition as a percentage of metered dose (or ex-valve dose) is likely to result in a slightly higher value than when expressed as a percentage of nominal dose (or label claim). Studies testing radiolabelled CFC-salbutamol pMDI (Ventolin®, GlaxoWellcome) used with an Aerochamber found lung depositions of 0.67% for preterm infants [3] and 1.97% for children under 5 years of age [4]. Our results indicate that the HFA-BDP, due to smaller particles, will give a much higher lung dose in infants than CFC-formulations with the same spacer.

Lung dose of HFA-BDP was not dependent on tidal volume, whereas lung dose of CFC-BDP decreased rapidly with increasing tidal volume. With increasing tidal volume, peak inspiratory flow rate increases. It has been shown in adults that fast inhalation leads to lower lung deposition compared with slow inhalation [24]. Flow will have a turbulent pattern with high inspiratory flow rate in the narrow upper airways. As a result, coarse particles are more likely to deposit in the upper airways by inertial impaction and thus lung dose will be lower. This appears not to be the case for the EFPD of CFC-BDP and HFA-BDP, which is largely independent of breathing pattern. Since 90% of the lung dose of HFA-BDP consists of particles smaller than 2.1 µm, the lung dose is much less dependent on breathing pattern compared with CFC-BDP. Only 13% of the lung dose of CFC-BDP has particles smaller than 2.1 µm.

The lungdose in our model indicates the dose delivered beyond the subglottic level. It does not give information on the distribution of drug in the lower airways. However, particle size gives an indication on where the aerosol may deposit as it has been shown in several theoretical and clinical aerosol deposition models that small particles deposit more peripherally in the airways than larger particles [25]. A lung deposition study in adults showed that the distribution of HFA-BDP was more peripheral in the lungs compared with CFC-BDP [7] The relation between particle size and deposition pattern is not known for infants. It is likely that the high EFPD of the HFA-BDP will improve peripheral deposition in infants.

The clinical consequences of the improved aerosol characteristics might be considerable. A high lung dose which is independent of inspiratory flow may be an advantage for children who are not co-operative during the administration of aerosol. It has been shown that crying reduces lung deposition from a pMDI/spacer to almost zero [10]. Almost 50% of young children are not cooperative during the administration procedure [5]. These children might benefit from HFA-BDP for control of asthma symptoms. With the increased lung dose in infants and potential for improved lung distrubution, it is expected that the daily dose of HFA-BDP needed to control asthma symptoms will be substantially reduced compared with CFC-BDP. In adults with asthma it was shown that the dose of HFA-BDP could be reduced 2.6 times to obtain the same improvement in lung function as with CFC-BDP [26]. Clinical efficacy studies are needed to assess the lowest effective dose of HFA-BDP in infants.

In conclusion, Aerosol deposition tests using the SAINT-model and simulated breathing show that HFA-BDP with spacer gives substantially higher lung doses than CFC-BDP with spacer. Furthermore, the large proportion of extra fine particles in HFA-BDP results in reduced variability in lung doses related to breahing pattern compared with CFC-BDP. Further research is needed to show that HFA-BDP improves treatment efficacy in infants.

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SUMMARY AND GENERAL DISCUSSION

CHAPTER 10

Summary, discussion and future research

10.1 SUMMARY

Aerosol therapy is an established means for treatment of asthma. The pressurized metered dose inhaler (pMDI) combined with spacer is the recommended aerosol delivery system for maintenance asthma therapy in children. The addition of a facemask makes the pMDI/spacer also applicable for young children, who cannot inhale through the mouth on command. There are many different spacer designs, each with its own characteristics that may work out positively or negatively for the efficiency to deliver aerosols to children. However, little is known on the performance of pMDI/spacers in young children. Knowledge about the inhaled dose and factors affecting this dose is necessary for optimal application of aerosol therapy. The aim of this thesis was to increase the knowledge of aerosol therapy in young children in order to improve clinical practice.

The studies presented in this thesis focus on the efficiency of different pMDI/spacers to deliver therapeutic aerosols to young children and the factors that may affect the dose delivered to the patient.

Chapter 1 gives a general introduction on the rationale of this thesis and explains the outlines and aims of the studies.

Chapter 2 provides extensive background information on the scientific and practical aspects of aerosol therapy in children. Indications for aerosol therapy, the basic principles of aerosol deposition and the methods to investigate the aerosol deposition are discussed. Finally, the currently available aerosol delivery systems are discussed, with respect to the use in children.

Chapter 3 presents a randomized cross-over study in which we assessed and compared within-subject dose variability of aerosol delivery of metal and plastic spacers in children in daily life. Seventeen children aged 1-4 years (group I) and sixteen children aged 5-8 years (group II) with stable asthma participated in the study. Dose of budesonide from the spacer was measured by means of filters placed between spacer and facemask (group I) or between spacer and mouth (group II). The dose on the filter represented the total dose delivered to the mouth. Each of the spacers was tested for one week at home in a randomized order. The dose delivered was 2 fold higher for the metal- compared with the plastic spacer in both groups. This could be explained by the presence of electrostatic charge in plastic spacers which reduced the dose delivered. A considerable within-subject dose variability was found, which was highest in the younger children. This means that dose reproducibility is poor when children use a pMDI/spacer at home, especially in the younger age group. This variability was lower for the metal than for the plastic spacer in children 5-8 yrs of age, but not different in younger children using a facemask.

Since dose variability seemed to be highest in young children, and few children under the age of 2 had been included in the first study, a second study was performed with this age group. This study, presented in **chapter 4**, further investigated dose

delivery, dose variability and factors affecting these variables in 25 wheezy children aged 5-26 months in daily life. The dose of budesonide from a metal spacer, and the dose of fluticasone from a plastic spacer were measured by filters in a randomized order. We also examined the dose from the spacer when electrostatic charge (ESC) of the plastic spacers was reduced by coating the spacer with household detergent. This study confirmed that dose variability is high in young children using pMDI/spacers at home. Dose variability of the metal spacer was significantly higher compared with both static and non-static plastic spacers, of which dose variabilities were similar. Poor co-operation during the administration procedure was the most important reason for a high dose-variability in all spacers. Detergent coating was effective to reduce ESC, and to increase dose delivery, but had no effect on dose variability. We speculated that the relatively high dose variability in the metal spacer could be explained by a suboptimal fit of the face mask, which was observed on video recordings. Despite repeated instructions, many mistakes were made in the administration procedure, which resulted in reduced or no drug on the filters. Good co-operation was observed in only half of the children. Hence, the study shows that lack of co-operation during the administration procedure is an important problem for almost 50% of young children treated with aerosol therapy.

In filter studies the dose from a spacer which is delivered to the mouth is measured. This does not give information on the distribution in the airways and the amount of drug delivered to the lung. We therefore did a lung deposition study, which is described in **Chapter 5.** Lung deposition in asthmatic children aged 1-12 years was assessed using radiolabelled salbutamol delivered by a pMDI attached to a plastic spacer. The spacers were detergent-coated to minimize electrostatic charge on the surface. Mean lung deposition, expressed as a percentage of the actuated dose was 16.4 to 41.8% in children aged 1-12 years. Lung deposition increased with age, but the dose per kilogram bodyweight was equal for all ages. It was concluded that plastic spacers with reduced electrostatic charge by detergent coating produced much higher lung deposition than was previously found by others, who used electrostatic spacers.

To study in detail how breathing patterns affect aerosol deposition in young children we developed an upper airway model of an infant. **Chapter 6** describes the making of the Sophia Anatomical Infant Nose-Throat (SAINT)-model; an anatomically correct upper airway model of an infant, which can be used as a tool to study aerosol deposition mechanisms in infants. The model was made with a stereolithographic technique using a UV-sensitive resin. The SAINT-model is made from a 3D-CT-scan of the head of a 9-months-old child. It includes the face, the nasopharynx and larynx down to the subglottic region. The nasal airway of the model is open for air passage and the oral airway is closed. The CT-scan of the model matched the original in-vivo CT-scan closely. Aerosol deposition measurements showed that the dose leaving the subglottic region of the model or 'lung dose' was comparable with in vivo lung deposition data.

Chapter 7 presents a study with the SAINT-model investigating the influence of tidal volume and respiratory rate on aerosol deposition from 4 pMDI/spacer combinations, which are used for infants. Budesonide pMDI and fluticasone pMDI were each tested with two different spacers. Spacer output and lung dose were measured using filters. Particle size distribution of the lung dose was assessed with an impactor during simulated breathing. Spacer output increased with increasing tidal volume, but was not affected by changing respiratory rate. The lung dose increased with increasing tidal volume, from tidal volumes of 25 up to 50 or100 ml, depending on which spacer was used. However, the lung dose decreased with further increase in tidal volume. Furthermore, lung dose decreased with increasing respiratory rates. The results could be explained by the higher inspiratory flows with increasing tidal volume and respiratory rate. High flow rates cause increased deposition of large particles in the upper airways and subsequently produced a lower dose into the lungs. Deposition of particles <2.1 μm was largely independent of flow. Furthermore, we found that lung dose was dependent of pMDI and independent of spacers if electrostatic charge of plastic spacers was reduced.

As was shown in chapter 3, co-operation during the adminstration of aerosols is a major problem in young children, and may cause failure of treatment. To overcome this problem, it has been suggested to adminster the aerosols during sleep. However, the efficiency of administration during sleep is not known. In **chapter 8** the dose delivered to the lungs from a pMDI/spacer was measured using the SAINT-model and simulated breathing patterns, which were recorded during sleep and wakefulness in 18 children under 2 years of age. The lung dose was significantly higher for the sleep breathing patterns compared with the wake breathing patterns. This could be explained by the irregularity of the wake breathing patterns. Administration of aerosols during sleep might, therefore, be an efficient alternative to treat unco-operative toddlers. Further research is needed to study the clinical efficacy of administration during sleep.

In **chapter 9** lung dose of a new hydrofluoroalkane–134a beclomethasone dipropionate (HFA-BDP) pMDI, containing a high proportion of particles <2.1 μm, was compared with lung dose of a conventional chlorofluorocarbon (CFC)-BDP pMDI, which mainly contains particles between 2.1 and 4.7 μm. This was studied with the SAINT-model connected to an impactor during simulated tidal breathing. A small volume detergent coated plastic spacer was used. It was found that HFA-BDP delivered a 4 to 14 fold higher dose to the lungs compared with CFC-BDP. Furthermore it was found that lungdose with HFA-BDP did not alter significantly with tidal volume, whereas lung dose with CFC-BDP decreased with increasing tidal volume. The results implicate that the use of HFA-BDP with a high dose of extra fine particles increases the dose delivered to the lungs and reduces the variability related to the breathing pattern, compared with a CFC-BDP pMDI with larger particles in infants. We speculate that the daily dose of HFA-BDP necessary to treat asthma in young children will be substantially reduced compared with CFC-BDP.

10.2 GENERAL DISCUSSION

In our studies we investigated many factors that can affect the aerosol delivery from pMDI/spacers in young children. In the following section we will discuss these factors and the implications for clinical practice. Doses mentioned in the text below are expressed as a percentage of the nominal dose unless stated otherwise.

10.2.1 FACTORS AFFECTING AEROSOL DELIVERY FROM PMDI/SPACERS IN YOUNG CHILDREN

PATIENT-RELATED FACTORS

Co-operation

Within subject dose variability was found to be high in young children when using a pMDI/spacer at home. Co-operation during the administration procedure was the major factor for children under 2 years of age causing high within-subject dose variability.

Our study showed that almost 50% of children under 2 years of age did not co-operate sufficiently during the adminstration of aerosol. This is in agreement with other studies where it was shown that crying resulted in decreased lung dose [1,2]. Clearly, we have to consider the fighting toddler as an important risk factor for failure of aerosol therapy. It is important for the clinician to be aware of any co-operation problems when prescribing aerosol therapy in young children. Parents have to be instructed that good co-operation during the administration procedure is crucial. To date no methods have been developed to improve the acceptibility of pMDI/spacer treatment in young children.

In search for a method to treat unco-operative infants, we examined the possibility to deliver aerosol to the lungs during sleep. To study this we made use of the SAINT-model. Inhalation from a pMDI/spacer during sleep breathing resulted in a higher lung dose compared with wake breathing. Therefore, aerosol delivery during sleep may be a good alternative to treat fighting toddlers. However, the feasibility and effectiveness of this method should be studied in vivo.

Breathing pattern

Young children have variable breathing patterns during inhalation of aerosol [3]. The breathing pattern has important influence on the dose reaching the lungs. This was shown in several studies in adults, where fast inhalation results in lower lung deposition compared with slow inhalation [4-6]. To our knowledge we were the first to study the relation between tidal breathing patterns and lung dose for young children. In our SAINT-model, the lung dose was found to increase with increasing tidal volume, up to a tidal volume of around 50 ml. However, the lung dose decreased with further increase in tidal volume. Furthermore, lung dose decreased with increasing respiratory rates. The results could be explained by the higher inspiratory flow rates with increasing

tidal volume and respiratory rate. This causes increased impaction of coarse particles in the upper airways and subsequently a lower lung dose. The differences in inspiratory flow rates also explain why the lung dose with sleep breathing patterns is higher compared with wake breathing patterns. Inspiratory flow rates were significantly higher for the wake breathing patterns.

Consequently, in case a child has a tidal volume smaller than 50 ml, or is tachypnoeic a lower dose may reach the lungs and a higher dose is deposited in the upper airways.

Administration technique

The spacer was introduced to simplify the inhalation of aerosol from a pMDI. However, we and others showed that many mistakes are made during the administration procedure using a pMDI/spacer, even after repeated instructions [7-9]. Some mistakes can substantially influence the dose delivered to the patient [8]. In our study we found spacer-ouputs of zero, caused by leaving the cap on the pMDI and doses of more than 100% suggesting that more than the subscribed dose was actuated into the spacer. Aspects of inhalation technique requiring good co-operation of the child, like inhaling for 30 seconds through the spacer, or keeping the facemask on the face during the inhalation were scored correctly in only half of the study group. The pMDI/spacer was often not shaken before use. This may result in variations in dose up to 25% [10]. Therefore, mistakes in the administration procedure contribute to high dose variability and can even result in no drug being inhaled. To achieve optimal aerosol delivery it is first of all important that the clinician prescribing the aerosol therapy is well aware of the optimal administration technique. In addition, the adminstration technique should be carefully instructed, checked and corrected regularly.

Age

We and others found that spacer-output does not depend on age in children 0.5 years and older [11-13]. An age dependent spacer-output was found when a large volume plastic spacer with a high resistance valve was used in children 0.5-4 years of age [14]. Our lung deposition study showed that the total lung dose increased with age, but that the amount of drug per kilogram bodyweight was about equal for all age groups. This is in support of the idea that the same nominal doses can be prescribed for all ages as has been suggested by other authors. However, in our radiolabelled aerosol study we found that a greater proportion of the dose inhaled is deposited in the upper airways of young children compared with older children.

DEVICE RELATED FACTORS

Electrostatic charge

It has been shown that electrostatic charge on the inner surface of a plastic spacer attracts aerosol to the spacer wall, thus reducing spacer output [15-17]. We hypothesized that electrostatic charge of the spacer would be a major factor for dose variability in

daily life use. Though electrostatic charge reduced spacer-ouput, it appeared to play only a minor role in dose variability. Other factors, like co-operation of the child, appeared to be more important for dose variability. We and others showed that the spacer-output from a static (non-detergent coated) plastic spacer was reduced two fold compared with a non-static (detergent coated) plastic spacer or a metal spacer [11,14]. On the other hand, we showed that the dose of a bronchodilator delivered to the lungs in young children by using non-static plastic spacers was up to 10 fold higher compared with previous lung deposition studies using static spacers [2,18]. Furthermore, it has been shown that the use of a non-static plastic spacer increases the bioavailability of salbutamol by 2.4-4 fold in children 7-12 years of age [19].The clinical significance of this finding with regard to bronchodilators is not clear. A study in children aged 4-8 years comparing the efficacy of a bronchodilator delivered by static plastic spacers with non-static plastic spacers or the metal spacer showed no differences in post-bronchodilator peak expiratory flows [20]. For inhaled corticosteroids we found a 5-fold increase in lung dose using a non-static plastic spacer compared with a static spacer. It is likely that a higher lung dose of inhaled corticosteroids will results in a better clinical effect. In a number of studies a significant dose-response relation for inhaled corticosteroids has been shown [21-25]. Therefore, for efficient use of a pMDI/spacer we recommend that electrostatic charge should be avoided as much as possible by using a metal spacer or by coating a plastic spacer with detergent once a week.

Face mask

A face mask attached to the spacer is necessary to enable young children, who cannot breath through a mouth piece, to inhale the aerosol [26-29]. It is important to keep the face mask airtight on the face during inhalation. An incomplete seal of the face mask on the face can lead to air entrainment from the side of the face mask, which results in decreased spacer-output. In nebulizers it has been shown that holding the face mask 1 or 2 cm from the face reduced the dose delivered to the patient 2 to 6 fold [30]. Therefore, in the instructions of parents in the use of pMDI/spacers, the importance of an optimal seal of the face mask should be stressed. We speculated that the effect of poor co-operation on dose variability was partly caused by the incomplete seal of the face mask to the face. In video observations, interruption of the seal was observed many times in relation to movements of the head. In addition many children showed a sub-optimal fit of the face-mask itself. The shape and flexibility of the facemask seemed to be important to obtain a good seal. The face mask of the metal Nebuchamber is preshaped to the facial contours, has a flat rim and is rather stiff (figure 1). The face mask of the plastic Babyhaler is round, has an inward curled rim and is soft and flexible (figure 2). In many children, we observed a suboptimal fit of the facemask of the metal spacer, which also had the highest dose variability. Furthermore, both dose delivery and dose variability of the metal spacer were correlated to co-operation. The round face mask appeared to have a better seal on the face. Therefore, we think it likely that for

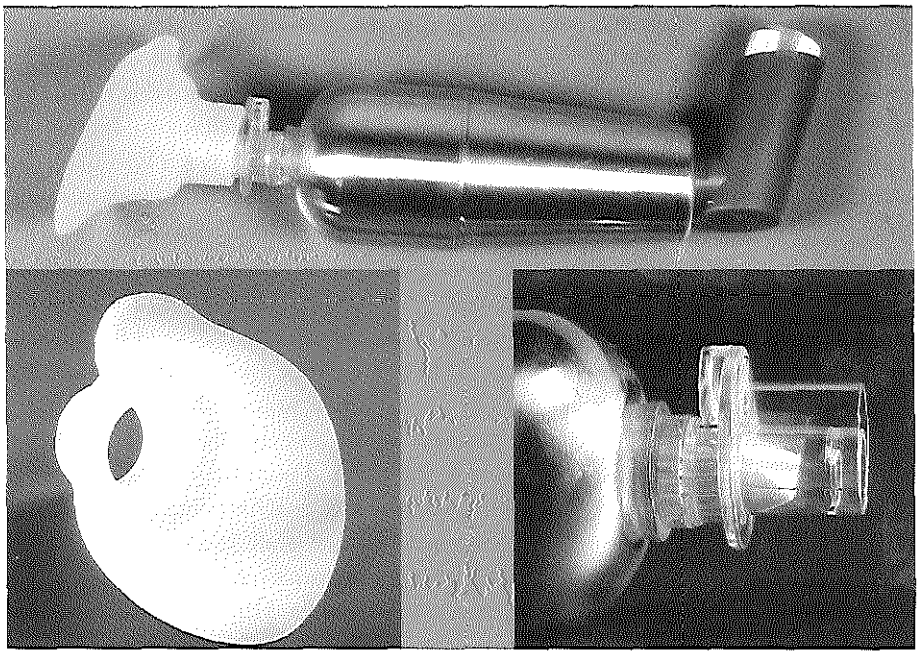

FIGURE 1. Nebuhaler® with detail of mask and valves.

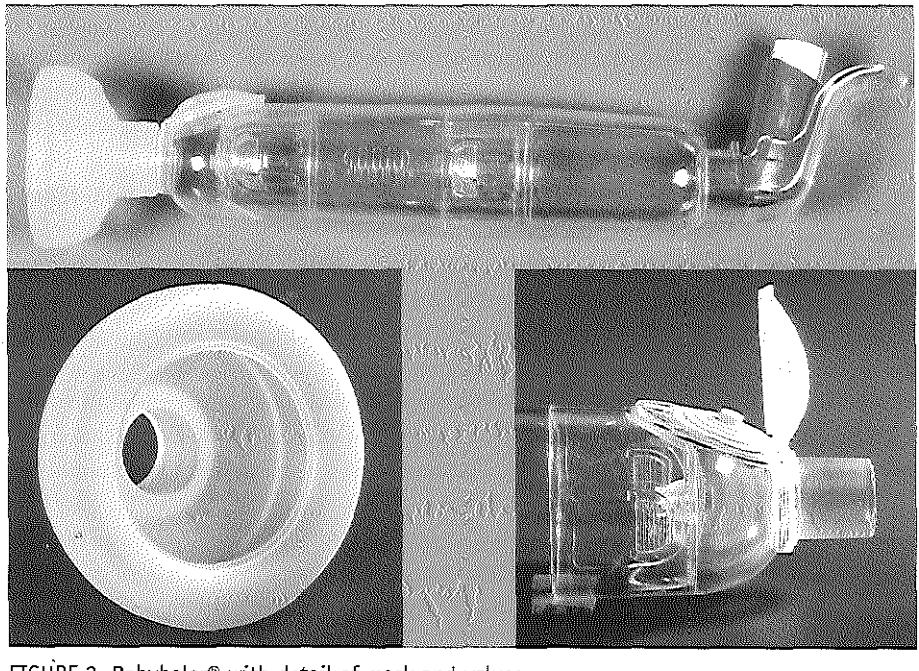

FIGURE 2. Babyhaler® with detail of mask and valves.

uncooperative children with a sub-optimal fitting facemask on the Nebuchamber, aerosol delivery can be approved by using a round flexible facemask with an inward curled rim. This should be investigated in further studies.

Particle size

The respirable range of particle size is considered to be 1 to 5 μm. However, this range is based on studies in adults. The respirable particle size for children is not known, and likely to be dependent on age and size of the child. Even in adults, it is likely that the respirable range of an aerosol will vary from patient to patient. Furthermore, the optimal particle size for an aerosol will also depend on the target area in the bronchial tree. It has been shown that with a particle size of around 2.8 μm for a β_2-agonist an optimal dose-response relation is achieved in asthmatic adults [31,32]. Taking into account the small airway diameters and relatively high flow rates in the central airways of children [33], we hypothesize that the optimal particle size for young children will be substantially smaller compared with adults. Simulation experiments with the SAINT-model showed that the lung dose from all pMDI/spacers tested consisted mainly of particles smaller than 4.7 μm. This implicates that particles from 4.7 μm and smaller were able to pass the upper airways of a child of 9-month-old, and can be considered 'respirable'. However, when inspiratory flow rate increased the MMAD of the lung dose decreased. In other words, only small particles were able to pass the upper airways. Interestingly, deposition of particles smaller than 2.1 μm was largely independent of breathing pattern. Therefore it was not surprising that the lung dose of the HFA-BDP (MMAD = 1.1 μm) was independent of the breathing pattern. Furthermore, the total lung dose of pMDI's with smaller particles (fluticasone, HFA-BDP) were found to be higher compared with pMDI's with larger particles (budesonide, CFC-BDP), The lung dose appeared to be independent of the spacer used. We did not measure the regional deposition in the lungs in relation to different particle sizes, but it has been shown that smaller particle are more likely to deposit in the peripheral airways [34-36]. In addition, it has been shown that in asthma CF and BPD morphological changes are more severe in peripheral compared with central airways [37-40]. Therefore, it makes sense that for the delivery of inhaled corticosteroids in young children pMDI's should be used with a low MMAD of around 1 μm. This is likely to improve lung deposition and reduce variability related to breathing pattern. We hypothesize that the use of these types of aerosols will improve clinical efficacy. This should be further investigated in clinical studies.

Spacer-design

There are 4 types of spacers commercially available in the Netherlands. The plastic spacers: Volumatic® (GlaxoWellcome, Zeist, the Netherlands), Babyhaler® (GlaxoWellcome) and Aerochamber® (Boerhinger Ingelheim, Alkmaar, the Netherlands) and the metal spacer: Nebuchamber® (AstraZeneca, Zoetermeer, the Netherlands). Each

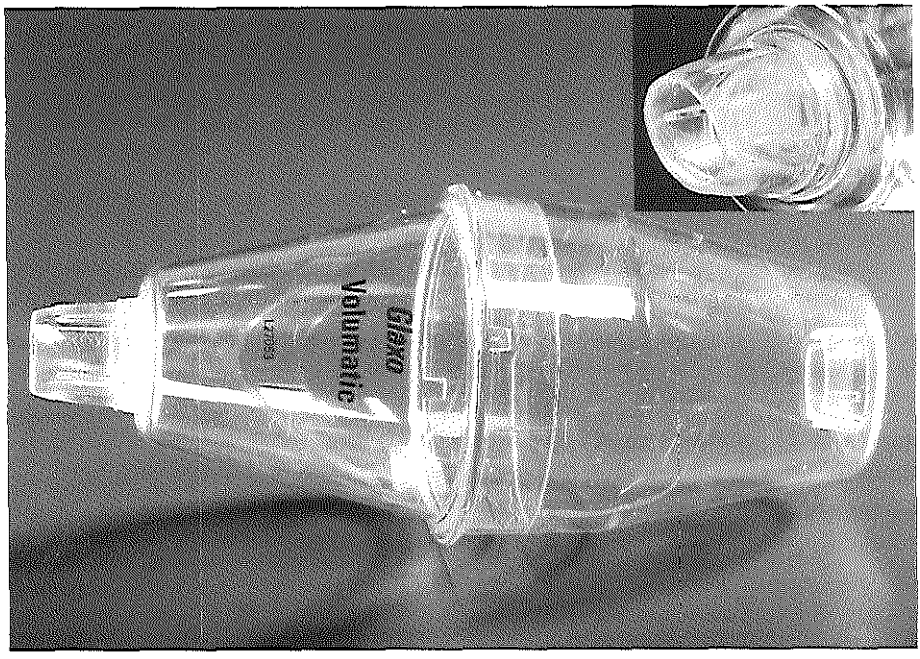

FIGURE 3. Volumatic® with detail of valve.

spacer can only be used with the pMDI's of its manufacturer, except for the Aerochamber, which has a universal inlet fitting all pMDI's. All 4 types of spacers were tested in our studies. Each spacer has its own properties which affect the dose delivered in a particular patient positively or negatively. As discussed previously, electrostatic charge is an important factor that can reduce dose delivery. However, we found that when electrostatic charge of spacers is optimally reduced the lung dose is dependent on the particle size distribution of the pMDI and relatively independent of the spacer. In the following section each spacer is discussed seperately.

The *Volumatic* (figure 3) is the only large volume (750 ml) polycarbonate spacer. It is a conical spacer with one round hard plastic inspiratory valve. Exhaled air flows through holes in the mouthpiece. The relatively high resistance valve needs sufficient flow to function properly, which can often not be achieved by young children or dyspneic adults [41,42]. The Volumatic is only available with a mouthpiece. The spacer is made of polycarbonate plastic, therefore it can accumulate electrostatic charge. We found a relatively low spacer output and high dose variability when the Volumatic was used at home, without detergent coating and with a Pulmicort® 200 µg pMDI. However, lung deposition of 28% up to 41.8% of metered dose from a Ventolin® 100 µg pMDI could be achieved in children 5-12 years of age. In this study the spacer was detergent coated and used with tidal breathing, or a single deep breath and breath-hold. The Volumatic can only be used for children of 4 years and older who are able

to breath through the mouth, because of the large volume, the high resistance valve and the inability to use it with a face mask this spacer.

The *Babyhaler* (figure 2) is a small volume (350 ml) polycarbonate tube-shaped spacer, with separate round in- and expiratory valves. The valves are fixed in the centre, allowing the aerosol to pass along the sides. The Babyhaler is provided with a round facemask. Our study showed that with the Babyhaler facemask it is relatively easy to obtain a good seal on the faces of young children. A disadvantage of the face-mask is that it is quite large and adds 20-30 ml dead space to the system. In addition, the dead-space between the valves is 35 ml. Therefore, the total dead space of the Bayhaler is quite large. This explains the relatively low spacer output and low lung doses which we found when small tidal volumes were used in the SAINT-model. Another disadvantage of the Babyhaler is that it can get electrostatically charged. We found a 5 fold reduction in lung dose for both fine and extra fine particles using a static Babyhaler compared with a non-static Babyhaler. However, if the Babyhaler is detergent coated and tidal volumes larger than 50 ml are used, the spacer output can increase to 60%, providing a lung dose up to 20% of metered dose. Because of the relatively large dead space we do not recommend the Babyhaler for children with tidal volumes smaller than 50 ml. The Babyhaler is suitable for children of 1 to 4 years of age.

The *Aerochamber* (figure 4A) is the smallest volume (150 ml) spacer available. It is a tube shaped spacer with a low resistance inspiratory valve. Expiratory flow goes through a valve integrated in the facemask or through holes in the mouthpiece. The Aerochamber has an inspiratory valve which consists of four flaps. The aerosol passes through the centre of these 4 flaps. Malfunctioning of the spacer valves are frequently observed in the out-patient clinic of the Sophia Children's Hospital. The Aerochamber is available with 3 different sizes of facemasks (infant, child and adult) or with a mouth piece. The facemask of the Aerochamber looks similar to the facemask of the Babyhaler, but is also available in smaller sizes. The dead space of the Aerochamber is small. It is made of Ektar® plastic and electrostatic charge can also build up on the surface. It should be detergent coated at least once a week. Spacer-ouput from the Aerochamber was lower with both Flixotide and Pulmicort compared with the other spacers. However, the lung dose of these pMDI's with the detergent coated Aerochamber were equal to the lung doses of the Flixotide with detergent coated Babyhaler and the Pulmicort with the Nebuchamber. This explains why the upper airway deposition was lowest for the Aerochamber. The Aerochamber is suitable for children of all ages because of the small volume, small dead space and low resistance valves, and the availability of different sized face masks and a mouthpiece. Recently a new design of the Aerochamber was introduced (Aerochamber Plus® (figure 4B)). The new Aerochamber Plus has a low resistance annular valve, which allows the aerosol to pass from the side. The facemask of the Aerochamber Plus is smaller compared with the old one, with a smaller dead space and a droplet-like shape. There is still little information available on the functioning of this new spacer.

FIGURE 4. A. Aerochamber® with detail of infant and child masks, and valves (old design).

FIGURE 4. B. Aerochamber Plus® with detail of infant and child masks, and valves (new design).

The *Nebuchamber* (figure 1) is a small volume (250 ml) pear shaped metal spacer with separate low resistance in- and expiratory valves. The inspiratory valve consists of two flaps which form a slit allowing the aerosol to pass centrally. The in- and expiratory valves are integrated in the mouthpiece and this needs to be replaced about every 6 months, because the valves wear out. There is no dead space between the valves [43]. It can be used with or without facemask. The facemask was designed to minimize the dead space added to the pMDI/spacer. As discussed previously, it is difficult to obtain a good seal between the faces of young children and the facemask of the Nebuchamber. In our study we showed a high dose variability in young children using the face mask, but significantly lower dose variability when used without face mask in children 5-8 years old. An important positive point of the Nebuchamber is that electrostatic charge is no issue because it is made of stainless steel. This makes the Nebuchamber less complicated to use and also less fragile. Using the SAINT-model we found a spacer-ouput from 30% at a tidal volume of 25 ml up to 45% at a tidal volume of 200 ml with Pulmicort®-pMDI. The maximum lung dose found with the Pulmicort®-pMDI was 10.6% at a tidal volume of 50 ml. The upper airway deposition was higher for the Nebuchamber with the Pulmicort®-pMDI compared with the Aerochamber with Pulmicort®-pMDI. The Nebuchamber is suitable for children of all ages, because of the small volume, small dead space and low resistance valves.

In conclusion, each spacer design has its own advantages and disadvantages, making it suitable or less suitable for certain ages. Obviously there is room for improvement for the face mask and valve design. Electrostatic charge need to be avoided at all times.

10.3 CONCLUSIONS

The use of pMDI/spacers for aerosol therapy in young children requires special attention for those factors that may cause failure of treatment. Aerosol therapy in young children can be improved by good co-operation during the administration procedure, quiet breathing, a good fitting face mask, avoidance of electrostatic charge of the spacer and aerosols with a high proportion of small particles.

10.4 DIRECTIONS FOR FUTURE RESEARCH

Our study showed that there are many toddlers who do not co-operate during the adminstration of aerosols, resulting in inefficient dose delivery from the pMDI/spacer. Future research should focus on optimizing aerosol therapy in the group of fighting toddlers. This may be accomplished by:

- Development of a face mask that fits airtight on the face and is less sensitive for movements of the head.
- Studying feasibility and clinical efficacy of administration during sleep.
- Development of training programs for children and their parents to increase the number of children that accept the aerosol therapy with pMDI/spacer.

Furthermore, we showed that the optimal particle size for young children to inhale therapeutic aerosols is probably substantially smaller than what is produced by most pMDI's. The optimal particle size of therapeutic aerosols will also depend on the site of action of the drug. Inhaled steroids may need to be deposited as far as the alveoli, whereas bronchodilators may be deposited more centrally in the lung. Also the use of new agents like antibiotics, inhaled insuline, vaccins, requires knowledge about the area where the aerosol should be deposited Future reasearch should focus on:

- Defining the target of the inhaled drug: Where in the lung should the drug be deposited?
- Determination of the optimal particle size for different inhaled drugs and for children of different ages.

The SAINT-model appeared to be a useful tool to study the influence of different parameters on aerosol deposition in children. However, our results provide only information on the total lung dose and the particle size distribution, but not on the deposition location of the aerosol in the lungs. It is difficult to study this in vivo. Therefore, there is need for a model of the bronchial tree of a child to study lung deposition in children in detail. Detailed knowledge of airway geometry at different ages is required to develop adequate bronchial airway models of children.

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SAMENVATTING

Het inhaleren van medicamenten in a vorm wordt veel gebruikt voor de behandeling van astma. Bij kinderen wordt vooral de dosisaërosol (pMDI) met een voorzetkamer als toedieningsvorm gebruikt om onderhoudstherapie te geven. Om jonge kinderen anti-astma medicijnen toe te dienen wordt gebruik gemaakt van een voorzetkamer uitgerust met een kapje. Jonge kinderen ademen immers vooral door de neus en kunnen meestal niet bewust via de mond inhaleren. Er zijn veel verschillende soorten voorzetkamers op de markt. De efficiëntie van deze voorzetkamers is onderling verschillend en elke voorzetkamer heeft zijn voor- en nadelen. Over het functioneren van voorzetkamers bij jonge kinderen is slechts zeer weinig bekend. Om optimale therapie te geven is het belangrijk te weten hoeveel medicament er uit de pMDI-voorzetkamer door het kind wordt geïnhaleerd (dosisafgifte). Tevens, moet men de variabelen kennen die de hoogte van de geïnhaleerde dosis beïnvloeden. De studies in dit proefschrift concentreren zich met name op de efficiëntie waarmee verschillende dosisaërosol/voorzetkamer combinaties aërosol afgeven aan jonge kinderen en de factoren die daarop van invloed zijn. De bevindingen uit dit proefschrift kunnen bijdragen aan het verbeteren van de astmatherapie voor jonge kinderen.

Hoofdstuk 1 geeft een algemene inleiding van het proefschrift en worden de doelen van de studies uitgelegd.

Hoofdstuk 2 geeft uitgebreide achtergrond informatie over de wetenschappelijke en praktische aspecten van aërosoltherapie bij kinderen. Verder worden de indicaties voor aërosoltherapie, de basis principes van aërosoldepositie en de methoden om aërosoldepositie te onderzoeken besproken. Tevens worden de huidige methoden om aërosoltherapie aan kinderen te geven besproken.

REPRODUCEERBAARHEID VAN DE DOSIS

Een voorspelbare en reproduceerbare dosisafgifte van de pMDI-voorzetkamer is belangrijk om de goede dosis te kunnen voorschrijven. Hierbij streeft men naar een maximum aan therapeutisch effect en een minimum aan bijwerkingen. Vreemd genoeg is de reproduceerbaarheid van de dosisafgifte van de pMDI-voorzetkamers bij kinderen niet bekend. Er zijn vele factoren die de dosisafgifte van voorzetkamers kunnen beïnvloeden. Een belangrijke factor is de elektrostatische lading die aanwezig kan zijn op het oppervlak van plastic voorzetkamers. Het is aangetoond dat elektrostatische lading de dosisafgifte van een voorzetkamer aanzienlijk kan verlagen. Een metalen voorzetkamer is niet elektrostatisch geladen. In verscheidene studies bij kinderen werd aangetoond dat een metalen voorzetkamer een hogere dosis afgeeft dan een statische plastic voorzetkamer. Echter deze studies werden gedaan onder goed gecontroleerde omstandigheden in een laboratorium. Het mag duidelijk zijn dat dit waarschijnlijk niet de thuissituatie reflecteert. In **hoofdstuk 3** wordt een gerandomiseerde cross-over studie beschreven waarin de reproduceerbaarheid van de dosisafgifte werd gemeten in de

thuissituatie. Deze reproduceerbaarheid wordt uitgedrukt als (binnen-persoons) dosisvariabiliteit door de variatiecoëfficient van de dosisafgifte te bepalen. Deze werd bepaald voor een metalen voorzetkamer en twee plastic voorzetkamers bij kinderen in de thuissituatie. Zeventien kinderen van 1-4 jaar (groep I) en 16 kinderen van 5-8 jaar (groep II) met stabiel astma namen aan de studie deel. Het medicament dat werd onderzocht was het inhalatiesteroïd budesonide. De dosisafgifte van budesonide uit de pMDI-voorzetkamer werd gemeten door een filter te plaatsen tussen voorzetkamer en masker (groep I), of tussen voorzetkamer en mond (groep II). De dosis op het filter was representatief voor de totale dosis die in het lichaam zou zijn gekomen als de filter er niet had gezeten. Elke proefpersoon gebruikte de metalen en één van de twee plastic voorzetkamers twee keer per dag, elk gedurende 1 week. De volgorde waarin de verschillende voorzetkamers werden gebruikt was gerandomiseerd. De dosisafgifte van de metalen voorzetkamer bleek 2 keer zo hoog te zijn in vergelijking met de beide plastic voorzetkamers. Dit kon worden verklaard door de aanwezigheid van elektrostatische lading in de plastic voorzetkamers. De dosisvariabiliteit bleek aanzienlijk te zijn voor alle drie de voorzetkamers. Deze variabiliteit was het hoogst voor de jonge kinderen in groep I voor zowel de metalen als de plastic voorzetkamer en het laagst voor kinderen in groep II voor de metalen voorzetkamer. Dit betekent dus dat bij met name de jonge kinderen die de pMDI-voorzetkamer thuis gebruiken de reproduceerbaarheid van de dosisafgifte slecht is. De dosisvariabiliteit leek bovendien toe te nemen naarmate de kinderen jonger waren. Dit vormde de reden om een tweede studie op te zetten naar de dosis variabiliteit bij kinderen jonger dan 2 jaar. Deze studie, die beschreven is in **hoofdstuk 4**, had tot doel de dosisafgifte en dosisvariabiliteit van voorzetkamers van kinderen 0-2 jaar nader te onderzoeken en te bestuderen welke factoren daarop van invloed zijn in de thuissituatie. In deze studie werden 25 kinderen geïncludeerd in de leeftijd van 5-26 maanden die allen behandeld werden met anti-astma medicatie. In een gerandomizeerde cross-over studie werd de dosisafgifte van een budesonide-pMDI met metalen voorzetkamer en van een fluticasone-pMDI met plastic voorzetkamer gemeten met behulp van filters. De invloed van elektrostatische lading werd gemeten door een (elektro)statische met een niet-(elektro)statische plastic voorzetkamer te vergelijken. Een plastic voorzetkamer werd ontdaan van elektrostatische lading door deze af te wassen in een sopje met huishoudafwasmiddel vervolgens niet af te spoelen en daarna aan de lucht te laten drogen. Als de voorzetkamer wel werd afgespoeld met water, was er wel electrostatische lading aanwezig. Opmerkelijk was dat de dosisvariabiliteit van de metalen voorzetkamer significant hoger was dan die van zowel de statische als de niet-statische plastic voorzetkamers. De dosisvariabiliteit tussen de statische en niet statische plastic voorzetkamers verschilde niet. De belangrijkste factor voor de dosisvariabiliteit van alle voorzetkamers bleek de coöperatie van het kind te zijn. Het 'coaten' van de voorzetkamer met afwasmiddel bleek effectief om de elektrostatische lading voor een week te reduceren en dientengevolge de dosisafgifte te verhogen. Er was echter geen meetbaar effect op de dosisvariabiliteit bij deze jonge

kinderen. De relatief hogere dosisvariabiliteit van de metalen voorzetkamer werd waarschijnlijk veroorzaakt door het onvoldoende aansluiten van het masker op het gezicht van met name de niet-coöperatieve kinderen. Uit analyse van video-opnamen bleek namelijk dat ongeveer de helft van de kinderen niet goed meewerkte tijdens de aërosoltoediening en dat daarbij het masker vaak niet goed aansloot op het gezicht. Tevens bleek uit deze opnamen dat er veel fouten werden gemaakt tijdens de toedieningsprocedure wat resulteerde in een verminderde dosisafgifte. Deze studie laat zien dat coöperatie tijdens het toedienen van een aërosol essentieel is. Het niet goed meewerken van bijna de helft van deze kinderen van 0 tot 2 jaar resulteerde in een onvoorspelbare dosisafgifte.

LONGDEPOSITIE

De twee bovenstaande studies zijn filterstudies, waarin de dosisafgifte van een pMDI-voorzetkamer wordt gemeten aan de mond. Dit geeft geen informatie over de hoeveelheid medicament die uiteindelijk in de longen terechtkomt of de distributie van de dosis over de luchtwegen. Om dit te onderzoeken werd een longdepositiestudie opgezet, die beschreven wordt in **hoofdstuk 5**. De longdepositie in astmatische kinderen van 1 tot 12 jaar werd gemeten door middel van radio-actief gelabeld salbutamol, toegediend via een plastic voorzetkamer. De voorzetkamers waren met afwasmiddel behandeld om de elektrostatische lading te verminderen. De gemiddelde longdepositie, uitgedrukt als een percentage van de afgevuurde dosis, was 16.4 tot 41.8 % in kinderen van 1 tot 12 jaar oud. De longdepositie nam toe met de leeftijd, maar de dosis per kilogram lichaamsgewicht was gelijk voor alle leeftijden. Er kon worden geconcludeerd dat de gebruikte plastic voorzetkamers die met afwasmiddel waren gecoat een veel hogere longdepositie gaven dan voorheen werd aangetoond in andere studies, waarin statische voorzetkamers gebruikt werden.

ADEMHALINGSPATRONEN EN DEPOSITIE

Om in detail de invloed van ademhalingspatronen op aërosoldepositie in kinderen te kunnen bestuderen ontwikkelden we een model van de bovenste luchtwegen van een jong kind. **Hoofstuk 6** beschrijft het ontwikkelen en het maken van het "Sophia Anatomical Infant Nose-Throat (SAINT)"-model: een anatomisch correct bovenste luchtweg model van een kind. Dit model is een belangrijk hulpmiddel om in-vitro mechanismen van aërosoldepositie in kinderen te bestuderen. Het SAINT-model werd gemaakt met behulp van een driedimensionale CT-scan van het hoofd van een 9 maanden oud kind. Deze scan werd met met een stereolithografische techniek, dat gebruik maakt van een UV-gevoelig kunsthars, omgezet in een model. Het model is een kopie van een deel van het gezicht en de bovenste luchtwegen van de neus tot net onder de stembanden. De ademweg via de neus is open, maar via de mond gesloten. De CT-scan van het model en de originele CT-scan kwamen nauwkeurig overeen met elkaar. Aërosoldepositie metingen met het SAINT model toonden aan dat de aërosol

dosis die net onder de stembanden werd gemeten ("de longdosis") vergelijkbaar was met in-vivo longdepositie waarden uit andere studies.

In **hoofdtsuk 7** wordt een studie met het SAINT-model beschreven waarin de invloed van teugvolume en ademhalingsfrequentie op de bovenste luchtweg- en longdepositie wordt bestudeerd van vier verschillende pMDI-voorzetkamer combinaties. De budesonide pMDI werd getest in de Nebuhaler® en de Aerochamber® en de fluticasone pMDI werd getest in de Babyhaler® en de Aerochamber®. Dosisafgifte van de voorzetkamers en longdosis werden gemeten door middel van filters. Deeltjesgrootteverdeling van de longdosis werd bepaald met een impactor tijdens gesimuleerde ademhaling. De dosisafgifte van alle voorzetkamers nam toe met het teugvolume, maar werd niet beïnvloed door de ademhalingsfrequentie. De longdosis nam toe met het teugvolume, voor volumes van 25 tot 50 ml, afhankelijk van de gebruikte voorzetkamer. Echter bij verdere toename van het teugvolume, nam de longdosis weer af. De longdosis nam ook af met een snellere ademhalingsfrequentie. De resultaten kunnen worden verklaard door de hogere inspiratoire flows bij toenemend teugvolume en ademhalingsfrequentie. Bij hoge inspiratoire flows neemt de depositie door impactie van met name grotere deeltjes toe in de bovenste luchtwegen. Dit resulteert in een hoge bovenste luchtweg depositie en een lage longdosis. De depositie van deeltjes kleiner dan 2.1 µm was onafhankelijk van het gebruikte adempatroon. De fluticasone pMDI had een wat hoger percentage deeltjes < 2.1 µm dan de budesonide pMDI. De longdosis bleek vooral afhankelijk te zijn van de pMDI en in veel mindere mate door de voorzetkamer mits de elektrostatische lading van de plastic voorzetkamers was gereduceerd door middel van een afwasmiddel coating.

In hoofdstuk 3 werd aangetoond dat de coöperatie tijdens de toediening van een aërosol een belangrijk probleem vormt bij jonge kinderen. Als oplossing voor dit probleem wordt wel gesuggereerd dat bij deze kinderen aërosol toediening beter tijdens slaap kan plaatsvinden. Het is echter nooit onderzocht of er voldoende aërosol in de longen terechtkomt bij toediening tijdens slaap. In **hoofdstuk 8**, wordt de longdosis van een pMDI-voorzetkamer gemeten tijdens gesimuleerde waakademhaling en slaapademhaling, gebruikmakend van het SAINT-model. De adempatronen werden opgenomen bij 18 kinderen onder de 2 jaar tijdens slaap en in wakkere toestand. De longdosis voor de slaapademhaling was significant hoger vergeleken met de longdosis tijdens waakademhaling. Dit kon worden verklaard doordat de waakademhaling veel onregelmatiger was ten opzichte van de slaapademhaling. Toediening van een aërosol tijdens slaap zou dus een efficiënt alternatief kunnen zijn voor de tegenstribbelende peuter. Verder onderzoek is nodig om de praktische toepasbaarheid hiervan te onderzoeken.

DEELTJESGROOTTE EN DEPOSITIE

Het drijfgas van de pMDI's bevatten chloorfluorkarbonen (CFK's). Deze gassen tasten de ozonlaag aan. Daarom moeten alle CFK's vervangen worden voor milieuvriendelijker alternatieven, zoals de hydrofluoralkanen (HFA). Een nieuw

ontwikkelde HFA-pMDI met beclomethasondipropionaat (BDP) heeft niet alleen een ander drijfgas maar produceert ook veel meer kleine deeltjes (< 2.1 µm) vergeleken met de conventionele CFK-BDP pMDI, die voornamelijk deeltjes van 2.1 tot 4.7 µm bevat. In **hoofdstuk 9** wordt de longdosis van de nieuwe HFA-BDP vergeleken met de longdosis van de oude CFK-BDP bij verschillende teugvolumes. Dit werd onderzocht door het SAINT-model te bevestigen aan een impactor en een ademhalingssimulator. Een gecoate Aerochamber® met masker werd gebruikt voor de toediening van beclomethason. De HFA-BDP-Aerochamber® gaf een 4 tot 15 maal hogere longdosis vergeleken met de CFK-BDP-Aerochamber®. Daarbij veranderde de longdosis van de HFA-BDP niet significant met het teugvolume, terwijl de longdosis van de CFK-BDP afnam met toenemend teugvolume. De studie toont aan dat het gebruik van HFA-BDP dosisaërosol met veel extra kleine deeltjes de longdosis aanzienlijk verhoogt en de dosisvariabiliteit door adempatronen vermindert bij jonge kinderen vergeleken met CFK-BDP dosisaërosol met relatief grotere deeltjes. Waarschijnlijk zal de benodigde dagelijkse dosis om astma te behandelen met HFA-BDP aanzienlijk lager zijn dan met CFC-BDP. Dit moet in een klinische studie nader worden onderzocht.

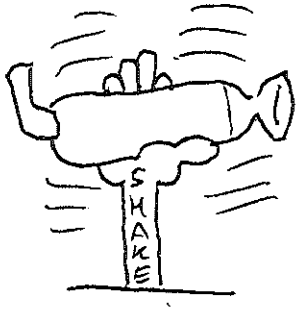
Hoofdtuk 10 geeft een samenvatting van het proefschrift en gaat in een discussie in op de gevonden resultaten. Factoren die van invloed zijn op de dosisafgifte van pMDI-voorzetkamers bij jonge kinderen worden besproken en er wordt ingegaan op hoe de efficiëntie van aërosoltherapie bij deze kinderen verbeterd zou kunnen worden. Patiënt gerelateerde factoren komen aan bod zoals: coöperatie; adempatronen; toedieningstechniek; en leeftijd. Tevens worden factoren besproken die gerelateerd zijn aan het toedieningssysteem zoals: electrostatische lading; masker; deeltjesgrootte; en ontwerp van de voorzetkamer. Tevens worden de voor en nadelen van de in Nederland beschikbare voorzetkamers besproken. Als laatste worden er suggesties gedaan voor verder onderzoek om meer inzicht te krijgen in aërosoltherapie bij jonge kinderen.

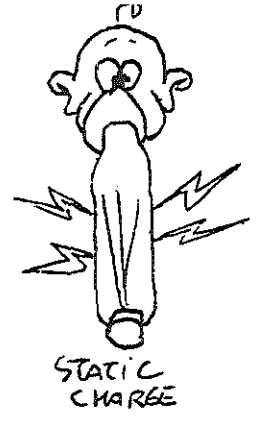
CONCLUSIES

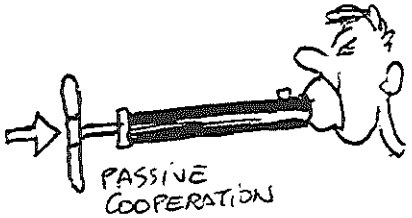
Aërosol therapie bij jonge kinderen kan aanzienlijk worden verbeterd door het stimuleren van goede coöperatie en rustige ademhaling tijdens de toediening. Een goed passend maskertje, vermijden van elektrostatische lading van de voorzetkamer en het gebruik van een aërosol met een voldoende hoog percentage aan kleine deeltjes zijn eveneens belangrijk. Toediening van een aërosol tijdens slaap kan een alternatief zijn voor niet coöperatieve kinderen. Verder onderzoek zou zich moeten richten op het ontwikkelen van een goed passend maskertje, de klinische toepasbaarheid van toediening tijdens slaap en het bepalen van de optimale deeltjesgrootte voor ieder specifiek inhalatiemedicijn voor kinderen.

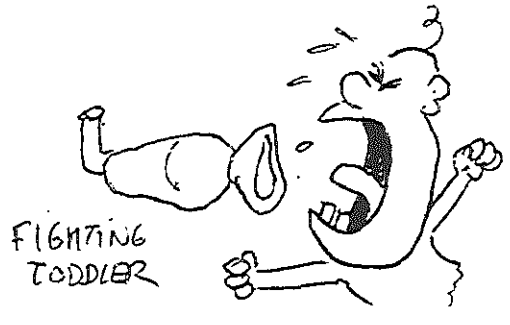
Aerosol therapy in young children:

DO'S and DONT'S









CONCEIVED BY
JOHAN C. DEJONGSTE
MD PhD, FPRM, HDPRM

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CURRICULUM VITAE

Hettie Mathilde Janssens was born in Seoul, Korea, on July 8th, 1970. Together with her younger sister, she went to the Netherlands in 1974, where they were adopted by Dutch parents. She passed her secondary school exam (VWO) at the "Visser 't Hooft Lyceum" in Leiden in 1988. From 1988 to 1996, she followed her medical training at the Medical Faculty of the University of Leiden. During her study she was a member of the introduction committee for first year medical students and committee member of the medical debating society "Cave Fungos". As a student, she followed an autopsy training for 2 months in 1992 at the department of Pathology of the University of Leiden. In the same year she went to Turkey for one month for a training at the department of Gynaecology and Obstetrics of the University Hospital in Trabzon, as part of a student exchange programm (EMSA). During her study she did several research projects at the Department of Neonatology in the University Hospital of Leiden (Prof. dr. M. van de Bor, Dr. A.J. de Beaufort, Dr. M.J.J. de Haan) and in the Neonatal Centre of the Royal Infirmary of Edinburgh, University of Edinburgh, Scotland (Prof.dr. N. McIntosh, Dr. G.C. Halley). In 1996 she did a clinical training at the Department of Pediatric Respiratory Medicine of the Sophia Children's Hospital, Erasmus University, Rotterdam (head: Prof. dr. J.C. de Jongste). After obtaining her medical degree in 1996, she started a research fellowship at the same department under the supervision of Dr. H.A.W.M. Tiddens, on a grant by AstraZeneca. The research performed during this period is presented in this thesis. Part of the research was done at the Department of Pediatric Respiratory Medicine of the Princess Margaret Hospital for Children in Perth, Australia (head: Prof. dr. P.N. LeSouëf) in 1997. In April 2001, she started to work as a junior registrar (AGNIO) at the Sophia's Children Hospital, Rotterdam (head: Prof. dr. H.A. Büller). She is married to Joost Haasnoot, a molecular biologist and artist.

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LIST OF ABBREVIATIONS

ANOVA	: analysis of variance
BDP	: beclomethasone dipropionate
BW	: body weight
CFC	: chlorofluorocarbon
CT-scan	: computer tomography scan
CV	: coefficient of variation
DC	: detergent coated
non-DC	: non detergent coated
DPI	: dry powder inhaler
EFPD	: extra fine particle dose (particles < 2.1 μm)
ESC	: electrostatic charge
F_i	: balanced inflow
F_{ai}	: flow to Anderson impactor
FEV_1	: forced expiratory volume in 1 second
FPD	: fine particle dose (particles < 4.7 μm)
GSD	: geometric standard deviation
HFA	: hydrofluoroalkane
HPLC	: high performance liquid chromatography
MMAD	: median mass aerodynamic diameter
MSLI	: multistage liquid impinger
p	: level of significance
P:C ratio	: peripheral : central lung deposition ratio
pMDI	: pressurized metered dose inhaler
SAINT-model	: Sophia Anatomical Infant Nose-Throat model
SD	: standard deviation
SEM	: standard error of the mean
R	: Spearman's correlation coefficient
RR	: respiratory rate
Vt	: tidal volume