Improving the Efficiency of Inhalation Therapy in Young Children

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Improving the Efficiency of Inhalation Therapy in Young Children

Het verbeteren van de efficiëntie van inhalatietherapie bij kleine kinderen

Proefschrift

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Stichting Asthma Bestrijding

Voor mijn dochters
Anna Maria, Christina en Elena

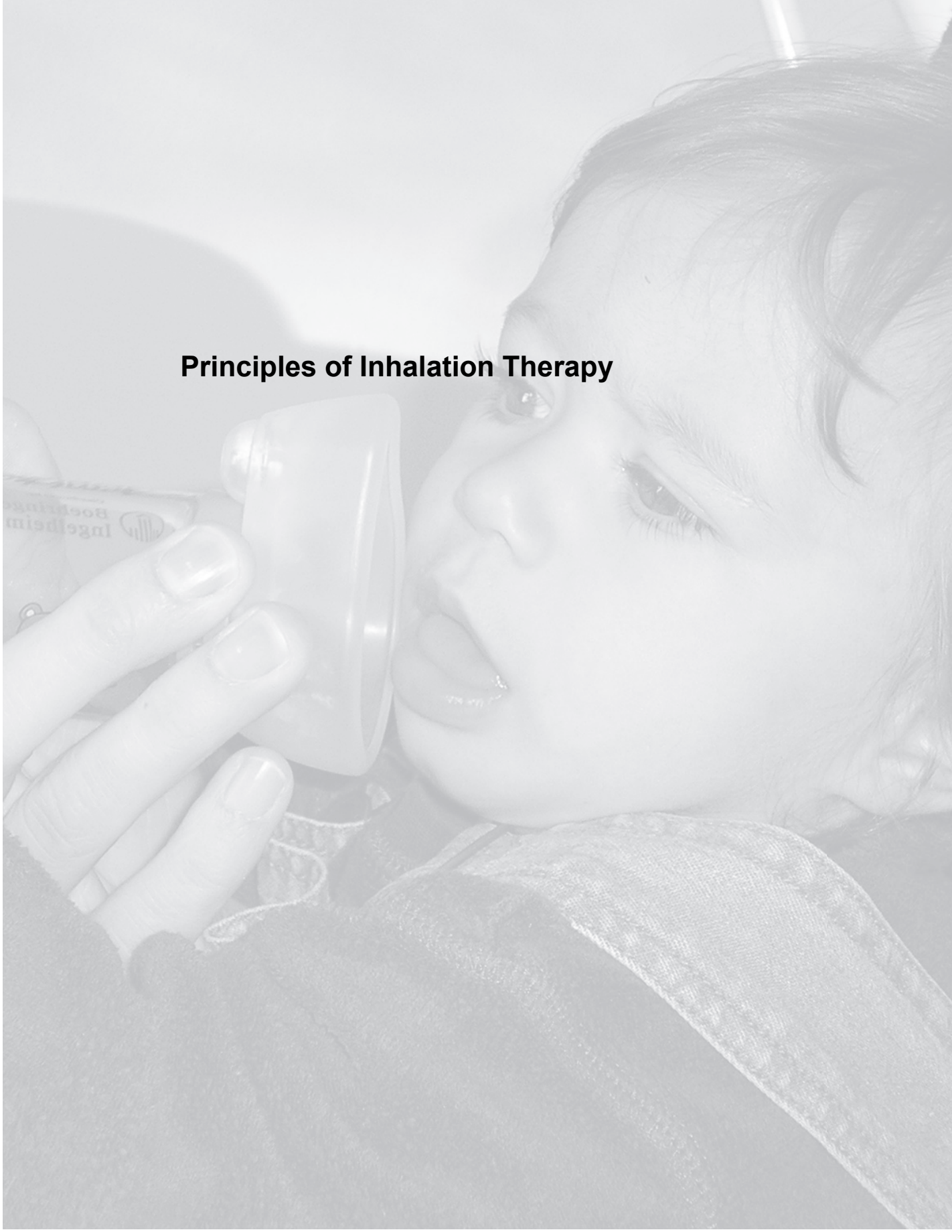
Table of Contents

List of Abbreviations

ANCOVA	:	Analysis of Covariance
ANOVA	:	Analysis of Variance
APS	:	Aerodynamic Particle Sizer
ATS	:	American Thoracic Society
AUC	:	Area Under the plasma Concentration/time curve
BDP	:	Beclomethasone Dipropionate
BMP	:	17- Beclomethasone MonoPropionate
BPD	:	Bronchopulmonary Dysplasia
CF	:	Cystic Fibrosis
CFCs	:	Chlorofluorocarbons
CI	:	Confidence Interval
Cmax	:	Maximal concentration after inhalation
COPD	:	Chronic Obstructive Pulmonary Disease
CV	:	Coefficient of Variation
DPI	:	Dry Powder Ihaler
EHDA	:	Electrohydrodynamic Atomization
eNO	:	exhaled Nitric Oxide
FEV_1	:	Forced Expiratory Vlume in 1 second
GSD		Geometric Standard Deviation
HFAs	:	Hydrofluoroalkanes
HPLC	:	High Performance Liquid Chromatography
K_{el}	:	Apparent terminal elimination rate constant
LnAUC:	:	Ln-transformed Area Under the plasma Concentration-time curve
LnC	:	Ln-transformed maximum plasma Concentration,

LOQ	:	Limit of Quantification
MMAD	:	Mass Median Aerodynamic Diameter
PCD	:	Primary Ciliary Dyskenisia
PET	:	Positron Emission Tomography
pMDI	:	Pressured Metered Dose Inhaler
REM-sleep	:	Rapid Eye Movement sleep
Rint	:	Respiratory resistance with the interrupter technique
SAINT-model	:	Sophia Anatomical Infant Nose Throat model
SD	:	Standard Deviation
SPE	:	Solid Phase Extraction
SPECT	:	Single Photon Emission Computed Tomography
$T_{½}$	:	Apparent terminal half-life

Principles of Inhalation Therapy



Chapter 1

Principles of Inhalation Therapy

1. Introduction

There are several ways to administer medication to patients. Since the early seventies drug delivery via inhalation has become the most important way of administration in pulmonary diseases such as asthma. Various aerosol delivery systems have been developed to this end, for use in adults, and only later modified for use in children. This is why much is known about inhalation therapy in adults, and only little about its use in young children (1). The studies presented in this thesis, therefore, mainly focused on inhalation therapy applied to young children.

This introductory provides the essential background information about inhalation therapy. This knowledge should enable the reader to better understand the aims and results of the studies presented in the next chapters. In addition, it highlights the key factors that influence efficiency and efficacy of inhalation therapy. Finally, an overview of radio-labeled deposition studies and clinical efficacy studies is given.

2. Inhalation Therapy

Inhalation therapy, or aerosol therapy, can be described as the inhalation of an aerosol targeted at treating diseased areas of the respiratory tract. Inhalation therapy has been practiced since ancient times, when patients were recommended to breathe the fumes carrying sulfuric vapors from the slopes of the Vesuvius (2). Throughout the centuries, a variety of inhalation therapies – inhaling smoke of burning plants and the “asthma cigarette” (Figure 1) – have been used for therapeutic purposes (2, 3). It is through the development of devices designed to aerosolize medication that inhalation therapy has become the preferred method to treat respiratory diseases (4). Asthma and chronic obstructive pulmonary disease (COPD) used to be the major diseases treated by aerosol therapy. To these have now been added other respiratory diseases such as: bronchopulmonary dysplasia (BPD)(5, 6); cystic fibrosis (CF) (7-10); primary ciliary dyskenisia (PCD) (11, 12); chronic bacterial bronchitis; atelectasis (13-15); and laryngitis (croup) (16-18). The most recent development is the introduction of inhalation therapy for non-respiratory diseases such as pulmonary hypertension, diabetes, and massive burn and smoke-inhalation injury (19-25). Furthermore, in vaccination campaigns the inhalation of aerosolized antigens is used as an alternative to subcutaneous injection (26-28).

Figure 1. Asthma cigarettes (29)

Inhalation therapy for pulmonary diseases has the advantage of direct delivery of the medication to its site of action. This should produce a more rapid therapeutic effect. Furthermore, less medication is needed to get the same therapeutic effect that systemically delivered medication would produce. As a consequence, inhalation therapy has a high efficacy/toxicity ratio (1, 3).

A disadvantage of inhalation therapy, however, is its great complexity compared with systemic therapy. Firstly, the aerosolized drug is delivered to the lung, which is an organ specialized to exclude foreign material (1, 4). Secondly, many types of aerosol delivery devices are available, each with its own specifications and limitations. Knowledge of the various features is needed to select the most efficient device for a particular patient. Inhalation therapy in the pediatric age group is even more complex than in adults, as it

includes different patient categories in terms of anatomy and psychological developmental level (1). Each category, from neonates to teenagers, would therefore require a special approach.

To achieve efficient and effective inhalation therapy, i.e. the highest efficacy/toxicity ratio, the first concern is to deliver the right amount of drug to the patient. The next concern is to have this amount of drug deposited at the right site of action in the lung (30). Furthermore, for successful inhalation therapy, the prescribing clinician should have knowledge of the properties, behaviors and physical principles of therapeutic aerosols, and of device- and patient-related factors influencing efficiency and efficacy.

Figure 2 illustrates the different aspects of inhalation therapy. The numbers in this figure correspond to the following sections in this chapter in which they are discussed.

3. Aerosols

An *aerosol* is a collection of solid or liquid particles suspended in a gas (3, 31). Dust, smoke, mist, fog, haze, and smog are examples of aerosols. Aerosol particles may vary in shape, size and density. Their description is simplified by the concept of *aerodynamic diameter*, i.e. the diameter of a sphere with a unit density that has aerodynamic behavior identical to that of the aerosol particle. Particles having the same aerodynamic diameter may have different dimensions, shapes, and densities (3, 31). The range of diameters of aerosol particles is between 0.01 and 100 μm. Particles larger than 100 μm normally do not remain suspended in air for a sufficient amount of time. In general, aerosols do not remain indefinitely stable in air.

Therapeutic aerosols usually contain particles with a wide range of aerodynamic diameters and are then referred to as *polydisperse* aerosols. Polydisperse aerosols are described by their *mass median aerodynamic diameter* (*MMAD*) and their *geometric standard deviation* (*GSD*) (3). The MMAD is defined as the aerodynamic diameter for which half of the aerosol mass consists of larger particles and half the aerosol mass of smaller particles (3, 31, 32). The GSD describes the particle size distribution and is defined as the ratio of the diameter of the particle on the 84.2th percentile and the median diameter (3). A second type of aerosols, *monodisperse aerosols*, contain particles with a small range of aerodynamic diameters: the GSD is smaller than 1.2. The distinction between monodipserse and polydisperse is quite essential, as the lung deposition pattern of a polydisperse aerosol with a

certain MMAD may be different from that of a monodisperse aerosol with the same MMAD (3).

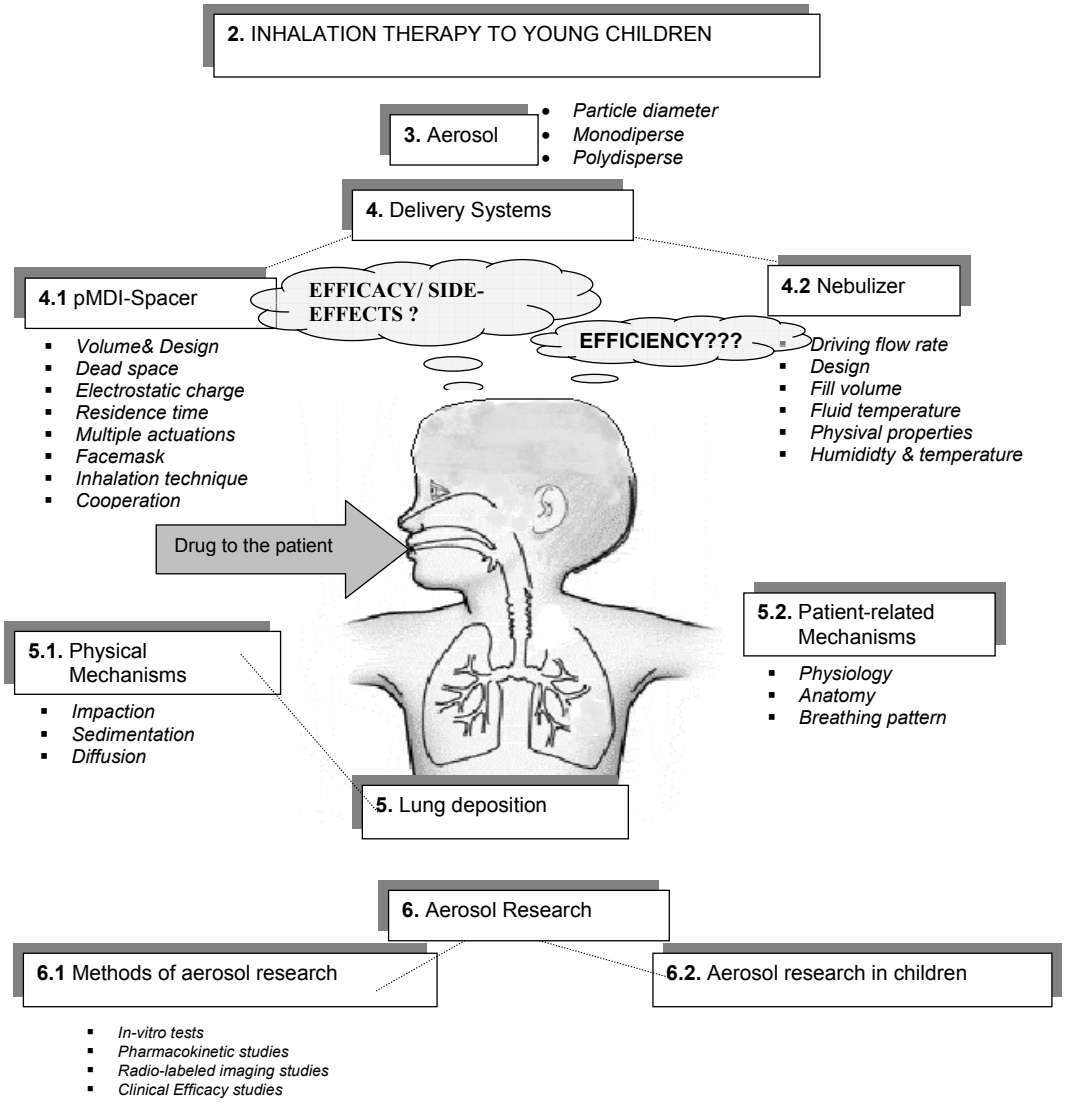


Figure 2. Overview of contents Chapter 1: Complexity of Inhalation Therapy.

Therapeutic aerosols with a MMAD ranging between 1 and 5 μm are believed to have the highest probability of deposition in the lower respiratory tract and are often referred to as respirable aerosols (Figure 3) (3).

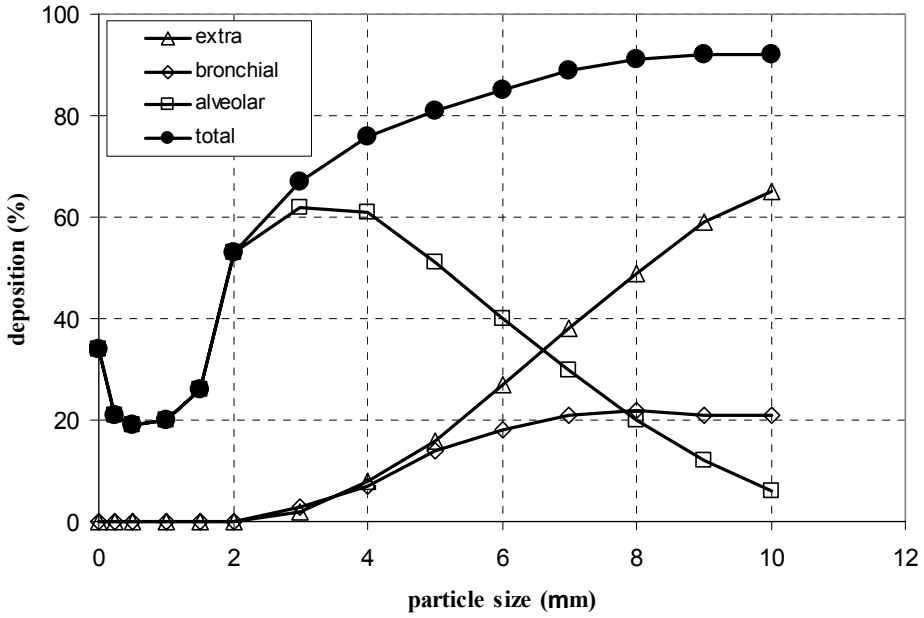


Figure 3. In-vivo deposition of particles in the human airways. (33) based on ref. (34) (flow rate: 250 ml/s, tidal volume: 1000ml)

In general, smaller particles have a higher likelihood of being deposited more peripherally than have larger particles. Particles larger than 10 μm are less likely to enter the tracheobronchial tree. While particles between 0.1 μm and 1 μm have a higher probability to penetrate deep into the lung, they also have a higher probability to be exhaled. For particles smaller than 0.1 μm, deposition efficiency increases again due to diffusion (see section 5.1).

4. Aerosol Delivery Systems

Aerosols are delivered to patients by means of aerosol delivery systems, of which many types are available. They are classified into three main categories: pressurized metered dose inhalers (pMDIs), dry powder inhalers (DPIs), and nebulizers (30, 32). The first category, the pMDIs, can

be further classified into two sub-categories, based on their operating technique: the breath-actuated method and the press-and-breath method with or without spacer. Most aerosol delivery devices were primarily designed for use in adults and subsequently modified for use in children. Nebulizers and pMDIs with spacers are currently the most efficient delivery systems for young children and are discussed in detail in this section. By contrast, DPIs and breath-actuated pMDIs are not used in young children and are, therefore, only briefly mentioned.

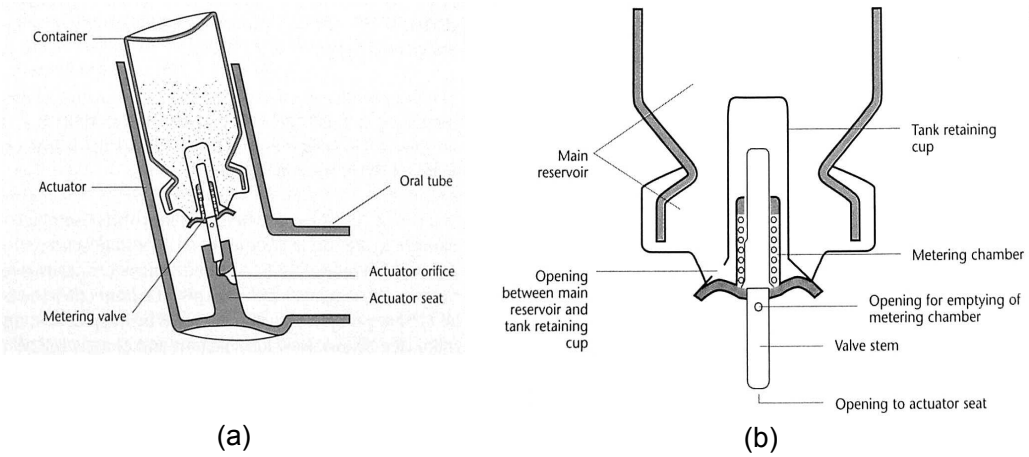


Figure 4. Schematic cross-section of a pMDI (a) and detail of the container (b) (32).

4.1 pMDI-Spacer

Pressurized Metered Dose Inhaler

Launched in 1956, the pMDI has since then become very popular because it is small, is noiseless during administration, and has a short administration time. Nowadays, it is the most frequently prescribed method for therapeutic aerosol delivery. The pMDI consists of a pressurized canister containing micronized drug, propellant, and surfactant (Figure 4). As the medication is usually suspended rather than dissolved in the propellant-surfactant mixture, the pMDI must be shaken vigorously before use, so as to mix the medication with the propellant and surfactant (3, 35, 36). After shaking, the pMDI should be fired directly, seeing that the mixture of medication, propellant and surfactant will rapidly separate within the canister (3). The propellant in the mixture serves as the energy source for expelling the drug from the canister into the air. The surfactant reduces aggregation

within the chamber and lubricates the valve stem (3). The propellant/surfactant/medication mixture is released from the canister through the metering valve and the stem. The stem fits in an actuator boot designed and tested to work with that specific propellant/surfactant/medication mixture (35-37). As small changes in actuator design can substantially change the pMDIs aerosol characteristics and output, a canister should be used with a specifically designed actuator (35, 36).

During actuation, the metering chamber is closed to the canister and open to the atmosphere. An aerosol cloud containing the propellant/surfactant/medication mixture leaves the actuator at high velocity. The released aerosol particles rapidly decelerate due to the resistance of the air and decrease in size as the propellant evaporates (3). If fired directly in the mouth, approximately 80% of the dose leaving the actuator will impact on the oropharynx due to the high velocity of the aerosol cloud (38). The dose deposited in the mouth may cause local side effects such as a candida infection (39). In addition, the drug will be swallowed and/or absorbed from the mucus of the oropharynx and may thus also contribute to systemic side effects (40-42).

Until recently, chlorofluorocarbons (CFCs) were used as propellants in pMDIs. However, in accordance with the Montreal Protocol on Substances that Deplete the Ozone Layer, most CFCs have now been replaced with the more environment-friendly hydrofluoroalkanes (HFAs). The transition from CFCs to HFAs was used as an opportunity to improve pMDI technology. The first HFA-pMDI, containing salbutamol, had an adapted valve design that resulted in a more constant dose from the first to the last actuation. The dose having become less temperature-dependent as well, dose variability was further reduced (43). Furthermore, the lower velocity of the aerosol cloud traveling from the actuator reduced the oropharyngeal deposition due to lower impaction (see section 4.1.1) (44). HFA-pMDIs containing beclomethasone dipropionate (BDP) deliver aerosols with a MMAD of 1.1 μm (45). These small particles are of particular relevance for aerosol therapy in young children. In a laboratory study using an upper-airway model of a 9-month old child (SAINT-model), Janssens et al. showed that the HFA-BDP pMDI yields substantially higher lung doses than does the CFC-pMDI (46). Moreover, the large proportion of extra-fine particles in the HFA-BDP pMDI reduced the breathing pattern related variability in lung dose when compared with the CFC-pMDI (46).

A problematic feature of pMDIs that are based on the press-and-breath method, is synchronizing the moment of dose actuation with time of

inhalation (32, 47, 48). To overcome this hand-breath coordination problem, a breath-actuated system was developed in the 1990s. This system makes it possible for the inspiratory flow rate to release a dose at the onset of an inhalation. Once the inspiratory flow rate exceeds 30 L/min, a vane is moved. This presses the canister in the actuator and subsequently the pMDI is fired. Although the breath-actuated system eliminates the coordination problem, it does not yet eliminate the high oropharyngeal deposition. In addition, the minimum flow rate presents a problem for young children, who generally will not be able to reach a flow rate of 30 L/min. Therefore, the breath-actuated pMDI is not recommended for young children (35, 36).

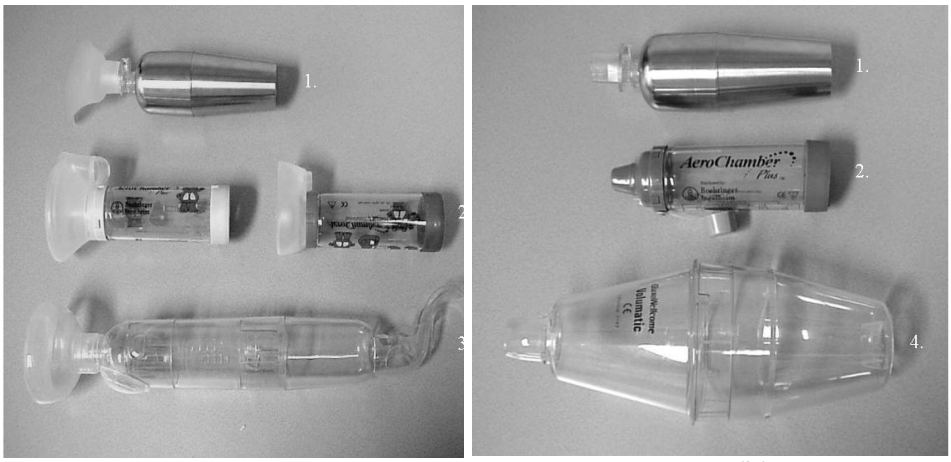
Spacers

In the 1980s, attempts to overcome the problem of hand-breath coordination were made by developing so-called spacers (Figure 5) (49-52). In addition, spacers carry the advantage of substantially reducing the oropharyngeal deposition. Spacers allow the aerosol cloud to expand and the aerosol particles to decelerate and evaporate (36, 50, 53). In addition, coarse aerosol particles are likely to impact on the spacer's inner surface. The dose inhaled from a spacer consequently contains a large proportion of fine particles (36, 54). In adults, the use of a pMDI-spacer combination improves the therapeutic effect by its improved efficiency of aerosol delivery (51, 52, 54, 55). Radio-labeled studies in adults using a pMDI-spacer combination showed a lung deposition between 20 and 45% of the metered dose (56, 57).

The pMDI-spacer combination is particularly useful in the treatment of children. Inspiration and expiration valves incorporated in the spacer enable inhalation with multiple breaths, which is of help to children who cannot clear the aerosol cloud from the spacer in a single inhalation. Low-resistance valves incorporated in the spacer even enable children with low tidal volumes to effectively open and close the valves (58). Importantly, for use in young children who are unable to breathe through a mouthpiece, the spacer should be fitted with a facemask. This would allow them to inhale the aerosol using tidal breathing (3, 35, 36, 59). In young children, nevertheless, the doses delivered to the lung by means of pMDI-spacer are still low. Radio-labeled studies in children younger than 4 years showed lung depositions between 0.67% and 16.4% of metered doses (60-62). In children older than 8 years, lung deposition was 41.8% of the metered dose (60). Strong attempts should be made, therefore, to improve the efficiency of aerosol delivery in young children.

pMDI-Spacer Interaction

Factors such as aerosol output, particle size distribution, and dose variability are determined by a variety of features related to the pMDI-spacer combination. These features are discussed below.



(a) (b)

Figure 5 Example of commercially available spacers in the Netherlands. (a): Spacers fitted with facemask. (b): Spacers with mouthpiece. 1 is NebuChamber® (AstraZeneca), 2 is Aerochamber plus® (Trudell Medical International), 3 is Babyhaler® (GlaxoSmithKline), 4 is Volumatic® (GlaxoSmithKline).

Spacer Volume & Design

Spacer volume determines aerosol dose and -concentration within the spacer. The use of a small volume spacer generally results in a high initial concentration of the actuated dose in the spacer, but also in high particle impaction on the spacer's inner surface. The use of a large volume spacer is associated with less impaction, and consequently with a greater dose available for inhalation. Patients with large tidal volumes can easily clear the aerosol cloud from a large volume spacer. However, young children with low tidal volumes need more time to do so. During inhalation, the aerosol particles will sediment on the spacer's inner surface. A small volume spacer will therefore be more efficient for young children with low tidal volumes, as it involves a shorter time for emptying the aerosol cloud (58).

The shape of the aerosol cloud leaving the actuator is different for each pMDI. Therefore, both form and volume of the spacer will determine the

amount of aerosol particles deposited on the spacer's inner surface (58, 63). In a controlled laboratory setting using the SAINT-model with the electrostatic charge of the spacer having been eliminated, lung dose was shown to be primarily affected by the pMDI and not by the type of spacer (64).

Valves

Adults with acute asthma have been shown to have expiratory flows that may be insufficient to close the valve of a spacer. If so, exhaled breath will re-enter and blow the remaining aerosol out off the spacer. This phenomenon has been claimed to contribute to the poor response sometimes observed when spacers are used in acute asthma (58, 65). For use in children, the valve incorporated in the spacer must be of low resistance and operate efficiently at low tidal volumes. Partially open or deformed valves are likely to significantly impair drug delivery, since aerosolized drug may be lost by impaction on the incompletely opened valve (Figure 6) (58).

Dead Volume Space

A large dead volume space between the mouthpiece or facemask and the inspiratory valves may substantially reduce spacer efficiency in young children. In an in-vitro study it was shown that adding a 50 ml dead volume space to the spacer halved the dose output from the spacer at a tidal volume of 50 ml (58).

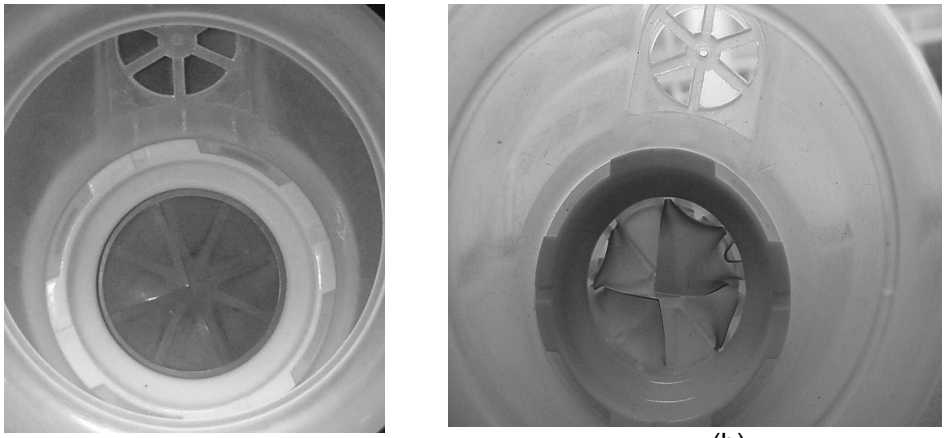


Figure 6. Aerochamber mask® (a) Normally closed inspiratory valve with small, closed expiratory valve. (b) Deformed valve with missing expiratory valve.

Electrostatic Charge

The inner surface of plastic spacers may show electrostatic charge. Attracting aerosol particles to the spacer wall, this could significantly reduce dose output (66). A metal spacer was developed, therefore, to overcome the problem of electrostatic charge (67, 68). The electrostatic charge of plastic spacers can be substantially reduced for about one week, however, by coating with household detergent (66, 69-71). Coating in practice involves washing the plastic spacer thoroughly with household detergent and leaving it to drip dry. Dose outputs of detergent-coated spacers have been shown to equal those of metal spacers (66). Storing plastic spacers in nylon or plastic bags will induce electrostatic charge, so this is best avoided.

Residence Time

Time between actuation and inhalation is defined as the residence time. During this time aerosol particles will sediment to the spacer's inner surface. Long residence time is associated with a high amount of aerosol particles settling to the spacer's inner surface, leaving few aerosol particles available for inhalation (70, 71). This effect will be stronger for electrostatically charged spacers, as the electrical field causes the aerosol particles to settle more rapidly (70, 71).

Multiple Actuations

Multiple actuations may substantially reduce the dose delivered to the patient, as it causes aerosol particles to merge into larger aggregates that will more easily impact onto the spacer's inner surface (70, 71). In case more actuations are needed, each actuation should immediately be followed by inhalation of the dose. This procedure should be repeated until the prescribed number of doses has been inhaled.

Facemask

Several studies suggest that facemask design is important for the efficiency of drug delivery (66, 72, 73). A facemask should tightly fit to the face to avoid air leaks and to minimize dead space volume. Janssens et al. in a daily-life study observed that it is difficult to obtain and maintain a good seal between the mask and the face, especially in uncooperative young children (66). To date, the precise effects of facemask leak size and position on drug delivery efficiency have not yet been investigated.

Inhalation Technique

The recommended technique for the use of a pMDI-spacer combination consists of the following steps: First, shake the pMDI-spacer combination for 10 seconds; Second, with the child sitting in an upright position, place the facemask on child's face or the mouthpiece between the teeth; Third, actuate a single puff in the spacer within 5 seconds after shaking; Fourth, let the child quietly inhale for at least 15 seconds using tidal breathing. Repeat this procedure if more puffs are needed. Although this technique seems easy, it is prone to errors leading to unpredictable dose output (66). In order to optimize aerosol delivery, both patients and parents should be properly instructed in applying the recommended technique of inhalation devices. In addition, the inhalation technique should be regularly checked (36, 74). Medical and nursing staff, therefore, should have up-to-date knowledge on proper inhalation techniques and the factors that influence aerosol delivery.

Cooperation & Breathing Pattern

An important determinant for efficient aerosol therapy to young children is the child's degree of cooperation. Janssens et al. found that one-third of children under the age of 2 years become distressed during aerosol administration, resulting in high dose variability and low dose output from a spacer (66). Children in distress have highly irregular breathing patterns, characterized by high inspiratory flow rates and long intervals between breaths. Studies using radio-labeled aerosols showed highly inefficient delivery of aerosols to crying or upset children (61, 75). Clinicians, therefore, have recommended aerosol administration during sleep, which in theory may be an interesting alternative. In a laboratory study, Janssens et al found lung deposition with sleep-breathing patterns to be significantly higher than that with wake-breathing patterns (76). However, the feasibility and efficacy of aerosol administration during sleep have not yet been studied in daily life.

4.2 Nebulizers

Types of nebulizers

The nebulizer has been the mainstay of aerosol therapy for many years. However, with the development of other delivery systems, such as the pMDI, the nebulizer is no longer the first choice in the treatment of asthma. It is

nowadays mainly used to deliver medications, such as inhaled antibiotics, that are only available as fluids. Furthermore, the nebulizer is applied for delivering high doses of bronchodilators in case of acute asthma, or when other delivery systems are not well accepted by the patient (3).

Two types of nebulizer systems are available, distinguished by principle of aerosol generation: the jet nebulizer and the ultrasonic nebulizer (Figure 7). The jet nebulizer uses a jet of compressed air, which is forced through a nozzle under high pressure. In the nozzle the air moves at high velocity (77). At the end of the nozzle, an abrupt decrease in pressure creates a vacuum, causing the drug solution to be driven through a narrow tube. Subsequently, the drug solution aerosolizes and long filaments are formed. These filaments break into droplets as a result of the effects of surface tension. Consequently, a wide range of aerosol droplet sizes is created (3, 77). A baffle placed above the nozzle ensures that only smaller droplets can leave the nebulizer chamber. Most aerosol particles impact on the baffle and the chamber sidewalls, and subsequently fall back in the drug solution for re-nebulization. Most nebulizer baffles are designed to ensure that the particle size distribution is in the range of 2-5 μm (3, 35, 77).

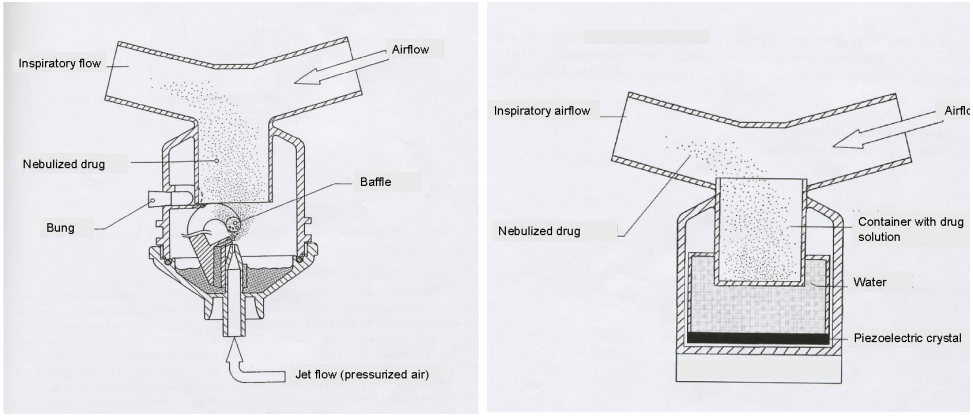


Figure 7. Cross-section of : A. Jet nebulizer; B. Ultrasonic nebulizer (78)

In the ultrasonic nebulizer, kinetic energy aerosolizes the drug solution. The kinetic energy is produced by a piezoelectric crystal that vibrates when a current is passed through (3). The frequency of the vibrating crystal determines the particle size of the droplets. Aerosol particles generated by the ultrasonic nebulizer are typically coarser than those

generated by the jet nebulizer (3, 77). Ultrasonic nebulizers are not suitable for suspensions, such as steroids, or for viscous fluids, such as antibiotics (79). The following section focuses on jet nebulizers, as these are most frequently used to treat children with pulmonary diseases.

Interacting factors

Various factors may affect the aerosol output and particle size distribution of a jet nebulizer.

Driving airflow rate

In jet nebulizers, the airflow rate through the nozzle determines droplet size and nebulization time. High flow rates (*e.g.* 8 L/min) result in smaller droplets and shorter nebulization times than do low flow rates (*e.g.* 4 L/min) (80). For many jet nebulizers a flow rate of 8 L/min is recommended (3, 77).

Nebulizer design

The design of the baffle is one of the determinants of nebulizer performance. The higher the fraction of aerosol particles intercepted by the baffle, the smaller the aerosol particle size but the longer the nebulization time (3, 77). In conventional jet nebulizers aerosol is continuously produced during inspiration and expiration. Continuous nebulization, however, wastes medication because aerosol generated during expiration is largely lost into the air (35). Modifications in jet nebulizer design have improved the efficiency of the nebulization process. Firstly, an *open-vent system* was developed, which allows additional air entrainment during inhalation causing a shorter nebulization time. However, open-vent systems are not efficient in young children, as their inspiratory flow rates do not exceed the output flow rate of the compressor (59, 81). Secondly, a *breath-enhanced open-vent device* was developed, which allows the patient to inhale additional air through an inspiratory vent. On exhalation, the inspiratory vent closes, and aerosol can only exit via a one-way valve near the mouthpiece. The breath-enhanced open-vent device increases the amount of aerosol particles to inhale, without increasing the amount of aerosol particles lost during exhalation (35). Thirdly, a *breath-actuated device* was developed, which follows the patient's breathing pattern. Nebulization takes place only during a predetermined fraction of the inspiration time. A breath-actuated device improves dose reproducibility and reduces loss of aerosol during exhalation. This improves the efficiency of drug delivery. However, using this device nebulization of the entire dose takes 3-4 times longer (delivering 3-4 times

more drug) than it does using a continuous operating jet nebulizer (35, 82, 83).

Fill volume and residual volume

The residual volume is the volume of liquid that remains in the nebulizer after completion of nebulization. Residual volumes ranges from 0.5 to 1.5 ml (35, 77). Consequently, at an initial small *fill volume* of 2 ml, more than 50% of the medication placed in the nebulizer will be retained. A larger fill volume gives a relatively smaller residual volume, allowing for a larger quantity of active medication to be nebulized (3).

Fluid temperature

In jet nebulizers, fluid temperature may drop approximately 7 °C during nebulization due to evaporation of the fluid. This temperature drop is associated with a decrease in particle size (84). In some ultrasonic nebulizers, fluid temperature may increase approximately 20 °C during nebulization. This is a potential problem for medication that is subject to denaturation, such as proteins(3, 35, 77).

Physical properties of drug solution and suspension

The viscosity of suspensions and solutions influences the rate of medication delivery. In case a jet nebulizer is used with a relatively low driving flow rate (6 L/min), the nebulization time for more viscous suspensions, such as antibiotics, can be relatively long. Hence, a driving flow rate of at least 8 L/min is generally recommended (3).

Humidity and temperature

High temperatures and relative humidity may give rise to hydroscopic growth of aerosol particles, i.e. an increase in particle diameter resulting from association with water vapor (85). When aerosol particles entrain into a warm and fully water-saturated air stream, they will increase in size. Additionally, they may coalesce and even further increase in size (35).

Facemask

It is of great importance that facemasks used in combination with a nebulizer are close-fitting. Keeping the facemask at a distance of 1 cm from

the face was found to halve the maximal inspired dose. At a distance of 2 cm, reduction amounted to 80% of the maximal inspired dose (86).

Table 1. Advantages and disadvantages of aerosol delivery devices for use in children. Adapted from ref. (32)

Device	Advantages	Disadvantages
Nebulizer	• Suitable for all ages • Tidal breathing possible • Delivery of high doses over prolonged period • Facemask can be used	• Cumbersome • Noisy • Time consuming • Need of voltage supply • Risk of bacterial contamination • Poor reproducibility of dose and particle size • Large inter-device variability • Maintenance of compressor • Expensive
pMDI	• Small, handy • Quick • Low dose-to-dose variability	• Complicated hand-mouth coordination • High oropharyngeal deposition caused by high velocity of aerosol • Not suitable for children
pMDI breath-actuated	• Small, handy • Quick • No hand-mouth coordination required	• High oropharyngeal deposition caused by high velocity of aerosol • Deep inspiration required • Not suitable for children younger than 7-8 years • High inspiratory rate required
pMDI/spacer	• All ages • Tidal breathing possible • Facemask can be used • Quick • Reduced oropharyngeal deposition, and therefore less local side effects	• Electrostatic charge of plastic spacers • Large size of spacer • Correct administration procedure is critical
DPI	• Small, handy • Quick • No hand-mouth coordination required • Propellant free • Reduced oropharyngeal deposition, and therefore less local side effects	• High inspiratory flow rate required • Efficiency dependent on strength of patient • Not suitable for mostchildren younger than 7-8 years

4.3 Advantages and disadvantages of aerosol delivery devices

The advantages and disadvantages of the various aerosol delivery devices for use in children are presented in **Fout! Verwijzingsbron niet gevonden.** (32). Nebulizers and pMDI-spacers both have the advantage of facemask use, and require only tidal breathing. Therefore, patients of all ages can use these devices. An additional advantage of the pMDI-spacer over the nebulizer is that it is cheap, silent, small, time-efficient, and does not need power supply. On the other hand, the pMDI-spacer has a critical administration procedure: any deviation from the recommended procedure may increase dose variability and reduce the amount of medication available for inhalation (66). One advantage of nebulizers over pMDI-spacers is that a higher dose of medication can be nebulized. In addition, nebulizers can be used in combination with oxygen. Hence, in most emergency rooms nebulizers are the first choice in the treatment of an acute asthma attack (3).

5. Drug deposition in the lung

Upon inhalation of an aerosol, particles may deposit anywhere within the respiratory tract or may be exhaled (3). Three factors influence the quantity of medication deposited in the lung and the distribution pattern of deposition:

1. Physical properties of the aerosol;
2. Physical deposition mechanisms;
3. Patient-related mechanisms.

Physical properties of the aerosol have been discussed in section 3. Physical deposition and patient-related mechanisms are discussed below.

5.1 Physical deposition mechanisms

Deposition of inhaled particles is primarily governed by three physical mechanisms: inertial impaction, sedimentation, and diffusion. The relative contribution of each mechanism is determined by the characteristics of the inhaled particles, and by patient-related mechanisms, such as breathing pattern and respiratory tract anatomy (30, 32). The impact of the three physical mechanisms on the lung deposition as function of particle size is shown in Figure 8.

Inertial impaction

A parameter describing an airborne aerosol particle is the momentum. The momentum is the product of particle mass and particle velocity. Particles with large mass and/or large velocity have larger momentums. Upon changes in airflow direction, i.e. in the pharynx, the particle's momentum determines whether the particle is able to follow the change in airflow direction or will impact onto the pharynx wall. The likelihood of impaction increases with increasing airflow rate and particle size. Impaction is the most important deposition mechanism in the upper and central airways and at or near bronchial bifurcations (Figure 9) (3, 30, 88).

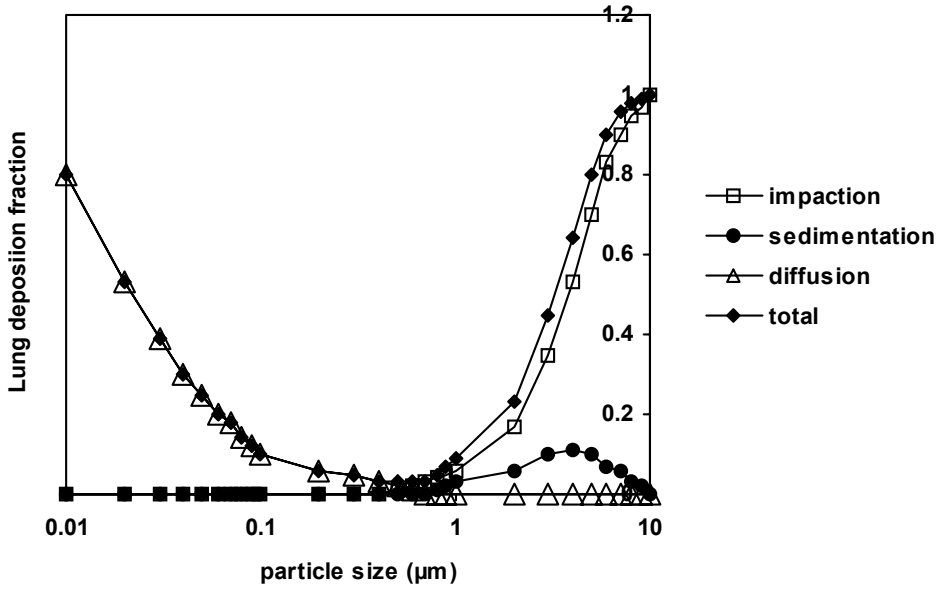


Figure 8. Efficiencies of the particle deposition mechanisms of inertial impaction, sedimentation, and diffusion in relation to particle size (87).

Sedimentation

The total cross-sectional area of the more peripheral airways is substantially larger than that of the central airways. The flow, however, remains constant throughout the entire respiratory tract. The flow is defined as the product of cross-sectional area and flow rate. At a constant flow,

therefore, the flow rate in the peripheral airways is lower than that in the central airways (89). In peripheral airways, sedimentation is consequently the most likely deposition mechanism. Sedimentation is governed by gravitational forces and is a time-dependent process (Figure 10). The likelihood of sedimentation increases with residence time in the airway. For this reason, the breath-holding maneuver after inhalation increases the efficiency of lung deposition by means of sedimentation (3, 30, 89).

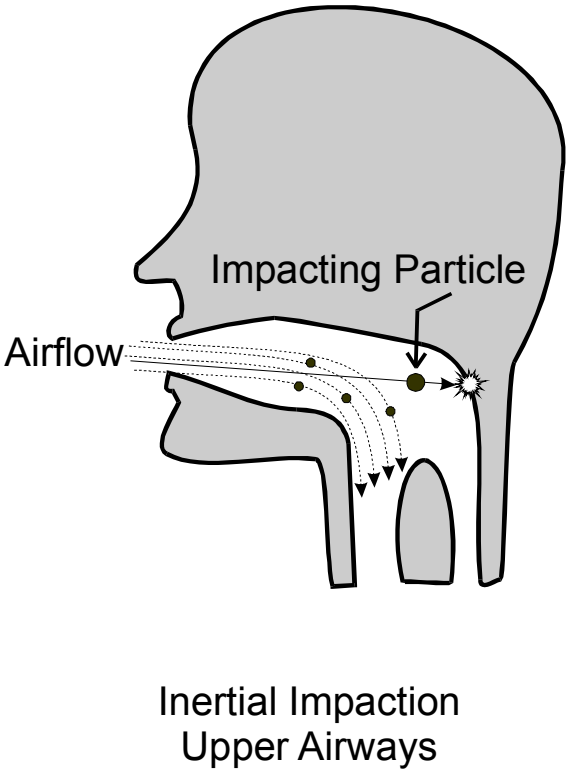
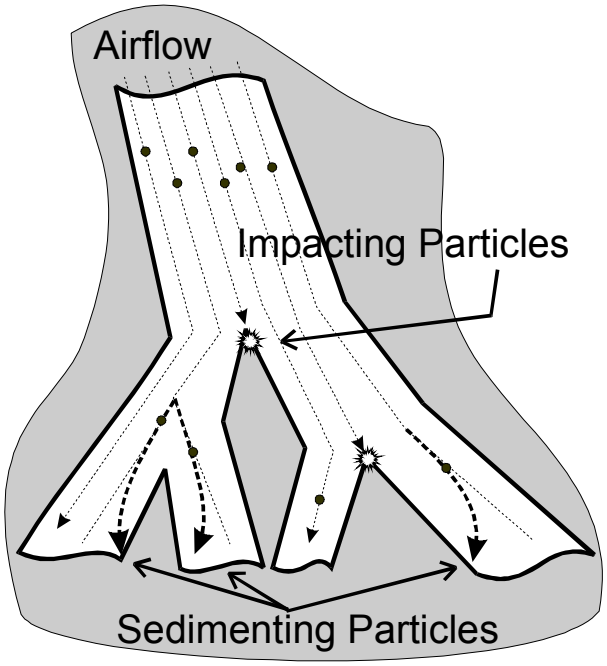


Figure 9. Inertial impaction.



Sedimentation and Inertial Impaction
Central Airways

Figure 10. Sedimentation and inertial impaction in the central airways.

Diffusion and Brownian motion

Diffusion is the primary transport mechanism for particles less than 0.1 μm in diameter (Figure 8). When these particles are close to the airway wall, i.e. in the bronchioles and alveoli, diffusion is the most important mechanism of deposition. Collision of gas molecules with small aerosol particles in still air causes an irregular wiggling motion of the aerosol particles. This motion, called the *Brownian motion*, is the cause of the diffusion mechanism (Figure 11). Diffusion of aerosol particles is defined as the *net* transport of these particles in a concentration gradient. This transport is always from a region of higher concentration to a region of lower concentration. For particles less than 0.05 μm, both diffusion and Brownian motion are characterized by the particle diffusion coefficient, which is inversely proportional to the particle size. For example, a 0.01 μm particle will be transported by diffusion 20.000 times faster than a 10-μm particle (3, 30, 31).

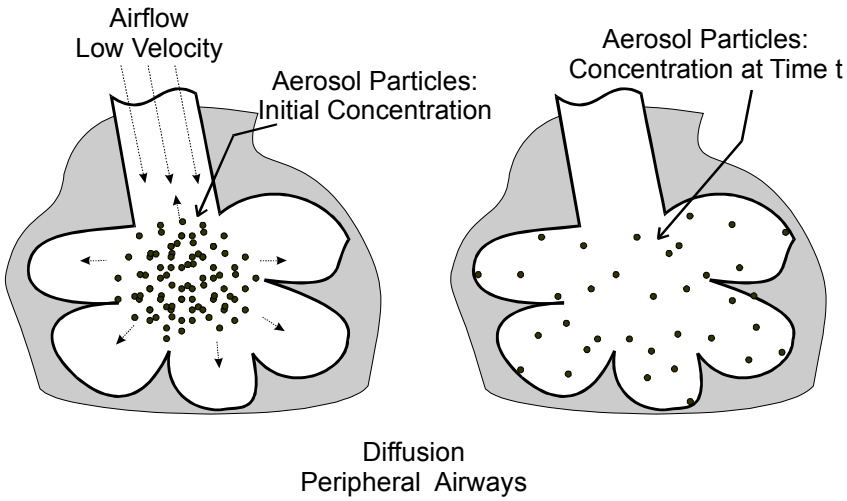


Figure 11. Diffusion of aerosol particles in the peripheral airways.

5.2 Patient-related mechanisms

Quantities of particles deposited and site of deposition are influenced by the following patient-related factors:

- Physiology of the airways (30, 35, 89-92);
- Airway anatomy and pathology (90-94);
- Breathing pattern, including frequency, flow rate, and tidal volume (30, 90, 91, 95-98).

Airway physiology

The respiratory tract includes defense mechanisms for the elimination of foreign material. For example, one of the functions of the nose is to filter particles. Deposition in the nose mainly results from impaction caused by turbulence occurring at the internal ostium (3). Hence, nasal filtration is greater for larger particles than it is for smaller particles. As young children are obligate nose breathers, they have a considerable chance of upper airway deposition (3, 30, 35, 90).

Airway anatomy and pathology

Airway caliber is an important determinant of aerosol deposition. The mean airway lumen diameter of the respiratory tract between the main bronchi to the bronchioli increases two-threefold between birth and adulthood (90, 91, 99). The small airway caliber in infants and young children favors central airway deposition by impaction. In addition, lung pathology may further narrow small caliber airways (Figure 12) (90, 91, 99). Inflammation, edema, mucus, bronchoconstriction, and abnormal anatomy lead to changes in flow patterns and, consequently, in aerosol deposition patterns. Studies using radio-labeled aerosols have shown increased central deposition and reduced deposition in the peripheral airways in both adults and children with airway obstruction (61, 99-103).

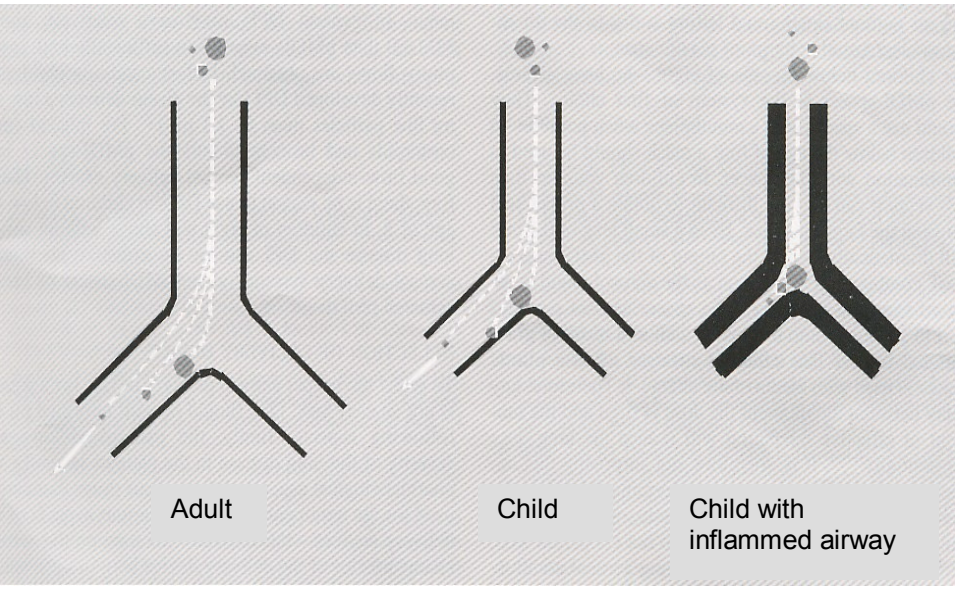


Figure 12. Deposition by impaction. While in healthy adults large particles may penetrate into the peripheral airways, in children with inflammatory lung disease only the smallest particle have a chance to penetrate into the peripheral airways (88).

Breathing pattern

The breathing pattern during aerosol inhalation greatly influences particle deposition in the respiratory tract (83, 91, 98, 104). A person's

breathing pattern is characterized by factors such as flow rate and flow volume. Young children show a highly variable breathing pattern (Figure 13) (76, 83, 99). When crying, the child's inspiratory flow rate will increase (75). High inspiratory flow rates, however, enhance the impaction of particles in the oropharynx and the central airways on account of a more turbulent airflow. This results in a lower lung deposition (75, 91). Furthermore, young children with low tidal volumes show reduced aerosol delivery, as they need more time to inhale the aerosol. During this time, aerosol particles tend to settle onto the spacer's inner surface (58).

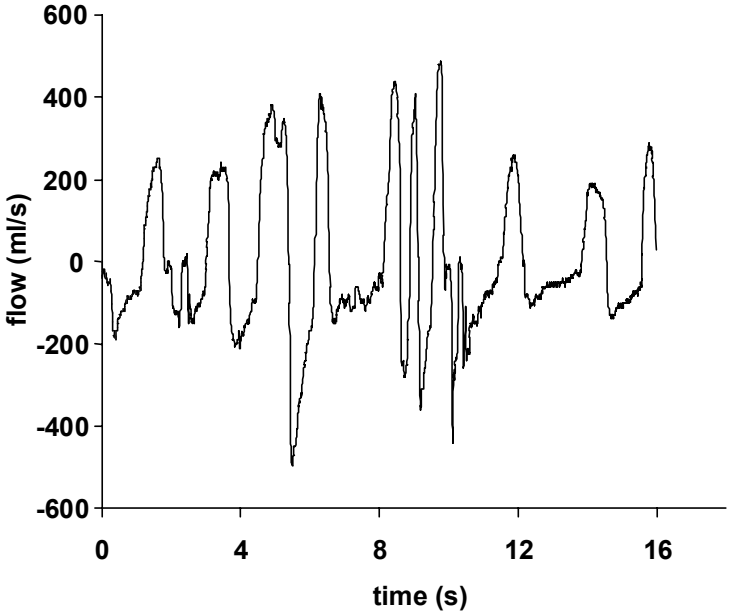


Figure 13. A young child's typical breathing pattern (76).

Older children and adults are able to inhale slowly and steadily, and to hold their breath for 5-10 seconds after inhalation. The slow and steady inhalation increases the fraction of inhaled particles that penetrates into the peripheral airways (30, 98, 104). A breath-holding period of 10 seconds after inhalation allows particles to be deposited by sedimentation (see section 5), and therefore, enhances peripheral lung deposition. Not being able to inhale slowly and steadily and to hold their breath, young children will generally inhale the administered aerosol by tidal breathing. Tidal breathing results in a

larger proportion of the inhaled aerosol being exhaled (58). Finally, the effect of breathing pattern on lung deposition cannot be seen separately from particle size. In an in-vitro study Janssens et al. showed that the lung dose of extra fine particles (MMAD <2.1 μm) was not associated with tidal volume, whereas the lung dose of particles between 2.1-4.7 μm decreased rapidly with increasing tidal volume (46).

6. Aerosol research in young children

The previous sections discussed the many factors that influence the efficiency and efficacy of aerosol therapy. It was pointed out that many types of aerosol delivery devices are available, each with its particular characteristics that may influence aerosol therapy. These characteristics should be taken into account when opting for a device to be applied in the individual patient. We have to realize that data from studies in adults cannot be extrapolated to children, because children have different physiology, anatomy, pathology, and breathing patterns. Therefore, in order to optimize aerosol therapy in children, we need data from studies in children. This section presents a short overview of aerosol research methods and an overview of clinical efficacy and radio-labeled deposition studies in young children.

6.1 Aerosol research methods

The efficiency of aerosol therapy can be studied in-vitro or in-vivo. In-vitro studies are useful to investigate factors that may influence the efficiency of aerosol delivery and to estimate lung deposition (105, 106).

Pharmacokinetic, radio-labeled imaging, and clinical efficacy studies are examples of in-vivo studies. While the first two are used to quantify lung deposition (105, 107), clinical efficacy studies are used to evaluate the efficacy and safety of aerosol therapy (97, 108).

In-vitro studies

Impactors or laser diffraction systems are used to analyze an aerosol's particle size distribution. Knowledge of particle size distribution is important for the development of new aerosol delivery devices. However, as in-vitro studies are known to overestimate the amount of drug reaching the lungs with

respect to the in-vivo situation (109), in-vitro studies are mainly used comparatively (105, 110).

Upper airway models connected to computer-controlled breathing simulators are used to study factors that influence the efficiency of aerosol delivery devices. A filter placed between the device and the model measures the total dose delivered to the model at a certain breathing pattern. This method estimates total body deposition, but does not give information about the deposition pattern (46, 64, 76, 111).

Pharmacokinetic studies

In pharmacokinetic studies, lung deposition can be estimated by quantification of the amount of drug or metabolites in plasma or urine. Figure 14 shows schematically what happens to an inhaled drug. In general, systemic drug levels represent drug absorbed via the lungs as well as via the gastrointestinal tract. They will, therefore, reflect only lung deposition when absorption via the gastrointestinal tract is prevented or when it is completely eliminated by the first-pass metabolism. Activated charcoal can be used to block the absorption from the gastrointestinal tract (41, 105, 113). Pharmacokinetic studies are of somewhat limited value in that they do not demonstrate regional lung deposition patterns (105, 113).

Radio-labeled imaging studies

Regional lung deposition pattern of inhaled aerosols can be assessed, nevertheless, by radionuclide imaging. Gamma scintigraphy, the most widely used imaging method, generates a 2-dimensional image (105, 107). Gamma scintigraphy uses drug formulations labeled with a radionucleotide, such as ^{99m}Tc. After inhalation, these enable the lungs and oropharynx to be imaged in 2 dimensions by a gamma camera. The images distinguish lung zones representing the large, median and small airways, respectively. However, as the zones are arbitrarily demarcated, it is only possible to obtain an estimation of the deposition in the different zones. A more detailed deposition pattern can be provided by 3-dimensional imaging techniques, such as single photon emission computed tomography (SPECT) or positron emission tomography (PET) (106).

These techniques are able to relate lung deposition patterns to different airway sizes with higher precision than does gamma scintigraphy. However, SPECT and PET are expensive and complex, requiring large quantities of radiotracers and long scanning times. In addition, they have not been

validated as adequately as the 2-dimensional gamma scintigraphy method (106).

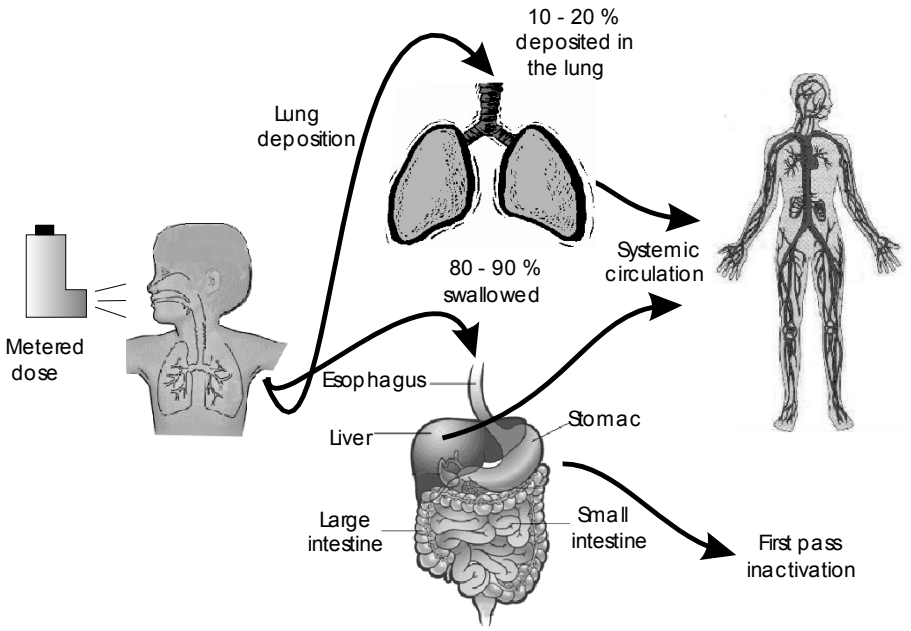


Figure 14. Pharmacokinetics of inhaled drugs. After inhalation, the metered dose is partly deposited in the lung and partly deposited in the upper airways and subsequently swallowed. The systemic plasma concentration of an inhaled drug is the sum of the fraction absorbed directly from the lung and the fraction absorbed in the gastro-intestinal tract that is not eliminated by the first-pass metabolism. Based on ref. (112)

Clinical efficacy studies

Clinical efficacy studies may serve to test efficacy and safety of the inhalation therapy, provided they are designed as randomized, double-blind, placebo-controlled trials (114). Efficacy of bronchodilators is determined by lung function tests before and after inhalation of a bronchodilator. As bronchodilators show a rapid response after inhalation, reliable results can be obtained in small groups of patients. By contrast, a therapeutic effect of inhaled corticosteroids on chronic airway inflammation can not be measured until after 6 weeks (115-117). Consequently, measuring clinical efficacy of

inhaled corticosteroids demands long term studies with large numbers of patients, frequent lung function testing, registration of symptoms, hospital admissions, exacerbation, and concomitant administration of other drugs (32).

6.2 Aerosol research in children

Only few clinical efficacy and lung deposition studies in young children have been published. Most countries forbid lung deposition studies using radioactive aerosols in children for ethical reasons, as the long-term risks of high local deposition are still unknown. Table 2 gives an overview of the results of the available radio-labeled imaging studies in young children. Clinical efficacy studies in young children are few because it is difficult to make the diagnosis of asthma in children younger than 4 years. Furthermore, reproducible end-points that can be used to study large numbers of young children are lacking. Routine lung function testing is feasible in most children older than 6 years. Lung function testing in younger children is technically difficult and time consuming, and is restricted, therefore, to only a few centers.

Recently developed, non-invasive methods to measure airway resistance and inflammation might be of help in aerosol research in young children. One of these, the respiratory resistance with the interrupter technique (Rint), enables to determine airway resistance during tidal breathing in children older than 3 years (118, 119). Another non-invasive method is the measurement of exhaled Nitric Oxide (eNO), which is a "surrogate marker" of airway inflammation (120-124). Both methods have recently been validated and reference values are now available (119). Seeking to improve aerosol therapy, several studies using eNO as an end-point were conducted in children older than 6 years (124, 125). To date, however, there is no evidence that eNO and Rint might be useful as end-points in clinical efficacy studies. Table 3 gives an overview of clinical efficacy studies in young children with recurrent wheeze.

Table 2. An overview of radio-labeled studies in young children

Reference	Age (range)	Disease	No. Subjects	Aerosol Delivery device	Lung deposition	Deposition expressed as
Wildhaber(62)	2-4 yr	Stable asthma	8	Nebulizer and pMDI-AC (DC)	5.4 %	% of metered dose
Wildhaber(60)	< 4yr	Stable asthma	8	pMDI-BH (DC)	16.4 %	% of total actuated dose
Tal(61)	3 mo-5yr	7 asthma, 4 CF, 4 BPD	15	pMDI-AC (non-DC)	2%	% of inhaled drug??
Amirav(101)	1-14 mo	Acute RSV	12	Nebulizer	1.5 % in right lung	% of nebulizer output
Zar(126)	3-7 yr	Stable asthma	40	BH (DC) and AC (DC) using mouthpiece or facemask	BH: 25% AC: 21% Use of facemask = Mouthpiece	% of inhaled drug??
Mallol(102)	3-24 mo	CF	20	Nebulizer using 2 different particle sizes	0.97%	% of total dose placed in nebulizer
Chua(99)	4-15 mo	CF	12	Nebulizer	1.3%	% of nebulizer output

AC: Aerochamber, BH: Babyhaler, DC: detergent-coated, CF: cystic fibrosis, BDP: bronchopulmonary dysplasia, RSV: respiratory syncytial virus

Table 3. Overview of clinical efficacy studies in young children with recurrent wheeze.

Ref.	Age (range)	Subjects	Design	Duration	Drug+Device	End-points	Outcome
Barrueto (127)	14-18 mo	31	DB PC	8 weeks	BDP/salb + AC (non-DC)	Symptom scores	Symptom scores ~
Bisgaard (128)	11-36 mo	77	DB parallel-group	12 weeks	BUD + NH (non-DC)-facemask	Symptom scores	Symptom scores ↑
Bisgaard (129)	12-47 mo	625	Parallel-group, open-label	52 weeks	FP + BH (DC?) / SCG + NH (DC?)	Symptom scores	FP better efficacy than SCG
Bisgaard (130)	12-47 mo	237	DB PC	16 week	FP + BH (non-DC)	Symptom scores	Symptom scores ↑
Chavasse (131)	3-12 mo	48	DB PC	2 months	Salb + BH (non-DC)	Diary cards + ILFT	Vmax FRC + symptom scores ~, increase in airway resistance
Chavasse (132)	3-12 mo	37	DB PC	12 weeks	FP + BH (DC?) - facemask	Symptom scores	Symptom scores ↑
Conner (133)	6-36 mo	25	DB PC	2 weeks	Salb + AC (non-DC)	Symtom scores	Symptom scores ↑
Connet (134)	1-3 yrs	26*	DB PC	6 months	BUD + NH (non-DC)-facemask	Symptom scores	Symptom scores ↑
Hofhuis (135)	6-22 mo	17	Retrospective		Terb + NH / Salb + BH	ILFT	Vmax FRC ~
Hofhuis (136)	4-24 mo	65	DB PC	16 weeks	FP + BH (DC) - facemask	ILFT+ symptom scores	Vmax FRC + symptom scores ~
Jackson (137)	4-20 mo	16		1 day	Albuterol + BH	ILFT	Airway resistance ~
Kraemer (138)	2-25 mo	29	DB PC	6 week	BDP/ Salb +BH (non-DC)	ILFT + symptom scores	Lung function + symptom scores ↑
Noble (139)	4 -18 mo	15	DB PC	6 weeks	BUD + NH (non-DC)	Symptom scores	Symtom scores ↑
Mandelberg (140)	10-48 mo	42**	DB PC	1 day	Salb + NC-facemask vs Salb + nebulizer	RR, HR, PO clinical symptom measures	Symptom scores ↑ Equal efficacy for NC and nebulizer
Mellon (141)	6-48 mo	214	DB PC	12 weeks	BUD + nebulizer-facemask vs mouthpiece	Symptoms scores	Symptom scores ↑ Equal efficacy for Facemask and mouthpiece
Primhak (142)	8-45 mo	33	DB two-period, four-treatment		Salb + BH (non-DC)-facemask	Metacholine provocation test	50-100 µg salbutamol is bronchoprotective
Stick (143)	5-18 mo	38	DB PC	9 weeks	BDP + NH (non-DC)	ILFT + symptom scores	Vmax FRC + symptom scores ~
Teper (144)	7-24 mo	30	DB PC	6 months	FP + AC (DC)	Symptom scores	Symptom scores ↑
Van Bever (145)	3-17 mo	23	DB PC	10 weeks	BUD + nebulizer	Symptom scores	Symptom scores ~

Abbreviations:
DB: double-blind. PC: placebo-controlled. BUD: budesonide. BDP: beclomethasone dipropionate. FP: fluticasone dipropionate. Salb: salbutamol. SCG: sodium cromoglycate. Terb: terbutaline. AC: Aerochamber. BH: Babyhaler. NC: NebuChamber. NH: Nebuhaler. DC: detergent-coated. Non-DC: non-detergent-coated. ILFT: Infant Lung Function Testing. PO: pulse oximetry

Symbols:
*severe asthmatics
** acute wheeze
~ : no significant improvement, ↑ : significant improvement

7. Remarks

A wide variety of factors that influence the efficiency and efficacy of inhalation therapy were discussed in this chapter. Mask design, cooperation and particle size seem to be the critical factors that affect inhalation therapy in young children. Many young children do not cooperate during aerosol administration, which makes it difficult to obtain a good seal of the mask on the face. In addition, crying during inhalation therapy gives high inspiratory flow rates, which result in high oropharyngeal deposition and low lung deposition. Moreover, obviously children have smaller airways than adults. They will, therefore, most likely benefit from smaller particle sizes, which most of the currently available devices unfortunately are not able to deliver.

From a review of the literature it appears that the above factors have not been extensively investigated. Although many studies investigated the efficiency of aerosol therapy, only few concerned young patients. Detailed knowledge of these factors, however, is crucial to further optimize aerosol therapy in young children.

8. Aims and outline of this thesis

The overall scope of this thesis is to contribute to the optimization of inhalation therapy in young children. The complexity of inhalation therapy in all its aspects was described in detail in the previous sections. One of the crucial factors for the efficiency of drug delivery to young children appeared to be the fit of the mask to the face (66, 73). In a daily life study using the pMDI-spacer combination, it was observed that obtaining and maintaining a good seal between the mask and the face is especially difficult in uncooperative young children (66). A few studies are available investigating the effect of facemask fit on drug delivery (72, 73, 146, 147). These studies, however, did not investigate whether and how size and position of the leak might affect the efficiency of drug delivery. We, therefore, set up an in-vitro study using the SAINT-model and a breathing simulator, aimed at investigating possible effects of size and position of a facemask leak on spacer output and lung dose (**Chapter 2**). Furthermore, in daily life study in young children using a spacer we examined how facemask design affects the efficiency of aerosol delivery (**Chapter 3**).

A tight fit of the facemask is also important for the efficiency of drug delivery by means of a nebulizer (146). For nebulizers, a tightly fitted mask will minimize room air entrainment. The estimated maximal dose that is

likely to reach the patient, ranges between 11 and 14% of the nominal dose (148). A loosely fitted mask may cause adverse events due to exposure of the patient's eyes and skin to the aerosolized drug (148). The current literature provides no information on patterns of aerosol loss associated with commercially available facemasks-nebulizer combinations. This is why we studied, from video-recordings, patterns of aerosol loss from various pediatric facemasks combined with a nebulizer (**Chapter 4**).

Another important determinant for efficient aerosol therapy to young children is a child's degree of cooperation. A daily life study found that one-third of children under the age of 2 years become distressed during aerosol administration. This results in a high dose variability and a low dose output from a spacer (66). This is why administration of aerosols during sleep has been suggested as an alternative for uncooperative children (61, 76, 149). In **Chapter 5,** we present a study in which the feasibility of drug administration by means of pMDI-spacer in sleeping young children indeed was investigated.

To achieve optimal efficacy of inhalation therapy, the aerosolized drugs should be delivered to the target regions in the lung. One of the factors influencing the efficacy of inhalation therapy is the particle size of the inhaled drug. To define the optimal particle size, clinical efficacy and systemic side effects of the inhaled drug should be determined (150, 151). Bronchodilators with a MMAD of 2.8 μm were shown to give the best improvement in lung function and the lowest systemic side effects in mild and severely affected asthmatic adults (150, 151). It is not known, however, whether inhaled steroids with a MMAD of 2.8 μm are also the most efficacious in asthmatic adults. To define the optimal particle size for inhaled corticosteroids, we set out to investigate the systemic absorption as function of aerosol size in adults with mild asthma, using monodisperse beclomethasone dipropionate (BDP) aerosols (**Chapter 6**).

In **Chapter 7**, the results of the studies presented in this thesis are summarized and discussed, and suggestions for further research are proposed.

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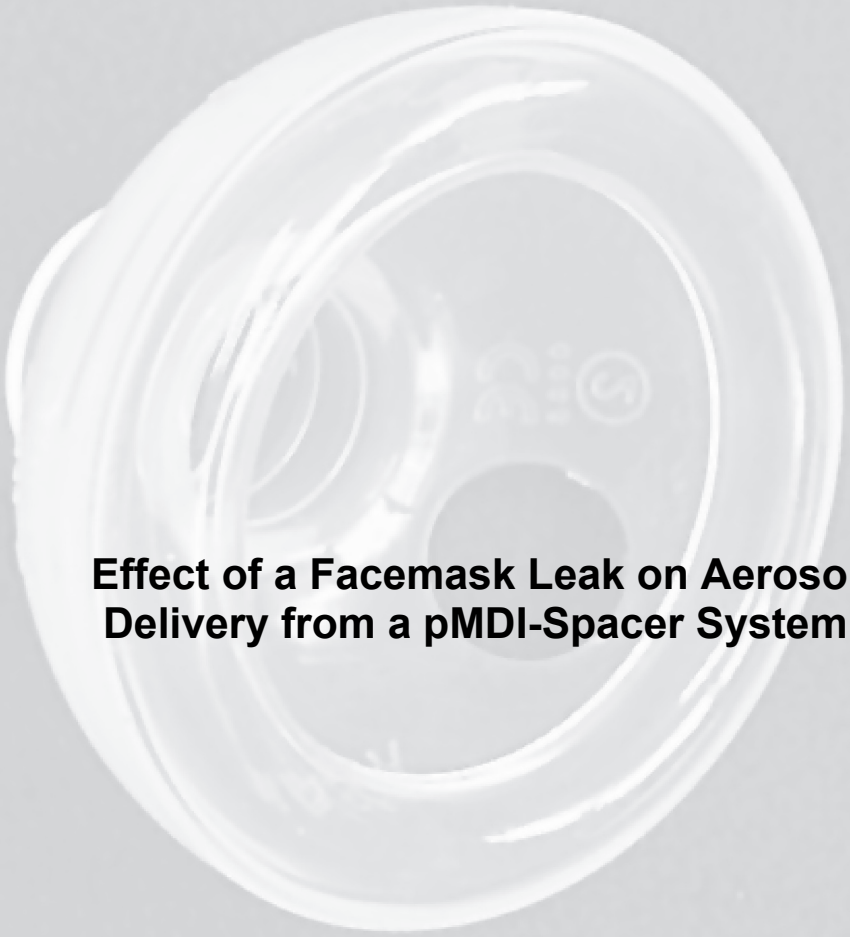

Effect of a Facemask Leak on Aerosol Delivery from a pMDI-Spacer System

Chapter 2

Effect of a Facemask Leak on Aerosol Delivery from a pMDI-Spacer System

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Abstract

Aim: The objective of this investigation was to study the relation between size and position of a mask leak on spacer output and lung dose.

Method: An upper-airway model (SAINT-model, Erasmus MC) was connected to a breathing simulator. Facemasks with leaks ranging between 0 and 1.5 cm^2 were examined. Leaks were located close to the nose or close to the chin. During simulated breathing, 200µg budesonide (Pulmicort®, AstraZeneca) was delivered to the model via NebuChamber® (AstraZeneca) with facemask. Spacer output and lung dose were measured by placing a filter between spacer and facemask or between model and breathing simulator, respectively. Budesonide trapped on the filter was quantified by means of HPLC, and expressed as % of the nominal dose.

Results: Mean spacer output doses for the nose position were 50, 38, 28, 12, 10, 6 and 0%, and for the chin position were 50, 40, 31, 11, 9, 4, and 0% for leaks of 0, 0.05, 0.1, 0.16, 0.2, 0.3 and larger than 0.4 cm2, respectively. Mean lung doses for the nose position were 10, 8, 6, 3, 3, 1, 0, 0, 0, 0%, and for the chin position were 10, 9, 8, 6, 6, 5, 1, 1, 0 and 0% for leaks of 0, 0.05, 0.1, 0.16, 0.2, 0.3, 0.4, 0.5, 1 and 1.5 cm^2.

Conclusions: Efficiency of a pMDI-spacer-facemask strongly depends on the size of a facemask leak. Spacer output did not depend on the position of the leak. Lung dose was higher for leaks near the chin than for leaks near the nose.

Introduction

Over the past years, many inhalation devices have been developed to treat young children. The pMDI-spacer combination with a facemask is the first choice device for infants and young children.[1,2] Clinical studies in young children have shown that many factors can affect the efficiency of the pMDI-spacer-facemask.[3-10] Factors like spacer volume, multiple actuations, electrostatic charge, breathing pattern of the child all influence the drug delivery to young children.[3-10] In addition, it has been suggested that the fit of the mask to the face plays a role in the efficiency of drug delivery.[1,3,10,11] In an *in vivo* study, it was observed, that it was difficult to obtain a tight facemask seal in non-cooperative children.[3,10] There are only few studies performed in which the effect of the fit of the mask to the face on drug delivery was investigated.[11-14] In an *in vitro* study, a 50% reduction in drug delivery was found when the mask of a nebulizer was removed 1 cm from the face.[12] A distance of 2 cm from the face resulted in an 80% reduction in drug delivery. Recently, it was shown for both a nebulizer and a pMDI-spacer combination, that a leak between mask and face reduced drug delivery.[14] However, these studies did not investigate the relation between the size and position of the leak and the efficiency of drug delivery. The aim of our *in vitro* study was to investigate the relation between the size and position of a facemask leak on spacer output and lung dose. We hypothesized that, with an increase of the leak, less drug would be delivered to the patient and to the lungs. Furthermore, we hypothesized that the position of the leak would influence spacer output and lung dose.

Materials & Methods

Upper Airway Model

The Sophia Anatomical Infant Nose-Throat (SAINT) model was used for aerosol deposition measurements. The SAINT-model is a CT scan-derived, stereolithographically made, anatomically correct, and validated model of the upper airways of a 9-month-old infant.[15] The model includes the face, nasal cavity, pharynx, and the subglottic region. The nasal airway is open for air passage; the oral airway is closed. To simulate sticky mucosa and to eliminate electrostatic charge, the inner surface of the model is coated with a thin layer of glycerol/Brij-35 (polyoxyethylene 23 laurylether) mixture

pMDI-spacer-facemask

A budesonide pMDI, (Pulmicort® 200µg, AstraZeneca, Sweden) in combination with a metal spacer (NebuChamber®, AstraZeneca, Sweden) was used for the experiments. Before testing, a new pMDI was primed by shaking and firing 10 waste puffs. The NebuChamber was used in combination with a round-shaped resuscitation facemask (Galemed®, Taiwan). A round facemask was chosen for practical reasons; it allowed us to create leaks of various sizes, which could easily be placed at different positions. Nine leaks ranging from 0.05, 0.1, 0.16, 0.2, 0.3, 0.4, 0.5, 1, to 1.5 cm^2 were drilled in the facemask (Fig. 1).

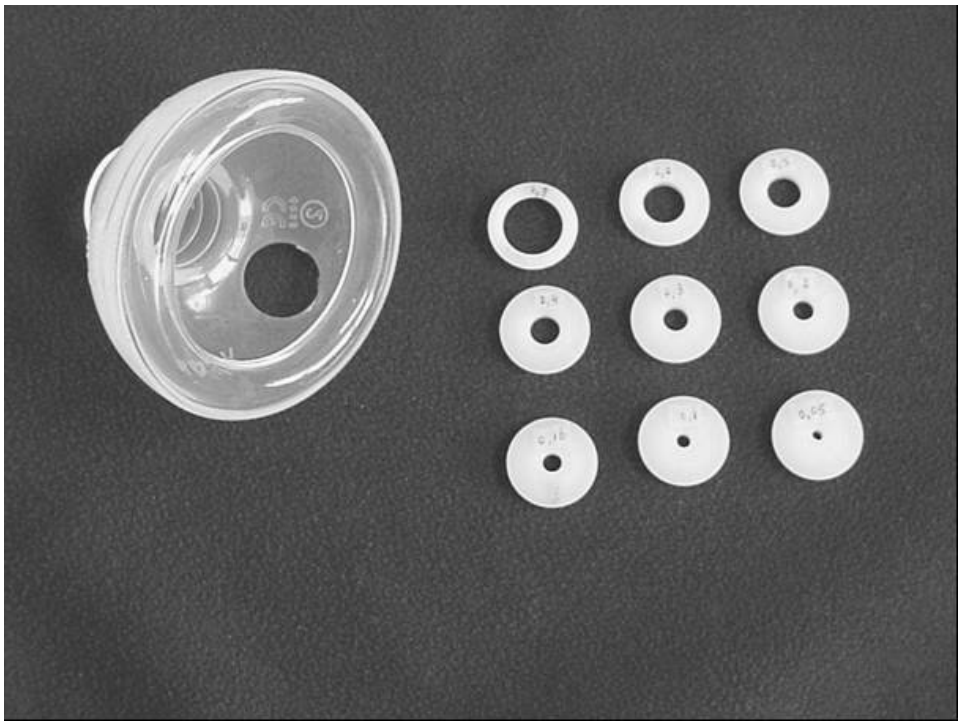


Figure 1. Round-shaped resuscitation facemask (Galemed®, Taiwan). Leaks of various sizes were drilled in the facemask.

Experimental set-up

The SAINT-model was connected to a custom made computer-controlled breathing simulator, which simulates infant breathing patterns[16] (Fig. 2). Filters (MQ303, Marquest®, USA) were used to collect the drug delivered from the pMDI-spacer-mask combination. For each measurement a new filter was used. Spacer output was measured by positioning the filter between the spacer and the facemask. Total lung dose was measured by positioning the filter between the SAINT-model and breathing simulator. Spacer output and lung doses are expressed as a percentage of the nominal dose. The influence of the position of the leak on spacer output and lung dose for different leak sizes was studied by placing the leak at the part of the mask placed over the nose (N) or at the part of the mask placed over the chin (C). Aerosol delivery was tested using a sinusoidal tidal breathing pattern, with a ratio of inspiratory time/total respiratory cycle time 0.42, tidal volume 100 ml, and respiratory rate 30 breaths/minute. These settings are in accordance with the reference values appropriate for the age of the subject used to construct the model.[17] The experiments were performed in ambient conditions with humidity of 30-40%.

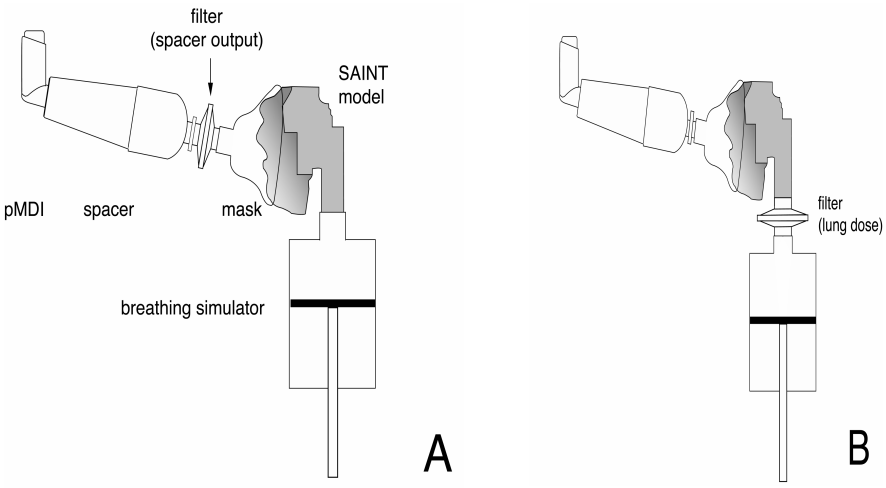


Figure 2. Experimental set-up to measure spacer output (A), and lung dose (B). Dose of drug is delivered by pMDI into a spacer/facemask and inhaled by the SAINT-model connected to a breathing simulator. “Reprinted by permission from Ref.15.”

Study procedure

The SAINT-model was attached to the breathing simulator. Next, 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 after shaking, one puff of budesonide was actuated into the spacer, just before the start of an inspiration. Aerosol drawn from the spacer by the breathing simulator was trapped on a filter during 30 seconds of simulated tidal breathing. All measurements were repeated six times. After 114 measurements the pMDI was replaced by a new pMDI.

Drug analysis

The drug trapped on the filter was analyzed at the laboratory of the department of Pharmacy of the Erasmus Medical Center Rotterdam. The budesonide on the filters was dissolved in 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 (5 μm particles, 5 * 0.46 cm (i.d.)). The coefficient of variation of this method was below 3%. Laboratory technicians were blinded for the experimental conditions of the filters.

Statistical and data analysis

The amount of budesonide on the filters is expressed as a percentage of the nominal dose. Results shown are means (±SEM). The data were linearised by plotting the logarithm of the mean spacer output or mean lung dose versus the leak size. Comparisons between spacer output and lung dose for different leaks and positions were tested using independent sample t-test. The following variables were tested: lung dose with a leak near the nose (LN), lung dose with a leak near the chin (LC), spacer output with a leak near the nose (SN), and spacer output with a leak near the chin (SC). The correlation between the leaks and these variables was investigated by using Pearson correlation coefficients (R). Analysis of covariance (ANCOVA) was performed to investigate the differences between the variables LN–LC and SN–SC. Regression analysis was used to fit the linearised data. Regression parameters were calculated at a confidence level of 95%.

Results

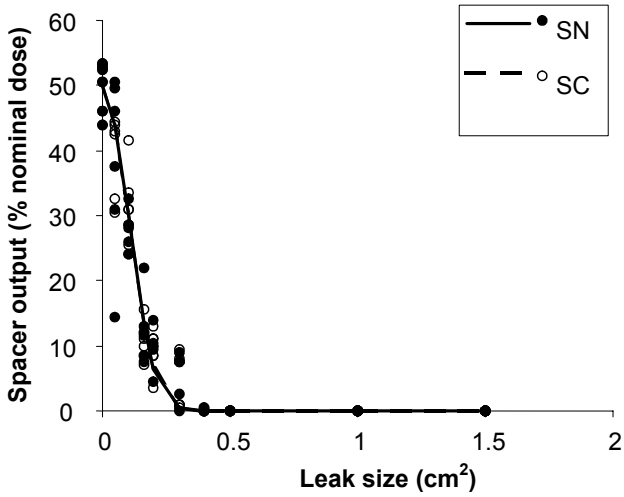
Spacer output and lung doses for various leak sizes are shown in Table 1. Spacer output (for SN and SC) correlated strongly to the increase of leak size ($R=-0.99$ and $p< 0.0001$) (Fig. 3A). Spacer output did not depend on the position of the leak. Lung dose versus leak size is shown in Figure 3B. Lung dose (for LN and LC) correlated strongly to the increase of the leak size (for LN $R=-0.99$ and $p<0.0001$, for LC $R=-0.91$ and $p<0.0001$). Lung dose was higher for leaks in the "Chin" position compared to the "Nose" position.

Discussion

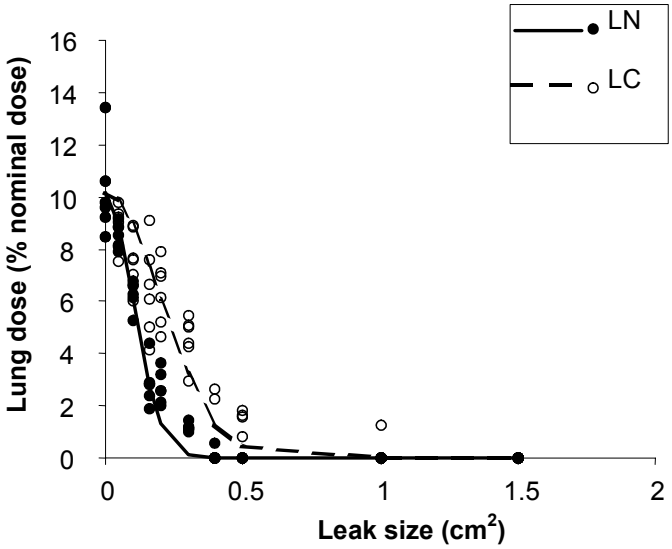
In this study we investigated how size and position of a facemask leak influences spacer output and lung dose during tidal breathing. The study was conducted on an anatomically correct upper airway model of a nine-month-old child. Both spacer output and lung dose decreased rapidly with increasing leak size. We showed that even a minor leak in the facemask was sufficient to reduce the lung dose by more than half compared to the lung dose obtained with a perfect mask seal.

Table 1 - Spacer output doses with a leak near the nose (SN), and chin (SC), and lung doses with a leak near the nose (LN) and chin (LC). Results are means (± SEM) and expressed as % of the nominal dose.

Leak (cm^2)	SN (%)	SC (%)	LN (%)	LC (%)
0	50(4)	50(4)	10(2)	10(2)
0.05	38(13)	40(6)	8(0)	9(1)
0.1	28(3)	31(6)	6(1)	8(1)
0.16	12(5)	11(3)	3(1)	6(2)
0.2	10(3)	9(3)	3(1)	6(1)
0.3	6(3)	4(4)	1(0)	5(1)
0.4	0(0)	0(0)	0(0)	1(1)
0.5	0(0)	0(0)	0(0)	1(1)
1	0(0)	0(0)	0(0)	0(1)
1.5	0(0)	0(0)	0(0)	0(0)



(a)



(b)

Figure 3. Part (a): Spacer output versus leak size. —— • SN: leak is positioned close to the nose.---- o SC: leak is positioned close to the chin. Part (b): Lung dose versus leak size. —— • LN: leak is positioned close to the nose. ---- o LC: leak is positioned close to the chin

Our study confirms previous studies, that a good facemask-face seal is important for the efficiency of drug delivery.[3,10-14] In a study with infants, it was observed that a poor facemask-face seal resulted in a low spacer output.[3,10] However, the relation between facemask seal and drug delivery was not systematically investigated. Several facemasks in combination with the NebuChamber were studied in an *in vivo* filter-study in a "hospital setting."[11] The NebuChamber was attached to a data-logger, which measured the inhaled volume. The type of facemask attached to a spacer device was important for the volume inhaled from the spacer and consequently the dose of drug delivered to the child. *In vitro* studies investigating the influence of facemask seal on aerosol delivery showed that the amount of inhaled aerosol was decreased when a leak was present. However, the effect of size and position of the leak on lung dose was not investigated.

To our knowledge, no systematic study on the relationship between leak size and drug delivery has been published. We found a strong negative correlation between the size of a leak and the lung dose. This result is especially relevant for inhalation therapy in children below the age of 2 years. Many of these children do not co-operate during the administration of a drug delivered by pMDI-spacer.[2,3,6,9-11,18] In non-cooperative children, it is difficult to obtain a tight seal between the mask and the face. In case of an incomplete seal, it is likely that the amount of drug delivered to the child will be drastically reduced.

Our study shows that not only the size, but also the position of the leak is important. Lung dose decreased more rapidly when the leak was positioned close to the nose relative to a leak located near the chin. However, spacer output did not differ for the nose or chin position. In the SAINT model used in the study, breathing is through the nose, as it is with most infants. A leak close to the nose may cause turbulence. Coarse particles are less able to follow turbulent airflow pattern and will impact on the face, inside the mask, or in the upper airways resulting in a reduction of lung dose.[19,20] When the leak is located more distantly from the airflow coming from the spacer, the interference with the flow pattern will be less. This could explain why the lung dose/spacer output ratio increases with leak size. A technical study on the flow dynamics of the mask in relation to the position of the leak is needed to confirm our hypothesis.

Clearly, our model study has its limitations. Firstly, spacer output dose only indicates the total dose delivered to the patient, and lung dose indicates the dose delivered beyond the subglottic level. They do not give any

information on the distribution of drug in the lower airways. Secondly, we used a round facemask instead of the original pre-shaped facemask of the NebuChamber. It is unlikely that the effect of leak size would be different for the pre-shaped NebuChamber mask. However, the effect of the position of the leak might be smaller since the dead volume of the NebuChamber mask is smaller. Thirdly, for purpose of standardization the shape and position of leaks in our study are different from those occurring in the every day administration procedures. However, it is likely that in real life any small leak between facemask and face will result in a similar reduction of lung dose as observed in our *in vitro* study.

In conclusion, we showed that even a small air leak in the facemask can drastically reduce spacer output and lung dose. A leak close to the nose reduces lung dose more compared to a leak close to the chin. The results of this study stress the importance of a perfect seal between facemask and face when treating young children with a pMDI-spacer-facemask combination. Therefore, care should be taken that the mask has a good seal to the face, especially in the proximity of the nose.

Acknowledgement

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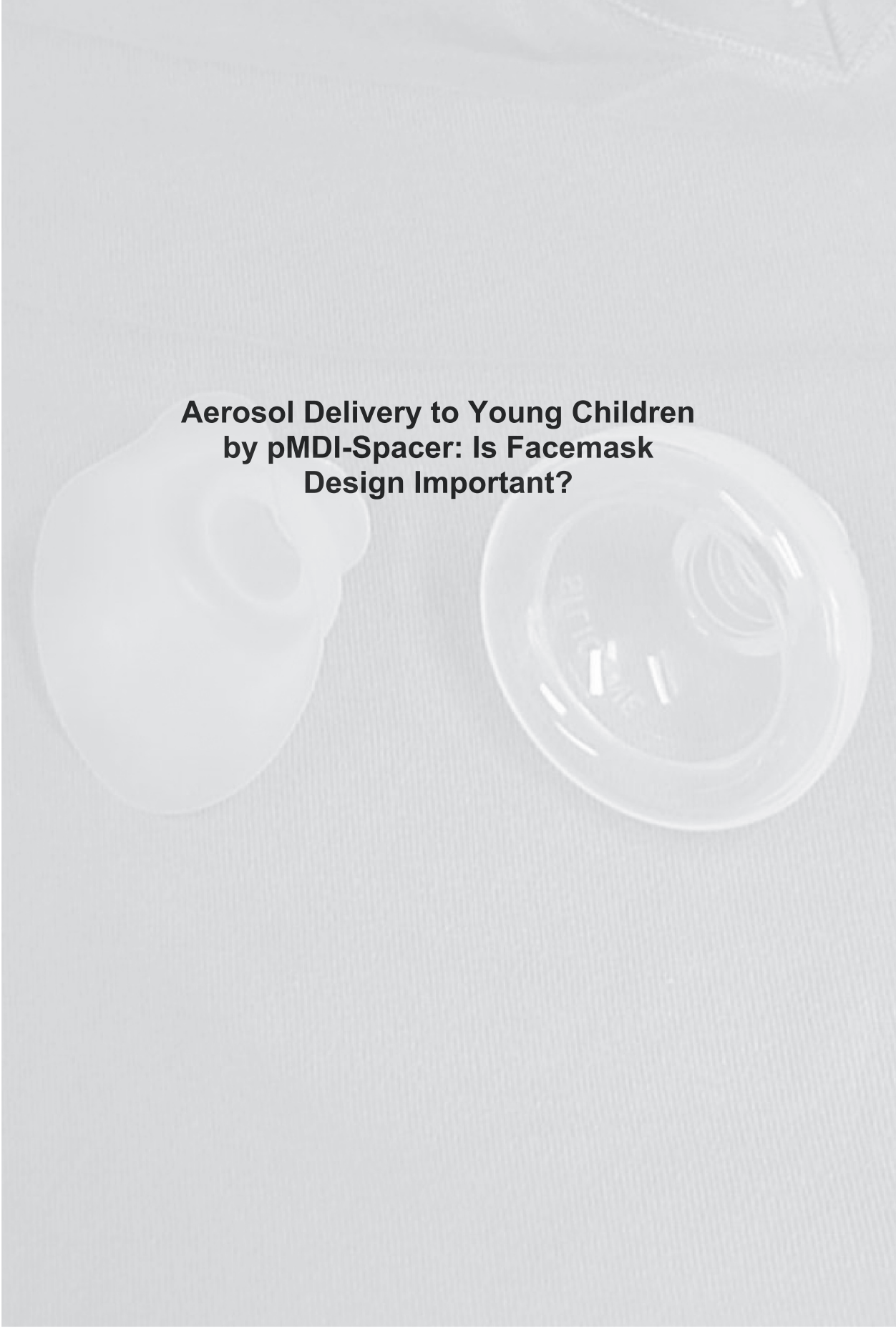
Aerosol Delivery to Young Children by pMDI-Spacer: Is Facemask Design Important?



Chapter 3

Aerosol Delivery to Young Children by pMDI-Spacer: Is Facemask Design Important?

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Abstract

Aim: This study aimed at identifying in a daily-life setting the influence of facemask design on drug delivery via a spacer to young children.

Method: In a 4-week randomized crossover study, 24 children (7-23 months old) with recurrent wheeze tested the AstraZeneca®, Galemed® and Hans Rudolph® facemask combined with the NebuChamber® at home. Each mask was tested twice daily for 7 consecutive days. Filters positioned between the NebuChamber and facemask trapped the budesonide aerosol (200 µg, Pulmicort®). Parents were asked to score the child's degree of cooperation during administration on diary cards. The administration procedure was evaluated through video recordings.

Results: Mean filter dose (standard deviation (s.d.)), expressed as % of nominal dose, was 39% (14), 47% (12) and 42% (11) for the AstraZeneca, the Galemed and the Hans Rudolph mask, respectively. Irrespective of the degree of cooperation, the Galemed mask gave significantly higher mean filter doses than the other masks (level of significance) ($p < 0.045$). Median (range) within-subject dose variability, expressed, as coefficient of variation (CV), was 37% (19-255), 32% (9-114) and 30% (9-115) for the AstraZeneca mask, the Galemed mask and the Hans Rudolph mask, respectively, not significant (ns). Dose variability increased with decreasing cooperation for all three masks ($p = 0.007$).

Conclusions: Drug delivery to young children with recurrent wheeze by means of the NebuChamber can be enhanced using the Galemed facemask. Dose variability seems to be independent of facemask design but mainly depends on cooperation.

Introduction

In infants and preschool children inhalation therapy with β_2-agonist and corticosteroids can be effective in the treatment of recurrent wheeze (1-6). The pressurized metered dose inhaler (pMDI)-spacer-facemask combination can be an efficient system to deliver aerosolized drug to young children. Efficiency, however, can be influenced by device-related factors – static charge, spacer volume, facemask design, and pMDI properties – and patient-related factors – breathing pattern, cooperation and administration technique (2, 4, 5, 7-11).

Previous studies suggest that facemask design is important for the efficiency of drug delivery (11, 12). In a daily-life study we observed that obtaining and maintaining a good seal between the mask and the face is especially difficult in uncooperative young children (11). We found that dose delivery relates to the degree of cooperation for the NebuChamber® (AstraZeneca, Sweden) fitted with a face-shaped mask, but not for the detergent coated Babyhaler® (GlaxoWellcome, UK) with a round facemask. In this study, however, we did not systematically evaluate the relationship between facemask design and the efficiency of aerosol delivery. Therefore, we performed a daily-life study examining how facemask design affects the efficiency of aerosol delivery to young children by means of a spacer (NebuChamber). Furthermore, possible factors influencing filter dose and dose variability – like cooperation, inhalation technique, age, and symptoms – were studied.

Materials and methods

Study population

Twenty-four children aged between 7 and 23 months, treated for recurrent wheeze with inhalation therapy twice daily, were recruited from the outpatient clinics of the Erasmus MC-Sophia (Rotterdam, the Netherlands), the Reinier de Graaf Gasthuis (Delft, the Netherlands) and the Albert Schweitzer Ziekenhuis (Dordrecht, 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 Ethics Review Committee of Erasmus MC approved the study.

Study design

In a 4-week randomized crossover study, we visited the children at home five times. Parents were asked to follow standardized instructions, which have been described previously (11), on the use of inhalation therapy. In addition, they were asked to administer the study medication before the child's regular inhalation treatment, which was continued using their own medication and device. In a 1-week run-in period, the children practiced with three different masks (see Materials) in combination with the NebuChamber. In the following three study weeks, the children tested in randomized order each mask-NebuChamber combination twice daily for one week. Each week the children received a clean NebuChamber and facemask. To assess drug delivery, the parents were asked to place a new filter between the NebuChamber and the mask before each administration. For each child a maximum of 42 filters could thus be obtained.

After every administration procedure parents were asked to fill out a diary card, evaluating cooperation and symptoms during the study period (11). Cooperation during administration was assigned a score ranging from 0 (good cooperation) to 3 (fighting). The symptoms cough, wheeze and shortness of breath were each assigned a score ranging from 0 (no symptoms) to 4 (severe symptoms). The total symptom score, with a maximum of 12, was defined as the sum of the scores for cough, wheeze and shortness of breath. At the end of each study week, we recorded the administration procedure on video. Three observers scored in random order all video recordings, using a video checklist as described previously (11).

Materials

A pMDI (Pulmicort® 200µg, AstraZeneca, Sweden) delivered budesonide aerosol through the metal NebuChamber® (250 ml, AstraZeneca, Sweden) in combination with three different masks: the original facemask of the NebuChamber, hereafter called the AstraZeneca mask, the Galemed® (Galemed Corporation, Taiwan) facemask and the Hans Rudolph® (Hans Rudolph, inc., USA) facemask (Fig. 1). The face-shaped AstraZeneca mask has a thin and rather stiff rim. The round Galemed mask has a thick and flexible rim. The face-shaped Hans Rudolph mask has a thick rim and a flap to stabilize the mask on the chin. A plastic adapter was used to fit the Hans Rudolph mask onto the NebuChamber.

Each child received a new budesonide pMDI, primed by shaking and firing 10 waste puffs. A filter (Marquest®, MQ303, USA) inserted between the spacer and the facemask trapped the aerosol discharged by the spacer. The filter holders fitted tightly to the mouthpiece of the Nebuchamber. The filter holder of a Marquest filter added 38 ml of dead space. The pressure drop over the filter is 230 Pa at 60 L/min (13).

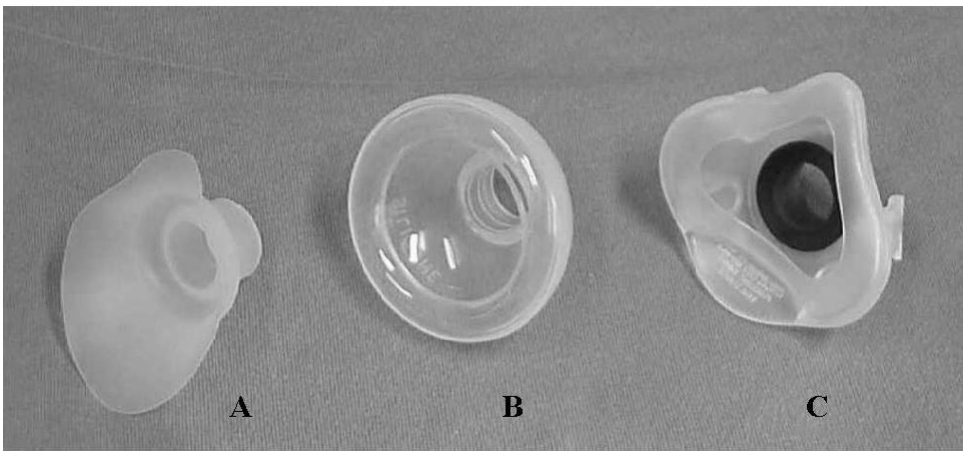

Figure 1. A. The AstraZeneca mask B. The Galemed mask C. The Hans Rudolph mask

Filter analysis

All filters were analyzed in a blinded fashion at the laboratory of the Erasmus MC department of Hospital Pharmacy (Rotterdam, the Netherlands). The filters were washed with ethanol containing an internal standard (fluocinolone acetonide). Budesonide amounts were measured by high performance liquid chromatography (HPLC), using an ethanol-water (43:57) mobile phase and a Supelcosil LC-18 column (5 μm particles, 5 * 0.46 cm (inner diameter)). Budesonide was detected by UV-spectrophotometry at a wavelength of 254 nm. The coefficient of variation of the method was < 3%.

Statistical analysis

SPSS for Windows version 9.0 and SAS were used for statistical analyses. Filter dose, calculated as the amount of budesonide deposited on the filter, was expressed as a percentage of the nominal dose. The filter dose variability was expressed as the within-subject coefficient of variation (CV).

Study week sessions that yielded less than 3 filters, either in the morning sessions or in the evening sessions, were excluded from analysis.

The mean (± SD) filter doses of the 14 samples collected each week was calculated for each child. T-tests were carried out to compare mean filter doses for each mask, after ensuring that the results were normally distributed. Wilcoxon's signed rank test was used to compare the CVs for the three masks. Relationships between filter dose and age, filter dose and cooperation score, filter dose variability and age, and filter dose variability and cooperation score were assessed using Spearman's correlation coefficient (r) and Repeated Measurements ANOVA (SAS PROC MIXED). Mean total symptom scores and mean cooperation scores obtained from the weekly diary cards were compared using the Friedman test. A p-value of ≤ 0.05 (two-sided) was considered to indicate significant differences.

Items on the video checklist relating to the child's cooperation, i.e. "Child breathes for at least 15 seconds through the facemask from the start of the administration" and "Child breathes quietly through the facemask from the start of the administration", were correlated with the filter dose obtained while the video recording took place, using Repeated Measurements ANOVA.

Results

Twenty-five children were enrolled into the study. One dropped out after the run-in period because of non-compliant parents. Twenty-four children (18 boys) completed the study. Median (range) age was 15 (7-23) months. Inhalation devices used before study entry were: NebuChamber (n=6), Babyhaler (n=9), AeroChamber® (Trudell Medicals, London, Ontario, Canada) (n=8) and nebulizer (n=1). A total of 285, 289 and 295 filters were collected for the AstraZeneca facemask, the Galemed facemask and the Hans Rudolph facemask, respectively. Only 5 (3.5%) of the total number of 144 week-sessions were excluded from analysis because less than 3 morning or evening filters were collected.

Filter dose

Mean filter dose (SD) was 39% (14), 47% (12) and 42% (11) for the AstraZeneca mask, the Galemed mask and the Hans Rudolph mask, respectively. Mean filter dose of the Galemed mask was significantly higher

than that of the AstraZeneca mask (p=0.003) and the Hans Rudolph mask (p=0.045). The AstraZeneca mask and the Hans Rudolph mask did not significantly differ in mean filter dose. Simultaneous evaluation of masks and cooperation scores showed significant differences between the AstraZeneca mask and the Galemed mask and between the Galemed mask and the Hans Rudolph mask for both good/moderate cooperation (score 0 and 1) and poor cooperation (score 2 and 3) (Figure 2). For good/moderate cooperation, mean filter dose (SD) was 43% (12), 49% (11), and 44% (9) for the AstraZeneca mask, the Galemed mask and the Hans Rudolph mask, respectively. For poor cooperation, mean filter dose (SD) was 32% (17), 45% (14), and 38% (13) for the AstraZeneca mask, the Galemed mask and the Hans Rudolph mask, respectively. Children showing good/ moderate cooperation had on average a 4.5% higher filter dose (p= 0.03) than children showing poor cooperation. However, the differences between the masks were not significantly different for the good/moderately cooperative children compared to the poorly cooperative children. Furthermore, the difference between good/moderate and poor cooperation for the AstraZeneca mask was not significantly different from the difference in cooperation score for the Galemed and Hans Rudolph mask. Filter dose did not correlate with age for any of the three masks.

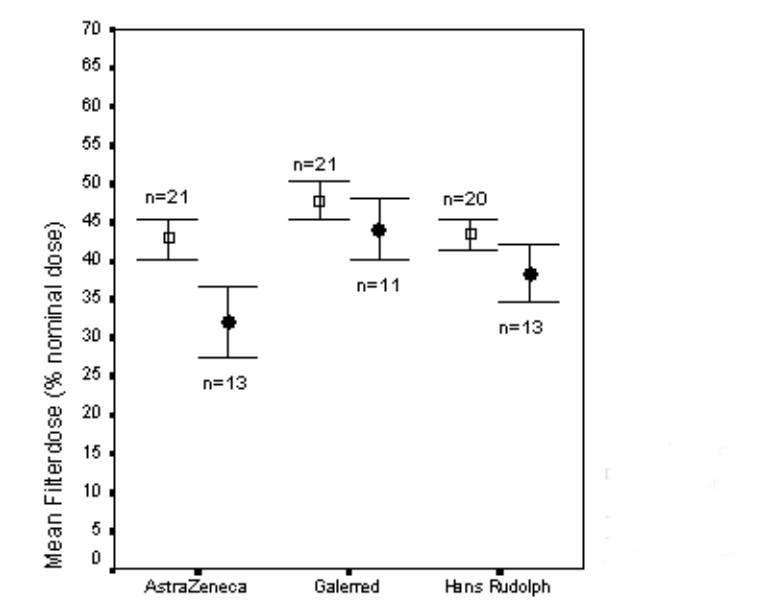

Figure 2. Mean filter doses expressed as percentage of the nominal dose (± SEM) for children with good/moderate cooperation (□) and with poor cooperation (●) for the AstraZeneca, the Galemed, and the Hans Rudolph masks.

Filter dose variability

Median (range) filter dose variability was 37% (19-255), 32% (9-114) and 30% (9-115) for the AstraZeneca mask, the Galemed mask and the Hans Rudolph mask, respectively (ns). The AstraZeneca mask and the Galemed mask showed a significant positive correlation between the filter dose variability and the cooperation score ($p<0.02$). The slopes of the regression curves of filter dose variability versus the cooperation score were not significantly different (figure 3). The slope of pooled data from the three masks showed a significant positive relation ($p=0.007$). An increase of 1 point on the cooperation scale (worse cooperation) led to a 32% increase in filter dose variability. Filter dose variability showed a negative correlation with age only for the Hans Rudolph mask ($r=-0.5$, $p=0.01$).

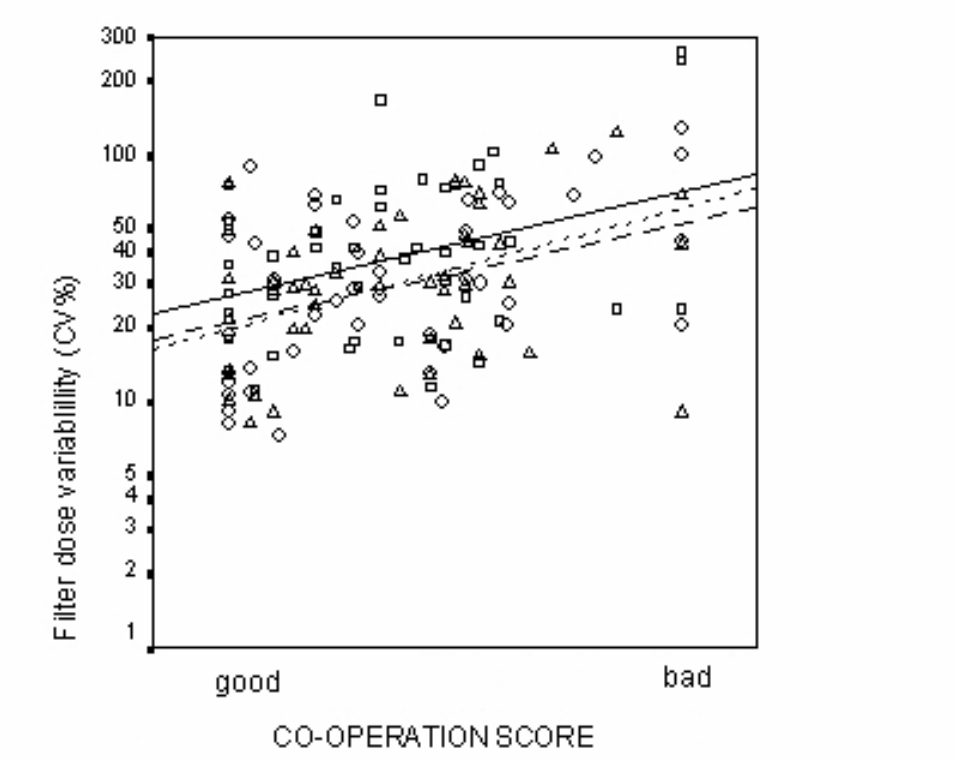

Figure 3. Scatter plot of the filter dose variability (CV%) on a logarithmic scale versus cooperation score for the AstraZeneca, the Galemed, and the Hans Rudolph masks. ——, □ AstraZeneca mask; ·····, × Galemed mask; ----, Δ Hans Rudolph mask.

Symptom and cooperation scores

Median (range) symptom scores for the AstraZeneca mask, the Galemed mask and the Hans Rudolph mask were 0.2 (0-9), 0.5 (0-8) and 1.3 (0-10), respectively (ns).

Median cooperation score was 1.1, 0.9 and 1.1 for the AstraZeneca mask, the Galemed mask and the Hans Rudolph mask, respectively (ns). Poor cooperation (score 2 or 3) during the administration procedure was assigned in 28%, 33% and 36% of all scores for the AstraZeneca mask, the Galemed mask and the Hans Rudolph mask, respectively.

Video recordings

Children breathing at least 15 seconds through the facemask from the start of administration had significantly higher filter doses ($p<0.03$). Filter doses of children breathing quietly during administration did not differ from that of children crying during administration.

Discussion

This daily-life study was carried out to examine the influence of facemask design on the efficiency of aerosol delivery by means of the NebuChamber to young children with recurrent wheeze. We found that the round facemask (Galemed) gave a significantly higher filter dose than the pre-shaped facemasks (AstraZeneca and Hans Rudolph).

Few studies have suggested that facemask design affects the efficiency of aerosol delivery (11, 12). However, the systematic evaluation of the relationship between facemask design and efficiency of aerosol delivery in daily life has only been attempted by Amirav et al (14). They found filter doses (as % of the nominal dose) of 28.1% and 21.6% for a round facemask and the AstraZeneca facemask, respectively (14). Although, the magnitude of difference between the round facemask and the AstraZeneca mask in this study is similar to ours, it is striking that mean filter doses in Amirav's study are less than half of the filter doses found in our study and previous filter studies (7, 11, 15, 16). The filter dose for the round mask in Amirav's study was even lower than the lowest filter dose in our study. Differences in the mean filter doses between Amirav's study and our study can be explained by

the differences in study design. In Amirav's study the observational period started immediately after instruction. In contrast, in our study subjects practised one week with the spacer, masks and the filter method before they were randomised, such that learning effects were reduced. In addition, in Amirav's study subjects inhaled once daily two puffs, whereas our study subjects inhaled twice daily one puff. As a result we collected not only twice as many filters for each subject, but most likely fewer mistakes per administration procedure were made because of the single-puff-dosing (4, 8, 17).

As suggested previously by other authors, our study supports the view that patient-related factors are important for the efficiency of aerosol delivery (7, 11, 18, 19). Moreover, in children younger than 2 years patient-factors, such as cooperation, are probably more important than facemask design. Young children often fight the administration procedure, such that it is difficult to obtain and maintain a complete facemask seal (7, 11, 20). Since our in-vitro work showed that even a small leak dramatically reduces filter dose, the significantly lower filter doses in uncooperative children can be explained by the incomplete seal (21). The uncooperative children had significantly lower filter doses for all masks, and the differences in filter doses between the masks did not relate to cooperation. Hence, we may conclude that, independent of the facemask design, it is difficult to obtain a tight seal when the child is uncooperative. We also found that the dose variability increased significantly when a child did not cooperate. However, we did not find significant differences between the filter dose variability of the different masks, while we expected that the filter dose variability would be highest for the mask with the lowest filter dose. Furthermore, we did not find a difference in cooperation score between the masks. It is, therefore, unlikely that facemask design influences cooperation. Clearly, many young children do not like to have any mask pressed on their face.

In this study, the filter dose represents the total amount of aerosol delivered to the patient. It does not provide information on lung deposition or clinical efficacy. Lung dose depends on various patient-related factors, such as airway anatomy and breathing pattern. In the video analysis we showed that mean *filter dose* of children breathing quietly during administration was not significantly different from that of children crying during administration. Although the mean filter dose was similar, *lung dose* in crying children will be very low, since most of the drug delivered to the patient will be deposited in the oropharynx (9). In cooperative children, however, it is likely that a higher percentage of the drug delivered to the patient will be deposited in the lung.

In conclusion, the efficiency of aerosol delivery can be improved using a round facemask. However, whether this improvement in delivery efficiency is clinically relevant can only be determined by clinical efficacy studies (22). Since such a high percentage of young children are fighting the aerosol administration and these children do not easily accept any mask on their face, we should focus more on the improvement in acceptability of aerosol therapy in young children.

Acknowledgements

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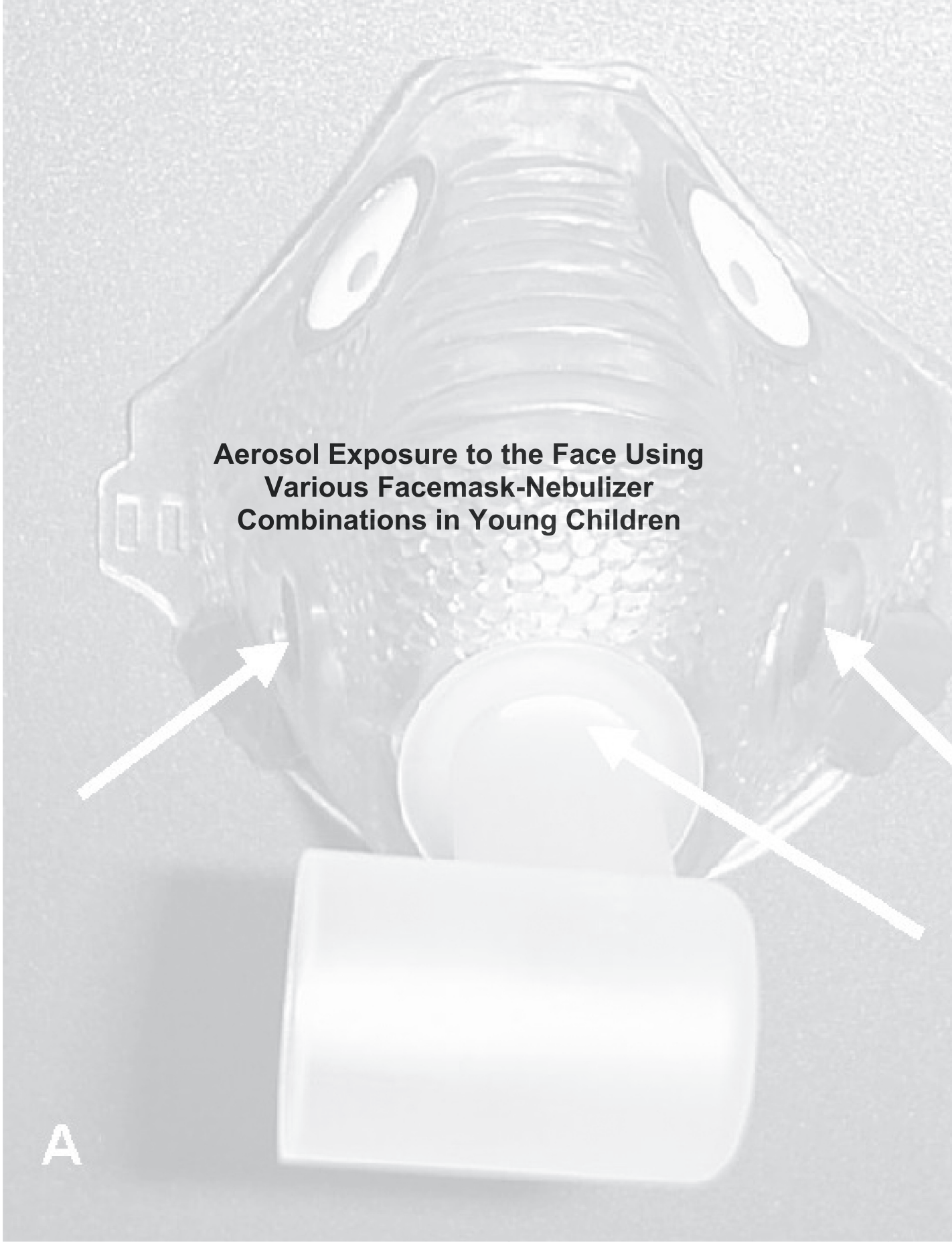
Aerosol Exposure to the Face Using Various Facemask-Nebulizer Combinations in Young Children



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Chapter 4

Aerosol Exposure to the Face Using Various Facemask-Nebulizer Combinations in Young Children

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Submitted

Abstract

Most nebulizers have a loose fitted facemask. Even when the mask is placed tightly to the face, aerosol loss can be observed. This aerosol loss may cause local side effects due to exposure of the eyes and skin of the patient to aerosolized drug.

Aim: To assess, by recording on video, the amount and the pattern of aerosol loss from various nebulizer-facemask combinations.

Methods: In a randomized cross-over study, 33 children below 4 years of age were recorded on video during nebulization. Four commercially available nebulizer-facemask combinations were tested. Four observers scored randomly the videos using a checklist. Aerosol loss was scored 1 (=none), 2 (= a little) or 3 (= a lot).

Results: 93 videos were available for analysis. For the analysis of aerosol loss, there was a good level of agreement between the 4 observers (mean intra-class correlation coefficient > 0.69). The mean (± SD) score for aerosol loss was 1.7 (0.37), 1.4 (0.25), 2.1 (0.34) and 1.4 (0.28), for the Pari "Bubbles the FishTM", the Pari BabyTM Size 2, Hudson Neb-U-Mask, and the Salter, vented facemask with flaps, respectively. Aerosol loss of the Hudson Neb-U-Mask was significant higher compared with the other tested masks ($p < 0.03$). Large quantities of aerosol from the Hudson Neb-U-Mask were directed towards the eyes. Aerosol loss from the other three masks did not show a preferred direction.

Conclusion: The Hudson Neb-U-Mask is likely to give a higher chance of local side effects due to a higher aerosol loss during nebulization compared with three other tested masks.

Introduction

Inhalation therapy is a common treatment for respiratory diseases such as asthma and cystic fibrosis. Aerosolized medication is delivered to young children by using nebulizers and pressurized Metered-Dose Inhaler (pMDI)-spacers combinations. Although nebulizers are noisy, cumbersome, expensive and time-consuming, they have the advantage of nebulizing most drugs, even as drug cocktails, in high doses (1-4). Furthermore, nebulizers are used in children who do not tolerate pMDI-spacers (4-8).

In general, young children will not be able to use specific breathing techniques (9). They need a facemask for delivering aerosolized drug during tidal breathing. Efficient drug delivery with nebulizers is thought to benefit from tight fit of the facemask. In an in-vitro study, Everard et al. showed that distancing the nebulizer mask 1 cm from the child's face, halved the inspired dose of medication. A distance of 2 cm even resulted in 80% dose reduction (8). Many nebulizers have loose fitting masks with open vents (10). In addition, aerosol loss through these vents may cause side effects, because the patient's eyes and the skin are exposed to the nebulized drug. For example, for nebulized steroids, it has been suggested that such exposure may induce a steroid rash over the face, and may even include a risk for cataract (1, 11, 12).

To date, there is no information available about patterns of aerosol loss using commercially available facemasks-nebulizer combinations in young children. Therefore, we aimed to assess, by video recording, patterns of aerosol loss from various facemasks combined with a nebulizer in young children.

Methods & Materials

Study population

Children younger than 4 years treated with inhalation therapy were recruited from the outpatient clinic of the pediatric pulmonology department in the Erasmus MC-Sophia Children's Hospital, the Netherlands. Those whose parents or legal guardians could not obtain a tight fit of the mask on the face during nebulization were then excluded. The study procedure was stopped if a child actively resisted the administration procedure. Written informed consent was obtained from all parents or legal guardians. The

National Ethics Committee (CCMO, The Hague, The Netherlands) approved the study.

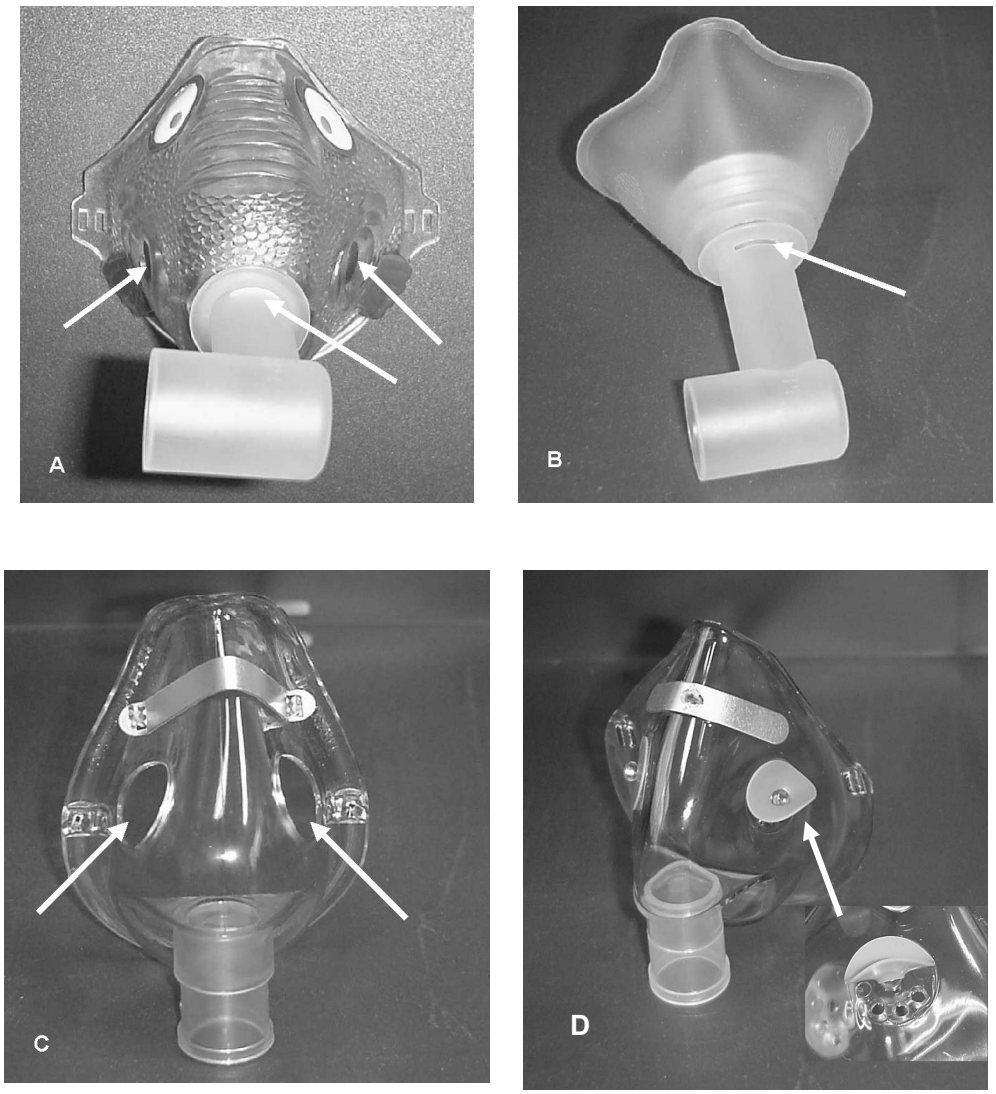

Figure 1. The four tested masks. Arrows indicate the position of the vents. A. Pari "Bubbles the FishTM" B. Pari BabyTM Size 2 C. Hudson Neb-U-Mask D. Salter, vented facemask with flaps.

Materials

The four nebulizer-facemask combinations used in this study are listed in Table 1. Vents positions for each mask are shown in Figure 1. The Pari LC Plus was combined with a Baby bend connection piece to attach the facemask to the nebulizer. All nebulizers were run using a PRONEB-Turbo compressor (Pari Respiratory Equipment, Inc., USA). Four ml of sterile Sodium chloride 0.9% was used for nebulization. New facemasks and nebulizers were used for each child.

Table 1. Nebulizer-facemask combinations

Facemask	**Nebulizer**
Pari "Bubbles the Fish™"[1]	Pari LC Plus[4]
Pari Baby™ Size 2[1]	Pari LC Plus[4]
Hudson Neb-U-Mask[2]	Hudson T-Updraft II[2]
Salter, vented facemask with flaps[3]	Hudson T-Updraft II[2]

[1] Pari Respiratory Equipment, Inc., Montgomery, CA
[2] Hudson Respiratory Care, Inc., Temecula, CA
[3] Salter Labs. Arvin, CA
[4] PARI Respiratory Equipment, Inc., Germany

Study design

In this randomized, cross-over study, each child was to test all 4 facemask-nebulizer combinations (Table 1). Figure 2 shows the experimental set-up. During aerosol administration, the child sat in the lap of an elder and was encouraged to sit as quiet as possible, while its favorite music played. Overall room light was dimmed and four specially designed lamps placed at both sides of the child were switched on for optimal visualization of the aerosol cloud. A digital camera (Sony, DCR-VX 1000, Sony Corporation, Japan) recorded the administration procedures from a frontal view for 90 seconds. Camera distance and settings were standardized.

Video analysis

After completion of the study all recordings were edited to show only episodes of active nebulization. Subsequently, 4 trained observers randomly

scored all edited recordings using a checklist including 4 items: 1. Visibility of the aerosol cloud; 2. Cooperation of the child; 3. Breathing pattern of the child; 4. Pattern of aerosol loss.

The first 3 items were scored to assess recording quality and suitability for analysis using a three-point scale: 1 = not at all; 2 = bad; or 3 = good. The end-point of the study, item 4, was scored using Figure 3, a four–quadrant division of the face. Aerosol loss in the quadrants was rated on a three-point scale: 1 = none; 2 = little; and 3 = a lot.

Each observer independently scored all recordings. Agreement between the observers was assessed by calculation of the kappa coefficient. Recordings were excluded for statistical analysis if the child did not comply with the protocol or when the aerosol cloud could not be visualized.

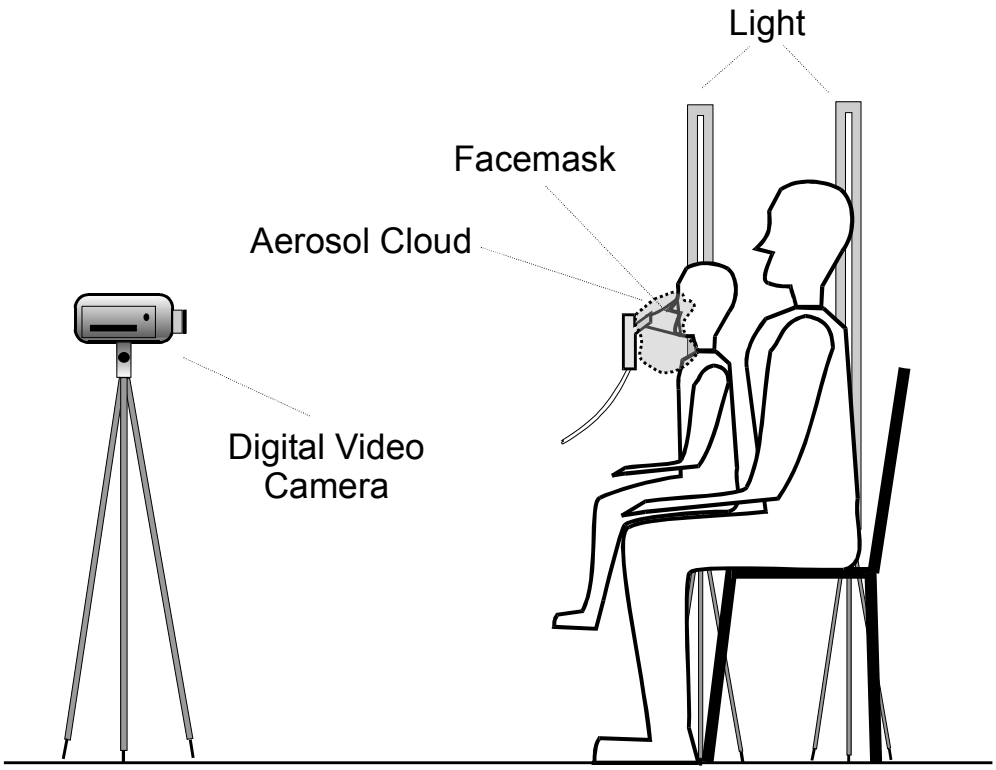

Figure 2. Experimental set-up, the child sits in the lap of the parent. Four specially designed lamps light the child's face, and visualize the aerosol cloud.

Statistics

SPSS for Windows version 10.1 was used for statistical analysis. Mean values of the 4 observers were used in the evaluation of the aerosol loss. Paired comparisons between the 4 masks were done using Wilcoxon's Signed Ranking tests. These tests were also used to compare aerosol loss for the 4 quadrants (Figure 3) within the mask.

	Not at all	Bad	Good
1. Good visible aerosol cloud			
2. Cooperative child			
3. Quiet breathing			

4. Aerosol loss in:

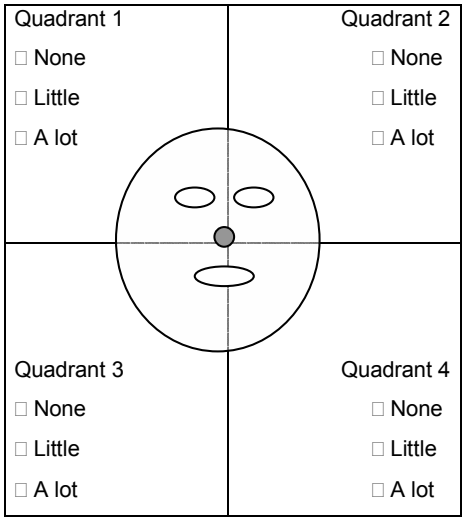

Figure 3. Checklist for scoring the video recordings.

Results

Thirty-three children were included in this study. Their characteristics are shown in Table 2.

Five children were later excluded because the parents and/or the child could not comply with the protocol. Nine children could not test all 4 masks, since they refused further cooperation at some point: three of these children had tested 3 masks, two had tested 2 masks and four had tested 1 mask. Nineteen children completed the entire study. In total 93 video recordings were available for assessment.

For assessment of aerosol loss, a good level of agreement between the 4 observers was found (mean kappa coefficient > 0.69). Fourteen of the 93 available videos appeared unsuitable for further statistical analysis, due to the child's restlessness and/or bad visibility of the aerosol cloud..

Aerosol loss

The mean total aerosol loss score was significantly higher for the Hudson Neb-U-Mask compared with the three other masks ($p < 0.03$). The mean (± SD) total aerosol loss score was 1.7 (0.37), 1.4 (0.25), 2.1 (0.34) and 1.4 (0.28), for the Pari "Bubbles the FishTM", the Pari BabyTM Size 2, Hudson Neb-U-Mask, and the Salter, vented facemask with flaps, respectively.

Table 3 shows the aerosol loss in the 4 quadrants for each mask. For the Pari "Bubbles the FishTM" mask, highest loss was in quadrant 4. For the Hudson Neb-U-Mask, substantial aerosol loss was observed in quadrants 1 and 2. Aerosol loss for the Pari BabyTM Size 2 mask and the Salter vented facemask was minimal, and there were no significant differences in aerosol loss between the quadrants.

Table 2. Patient characteristics

Age (yrs)	Sex	Diagnosis	Inhalation therapy history	No. of masks tested	No. of masks used for statistical analysis
0.6	F	CF	Nebulizer	3	1
0.6	M	BPD	PMDI-spacer	2	1
0.7	M	CF	Nebulizer	4	2
0.8	F	Recurrent wheeze	PMDI-spacer	3	2
0.9	M	CF	Nebulizer	4	2
1	F	CF	Nebulizer	4	4
1	M	CF	Nebulizer	1	1
1.5	F	Recurrent wheeze	PMDI-spacer	4	4
1.5	F	CF	Nebulizer	4	4
2	M	CF	Nebulizer	4	4
2	M	CF	Nebulizer	4	4
2	M	Recurrent wheeze	PMDI-spacer	1	0
2	M	Asthma	PMDI-spacer +	4	4
2	M	Recurrent wheeze	PMDI-spacer	4	4
2	M	Recurrent wheeze	Nebulizer	4	3
2.5	M	CF	Nebulizer	4	3
2.5	F	CF	Nebulizer	0	0
2.5	M	Recurrent wheeze	PMDI-spacer	4	4
2.5	M	Recurrent wheeze	PMDI-spacer	1	0
2.5	M	Recurrent wheeze	PMDI-spacer	0	0
2.5	M	Recurrent wheeze	PMDI-spacer	0	0
3	F	CF	Nebulizer	3	3
3	M	BPD	Nebulizer	0	0
3	M	Recurrent wheeze	PMDI-spacer	4	4
3.5	F	CF	Nebulizer	2	2
3.5	F	CF	Nebulizer	4	3
3.5	F	CF	Nebulizer	1	0
3.5	F	CF	Nebulizer	4	4
3.5	F	CF	Nebulizer	4	4
3.5	M	Asthma	PMDI-spacer +	4	4
4	F	CF	Nebulizer	4	4
4	M	CF	Nebulizer	0	0
4	M	CF	Nebulizer	4	4

+ PMDI-spacer plus nebulizer

Table 3. Aerosol loss scores over quadrants (range: 1= none; 2= a little; 3= a lot)

Mask	Quadrant 1	2	3	4
Pari "Bubbles the Fish™"	1.7	1.5	1.7	2.0*
Pari Baby™ Size 2	1.3	1.4	1.3	1.5
Hudson Neb-U-Mask	2.8*	2.9*	1.3	1.4
Salter, vented facemask with flaps	1.5	1.5	1.2	1.3

Discussion

During nebulization, young children are not able to use specific inhalation techniques (9). They, therefore, need a facemask to deliver aerosolized drug during tidal breathing. As most nebulizer masks fit loosely to the face and have open vents (10), aerosol will leak and aerosol delivery efficiency will be reduced. In addition, the patient's eyes and the skin will be exposed to aerosolized drug. This aerosol exposure may cause local side effects (1, 11, 12). In our study, the Pari "Bubbles the FishTM", the Pari BabyTM Size 2, and the Salter facemask showed little total aerosol loss during nebulization. On the contrary, the Hudson Neb-U-Mask showed a significant higher total aerosol loss compared with the other three masks. Therefore, use of the Hudson Neb-U-Mask is associated with a higher risk of local side effects of nebulization therapy, compared with the other three masks.

Although our study design indeed resulted in visualization of aerosol loss patterns, it is possible that the aerosol loss was not completely visualized on the video recordings. Lighting during recording is an important determinant of aerosol cloud image quality on video. An aerosol cloud is better visible when directly lighted. To this end, overall room light was uniformly dimmed and four specially designed lamps were focused on the patient in a standardized way. In addition, we included only children who were able to cooperate and sit quiet during nebulization. If children could not comply with these requirements, they were excluded for further analysis.

Another limitation of a video recording is that it gives a 2-dimensional image, providing for only a rough estimate of aerosol amounts spreading to the eyes and skin. Furthermore, we did not directly quantify doses deposited in the eyes and on the skin. However, the areas with the highest exposure to aerosol loss identified in our study will likely have the highest quantities of drug deposited on the face, and thus, will have the highest risk of local side effects.

A more reliable method to quantify eyes and skin exposure during nebulization would probably be a radio-labeled study using a 3-dimensional imaging technique. For ethical reasons, however, radio-labeled studies are limited in the pediatric population (4, 13-18). In addition, 3-dimensional imaging techniques are complex and very expensive (19).

Pattern of aerosol deposition in the eyes and on the face have previously been studied in-vitro using radio-labeled aerosols. A variety of facial and eye deposition patterns was found, depending on the nebulizer-facemask combination (20). Facial deposition was significantly less when the facemask was vented. The authors suspected that differences in facial deposition patterns were related to the insertion point of the nebulizers into the mask. The results of our in-vivo study suggest that size and position of vents in the mask-nebulizer combination probably have higher impact on differences in aerosol loss patterns than the insertion point of the nebulizer in the facemask. We found that the Hudson Neb-U-Mask and the Salter mask, both used in combination with the Hudson T-Updraft nebulizer, showed significantly different patterns of aerosol loss. In addition, the pattern of aerosol loss from the Salter mask was actually not different from that of the Pari Baby 2, which was combined with the Pari LC Plus nebulizer. Our study showed that the Hudson Neb-U-Mask, a mask with large vents close to the face, exposes the child's eyes and skin to large amounts of aerosol, especially during expiration. This effect can even be more dramatic in children under the age 2 years, as their inspiratory flow often does not exceed the driving flow of the nebulizer. In the youngest children, therefore, large amounts of aerosol can exit the mask-nebulizer combination even during inspiration (21).

The side effects of aerosol deposition on the skin and in the eyes have not been extensively studied. From our study it is clear that a risk of potential side effects is present. Therefore, a mask with minimal risk of unwanted eye and skin exposure to aerosol should be selected for children. Masks with vents in the nebulizer itself or between the nebulizer and the facemask seem to be the best choice. These masks allow the extra aerosol to exit the nebulizer-facemask combination at a greater distance from the face.

In conclusion, in view of its higher total aerosol loss, use of the Hudson Neb-U-Mask in young children is associated with a higher risk of side effects to eyes and skin compared with the other tested masks. Masks with large vents close to the face are less suitable for young children whose inspiratory flow does not exceed the nebulizer driving flow. Attempts should be made to design nebulizer-facemask combinations that reduce exposure of the eyes and skin to aerosol while preserving efficiency of aerosol delivery to the lungs.

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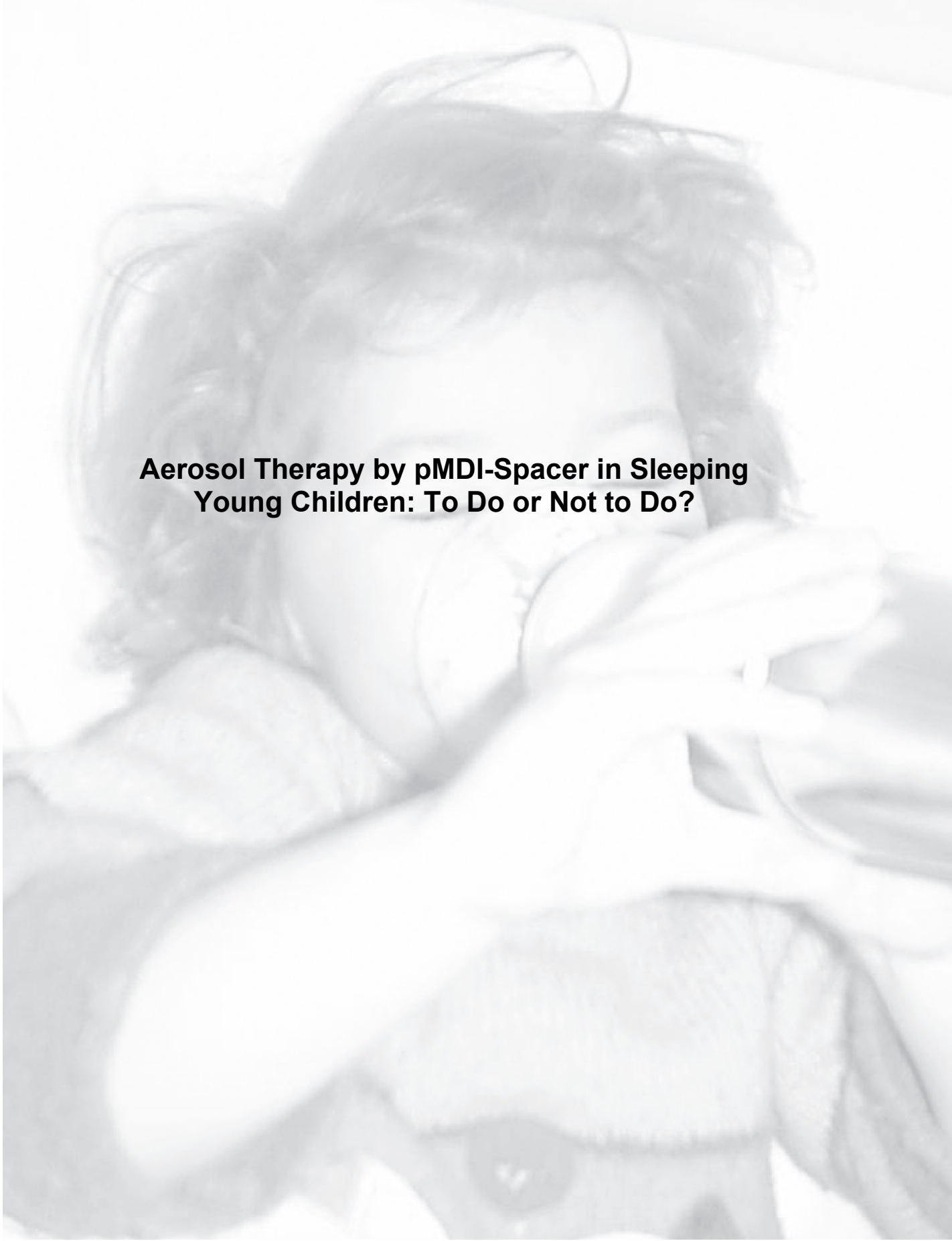

Aerosol Therapy by pMDI-Spacer in Sleeping Young Children: To Do or Not to Do?

Chapter 5

Aerosol Therapy by pMDI-Spacer in Sleeping Young Children: To Do or Not to Do?

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Submitted

Abstract

One-third of young children is distressed during inhalation therapy. It has been suggested that administration during sleep could be a good alternative for these children. A recent laboratory study in our department using an infant upper airway model showed significantly higher lung doses from a pMDI-spacer for sleep-breathing patterns compared with wake-breathing patterns.

Objective: We set up a daily life study to investigate the feasibility of aerosol administration by means of pMDI-spacer in sleeping young children.

Design: During three weeks, 30 children (6-23 months old) with recurrent wheeze daily inhaled 1 puff of budesonide aerosol (Pulmicort® 200 µg) while awake and 1 puff during sleep. Filters positioned between the NebuChamber® and facemask trapped the budesonide aerosol. Parents scored on diary cards the child's asthma symptoms, degree of cooperation, and feasibility of administration.

Results: In 69% of the sleep administrations the children woke up and 75% of these cases the children were distressed. Mean filter dose (expressed as % of the nominal dose) while awake was 47% and during sleep 16% ($p=0.007$). Median within-subject dose variability while awake was 50% and during sleep 110% ($p=0.007$).

Conclusion: Aerosol administration by means of pMDI-spacer during sleep offers no advantage and is not a feasible treatment option in most young children.

Introduction

The pressured metered dose inhaler (pMDI) combined with a spacer is commonly used to deliver inhalation medication to infants and young children (1-4). However, the efficiency of drug delivery by pMDI-spacer is influenced by device-related and patient-related factors (1, 5-10). An important patient-related factor in young children is the highly variable breathing pattern, which is affected by the child's level of cooperation (9-11). Cooperative young children with quiet tidal breathing have low breathing volumes and inspiratory flows. These children can efficiently clear the aerosol cloud from a small volume spacer, and generate relatively high lung depositions (3). Unfortunately, about 30% of young children are distressed during inhalation therapy (12, 13). When crying, they have high inspiratory flows and long pauses between breaths, resulting in low lung deposition and high oropharyngeal deposition (3, 9). Therefore, crying during the inhalation therapy is likely to reduce efficacy of the anti-asthma treatment.

Administering the aerosol during sleep has been suggested to overcome cooperation problems in young children (10, 14, 15). Indeed, in a model study we found significantly higher lung doses for sleep-breathing patterns compared with wake-breathing patterns (14). However, the feasibility of aerosol administration during sleep in a daily life situation was never studied systematically. Therefore, we carried out a daily life study to investigate the feasibility of drug administration by means of pMDI-spacer in sleeping young children.

Materials and methods

Study population

Thirty children aged between 6 and 23 months were recruited from the outpatient clinics of Erasmus MC-Sophia Children's Hospital (Rotterdam, the Netherlands), St. Franciscus Gasthuis (Rotterdam, the Netherlands), Reinier de Graaf Gasthuis (Delft, the Netherlands), and Albert Schweitzer Ziekenhuis (Dordrecht, the Netherlands). They all had been treated with twice-daily inhalation therapy for recurrent wheeze for at least the previous month. Children with cardiac disease or another disorder that might affect lung function were excluded from the study. Written informed consent was obtained from all parents. The Ethics Review Committee of Erasmus MC Rotterdam approved the study.

Materials

The metal NebuChamber® (250 ml, AstraZeneca, Sweden) in combination with the Galemed® (Galemed Corporation, Taiwan) facemask was used to administer 200 µg budesonide aerosol (Pulmicort® 200µg, AstraZeneca, Lund, Sweden) to the child. We used the Galemed mask – a round resuscitation mask with a thick and flexible rim– because it has been shown that use of this mask improved aerosol delivery compared with the pre-shaped NebuChamber facemask (13). Each child received a new budesonide pMDI, primed by shaking and firing 10 waste puffs. A filter (Marquest®, MQ303, USA) inserted between the spacer and the facemask trapped the aerosol inhaled from the spacer. The filter holders fitted tightly to the mouthpiece of the Nebuchamber. The filter holder of a Marquest filter added 38 ml of dead space. The pressure drop over the filter is 230 Pa at 60 $L \cdot min^{-1}$ (1).

Study design

The study period encompassed three weeks, i.e. one run-in week followed by two actual test weeks. Over these three weeks, we visited the children four times at home. Parents were asked to follow standardized instructions on the use of inhalation therapy, as previously described by Janssens et al. (12). Efficiency of drug delivery was assessed by adding twice-daily one puff of budesonide aerosol to the child's regular inhalation therapy, which was continued as before. Before each administration with study medication, parents placed a new filter between the NebuChamber and the mask to trap the budesonide aerosol. In the one-week run-in period, the parents practiced the study procedure with a placebo pMDI when the child was awake, and before regular inhalation therapy. In the mornings of weeks 2 and 3, they administered one puff of budesonide aerosol *before* the child's regular inhalation treatment, hereafter called "awake administration". In the evenings of weeks 2 and 3, they administered the child's regular inhalation treatment before the child went to bed. In addition, they administered one puff of budesonide aerosol *after* the child had fallen asleep, hereafter called "sleep administration" (Figure 1).

To monitor asthma symptoms and cooperation, parents filled out a validated diary card after each administration procedure (12). The symptoms cough, wheeze and shortness of breath were each assigned a score ranging from 0 (no symptoms) to 4 (severe symptoms). The total asthma symptom score, with a maximum of 12, was defined as the sum of the scores for cough,

wheeze and shortness of breath. Cooperation during administration was assigned a score ranging from 0 (good cooperation) to 3 (fighting).

In addition, parents addressed two questions about the "sleep administration" procedure. First: Did your child sleep throughout the administration procedure? Scores could range from 0 (slept through administration procedure), 1 (half-awake but tranquil), 2 (half-awake but distressed), 3 (fully awake but tranquil) and 4 (fully awake and distressed). Second: Was it easy to place the mask on the face? Scores could range from 0 (impossible), 1 (possible, but extremely difficult), 2 (possible, but difficult) and 3 (possible without any problems). If parents rated 0, 1 or 2, they were asked to clarify why it was difficult to place the mask on the face, by marking one of the two options: A (child's position in bed) or B (child's restlessness).

Figure 1. Aerosol administration in a sleeping young child. Failure to place the mask airtight on the face because of the position of the child in bed.

Filter analysis

All filters were analyzed in a blinded fashion by the Erasmus MC Hospital Pharmacy. The filters were washed with ethanol containing an

internal standard (fluocinolone acetonide). Budesonide amounts were measured by high performance liquid chromatography (HPLC), using an ethanol-water (43:57) mobile phase and a Supelcosil LC-18 column (5 μm particles, 5 * 0.46 cm (inner diameter)). Budesonide was detected by UV-spectrophotometry at a wavelength of 254 nm. The method's coefficient of variation was < 3%.

Statistical analysis

SPSS for Windows version 9.0 was used for statistical analyses. Filter dose, calculated as the amount of budesonide deposited on the filter, was expressed as a percentage of the nominal dose. Filter dose variability was expressed as the within-subject coefficient of variation (CV).

Mean (± SD) filter doses and CVs were calculated for each child. To determine efficiency of administration during sleep, only filter doses and CVs of children sleeping throughout the administration procedure were compared, using Wilcoxon's signed rank test.

Mean total symptom scores and mean cooperation scores obtained from the weekly diary cards were compared using the Friedman test. A p-value of ≤ 0.05 (two-sided) was considered to indicate significant differences.

Results

Thirty children (18 boys) entered the study. Results from three children were excluded from analysis because the parents had not complied with the protocol. Six children did not complete the third study week, because they were too distressed during the "sleep administration". The missing data for these children were accounted for in the analysis. Twenty-one children fully completed the study. A total number of 350 and 331 filters were collected for the "awake administration" and "sleep administration", respectively. Median (range) age was 15 (6-23) months. Mean symptom score (± SD) during the two actual study weeks was 1.4 (2.2).

Figure 2 shows the mean filter dose (A) and the mean filter dose variability (B) for the "awake administration" and the "sleep administration". Mean filter dose (± SD) for the "awake administration" was 47% (26) and that for the "sleep administration" 16% (13) (p=0.007).

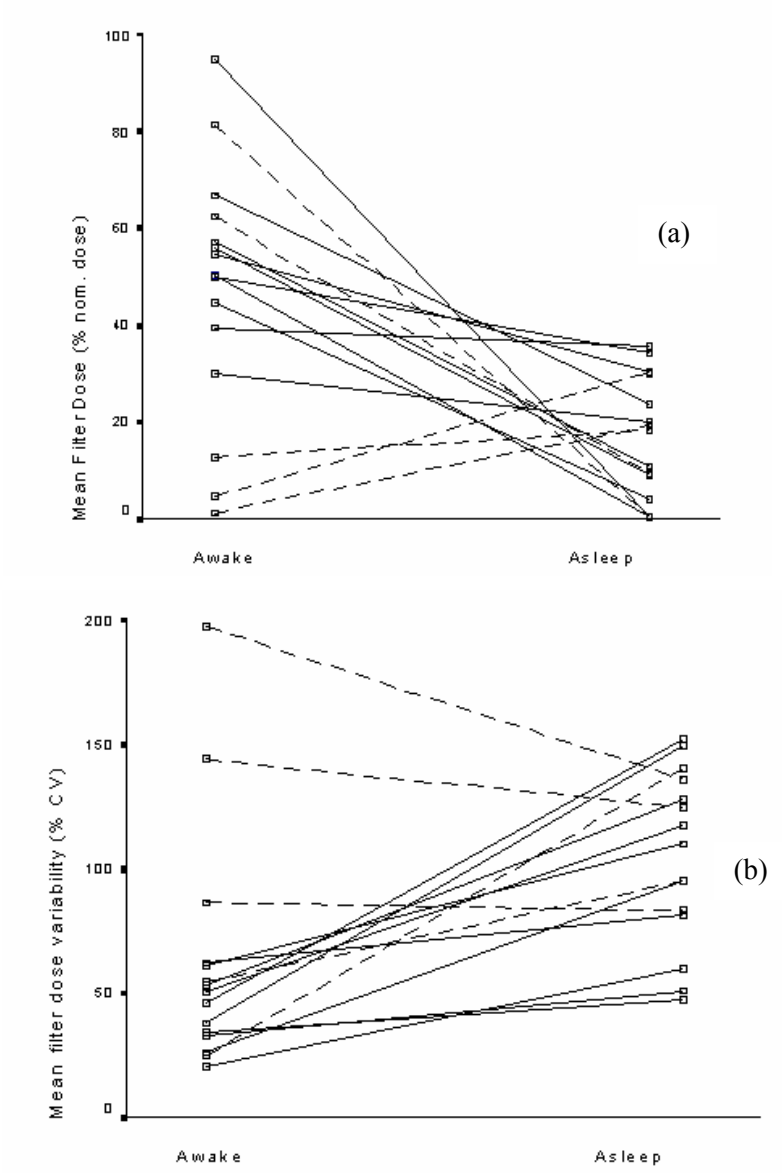

Figure 2. Part (a). Mean filter dose, expressed as % of the nominal dose, during the "awake administration" during the "sleep administration", for those children who slept through the administration procedure. ——— cooperative child and ----- uncooperative child during "awake administration". Part (b). Mean filter dose variability (CV%) during the "awake administration" and during the "sleep administration", for those children who slept through the administration procedure. ——— cooperative child and ----- uncooperative child during "awake administration".

Median filter dose variability (range) for the “awake administration” was 50% (21-198) and that for the “sleep administration” 110% (47-152) (p=0.007).

Poor cooperation (score 2 or 3) was recorded in 29% of the “awake administration” procedures. In 69% of the “sleep administration” procedures the child woke up, and in 75% of these cases the children were distressed. Seven children showed poor cooperation during three or more “awake administration” procedures. These seven children slept in 47% of the “sleep administration” procedures. In three of them, the sleep dose was higher than the awake dose (Figure 2A).

In 22% of the cases of children sleeping throughout the “sleep administration” procedure the parents reported mask-positioning problems. In 96% this was caused by the child’s position in the bed, and in 4% by the child’s restlessness.

Discussion

The aim of our study was to investigate the feasibility of aerosol administration in sleeping young children in a daily life situation. Administration during sleep was found to be possible in no more than one-third of the children. Moreover, filter doses of sleeping children were substantially lower than the filter doses obtained during the “awake administration”.

Several studies have shown that inhalation therapy by means of pMDI-spacer can be effective in the treatment of recurrent wheezing in young children (2, 3, 8, 16). However, up to 30% of the children below the age of 2 years can not be treated effectively because they become distressed during the administration procedure (12, 13). Distress, with its problems in obtaining a good facemask seal and its high inspiratory flows during crying, results in low lung deposition (3, 9). Aerosol administration during sleep has been suggested to be an option to treat these uncooperative children (10, 14, 15). In a previous laboratory study we first recorded the breathing patterns of 18 young children during sleep and while awake. Subsequently, an anatomically correct upper airway (SAINT-) model “inhaled” the drug with the recorded breathing patterns replayed by a computer-controlled breathing simulator. Lung dose was measured by placing a filter between the model and the breathing simulator. We found that the breathing patterns during sleep

resulted in significantly higher lung doses compared with the wake-breathing patterns (14).

How can we explain the discrepancy between the findings from this laboratory study and from our daily life study? First, the laboratory study was performed under optimal conditions with an ensured airtight fit of the mask on the SAINT-model, whereas in our daily life study the airtight fit of the mask on the child's face was not guaranteed. Fear of awaking the child may have withheld the parents to firmly press the mask on the child's face. Furthermore, about one-fifth of the parents indicated that it was difficult to place the mask, either because the child's position in bed or because of its restlessness. As shown in a previous study, even a tiny leak considerably reduces the amount of drug that can be inhaled from the spacer (17). Breathing patterns provide a second explanation for the discrepancy between the laboratory study and our daily life study. Breathing patterns used in the laboratory study were recorded prior to infant lung function testing while the children were awake and while they were sedated with chloralhydrate. We observed that the wake-breathing patterns were irregular and that the sleep-breathing patterns were regular (14). Apparently, the sedated children had all been recorded during quiet, non-Rapid Eye Movement (REM) sleep (14). In contrast, in our daily life study aerosol therapy was administered when the children were in a deep natural sleep. It is possible that at time of aerosol administration the children were in a REM sleep. During REM sleep the breathing pattern is irregular with variable respiratory rate and tidal volume and frequent central apneas (18-20). Therefore, the breathing pattern during REM sleep is likely to result in low doses inhaled from the spacer (21, 22).

Children who are uncooperative during inhalation therapy are the most important target group for aerosol administration during sleep. However, with this daily life study we demonstrate that the success rate of inhalation therapy during sleep is low, since most children woke up during the "sleep administration". Nevertheless, three of the seven uncooperative children obtained higher filter doses during "sleep administration" compared with "awake administration". Moreover, two uncooperative children, who showed higher filter doses during the "awake administration", had most likely been crying. In these children, filter doses are known to overestimate lung doses substantially (3, 9). Therefore, aerosol therapy during sleep could be appropriate in children who do not cooperate during the "awake administration" and remain asleep during the "sleep administration". Hence, inhalation therapy during sleep can be attempted in uncooperative children, however, with little chance of success.

It should be noted that, in this study, the dose found on the filters represents the amount of aerosolised drug delivered to the patient. It does not provide information on clinical efficacy or lung deposition. However, the filter method was sufficient to investigate the feasibility of aerosol administration during sleep.

In conclusion, many children were found to wake up when receiving aerosol therapy during sleep, and 75% of these cases the children were found to be distressed. In addition, in the children sleeping throughout the inhalation therapy filter doses were low and filter dose variability was high. Therefore, aerosol therapy by means of pMDI-spacer during sleep is not a feasible treatment option for most young children. Administration during sleep can be attempted in case of particularly uncooperative children. However, parents should be made aware that the success rate of inhalation therapy during sleep is low.

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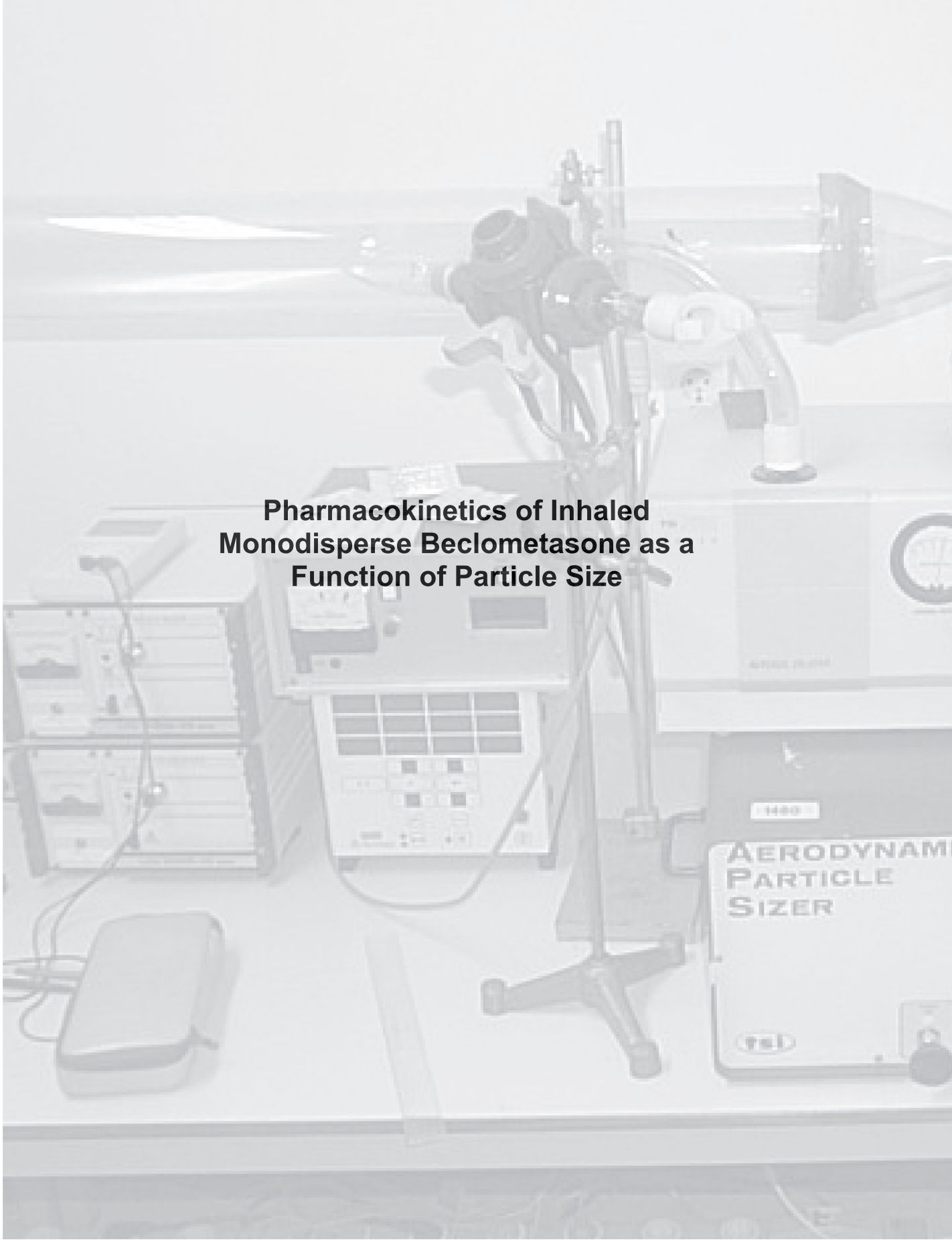

Pharmacokinetics of Inhaled Monodisperse Beclometasone as a Function of Particle Size

Chapter 6

Pharmacokinetics of Inhaled Monodisperse Beclometasone as a Function of Particle Size

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Submitted

Abstract

For optimal efficacy, anti-asthma drugs should be delivered to the desired region in the airways. To date, the optimal particle size for steroids in adults is not known.

Objective: To evaluate the pulmonary bio-availability for inhaled beclomethasone dipropionate (BDP) aerosols of different particle sizes.

Method: In a randomized single-blind cross-over trial, 10 mild asthmatic patients inhaled monodisperse BDP-aerosols of 1.5, 2.5 and 4.5 μm. Gastro-intestinal absorption was blocked by activated charcoal. Plasma levels of 17-beclomethasone monopropionate (17-BMP) were measured through liquid chromatography plus mass spectrometry.

Results: MMADs of 1.5 μm, 2.5 μm, and 4.5 μm gave mean maximum concentrations (C_{max}) of 17-BMP of 475 $pg \cdot mL^{-1}$, 825 $pg \cdot mL^{-1}$, and 1300 $pg \cdot mL^{-1}$, respectively. The area under the curve (AUC) values of 17-BMP for MMADs of 1.5 μm, 2.5 μm, and 4.5 μm were 2629 $pg \cdot h \cdot mL^{-1}$, 1161 $pg \cdot h \cdot mL^{-1}$, and 2276 $pg \cdot h \cdot mL^{-1}$, respectively. The mean terminal half-time of 17-BMP for all three aerosol sizes was around 1.5 hr.

Conclusions: Monodisperse BDP aerosols with a MMAD of 1.5 μm gave 2-3 fold lower values for C_{max} and AUC than those with MMADs of 2.5 and 4.5 μm.

Introduction

For decades, the administration of medication via the inhaled route has been the mainstay of therapy for respiratory diseases such as asthma or cystic fibrosis (1-3). More recently, inhalation therapy was also introduced for diseases such as diabetes mellitus, where insulin is delivered via inhalation to obtain systemic effects lowering blood glucose levels (4-7).

The efficacy of inhalation therapy – *i.e.* great beneficial effects and a low incidence of systemic side effects – largely depends on targeting a drug to the relevant regions in the lungs. Targeting is influenced by factors such as physiology, anatomy and pathology of the airways, breathing patterns, and the characteristics of the inhaled drug (8-14). Of these, the physiological, anatomical and pathological factors are hard to control. Breathing patterns, though, can be managed in theory, but in daily practice many flaws occur. However, it is the characteristics of the inhaled drug, such as particle size, that can be controlled effectively to enhance lung deposition.

For mild and severely affected asthmatic adults bronchodilators with a MMAD of 2.8 μm were shown to give the best improvement in lung function and the least systemic side effects (15, 16).It is not known, however, whether a MMAD of 2.8 μm is the most efficacious particle size for inhaled steroids in asthmatic adults. As the corticosteroid-receptor distribution is different from that of the β_2-receptors, inhaled corticosteroids are likely to require a different deposition pattern (9). Clinical efficacy and systemic side effects of inhaled steroids should be measured to define the optimal particle size. Systemic side effects are elicited by systemic absorbed steroids. Hence, we conducted a pharmacokinetic study using monodisperse beclomethasone dipropionate (BDP) aerosols to investigate the pulmonary bio-availability as function of aerosol size in adults with mild asthma. Since BDP is rapidly and completely converted to 17- beclomethasone monopropionate (17-BMP), which is more potent than BDP, we focused on the 17-BMP pharmacokinetics.

Materials and Methods

Study population

Non-smoking men and women with stable mild asthma, between the ages of 18-60 years, were invited to participate. Subjects had to comply with the ATS-criteria for asthma (17), and their baseline forced expiratory volume in one second (FEV_1) had to exceed 70% of the predicted value. Subjects had to show a reversibility of at least 9% of the predicted FEV_1-value after administration of 200 μg salbutamol. Subjects were excluded if they had a secondary illness, pregnancy, and/or treatment that might interfere with a reaction to bronchodilators. All patients gave their written informed consent before the entry of the trial, which was approved by the hospital ethics committee.

Study Design

The study was designed as a randomized single-blind cross-over trial. Patients were studied at the lung function laboratory at the University Hospital Utrecht on three separate days with one-week intervals. Oral anti-asthma medication was not allowed. Maintenance treatment with inhaled corticosteroids was discontinued 3 days prior to each study day. Long- and short-acting β_2-mimetic agents were stopped respectively 15 and 8 hours prior to the start of the trial. The baseline FEV_1 during each following session was not allowed to deviate more than 10% from that on day 1. Patients were first trained to inhale correctly. The inhalation maneuver consisted of a single inhalation from residual volume to total lung capacity with a constant flow of 40-60 L/min, followed by a 10 seconds breath-holding period and subsequently a slow exhalation. A hot wire anemometer placed close to the patient's mouth was used to measure inhaled volume and flow velocity. An indicator connected to the anemometer facilitated the patients to inhale at a constant flow. The amounts of aerosol deposited in the anemometer were negligible.

Aerosol Generation

In our experimental set-up (Figure 1), we used the electrohydrodynamic atomization (EHDA)-technique to generate

monodisperse aerosols. This EHDA-technique has been extensively described by IJsebaert et al.(18). Monodisperse BDP-aerosols (geometric SD < 1.2) of different Mass Median Aerodynamic Diameters (MMADs) – 1.5 μm, 2.5 μm and 4.5 μm – were generated from a BDP-ethanol solution. The generated monodisperse aerosols were collected in a large glass reservoir. Through an outlet at the end of the reservoir, part of the generated aerosols were sampled by an Aerodynamic Particle Sizer 33 (APS) (TSI, St. Paul, MN). The APS continuously measured particle size distribution and aerosol concentration (μg/l air) in the reservoir. Through another outlet patients inhaled 100 μg of the generated BDP-aerosols. The volume of inhaled air containing a dose of 100 μg BDP-aerosols was calculated by dividing this dose by the concentration of BDP-aerosols in the reservoir. As soon as the subjects had inhaled a dose of 100 μg BDP, they were switched over to ambient air to stop further inhalation of BDP-aerosols.

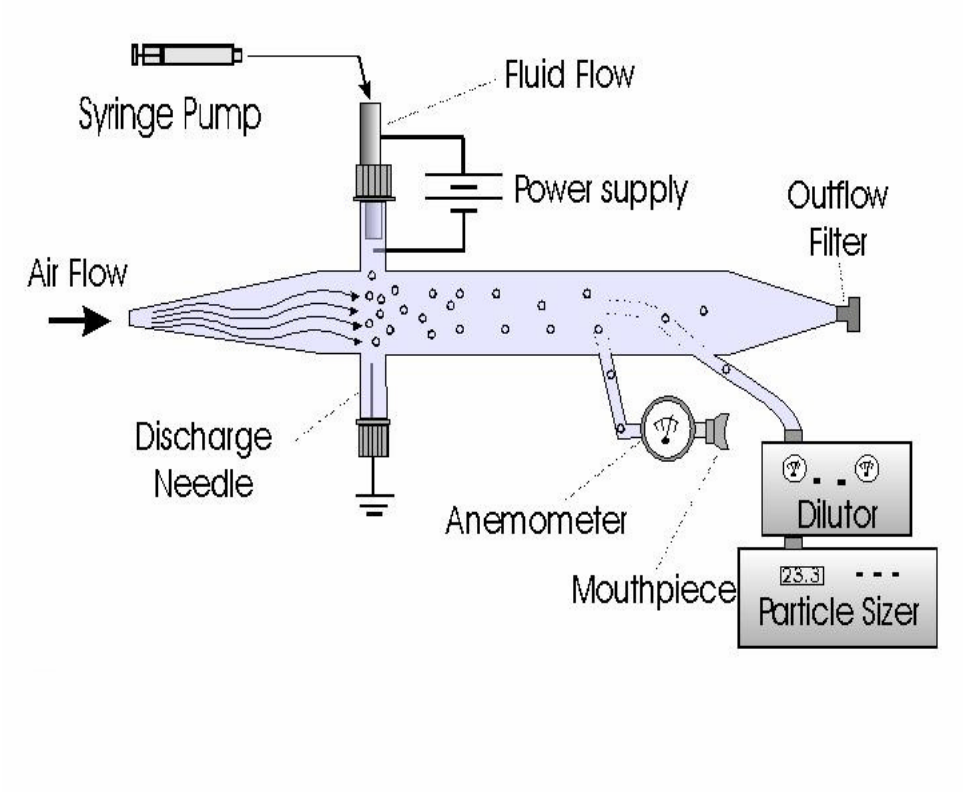

Figure 1. Schematic representation of the experimental set-up

Blood sampling

In order to be able to evaluate pulmonary bio-availability, gastrointestinal absorption was blocked by 5 grams activated charcoal prior to inhalation of the BDP-aerosols and 1, 2 and 4 hours after inhalation (19). An indwelling catheter (Becket Dickinson, Insythe W 18 gauge) was inserted into a forearm vein and a baseline blood sample was obtained. Consecutive blood samples were collected at 5, 10, 20, 30, 45, 60, 90, 120, 180, 240, 360 and 420 minutes after inhalation. The first 2 ml of blood of each sample was discarded. After collection of the sample, the indwelling catheter was flushed with 4 ml of saline 0.9%. The blood samples were collected in lithium-heparin tubes and immediately centrifuged in cooled centrifuges (7 ºC) for 10 minutes at 2200 g. Plasma was harvested and the plasma samples were frozen at - 70 ˚C within 1 minute after harvesting. This protocol was designed to ensure correct 17-BMP measurements, as any conversion from BDP to 17-BMP was instantly stopped.

Pharmacokinetic Analysis

Plasma concentrations of 17-BMP were analyzed using high performance liquid chromatography coupled simultaneously to a mass spectrometry (HPLC – MS-MS).

Calibration standards, study and control samples were thawed at room temperature, mixed thoroughly and centrifuged again for 10 minutes at 2200 g. Subsequently, the samples were extracted over a 50 mg C18 solid phase extraction (SPE) column. The SPE column was conditioned with 200 µl methanol (HPLC grade) followed by 400 µl water (Milli Q). Next, the column was loaded with a mix of 600 µl sample and 350 µl internal standard working solution. The eluate was dried under a stream of nitrogen at 40°C and reconstituted in 50 µl 40/60(v/v) acetonitrile/25 mM ammonium formate pH 5 buffer. 40 µl of the above-prepared sample was analyzed using a gradient elution on a 50 x 2.1 mm ODS3 5 µm column. The temperature of the column was kept on 40 °C at a flow rate of 0.8 ml/min.

The conditions for the MS-MS were: split ratio: 1 in 4; ionisation/interface: TurboIonspray @ 450°C; scan mode: selected reaction monitoring (SRM); cycle time: 3.5 minutes. The following transitions were monitored for BDP and BMP-17, respectively: m/z 521 → m/z 319 and m/z 527 → m/z 319.Data were acquired and processed using the software

package *Analyst*. LC-MS peaks were integrated and peak area ratios of BMP17 were calculated with respect to their internal standards.

Statistics

From the plasma concentration curves the following parameters were calculated:

- $AUC_{(0\text{-}t)}$ = Area under the plasma concentration/time curve from zero to the last measured time point (t) via the linear trapezoidal rule;
- $AUC_{(0\text{-}\infty)}$ = Area under the plasma concentration/time curve from time zero extrapolated to infinity, calculated as $AUC_{(0\text{-}t)} + C_{last}/K_{el}$.

With the sampling scheme of this study being rather long, the plasma concentrations at the last measuring points were frequently below the limit of quantification (LOQ): these concentrations were set to 0. If the latter was the case, the $AUC_{(0\text{-}\infty)}$ was not estimated and set equal to $AUC_{(0\text{-}t)}$; C_{max} = Maximal concentration after inhalation; K_{el} = Apparent terminal elimination rate constant; $T_{½}$ = Apparent terminal half-life.

The statistical analysis was carried out according to current bioequivalence guidelines (20). Hence, the individual $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}\infty)}$ and C_{max} data were log-transformed (natural logarithm) and subsequently analyzed using analysis of variance (ANOVA). The ANOVA model included subjects and aerosol sizes as main factors. The mean square error of the ANOVA was used to calculate the 90% confidence intervals of the $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}\infty)}$ and C_{max} ratios.

Results

Study population

Ten mild asthmatic patients (of which 9 women) completed the trial. The average age (SD) was 46.6 (10.7) years. Mean FEV_1 (SD) was 83.2 (15.9) percent of the predicted value. No adverse events were reported.

Pharmacokinetics

The mean plasma concentration/time profiles of 17-BMP for aerosols with MMADs of 1.5 µm, 2.5 µm, and 4.5 µm are shown in Figure 2. The derived pharmacokinetic parameters, *i.e.* ln-transformed $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}\infty)}$ and C_{max} and the geometric mean bioavailabilities following all three inhalations are presented in Table 1. The pharmacokinetic comparison of the threemonodisperse aerosols is shown in Table 2. AUC and C_{max} were significantly different between the 1.5 µm and the 2.5 µm aerosols ($p<0.003$) and between 1.5 µm and the 4.5 µm aerosols ($p<0.009$). There was no significant difference in AUC and C_{max} between the 2.5 µm aerosols and the 4.5 µm aerosols. The 2.5 µm and 4.5 µm aerosols produced 2 to 3 fold higher serum levels at all sampling times compared with the1.5 µm aerosols.

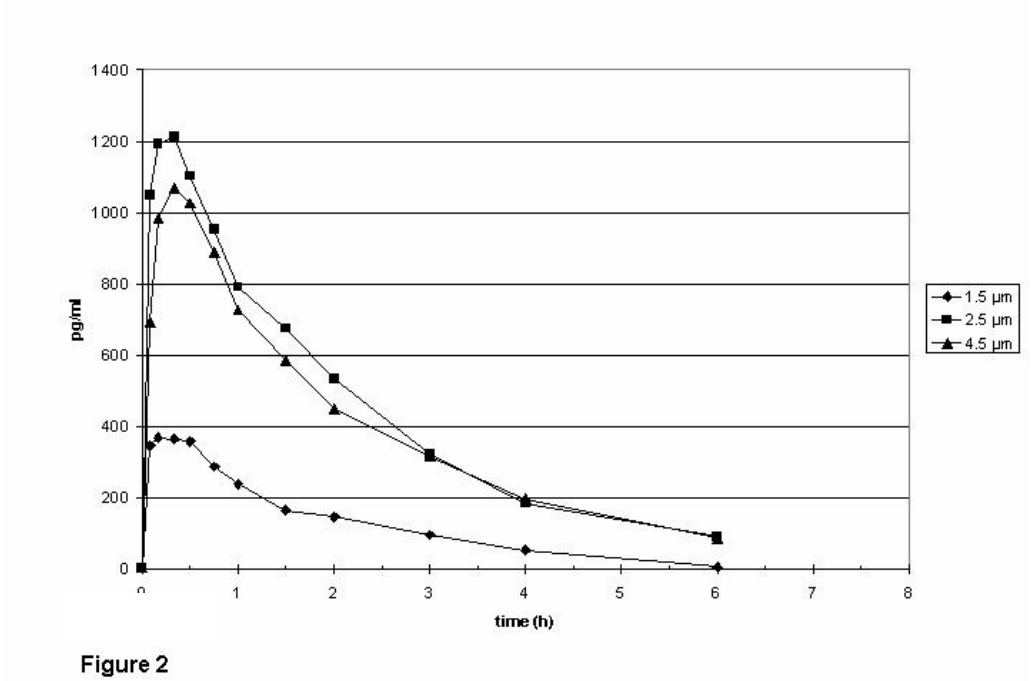

Figure 2

Figure 2. Mean plasma levels of 17 beclomethasone monopropionate (17-BMP) after inhalation of monodisperse aerosols with Mass Median Aerodyamic Diameters (MMAD) of 1.5 µm, 2.5 µm, and 4.5 µm. Gastrointestinal drug absorption was blocked by ingestion of charcoal.

Table 1. Ln-transformed plasma levels of beclomethasone 17-monodipropionate following inhalation of monodisperse aerosols with MMADs 1.5 µm, 2.5 µm and 4.5 µm

	1.5 µm				2.5 µm				4.5 µm			
Patient no.	$LnAUC_{(0-t)}$ ($pg \cdot h \cdot mL^{-1}$)	$LnAUC_{(0-\infty)}$ ($pg \cdot h \cdot mL^{-1}$)	LnC_{max} ($pg \cdot mL^{-1}$)	$T_{½}$ (h)	$LnAUC_{(0-t)}$ ($pg \cdot h \cdot mL^{-1}$)	$LnAUC_{(0-\infty)}$ ($pg \cdot h \cdot ml^{-1}$)	LnC_{max} ($pg \cdot mL^{-1)}$)	$T_{½}$ (h)	$LnAUC_{(0-t)}$ ($pg \cdot h \cdot mL^{-1}$)	$LnAUC_{(0-\infty)}$ ($pg \cdot h \cdot mL^{-1}$)	LnC_{max} ($pg \cdot mL^{-1)}$)	$T_{½}$ (h)
1	7.28	7.28	6.58	1.4	7.04	7.04	6.30	1.5	6.85	6.85	6.25	1.2
2	6.60	6.60	5.92	2.0	6.70	6.70	6.39	1.8	7.51	7.51	6.52	1.7
3	6.49	6.49	6.19	1.1	7.04	7.04	6.46	1.6	7.00	7.00	6.56	1.1
4	4.67	4.67	4.84	1.0	6.57	6.57	6.25	1.4	7.01	7.01	6.12	*
5	4.72	4.81	4.72	1.2	6.22	6.22	5.75	1.3	5.55	5.55	5.17	*
6	*	*	*	*	6.17	6.17	6.12	1.2	3.87	3.87	4.88	0.3
7	7.07	7.07	6.50	1.6	7.62	7.62	7.09	1.1	7.76	7.76	7.01	1.3
8	7.08	7.08	6.64	1.5	7.84	8.24	7.35	1.8	8.76	8.76	7.96	1.9
9	6.22	6.22	5.69	1.8	9.10	9.19	8.27	2.0	8.14	8.14	7.41	1.8
10	7.31	7.39	6.58	1.7	8.99	8.99	8.09	1.6	8.57	8.57	8.11	1.6
Mean	5.58	6.39	5.97		7.33	7.38	6.81		7.10	7.10	6.60	
Geometric	591.34	596.85	392.69		1521.99	1598.83	903.84		1217.29	1217.31	733.78	

LnAUC: Ln-transformed area under the plasma concentration-time curve, LnC_{max}*:* Ln-transformed maximum plasma concentration, $T_{½}$: apparent terminal half-life. * Missing values.

In almost all patients, the highest concentrations of 17-BMP for the 1.5 µm aerosols were seen at 10 minutes after inhalation and for the 2.5 µm and 4.5 µm aerosols at 20 minutes after inhalation. Six hours after inhalation 17-BMP was below the quantification limit in most patients. The median elimination half-life of 17-BMP was 1.5 hr for the 1.5 µm aerosols, 1.6 hr for the 2.5 µm aerosols and 1.4 hr for the 4.5 µm aerosols.

Table 2 Comparisons between the pharmacokinetic parameters of beclomethasone 17-monodipropionate for aerosols with MMAD 1.5 µm, 2.5µm and 4.5 µm.

	Comparison (A versus B)		
	1.5 µm vs 2.5	2.5 µm vs 4.5 µm	1.5 µm vs 4.5 µm
LnAUC	-2.933	0.223	-2.710
90% CI for	-4.415 to -1.451	-1.201 to 1.647	-4.192 to -1.227
p value	0.003	0.788	0.005
$\ln C_{max}$ ($pg \cdot mL^{-1}$)	-0.779	0.208	-0.570
90% CI for	-1.116 to -0.441	-0.116 to 0.533	-0.908 to -0.233
p value	0.001	0.279	0.009

LnAUC: Ln-transformed area under the plasma concentration-time curve, $\ln C_{max}$: Ln-transformed maximum plasma concentration, *CI*: confidence interval

Discussion

The aim of this study was to investigate the pulmonary bio-availability of different monodisperse BDP aerosol sizes in adults with mild asthma. We found that AUC and C_{max} were approximately 2-3 times lower for the 1.5 µm aerosols compared with the 2.5 µm and 4.5 µm aerosols.

Monodisperse aerosols are useful to investigate the relationship between aerosol particle size and systemic availability, as aerosol distribution curves show minimal overlap. The drawback of this approach is the great effort required to generate monodisperse aerosols. In the present study we

used the EHDA method, which is a validated and consistent method to produce monodisperse BDP-aerosols (18). Besides, it is a relatively easy method compared with the spinning top generator, vibrating orifice or Sinclair-LaMer generators.

For accurate charting of the systemic availability of monodisperse steroid aerosols as function of particle size, we controlled various factors that could affect lung deposition and lung dose. Firstly, patients inhaled the aerosol at a constant flow from a large volume glass reservoir, which acted like a spacer. Inhalation was followed by a 10 seconds breath-holding period. This procedure minimized oropharyngeal deposition and increased residence time, which in its turn enhanced deposition by sedimentation (21-24). Secondly, the concentration of aerosolized drug and the aerosol particle size in the glass reservoir were kept constant and were measured continuously by an aerodynamic particle sizer (APS). This minimized variations in inhaled dose between and within our patients, and between and within the different particle sizes. Thirdly, we controlled potential patient-factors by ensuring that the FEV_1 at start of each visit was within 10% of the patients screening value. Fourthly, the gastro-intestinal absorption was blocked by activated charcoal to ensure that the systemic availability represented only the drug absorption through the lung. The method of assessing the systemic bioavailability of the active metabolite 17-BMP, after inhalation of BDP with the charcoal block method, was described and validated previously (19, 25). The kinetic parameters of 17-BMP found in our study, such as T_{max} and $T_{½}$, are within the range found in previous pharmacokinetic studies (19, 25, 26). With the methodology used in our study, differences in the measured kinetic parameters were unlikely to be biased by the above-discussed factors.

The results of our study correspond to those presented by Heyder et al (27). In the latter, an in vivo-study with monodisperse aerosols, the alveolar deposition of particles between 2 and 6 μm was substantially higher than that of particles smaller than 2 μm.

The greater systemic availability of the 2.5 μm and 4.5 μm particles compared with the1.5 μm particles can be explained by the inhalation technique employed in our study. The constant and deep inhalation followed by a breath-holding period, presumably allowed the 2.5 μm and 4.5 μm particles to bypass the extrathoracic airways and to penetrate into the conducting and peripheral airways in high doses. The deposition of these particles was favored by sedimentation during inhalation and the breath-holding period. The 1.5 μm particles are typically able to pass through the extrathoracic and bronchial airways and to penetrate into the alveolar region.

However, a high proportion of these small particles will be exhaled again (27).

The results of our study seem to be conflicting with the results of previous pharmacokinetic studies comparing hydrofluoroalkane-134 (HFA)-BDP aerosols (MMAD 1.1 μm) with chlorofluorocarbon (CFC)-BDP aerosols (MMAD 3 μm). These studies showed that HFA-BDP yielded a 2-times greater systemic availability compared with the same dose of CFC-BDP (28, 29). This difference in systemic availability was explained by the smaller MMAD of the HFA-BDP compared with the CFC-BDP. However, differences in spray characteristics of the HFA- and CFC-pMDIs, as well as inhalation maneuver, were not considered to affect the results. A head-to-head comparison between these studies and our study cannot be made, because HFA-BDP and CFC-BDP aerosols are polydisperse aerosols and we used monodisperse aerosols. Polydisperse aerosols are aerosols with a large particle size distribution. Therefore, it is not possible to assess the contribution of the various particle sizes on the systemic availability. Hence, the increased systemic availability found for the HFA-BDP aerosols might well be due to the increased deposition of both small and large particles of the HFA-BDP aerosol in the conducting and peripheral airways.

Type of dispersity of the aerosol cannot solely explain the discrepancies in systemic availability between our study and the HFAs versus. CFCs studies (26, 28, 29). The HFA versus CFC studies followed a different study design. First, the HFA versus CFC studies did not use activated charcoal to block gastro-intestinal absorption and the systemic availability found in these studies, therefore, is a mixture of lung and GI-tract absorption (26, 28, 29). Second, the HFA versus CFC studies measured the first serum level of 17-BMP 0.5 to 1 hours after inhalation (26, 28, 29). However, as C_{max} can be reached 10 minutes after inhalation (19), the maximum concentration and a considerable part of the AUC might have been missed. Finally, one of the HFA-CFC studies measured the systemic availability via the beclomethasone plasma levels rather than the 17-BMP levels (29). Beclomethasone, however, is only a small component of the systemic available substance compared with 17-BMP (19, 28).

The goal of our study was to determine the systemic availability of inhaled corticosteroids with different aerosol particle sizes. The 1.5 μm aerosols gave a significant lower systemic availability compared with the 2.5 μm and 4.5 μm aerosols. However, our data give only an indication of total lung deposition. They do not allow to draw conclusions about the distribution of deposition in the lung and about the clinical efficacy. Furthermore, these

results obtained in adults are probably not applicable to young children. As children have narrower airways, the distribution of deposition in the airways, total deposition, and systemic availability will be different. To complete the definition of optimal aerosol particle size for inhaled corticosteroids in adults, clinical efficacy studies with monodisperse aerosols should be carried out.

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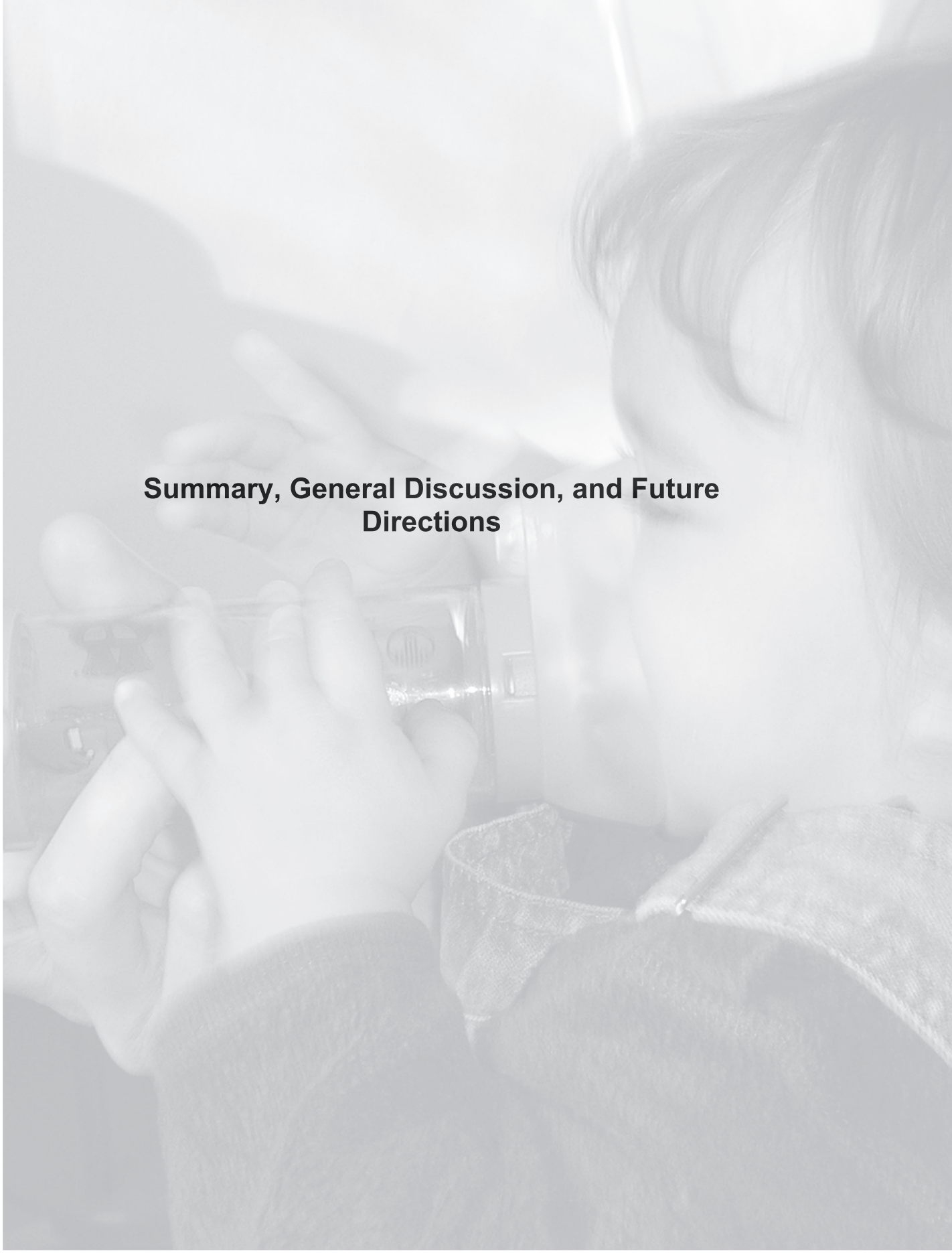

Summary, General Discussion, and Future Directions

Chapter 7

Summary, General Discussion, and Future Directions

Summary

Inhalation is the customary method to deliver medication to patients with lung disease (1). Delivering medication directly to its site of action, inhalation therapy has the advantage of a more rapid therapeutic effect. Furthermore, less medication is needed to get the same therapeutic effect of systemically delivered medication (2-4). However, it is difficult to deliver aerosolized drugs to the lungs efficiently and in a reproducible manner, especially in young children. Efforts are made, therefore, to improve efficiency and efficacy of inhalation therapy in young children. These can only be successful if clinicians have knowledge of the basics of inhalation therapy (1, 3, 4).

Chapter 1 of this thesis deals with the background of inhalation therapy. The major factors influencing efficiency and efficacy of inhalation therapy are presented, and radio-labeled and clinical efficacy studies in young children are reviewed. Finally, the aims of the studies presented in this thesis are discussed in detail. Mask seal, the child's cooperation, and particle size seem to be critical factors affecting inhalation therapy in young children. As appeared from our literature review, mask seal and particle size have not yet been extensively studied. Furthermore, alternatives to administer aerosolized medication to the uncooperative child have not been studied in daily life.

In **chapter 2**, we studied the effects of size and position of facemask leaks on spacer output and lung dose in-vitro, using an anatomically correct upper airway model of an infant (SAINT-model) and a computer-controlled breathing simulator. Spacer output and lung dose were measured from deposits on filters between spacer and facemask or between model and breathing simulator, respectively. We found efficiency of a pMDI-spacer-facemask combination to be strongly related to leak size. Even a small air leak in the facemask can drastically reduce spacer output and lung dose. Spacer output was not related to leak position. However, lung dose for leaks near the chin was higher than that for leaks near the nose. The results of this study underline the importance of a perfect seal between mask and face when treating young children using a pMDI-spacer-facemask combination.

Chapter 3 presents a four-week, randomized cross-over study in which we tested three commercially available facemasks in young children in daily life. The study aim was to examine how in young children facemask design affects the efficiency of aerosol delivery by means of pMDI-spacer. Spacer output was measured by placing a filter between spacer and facemask. The dose deposited on the filter represented the total dose delivered to the

patient. A round-shaped facemask gave significantly higher filter doses compared with face-shaped masks. We concluded that the efficiency of aerosol delivery to young children could be improved using a round facemask. However, many of the children were found to fight the therapy and did not easily accept any mask on the face.

In **Chapter 4**, we evaluated patterns of aerosol loss from various facemasks combined with a nebulizer. In a randomized cross-over study, children under the age of 4 years were recorded on video while testing four different nebulizer-facemask combinations. Patterns of aerosol loss were then assessed from the video-recordings. The mask with large open vents showed the highest total aerosol loss and greater exposure of the children's eyes and skin to aerosol compared with the other tested masks. We concluded, therefore, that masks with large vents are not suitable for nebulization therapy in young children.

Chapter 5 presents a study in which we evaluated the feasibility of drug administration by means of pMDI-spacer in sleeping young children. Spacer output was measured by placing a filter between spacer and facemask. For two weeks, the children inhaled aerosol twice daily, once when awake and once when asleep. It appeared that during most sleep administrations the children woke up and became distressed. In addition, the dose inhaled when the child was asleep was significantly lower than when awake. Furthermore, the within-subject dose variability when asleep was significantly higher than that when awake. Therefore, we concluded that aerosol administration during sleep offers no advantage and is not a feasible treatment option in most young children.

In **Chapter 6** the pulmonary bio-availability for inhaled beclomethasone dipropionate (BDP) aerosols of different particle sizes was investigated. In a complex experimental set-up, we generated monodisperse BDP aerosols with three different mass median aerodynamic diameters (MMADs). Adults with mild asthma inhaled each of the three generated monodisperse aerosols on separate days. Subsequently, we obtained blood samples at multiple time-points after inhalation. For each aerosol size, plasma concentration-time curves were derived. We found that the systemic availability for monodisperse BDP aerosols with a MMAD of 1.5 μm was 2-3 fold lower than for aerosols with MMADs of 2.5 and 4.5 μm.

General Discussion

Inhalation therapy in young children is an extremely complex procedure. Its efficiency and efficacy are determined by many factors (see Chapter 1). From the studies presented in this thesis, we obtained more detailed knowledge about some of these factors. This section discusses the most relevant findings of this thesis.

Facemask and pMDI-spacer

Seal

Our in-vitro study showed a strong negative correlation between leak size and lung dose. This result is especially important for aerosol therapy in young children, as many children under 2 years are uncooperative during inhalation therapy and may start crying. Crying children show high inspiratory flow rates, which enhance upper airway deposition and reduce lung dose (5). This, however, was not the only factor that reduced lung dose. If a child is uncooperative it is difficult to obtain a tight seal between mask and face, and leaks may then result. Our study revealed that even a small leak will drastically reduce lung dose.

Design

Facemask design is likely to play an important role in obtaining a good seal between mask and face. Therefore, we investigated how facemask design influences efficiency of aerosol delivery in daily life. The results of this study are consistent with aerosol therapy using a round-shaped facemask being more efficient compared with use of face-shaped facemasks. However, in children younger than 2 years patient-related factors, such as lack of cooperation, are probably more important than facemask design. This is confirmed by the results of our daily life study: uncooperative children had significantly lower filter doses for all masks. Furthermore, the differences in filter doses between the masks did not relate to cooperation. We conclude that, independent of the design of the mask, it is difficult to obtain a tight seal when the child is uncooperative. Furthermore, it is unlikely that facemask design influences the child's cooperation. This may be explained by the following arguments: First, filter dose variability in our study increased significantly when a child did not cooperate, but there were no significant differences between the filter dose variability of the different masks. Second, cooperation scores for the masks did not differ. The problem remains, however, that many young children will resist having any mask pressed onto the face.

Facemask and nebulizer

For nebulizers, the importance of a tight fitted facemask was shown by the results of an *in-vitro* study by Everard *et al.* When the nebulizer mask was moved 1 cm from the child's face, the inspired dose of medication was found to be as low as 50% of the dose delivered when the mask was closely fitting to the face. A 2 cm gap even resulted in 80% reduction of the dose delivered. Many nebulizers, however, have loose fitting masks with open vents. Thus, apart from reduced drug delivery, there may also be side effects from exposure of eyes and skin to aerosolized drug. When steroids are nebulized, a steroid rash may consequently develop over the face (6). In addition, there is a potential risk of cataract (6). An in-vitro study using radio-labeled aerosols found a variety of facial deposition patterns, depending on the nebulizer-facemask combination (7). Facial deposition was significantly less when the facemask was vented, as vents allow the extra aerosol to easily exit the mask rather than to impact on the face. However, in children younger than 2 years relatively large amounts of aerosols can exit the nebulizer-facemask combination through the vents during inspiration and expiration. This phenomenon is due to the fact that their inspiratory flow rates often do not exceed the driving flow of the nebulizer (8). Our study in children aged between 7 months and 4 years confirmed that their eyes and skin were substantially exposed to aerosol when using the mask with large vents close to the face. Therefore, we concluded that masks with large vents are not suitable for young children. Incorporating vents in the nebulizer or positioning them between the nebulizer and the facemask can, probably overcome the problem of aerosol exiting the mask and impacting on the skin or in the eyes. The extra aerosol will then exit further from the face.

Aerosol administration to uncooperative young children

In about 30% of the aerosol administration procedures, young children are found to become distressed (9). Distress makes it difficult to obtain a good seal between facemask and face. In addition, high inspiratory flows during crying result in low lung deposition (5, 10). Therefore, distress during aerosol administration obviously reduces the efficiency and, consequently, the efficacy of the anti-asthma treatment. An option to avoid the unwanted results of distress would be to administer the aerosol to the sleeping child. Janssens *et al.* in an *in-vitro* study found that lung dose obtained with sleep-breathing patterns was significantly higher than that obtained with wake-breathing patterns (11). However, this concept was never tested in real life.

From our daily life study we conclude that administration during sleep is not a feasible treatment option in most young children, since many children woke up, showing signs of distress in 75% of the cases. In addition, children sleeping throughout the inhalation therapy had low filter doses and high filter dose variability. The discrepancy between the *in-vitro* study and our daily life study can be explained as follows. First, airtight fit of the mask on the face could be ensured in the *in-vitro* study, whereas in our daily life study airtight fit was not ensured. About one-fifth of the parents indicated that it was difficult to position the mask correctly, either due to the child's position in bed or because of its restlessness. Furthermore, fear of awaking the child may have withheld the parents from firmly pressing the mask onto the child's face. Our *in-vitro* study, described in Chapter 2 of this thesis, showed that even a small leak will considerably reduce the amount of drug that can be inhaled from the spacer. Hence, it is likely that the incomplete seal resulted in reduced aerosol delivery to the patient. A second explanation may lie in possibly different breathing patterns between the *in-vitro* study and our daily life study. In the latter, sleep breathing patterns were likely to be less regular, since aerosol was administered during a deep natural sleep. Hence, less aerosol could be drawn from the spacer.

Particle size

The efficacy of inhalation therapy largely depends on successfully targeting a drug to the relevant regions of the lungs. Targeting is influenced by several factors, such as physiology, anatomy and pathology of the airways, breathing patterns, and characteristics of the inhaled drug (5, 12-17). An effective and controllable factor to enhance targeting is the particle size of the inhaled drug. Previous studies in adults showed that the optimal particle size for a β_2-agonist is 2.8 μm. For inhaled steroids, however, the optimal particle size is not known. It should be defined by investigating clinical efficacy and systemic side-effects for various particle sizes. We, therefore, studied pulmonary bio-availability as function of aerosol size using monodisperse aerosols. We found a higher systemic availability for the 2.5 μm and 4.5 μm particles compared with the 1.5 μm particles. These results are in agreement with findings reported by Heyder et al. (18), and can be explained by the constant and deep inhalation technique employed in our study. Most likely, this technique allowed the 2.5 μm and 4.5 μm particles to bypass the upper airways and penetrate into the conducting and peripheral airways in high doses. Deposition of these particles in the conducting and peripheral airways was favored by sedimentation during the inhalation and breath-holding periods. The 1.5 μm particles are able to pass, in general,

through the extrathoracic and bronchial airways and to penetrate into the alveolar region. However, a high proportion of these small particles will be exhaled again (18). The findings from our study give information only on the systemic availability of three different monodisperse particle sizes. Reflecting the probability of systemic side effects, the systemic availability gives only an indication of total lung deposition. Therefore, conclusions about drug distribution in the airways and about clinical efficacy could not be drawn.

Pharmacokinetic studies using monodisperse aerosols to investigate the pulmonary bio-availability as function of aerosol size in children would be very useful as well, seeing that they have smaller airways than adults. Deposition in children might take place in other sites, and thus total deposition and systemic availability may differ from those in adults. Unfortunately, the experimental set-up used in our study is not suitable for use in children. The major restricting factor is the impossibility of producing high concentrations of aerosolized drug in the reservoir. As a consequence, children cannot inhale a small dose of steroid in a single deep inhalation at a constant flow. With the maximum obtainable drug concentration, children would have to inhale at a constant flow for at least 7 to 10 minutes, which is physically impossible. Efforts should be made to find a suitable technique for such pharmacokinetic studies in children.

Conclusions

The design of the facemask, and consequently, the fit of the mask on the face, is an important determinant for the efficiency of aerosol delivery to children and for the occurrence of local side-effects. For use of the pMDI-spacer combination, however, the child's cooperation is probably even more important than facemask design. The alternative of aerosol administration during sleep is not feasible for very young children, as most of the children will wake up and become distressed.

In adults, monodisperse aerosols with a MMAD of 1.5 μm gave lower systemic availability compared with aerosols with MMADs of 2.5 μm and 4.5 μm. Pharmacokinetic studies using monodisperse aerosols are needed in children as well.

Future Directions

In view of improving the efficiency of aerosol delivery by pMDI-spacer combination in young children, future research should focus on ways of enhancing cooperation of the child during aerosol administration. There are several possibilities:

- Developing a spacer with a child-friendly appearance;
- Rewarding after completion of inhalation;
- Implementing an introductory program for parents and children at the start of the inhalation therapy to improve the acceptance rate;
- Implementing an intensive follow-up program and coaching by a qualified health-care worker.

Aerosol delivery by means of nebulizers would benefit from facemask-nebulizer combinations that reduce the amount of aerosol impacting on the eyes and skin of the patient but yet preserve the efficiency of aerosol delivery to the lung. Design efforts would have to focus, therefore, on positioning vents with a one-way valve in the nebulizer or connection piece at a greater distance from the face.

For children, deposition patterns and systemic availability will most likely differ from those in adults, as children have smaller airway diameters and show other breathing patterns. To improve the efficacy of inhalation therapy in children – *i.e.* great beneficial effects and low incidence of systemic side effects, it is essential to determine optimal particle size for inhaled corticisteroid therapy in children. To this aim, a reliable technique of producing monodisperse aerosols that is feasible in children should be developed first. Subsequently, pharmacokinetic and clinical efficacy studies need to be carried out to define the optimal particle size for corticosteroids in children.

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Samenvatting

Inhalatietherapie wordt vaak gebruikt bij patienten met longziekten. Het voordeel van inhalatietherapie is dat de medicijnen direct op de plek terechtkomen waar ze nodig zijn. Hierdoor kunnen ze dus sneller effectief zijn. Bovendien is er minder medicijn nodig om hetzelfde effect te bereiken dan wanneer hetzelfde medicijn oraal en/of systemisch wordt toegediend. Echter, om het medicijn elke keer in de juiste hoeveelheid in de longen te krijgen, is, vooral voor kleine kinderen, erg moeilijk. Het is belangrijk dat, met name bij kleine kinderen de inhalatietherapie wordt geoptimaliseerd, zodat er vaker een constantere hoeveelheid medicijn in de longen komt. Om de inhalatietherapie te kunnen verbeteren is het essentieel om basiskennis te hebben. In hoofdstuk 1 van dit proefschrift komt de achtergrond van inhalatietherapie aan bod. De belangrijkste factoren die de efficiëntie en effectiviteit van inhalatietherapie beïnvloeden zijn uiteengezet. Verder wordt er een overzicht gegeven van klinische effectiviteit studies en studies met radio-gelabelde aërosolen in kleine kinderen. Als laatste worden de doeleinden van de studies die in dit proefschrift worden gepresenteerd besproken.

De aansluiting van een masker op het gezicht, de coöperatie van het kind en de deeltjesgroottes van de aërosol zijn factoren die de inhalatietherapie aanzienlijk kunnen beïnvloeden. Uit de literatuur blijkt dat de aansluiting van het masker op het gezicht en de deeltjesgrootte niet grondig zijn onderzocht. Tevens zijn alternatieven voor inhalatietherapie bij het niet-coöperatieve kind nog niet in de dagelijkse praktijk onderzocht.

In **hoofdstuk 2** wordt bekeken wat het effect is van de grootte en de positie van een lek in het masker op de dosisafgifte van een voorzetkamer en de hoeveelheid medicatie die in de longen komt (“longdosis”). Om dit te onderzoeken hebben we gebruikt gemaakt van een bovenste luchtweg model van een kind (SAINT-model) in combinatie met een ademhalingssimulator. Dosisafgifte en longdosis werden gemeten door middel van filters, die geplaatst werden tussen respectievelijk de voorzetkamer en het masker en tussen het model en de ademhalingssimulator. De studie toont aan dat de efficiëntie van een dosisaërosol (pMDI) in combinatie met een voorzetkamer en maskertje sterk afhankelijk is van de grootte van het lek in het masker. Zelfs een heel klein lek kan de dosisafgifte en de longdosis sterk doen verminderen. De dosisafgifte werd niet beïnvloed door de positie van het lek, echter de longdosis was hoger wanneer het lek bij de kin zat in vergelijking

tot een lek dichtbij de neus. De resultaten van deze studie benadrukken nog eens dat een goede aansluiting van het masker op het gezicht van essentieel belang is voor de efficiëntie van inhalatietherapie met een pMDI-voorzetkamer.

In **hoofdstuk 3** wordt een gerandomiseerde cross-over studie beschreven waarin we de inhalatietherapie met behulp van een voorzetkamer gecombineerd met 3 verschillende maskertjes vergelijken bij kinderen onder de twee jaar in de thuissituatie. Het doel van deze studie was om de efficiëntie van de inhalatietherapie voor de verschillende maskertjes te onderzoeken door middel van het meten van de dosisafgifte van de voorzetkamer. De dosisafgifte werd gemeten door een filter te plaatsen tussen de voorzetkamer en het maskertje. De dosis op de filter was representatief voor de totale dosis die het kind zou hebben ingeademd als het filter er niet was geplaatst. Uit deze studie kwam naar voren dat het ronde maskertje een significant hogere dosisafgifte gaf in vergelijking met de gezichtsgevormde maskertjes. Wij concludeerden dat bij jonge kinderen de efficiëntie van inhalatietherapie met een metalen voorzetkamer verbeterd kan worden door gebruik te maken van dit ronde gezichtsmaskertje. Echter, een groot percentage (%) van de kleine kinderen was niet coöperatief tijdens de inhalatietherapie en accepteerde geen enkel maskertje op het gezicht.

In **hoofdstuk 4** hebben we het patroon van de aërosolwolk die tijdens het vernevelen ontsnapt ge-evalueerd voor 4 verschillende maskertjes gecombineerd met een vernevelaar. In een gerandomiseerde cross-over studie testten kinderen onder de 4 jaar vier verschillende masker-vernevelaar combinaties. De aërosolwolk die tijdens het vernevelen ontsnapte legden we vast op video. We konden uit deze studie concluderen dat de grootte van de aërosol wolk die ontsnapt over het algemeen meevalt. Het masker met grote ventilatiegaten liet echter een significant grotere aërosol wolk zien in vergelijking met de andere maskertjes. Wij concludeerden dat dit masker bij kleine kinderen wellicht een hoger risico op bijwerkingen voor ogen en huid kan geven dan de andere geteste maskers. Daarom is dit masker met grote ventilatiegaten minder geschikt voor verneveltherapie bij kleine kinderen.

In **hoofdstuk 5** wordt een studie beschreven waarin we hebben gekeken of inhalatietherapie tijdens de slaap mogelijk was en een goed alternatief is voor niet-coöperatieve kinderen. De dosisafgifte werd gemeten door een filter te plaatsen tussen de voorzetkamer en het maskertje. De dosis op de filter was representatief voor de totale dosis die zou zijn ingeademd als het filter er niet was geplaatst. Elke proefpersoon kreeg twee weken lang twee keer per dag inhalatietherapie met studiemedicatie, één keer als hij/zij

wakker was en één keer tijdens de slaap. Het resultaat van deze studie was dat de meeste kinderen wakker werden als zij inhalatietherapie tijdens de slaap toegediend kregen. Bovendien werden de meeste kinderen ook nog onrustig en huilerig. Verder bleek dat de dosisafgifte tijdens de slaap-toediening significant lager was dan tijdens de toediening als de patient wakker was. Ook de dosisvariabiliteit bleek significant hoger tijdens de slaap-toediening in vergelijking tot de toediening als de patient wakker was. Wij concludeerden dat inhalatie therapie tijdens de slaap voor de meeste kleine kinderen geen voordelen biedt en geen goed alternatief is.

In **Hoofdstuk 6** wordt een studie beschreven waarin we de systemische beschikbaarheid van geïnhaleerde beclomethasone dipropionate (BDP)-aërosolen in het bloed hebben gemeten. In een complexe opstelling maakten we monodisperse BDP-aërosolen met 3 verschillende mass median aerodynamic diameters (MMADs). Volwassenen met mild astma inhaleerden de drie verschillende monodisperse aërosolen op verschillende studiedagen. Gastro-intestinale opname van BDP werd geblokkeerd door tevoren actief kool (Norit) toe te dienen. Bloedmonsters werden genomen op verschillende tijdstippen na inhalatie. Voor elk deeltjesgrootte kon vervolgens de plasmaconcentratie curve in de tijd worden uitgezet. Wij vonden dat de systemisch beschikbaarheid voor monodisperse BDP-aërosolen met een MMAD van 1.5 μm 2-3 keer lager was dan de systemische beschikbaarheid voor monodisperse BDP aërosolen met een MMAD van 2.5 en 4.5 μm.

Conclusies

Voor efficiënte inhalatietherapie met een pMDI-voorzetkamer bij kleine kinderen is een goed passend gezichtsmaskertje erg belangrijk. De coöperatie van het kind lijkt echter nog de meest bepalende factor voor de efficiëntie van de inhalatietherapie. Verder bleek inhalatietherapie tijdens slaap geen goed alternatief voor het niet-coöperatieve kind.

Om bij verneveltherapie het risico op mogelijke locale bijwerkingen van huid en ogen te verlagen is het aan te bevelen om een goed passend maskertje te gebruiken met kleine ventilatiegaten in de vernevelaar of tussen masker en vernevelaar, zodat overtollig aërosol op enige afstand van het gezicht het systeem kan verlaten.

In de zoektocht naar het meest effectieve deeltjesgrootte voor inhalatie van corticosteroïden blijkt dat bij volwassenen met mild astma aërosolen met een MMAD van 1.5 μm een lagere systemische beschikbaarheid geven in vergelijking tot aërosolen met MMAD van 2.5 μm en 4.5 μm. Klinische effectiviteits studies met aërosolen van verschillende MMADs zouden

uitgevoerd moeten worden om te kijken welk deeltjesgrootte klinisch het meest effectief is. Dan pas is de optimale deeltjesgrootte te bepalen. Omdat kinderen geen kleine volwassenen zijn, ligt het in de verwachting dat effectieve inhalatietherapie bij kinderen een andere deeltjesgrootte vereist. Voor het verbeteren van inhalatietherapie bij kinderen zijn studies naar de meest effectieve deeltjesgrootte daarom ook bij kinderen nodig.

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Curriculum Vitae

José Festen was born in Groningen on October 16th, 1973. She passed her secondary school exam (VWO) at the "Lyceum de Grundel" in Hengelo in 1992. In the same year, she started her medical training at the Medical School of the University of Groningen. During her study she was member of the student association "Albertus Magnus", member and secretary of the board of the sailing association "Aeolus", and she played in the first team of the student hockey club "GCHC". As a student, she had clinical trainings at the department of neurology, Beatrix Children's Hospital in Groningen, and at the department of Gynaecology and Obstetrics at the University Hospital in Umea, Sweden. In 1996 she did a research project at the Montreal Neurological Institute and Hospital, Montreal, Canada. (Prof.dr. F. Andermann). Her internship she followed at the "Isala Klinieken" in Zwolle. The optional internship she did at the department of pediatrics at the "Reinier de Graaf Gasthuis" in Delft. After obtaining her medical degree in 1999, she started working as a resident at the department of pediatrics of the "Reinier de Graaf Gasthuis". In july 2000, she started a research fellowship at the department of Pediatric Pulmonology of the Sophia Children's Hospital, Erasmus Medical Center, University of Rotterdam (Prof. J.C. de Jongste) under supervision of Dr. H.A.W.M Tiddens. The research performed during this period is presented in this thesis. José is married to Gennaro Esposito, and they have three beautiful little princesses: Anna Maria (2000), Christina (2001) and Elena (2005).

List of Publications

JE Esposito-Festen, B Ates, FJM van Vliet, AFM Verbraak, JC de Jongste, HAWM Tiddens. Effect of a facemask leak on aerosol delivery from a pMDI-spacer system. *J Aerosol Med 2004; 17 (1): 1-6.*

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JE Esposito-Festen, H IJsselstijn, WCJ Hop, FJM van Vliet, JC de Jongste, HAWM Tiddens. Aerosol therapy by pMDI-spacer in sleeping young children: To do or not to do? *Submitted.*

JE Esposito-Festen, P Zanen, HAWM Tiddens, J-WJ Lammers. Pharmacokinetics of inhaled monodisperse beclomethasone as a function of particle size. *Submitted.*