Effect of a paediatric incentive spacer and reinforcement of inhalation technique training in preschool children

Jasminka Murdzoska

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Effect of a paediatric incentive spacer and reinforcement of inhalation technique training in preschool children.

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November 2006

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ABSTRACT

Incorrect inhaled drug delivery technique is a common problem in paediatric asthma [1-4]. Previously, device technique training has been shown to significantly improve inhaler skills, using subjective methods, namely check-list analysis [5-8]. However, more objective measures are needed to examine more comprehensively the effect of training in preschool children and parents.

Resistance to regular asthma therapy is also a frequent problem when attempting to treat young children. Reasoning with young children can be very difficult and parents often have to struggle with their child to achieve compliance [2]. The Funhaler spacer (FH) (Funhaler™; InfaMed, Australia) has been developed in an attempt to resolve this issue by incorporating incentive toys to distract the child from the drug delivery process. Based on parental questionnaire, the FH has been shown to improve inhalation technique and increase medication compliance in young children over a two-week period [1].

A total of 47 children participated in the present study; 24 were randomised to a standard Aerochamber plus spacer (AC+) (15 male, mean age 63.7 months, range 30-90 months), and 23 were randomised to the FH spacer (14 male, mean age 60.5 months, range 36-90 months). Of the 47, four children (AC+: n=2, FH: n=2), with a mean age of 51 months (36-60 months) were identified as nose breathers, and were analysed as a separate group. The results from the present study show that repeated clinic-based technique training had no significant effect on drug delivery (p=0.151). Furthermore, it was found that in the clinic setting, children who were using the FH.
spacer were more likely to 'play up' during the drug administration procedure, compared to children using the AC+ spacer. This was also reflected in the domiciliary setting, where children who were using the AC+ spacer exhibited significantly higher drug delivery consistently over the seven days, compared to the FH spacer group \( (p=0.032) \). In addition, the \textit{in vitro} data showed that drug delivery was significantly dependent on age, height, weight and breathing parameters (peak inhalation flow, tidal volume, inhalation volume, exhalation volume, peak exhalation flow) with the AC+ spacer; however this was not seen with the FH spacer. Although it was expected that dependence on parameters such as inspiratory volume would affect day-to-day drug dose, it was found that drug delivery was actually better in the home setting with the AC+ spacer than the FH spacer. Therefore, these findings suggest that children interact better with a standard spacer device, such as the AC+, compared to the incentive FH spacer.
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DEFINITION OF TERMS/ABBREVIATIONS

AC+: Aerochamber Plus® spacer; a commonly used small volume paediatric spacer.

Actuation: Activating the pMDI valve to release a predetermined dose of aerosolised drug particles.

Andersen Cascade Impactor: An in vitro system designed to measure output and particle size distribution of aerosolised drugs; consisting of eight stages, a jet stage and a throat model. Each stage represents a different particle diameter fraction.

Contrivance: Knowing how to use an inhaler/spacer device effectively but choosing to use it ineffectively.

Device Compliance: Maintenance of correct pMDI-spacer technique by both the parent and child.

Domiciliary setting: Home setting

FH: Funhaler® spacer, a novel incentive paediatric spacer manufactured by InfaMed, Australia.

Fine Particle Fraction (FPF): The amount of drug available in particles <4.7 μm in diameter.
**Flow-Volume Simulator (FVS):** Replicates human breathing traces by displacing air according to the breathing parameters of the trace.

**Mean Median Aerodynamic Diameter (MMDA):** represents the diameter of the aerosol particles at a cumulative distribution of 50%.

**Pressurised metered dose inhaler (pMDI):** (drug delivery device) - releases a predetermined dose of medication in an aerosol form. The drug is suspended in a propellant and each emitted particle contains the propellant with the drug inside.

**pMDI-spacer:** Pressurised metered dose inhaler used in combination with a spacer device.

**Pneumotachometer:** A device used to measure gas flow by converting differential pressure to a volumetric flow rate.

**Spacer:** (drug delivery device) - a holding chamber for aerosolised drug particles; allows the patient to breathe tidally. Spacers usually have inhalation and exhalation valves.
CHAPTER 1

INTRODUCTION

1.1 Background to the Study

In order to improve asthma care in the paediatric age group, it is important to isolate the sources of variability in drug delivery, and implement tactics to improve delivery of medication. Ineffective drug delivery due to poor inhaler technique is a common problem in young children [1-4], resulting in increased morbidity and greater number of hospital admissions [5-7]. Previous studies have shown that compliance to correct inhaler (pressurised metered dose inhaler- pMDI) technique ranges from 39-68% [7-11]. Non-compliance is believed to be a result of a combination of factors such as poor education on asthma and treatment, poor device training, boredom and apathy [12-14].

The most commonly prescribed delivery system for young children is a pMDI with a valved holding spacer [2]. Accurate use of a pMDI-spacer is imperative to reduce dose variability and increase drug delivery into the lungs [15, 16]. Former studies have not previously assessed the effects of clinic-based technique training by integrating a qualitative analysis (check-list score) with more objective measures, such as drug delivery [17-20]. Furthermore, it is not only crucial to assess drug delivery in a clinical setting, but also outside the clinic, in a more natural setting. The home provides a more realistic representation of drug delivery, as opposed to the clinic, where the child’s ‘best effort’ is normally measured.
Educating patients on asthma and the importance of achieving optimal device technique can be effective in adults and older children, but is less successful in young children [12, 19, 21], as these children cannot understand the benefits and needs of optimal treatment. Moreover, anti-inflammatory drugs do not provide immediate relief and are often delivered when the child is feeling well (symptom-free days) [2, 22]. Consequently, this may account for the low levels of compliance and contrivance (knowing how to use the device effectively but choosing to use it ineffectively) to anti-inflammatory medication [8, 23]. Reasoning with young children can be very difficult [2], particularly if they are under the age of five [21].

In an effort to address this problem a small volume paediatric incentive spacer (Funhaler®; InfaMed, Australia) has been developed. The spacer includes a number of unique features that distract the child from the drug delivery process and provide a means of self-reinforcing effective inhalation technique (Figure 2.3 p. 25). The Funhaler® (FH) consists of a toy arm containing a spinning disc and whistle which is located outside the expiratory valve of the spacer and is activated on exhalation. The toys perform optimally with deep tidal breathing, encouraging good technique by requiring the child to inhale deeply to achieve an adequate exhalation to make the disc spin and whistle sound. This novel device was designed to provide direct positive reinforcement for children on achieving effective inhalation technique [1].

The FH acts as an incentive for young asthmatics, making the drug delivery procedure more enjoyable, whilst encouraging optimal inhalation technique, conducive to effective asthma management. Based on a parental questionnaire, the FH has been shown to increase device compliance and improve inhalation technique in preschool children (2-6 years) over a two-week period [1]. A child's interaction
with the FH (compared to a standard spacer) over a longer period is not known. Additional evaluation, with more objective measures, is needed to verify if the previously observed effects of the FH are consistent.

Furthermore, in vitro breathing simulation methods can be used to assess the effects of inspiratory parameters on drug delivery. The influences of individual breathing parameters using actual human waveforms have not been previously studied [24, 25]. As variability in children is so large, it is essential to analyse each breath from each trace separately.

1.2 Significance of the Study

Poor technique and device compliance remains a major problem in paediatric asthma, resulting in ineffective drug delivery and severe health consequences [1-7]. In order to receive the full benefits of therapy, the prescribed dose must be inhaled into the lungs with each administration [15, 26]. Currently, there are no published studies examining the effects of pMDI-spacer technique training in young children and their parents using a measure of drug delivery. Non-compliance to maintaining proper device/inhalation technique is also a key issue, especially in young children. The FH spacer was developed in an attempt to increase compliance to optimal inhalation technique [1].

This study assesses the effect of clinic-based technique training in children and parents on drug delivery. It also evaluates the way in which children interact with an incentive device, with prolonged use (three-nine months), and the effect this has on drug delivery. Lastly, the influence of age, height, weight, spacer design and
individual breathing parameters are examined on drug delivery using a flow-volume simulator. Previous studies incorporating breathing simulation methods have assessed drug delivery using sinusoidal waveforms only; not actual human traces [24, 25]. This study allows the influence of different breathing parameters to be examined, by using an in vitro model to simulate actual human breathing traces.

1.3 Purpose of the Study

This study investigates the influence of inhalation technique training, using a pMDI-spacer, on drug delivery to preschool-age children. It also assesses if long-term use (three-nine months) of an incentive device (FH spacer) increased device technique compliance, and improved drug delivery, compared to a standard device (Aerochamber Plus spacer), in a clinic setting and a domiciliary setting. Finally, the effects of age, height, weight, spacer design and breathing parameters on drug delivery are evaluated using in vitro procedures. The results from this study will be useful in guiding the development of strategies to improve disease management and the quality of life of young asthmatics.
1.4 Research Questions

1. Will education and reinforcement of correct device technique in children and their parents improve drug delivery?

2. Will use of an incentive device (Funhaler spacer) improve inhalation technique and increase device technique compliance when compared to a standard spacer?

3. Is drug delivery using an inhaler and spacer better in a domiciliary setting compared to a clinical setting where the child is supervised by a health professional?

4. To what extent do breathing parameters, age, height, weight and spacer design affect drug delivery?
1.5 Aims

1. To determine if drug delivery is improved by regular reinforcement of:
   - Correct use of the pMDI-spacer by parents
   - Optimal inhalation technique by preschool children
   - The use of a paediatric incentive spacer

2. To assess intra- and inter-subject variability of drug delivery in a domiciliary setting in preschool-aged children.

3. To evaluate any differences in drug delivery between a clinical setting, where the child is supervised by a health professional, and a domiciliary setting where the 'white coat effect' does not exist.

4. To evaluate the effects of:
   - Breathing parameters
   - Age
   - Height
   - Weight
   - Spacer design

   on the efficiency of drug delivery using pMDI-spacers.
CHAPTER 2

LITERATURE REVIEW

2.1 Asthma

2.1.1 Definition

Asthma is characterised as a chronic inflammatory disease of the central and peripheral airways. Persistently inflamed airways become hyper-responsive [27, 28]; meaning that the smooth muscle around the airway is extremely sensitised, and exposure to an allergen can trigger an acute episode of coughing, wheezing, chest tightness and shortness of breath in susceptible individuals [15, 22, 26]. These episodes are associated with airway obstruction due to constriction and narrowing of the bronchioles, excessive mucus secretion and accumulation, and increased inflammation in the lining of the airways. If asthma is not well controlled, symptoms are recurrent and exacerbated at night, early in the morning, during exercise and when exposed to certain aeroallergens such as dust mites, animal dander, moulds, pollen and air pollution [4, 27, 28].

2.1.2 Airway Inflammation and Remodelling

Asthma is an inflammatory disease of the airways [27, 29, 30]. This inflammatory response occurs due to the interaction between an allergen and an IgE antibody bound on the surface of a mast cell. When the allergen binds to the IgE antibody (antigen-antibody interaction) the mast cell is activated and starts to release histamine and leukotrienes, causing smooth muscle contraction, and increased
vascular permeability and mucus secretion in the bronchioles of the airways [26, 31].
This response is immediate and starts the inflammatory cascade by attracting other
inflammatory cells such as eosinophils, neutrophils and basophils to the site, which
release more potent inflammatory mediators and directly contribute to the overall
inflammation of the bronchial mucosa. This is called the late phase response and the
process occurs within two hours to a few days [31]. The persistent inflammation
sensitises and disrupts the lining of the airways causing airway hyper-responsiveness
[27, 28].

Along with inflammation, structural changes of the airways, referred to as airway
remodelling, occur in all patients with asthma. It is not yet known whether
inflammation and remodelling occur independently or if inflammation is a result or
cause of airway remodelling [28, 32-34]. Airway remodelling consists of smooth
muscle hyperplasia and hypertrophy, sub-epithelial fibrosis, mucous and goblet cell
hyperplasia, and epithelial detachment and regeneration. Collectively, these
structural alterations cause thickening of the airway walls and are thought to be
responsible for airway obstruction and hyper-responsiveness [35].

2.1.3 Diagnosis
Asthma is diagnosed on the basis of family history of asthma or other atopic
diseases, and by recognition of one or more clinical symptoms such as coughing,
wheezing, chest tightness, and dyspnoea [36]. When a dramatic and apparent
response to corticosteroids is seen a patient is said to have asthma [23]. Although
most patients respond positively to inhaled and systemic corticosteroids, there is
however a sub-group of patients with ‘difficult to control asthma’ who are
corticosteroid resistant. These patients respond poorly to high doses of systemic corticosteroids, therefore to reduce serious side-effects early detection of corticosteroid resistance is crucial. Studies suggest that insensitive patients may fail to convert the steroid to an active form, may rapidly eliminate the steroid, may have incomplete glucocorticoid absorption or a reduction in glucocorticoid receptor ligand and DNA binding affinity due to uncontrolled immune activation, possibly triggered by allergens or infections [37, 38].

Three asthma phenotypes have been identified in children: transient wheeze which resolves by age three, non-atopic wheeze in toddlers, and atopic wheeze where 80% of cases begin after six years of age [39]. If severe asthma symptoms are experienced during childhood it is probable that symptoms will persist into adulthood. Conversely, in cases of mild childhood asthma, wheezing and other symptoms are likely to subside before adulthood [36, 40]. Some studies propose that if asthma is diagnosed early in life and if treatment is initiated before six years of age, persistent changes in lung function may be minimised [36, 41]. However, there is some conflict of opinion and more research is needed in this area [42].

2.1.4 Risk Factors for Asthma

2.1.4.1 Genetics

Previous literature has shown that there is a significant genetic component associated with the development of asthma [43, 44]. A study conducted in Northern Sweden revealed that a person with a family history of asthma has a 3-4 fold greater risk of developing asthma compared to someone with no genetic history of asthma [45]. Other studies have documented that the genetic contribution to childhood asthma can
be as high as 75% [46, 47]. Analysis of family pedigree patterns have been shown to best fit with models of polygenetic or oligogenetic inheritance types, indicating that multiple genes may be involved in determining an individual’s susceptibility to asthma [48].

2.1.4.2 Tobacco Smoke

An active smoker has a significantly higher risk of developing asthma as an adult. A study conducted in Northern Sweden documented that current or ex-smokers with a family history of asthma have a 7-fold risk of acquiring asthma when compared to people who have never smoked and have no family history of asthma [49]. Exposure to tobacco smoke in utero alters the development of the foetal immune system which may predispose children to allergic diseases such as asthma [50]. In addition, tobacco smoke exposure during foetal growth and early childhood has been shown to significantly impair lung growth and lung function [51-53]. A meta-analysis study evaluating the influence of tobacco smoke exposure on the development of childhood asthma found that there was a greater risk of acquiring asthma if the parents were smokers [54].

2.1.4.3 Diet/Nutrition

Changes in diet and eating habits may account for the increased rates in asthma cases over the last couple of decades. A current meta-analysis of 12 studies concluded that high body weight among school aged children increased the risk of developing childhood asthma by approximately 50%. The effect of high birth weight was less distinct but still significant [55]. Other studies have found that children in industrialised countries, who consumed high levels of polyunsaturated fats and processed foods,
had an increased risk of developing asthma; low intake of antioxidants and fresh fruits was also associated with an increased risk [56, 57]. A study involving asthmatic children between six to seven years of age showed that an increased consumption of fruits and vegetables daily provided a protective effect against wheezing, whereas large consumption of bread, butter and margarine increased asthma symptoms [57, 58].

2.1.4.4 Allergen Exposure

There is increasing evidence to suggest that exposure to high levels of indoor dust mite allergen is an important risk factor for the development of atopic sensitisation in children, which may facilitate the development of allergic respiratory disease [59-61]. A large prospective study following children from birth to seven years of age found that high exposure to house dust mite and cat allergen significantly increased the development of atopic sensitisation in the first three years after birth and up to seven years of age. Children with a family history of atopy were much more susceptible to asthma with even very low levels of exposure [62]. Conversely, more recent studies have shown that endotoxin exposure during infancy can provide a beneficial guard against allergen sensitization by enhancing type 1 immunity, and thus reducing the risk of allergic airway disease such as asthma [63-65].

2.1.5 Prevalence

Despite increased knowledge of the pathophysiology of asthma, and advances in treatment over the past several years, asthma still remains a major health issue in today’s society [26, 66]. Asthma affects 300 million people worldwide and is the cause of 1 in every 250 deaths worldwide [27]. Globally, the frequency of asthma is
greater in industrialised Western countries (i.e. Australia, New Zealand, UK) than in developing countries with a large rural population (i.e. Eastern Europe, India, Africa) [48, 67, 68]. In addition, data collected in industrialised countries over the last 40 years has shown a significant increase in the prevalence of childhood asthma [48].

A study conducted in 2001 found that Australia has the highest prevalence of asthma in pre-school children, compared to other industrialised countries such as the UK, Canada and USA [56]. The incidence of asthma in Australia is third highest in the world [69, 70] and is continually rising amongst Australian-born children [71]. In a national health survey, parents reported asthma as the biggest health issue affecting their children [72].

2.1.6 Impact of Asthma

Asthma can have a dramatic impact on the affected individual, their family and health services when the condition is not well managed. Poor symptom control leads to increased emergency department (ED) visits and hospitalisations, lost educational experiences due to school or work absence, sleep disturbance, inability to interact in sporting events and an overall lower quality of life [27]. Stanford and colleagues [73] reported that the cost of paediatric asthma related ED visits and hospitalisations in 1997 were approximately $157 million and $669 million respectively; these expenses are likely to have increased due to the rise in prevalence rates and cost of asthma medication. A survey conducted in New South Wales in 2001 revealed that 16% of children (2-12 years old) had visited an ED for an acute asthma episode over the past year [74]. Previous literature has also shown that children 0-4 years of age have the highest rates of ED attendance and hospital admissions in Australia as a result of
poor asthma management [69, 75]. In addition, a survey comparing a cohort of asthmatic and non-asthmatic children documented that overall expenditure for asthmatic children was 2.8 times higher than for non-asthmatic children [76].

It is very difficult to measure the burden of lost opportunities (i.e. decreased social activity, missed work/school days) for asthmatic people and their families. Collectively, people with asthma have over 100 million days of limited activity annually due to chronic symptoms [28]. A 2001 New South Wales health survey reported that 58% of children with asthma aged between 2-12 years could not perform normal daily activities to a satisfactory level in the last 12 months [74]. A study conducted in the United States examined the effects of sleep deprivation due to nighttime symptoms, and found that nocturnal disturbance and school absenteeism were closely associated. The study reported that 40% of children had experienced nocturnal symptoms in the previous month. During the same period, 35% of children were absent from school and 36% of parents reported that their child’s educational performance decreased due to their asthma. The study also showed that if the child’s sleep was disturbed one to three times in a month, 44% of parents missed work and if nocturnal wheezing had occurred on seven nights in the month, 56% missed work [77].

2.2 Asthma Treatment and Therapy

2.2.1 Asthma Triggers

An important aspect of treatment and symptom control is to identify specific triggers which exacerbate asthma symptoms. Asthma triggers can be identified through allergy testing. Patients should avoid exposure to these allergens by implementing
lifestyle and environmental changes. For example, individuals allergic to animal dander should remove pets from the house, and individuals with dust mite allergies should clean their mattresses, pillows and carpets regularly to reduce exposure [59, 78]. However, a study of house dust mite prevention measures has shown that such precautions do not effectively reduce levels of exposure, and that susceptible people are still at risk [79]. Therefore, asthma medication must be available.

2.2.2 Medication

When administered correctly, effective asthma therapy is able to control the pathophysiological processes of asthma in most patients by reversing airway obstruction and managing airway inflammation [80]. The most commonly used medications to treat asthma include short-acting beta\textsubscript{2} agonists, long-acting beta\textsubscript{2} agonists and anti-inflammatory drugs (preventer medication) [27, 28].

2.2.2.1 Beta\textsubscript{2} Agonists

Short-acting beta\textsubscript{2} agonists such as salbutamol, more commonly known as Ventolin\textsuperscript{®}, work by enhancing bronchodilation. These medications, also referred to as ‘rescue drugs’, provide immediate relief of acute asthma symptoms by binding to the beta\textsubscript{2} receptors on the smooth muscles of the bronchioles, causing them to relax and dilate. Symptom relief lasts up to three to four hours [4, 81, 82]. Short-acting beta\textsubscript{2} agonists should only be used to relieve acute symptoms, and if required more than three times a week, anti-inflammatory therapy should be commenced. Long-acting beta\textsubscript{2} agonists such as salmeterol (Serevent\textsuperscript{®}) enhance bronchodilation over a longer period of time. These drugs last up to 12 hours after administration and are used in conjunction with preventer/anti-inflammatory medications [4, 82].
2.2.2.2 Corticosteroids

Long-term therapy for chronic asthma should not be based only on 'rescue' medication and symptom relief. Airway inflammation is the primary cause of asthma symptoms, thus treatment should be focused on suppressing the inflammation with anti-inflammatory medications and normalising lung function. With this aim, day-to-day asthma symptoms will be reduced and a better quality of life will be obtained [82-84]. Prophylactic anti-inflammatory/preventer medications can include both oral and inhaled corticosteroids (ICS). Oral corticosteroids have generally been replaced with ICS in most cases of asthma; however, they are still used in situations of acute asthma exacerbations where the patient is not responding to beta\textsubscript{2} agonists [22].

Corticosteroids are the most potent and effective form of anti-inflammatory medications used to treat chronic asthma [83, 85]. Corticosteroids work by imitating the action of natural hormones produced by the adrenal cortex that are involved in regulating airway inflammation. These steroid hormones act on many cell types, which accounts for both their localised therapeutic effects, and unwanted systemic effects. Corticosteroids pass through the plasma membrane of cells and bind to the corticosteroid receptor in the nucleus, forming a corticosteroid-receptor complex. This complex can activate transcription factors or directly bind to specific DNA sites and alter gene expression. Through these mechanisms corticosteroids block active sites of proinflammatory genes at the molecular level and regulate the release of molecules involved in an inflammation response at the cellular level [85-87].
2.2.2.3 *Inhaled Corticosteroids*

Long-term use of ICS has been proven to reduce airway inflammation and bronchial hyper-responsiveness, thereby decreasing exacerbations and the need for rescue drugs. [22, 88, 89]. Furthermore, it has been shown that ICS provide a protective effect in children and significantly reduce the risk of asthma-related hospitalisations and ED visits [90]. Commonly used ICS include: budesonide, beclomethasone dipropionate (BDP), triamcinolone, flunisolide and fluticasone propionate (FP) [88]. The different ICS drugs vary greatly in terms of topical activity and adverse local and systemic side effects [15, 22]. FP has the benefit of an extensive first-pass hepatic metabolism, which means it has a low oral bioavailability (<1%) [86, 89, 91] and any drug deposited in the gastrointestinal tract is inactivated by the liver [22].

A new inhaled corticosteroid drug, ciclesonide (CIC), has been approved in many countries for use in adults and children over four years of age [2]. This novel drug has been designed as a ‘soft steroid drug’, which means it achieves high local concentrations to the target area with limited systemic exposure and adverse side effects [92]. CIC is inhaled as an inactive complex and is metabolised to its active form in the airways [84, 93]. Once activated, CIC exerts high localised anti-inflammatory activity in the lungs, and is then rapidly metabolised and inactivated [92]. In addition to these pharmacokinetic benefits, CIC has a low oral bioavailability (1%) and a high degree of protein binding (99%), reducing systemic activity and making it, at present, the safest ICS drug [84, 93, 94].
2.2.2.4 Adverse Systemic Side Effects with Inhaled Corticosteroids

Although administering corticosteroids via inhalation is associated with fewer systemic side-effects compared to oral administration, the risks of adverse side-effects are still significant with high doses of ICS. Thus, to reduce unwanted side-effects the minimum effective dose for optimal symptom management should be used, and the amount of drug particles inhaled into the bronchiole tree of the lungs maximised [28, 87, 95]. Local adverse effects in both adults and children can include dysphonia and oropharyngeal candidiasis due to oral deposition of drug particles. These effects can be minimised by implementing good oral hygiene (mouth rinsing and gargling) after use. Other adverse side-effects include adrenal suppression and depletion of bone mineral density [4, 22, 88, 93].

In pre-pubertal children the most concerning side-effect associated with long-term use of ICS is the impact on bone turn-over and growth. The effects on bone turn-over include inhibition of new bone formation and bone reabsorption. These adverse effects are especially troubling in children, who are acquiring bone mass quickly [4, 88]. However, studies examining the effects of moderate ICS use (doses less than 400 µg/day of FP or equivalent) on bone turn-over have not found a detrimental effect [4, 96].

Long-term follow-up studies have shown that growth during childhood can be suppressed with ICS use, however, this effect is short-term, and after the initial impact subsequent growth and final adult height are normal [4, 97-100]. Long-term therapy with doses of up to 200 µg/day of FP or equivalent in children is considered to be safe, with limited risk of adverse effects. The dose response curve for
fluticasone propionate starts to plateau with doses above 500µg/day, and at this point the danger of systemic side-effects is greater [88]. The risks associated with under-treated asthma can be far greater than the risks associated with ICS use. Studies have shown that poor asthma management can affect final adult height severely, as well as cause lung hyper-expansion which can lead to significant chest deformities [100-102].

2.2.3 Delivery Devices

The delivery system is a vital aspect of treatment [5]. Inhalation therapy is the preferred and recommended alternative to oral drug administration for both adults and children. Inhaled aerosol medications deliver the drug directly to the affected site (airways); this results in a rapid therapeutic response, with a lower drug dose required and less systemic side effects [9, 27, 103]. There are currently three main types of inhalational delivery devices for children: dry powder inhalers (DPis), nebulisers, and pressurised metered dose inhalers (pMDIs) with or without an attached spacer [4, 9, 104].

DPis are inspiratory-flow driven [22] and do not require hand-mouth synchronisation. However, the disadvantage of DPis is that the emitted drug dose is dependent on the inspiratory flow of the patient. A low inspiratory flow causes the drug particles to impact in the mouth and throat, and as a result the lung dose is reduced and systemic side effects are increased [105]. The inspiratory force required to receive an appropriate dose from a DPI is generally difficult to achieve for children under eight years, making these devices unsuitable for children below this age group [2, 4, 9].
The two other inhaler devices, nebulisers (Figure 2.1) and pMDIs with a valved holding spacer, are suitable for preschool-age children and do not require synchronising inhalation with the release of drug [106, 107]. The pMDI-spacer combination is more commonly used in this age group as nebulisers are expensive, difficult to operate, may need an external power source, are time consuming (each treatment session takes up to 10-15 minutes) and less convenient [82, 106, 108-110].

Figure 2.1: A nebuliser with a face mask for drug inhalation and a pump for drug aerosolisation.

In addition, up to 90% of the medication can be lost to the environment if the child’s inspiratory flow does not exceed the driving flow of the nebuliser [109, 111]. Studies have also shown that nebulisers significantly increase the heart rate after treatment when compared to pMDIs [106, 112-114], suggesting that there are greater adverse side-effects associated with nebulisation [115]. Furthermore, it has been shown that nebulisers require a much larger loading dose than pMDIs to achieve the same
intrapulmonary delivery [91, 106, 112]. It is estimated that 2000 μg of FP is needed via a nebuliser to achieve the same effect as 300 μg of FP via a pMDI [91].

pMDIs are relatively inexpensive, portable, convenient and require less time to use than nebulisers [106, 112, 113]. The main problem with the use of pMDIs in children under the age of six years is the difficulty of synchronising inhalation with actuation (compressing pMDI to release drug) [22, 106]. However, this can be overcome with the use of a spacer device, which is placed in between the pMDI and child’s mouth (Figure 2.2). A spacer provides a reservoir for the medication from which the child can breathe tidally, making synchronisation less important [104, 116]. Furthermore, spacers decrease the velocity of the emitted aerosol before it enters the mouth, and allow the propellant around the drug to evaporate so that the inhaled particles are smaller and diffuse further into the lungs with decreased oropharyngeal impact [22, 82, 104, 106, 111, 116].

Young children using a pMDI-spacer may need to take several breaths to clear the drug from the spacer [117, 118]; when larger spacers are used, the time taken to empty the drug from the spacer increases. Therefore, small volume spacers are the best option when treating young children, as they allow the drug to be inhaled from the spacer in a more concentrated form [116, 117, 119] before the particles agglomerate and are lost due to sedimentation [2].
Figure 2.2: A child using a pMDI with an Aerochamber Plus® spacer.

One of the problems with plastic spacers is that they can become electrostatically charged on the inside, causing the drug particles to adhere to the spacer wall, and thus compromising drug output [116, 120]. However, this problem can be overcome by coating the inside of the spacer with ionic detergent [118]. Detergent coating of spacers has been shown to significantly reduce electrostatic charge and increase drug delivery by up to 46-71% [121].

2.3 Factors Affecting Drug Delivery

2.3.1 Age, Height and Ventilatory Parameters

There are many factors which affect drug delivery in children, including age, height and breathing parameters such as tidal volume, peak inspiratory flow and inspiratory volume [116, 119, 122].

2.3.1.1 Breathing Simulation

The influence of age, height, weight and breathing parameters on drug delivery can be studied in vitro using a flow-volume simulator (FVS). Pre-recorded human
breathing traces can be simulated through a flow-volume simulator to replicate the patient's actual breathing pattern. The delivered dose of drug that would have been inhaled by the patient is captured on an inspiratory filter inserted between the drug delivery device (pMDI-spacer) and the breathing simulator [123]. While *in vivo* filter data can be correlated with markers of increasing lung size (age, height, and weight) the FVS can be utilised to examine the effects of individual inspiratory parameters, for example lag time, inspiratory volume and inspiratory flow.

Previous studies using breathing simulation methods have incorporated sinusoidal and square waveforms instead of actual human patterns. Investigators have created sine and square waveforms using the average measure for each breathing parameter (tidal volume, peak inspiratory flow, breathing frequency and inspiratory duty cycle) from several regular breathing traces [24, 25]. This method of investigation reduces the variability which is found from breath to breath and patient to patient, especially in children. As intra- and inter-variability is high in children it is vital to incorporate the actual trace for each patient and analyse each breath separately.

2.3.2 Technique, Training and Education

Incorrect use of inhaler devices significantly compromises drug delivery and increases adverse side-effects [5-7]. In order to achieve the full benefits of treatment, competent administration is essential [15, 26, 124]. Incorrect pMDI technique is common among many patients, including adults [125-128], but especially young children [129, 130]. Therefore, training and technique assessment by a health professional is crucial [5, 6, 19, 20, 125]. A study of 55 asthmatic children showed
that only 73% had a near correct technique that allowed any drug to enter the lungs [7].

In young children, the parent is responsible for administering the medication [131]; therefore the parent must be taught how to use the device correctly, and the child how to perform the optimal breathing manoeuvre [21]. The most common errors parents make when administering inhaled therapy include: not shaking the pMDI canister before actuating, not allowing five breaths to be completed before re-actuating and not co-ordinating actuation with the start of inhalation. Errors made by young children include: failure to keep their mouth tight over the mouthpiece of the spacer to stop the drug from escaping, inability to inhale the drug slowly and deeply to minimise impaction of particles in the proximal airways, breathing from the nose instead of the mouth, and forgetting to breath-hold after inhalation to maximise sedimentation of particles [103, 129, 132]. Previous studies suggest that the most beneficial form of education for adults and older children is one which includes both verbal counselling and a physical demonstration [133]; written instructions alone are not an effective measure [134, 135]. Toddlers learn by imitation and repetition, therefore video demonstrations or role-playing situations can be effective teaching methods [18].

Caregivers and patients who receive repeated training sessions are more likely to display competency in device implementation technique when compared to patients with no training [18, 19]. Kamps and colleagues [18] demonstrated that only 57% of children had correct technique after one training session and 98% after three sessions. In order to ensure the device is continually used effectively, monitoring and reinforcement is needed [19, 135, 136]. A previous study found that after patients
had established effective skills, only half continued to use the pMDI effectively in the 1-30 days following the official training session [137].

Contrivance (knowing how to use the device effectively but choosing to use it ineffectively) is also a problem in paediatric asthma [8, 23]. Education and strong communication between the physician and parent/guardian is a crucial determinant of therapeutic success [22, 131, 138, 139]. If the parent does not see their child’s asthma as a severe health problem due to lack of knowledge about the condition, it is likely that device compliance will be poor [28, 140, 141]. The aim of healthcare providers is to impart the importance of correct device technique, and continuous anti-inflammatory treatment, in order to attain better asthma control, reduce exacerbations and reduce the need for aggressive interventions [28, 142]. Education is an integral part of asthma management as it provides patients and their families with a greater understanding of asthma, device implementation skills (and the importance of device compliance), and emergency behaviours, leading to better symptom control and thus reducing associated morbidity [28, 143]. However, whilst education is an effective method for increasing co-operation in older children and parents, it is not so effective in young children, particularly if they are under the age of five where reasoning can be very difficult [12, 19, 21].

2.3.3 Device Compliance

In an attempt to address the issue of device technique compliance in young asthmatic children, an incentive spacer, the “Funhaler” (Funhaler®; InfaMed, Australia), has been developed (Figure 2.3). The spacer features a toy arm with a disc and whistle, so that when the child breathes deeply the disc spins and a whistle sound is created. The incentive toy encourages good technique (deep tidal breathing) and does not
interfere with delivery of medication, as it is separated from the main inspiratory route. The Funhaler (FH) is designed to address the needs of young asthmatic patients by making the delivery process more enjoyable and less boring in an attempt to increase device technique compliance. A two week preliminary study, based on a parental questionnaire, revealed that compliance in children (2-6 years of age) increased with the FH when compared to a standard spacer. However, the long-term effects of such an incentive device are not yet known [1].

**Figure 2.3:** Funhaler Spacer®. A: Parts of the Funhaler spacer. B: A 4-year-old child using the Funhaler spacer with a face mask.

### 2.4 Conclusion

From the review of literature it is apparent that there are many factors that can influence drug delivery in young children; incorrect inhaler technique, the child’s breathing parameters, contrivance and device compliance. The effect of inhaler technique training in preschool children (2-6 years) and their parents has not been extensively examined before. Previous studies have found that training improves
technique, however their results have been based on subjective measures, namely check-list analysis [17-19, 135]. Therefore, more objective methods of assessment are needed to conclusively evaluate the effects of inhaler training. Furthermore, the effect of clinic-based technique training on drug delivery in the home has not been examined. The home provides a more realistic representation of drug delivery as there is no clinical supervision and the child is in a more comfortable environment. Therefore, in addition to clinic-based training, this project assesses drug delivery in the home.

A preliminary study, based on a parental questionnaire, has indicated that the Funhaler® design improves device technique compliance in pre-school aged children (2-6 years) over short-term (two week) use [1]. This project examines the long-term effects of the FH, with more objective measures, on the common problem of device compliance.
CHAPTER 3

MATERIALS AND METHODS

3.1 Materials

3.1.1 Chemicals/Drugs

Methanol (Lab-Scan HPLC grade)

Sodium Hydroxide (NaOH) (Sigma, USA)

Liquid salbutamol Chemical Reference Standard (Glaxo, USA)

Salbutamol pMDI (100μg/actuation, Ventolin®)

3.1.2 Equipment

Inspiratory Filters (Hydrophobic membrane Uni-Filter Junior Datex-Ohmeda)

Aerochamber Plus Spacer® (AC+, Trudell Medical International, Canada, 135ml)

Funhaler Spacer® (FH; InfaMed, Australia, 225 ml)

Flow-Volume Simulator (Series 1120 Hans Rudolph, Kansas, USA)

Pneumotachometer (RSS 100 Hans Rudolph, Kansas, USA)

UV Spectrophotometer (UV-1601, Shimadzu Scientific, Japan)

Buchner flask

Reticulated vacuum/suction system

Digital Video Camera (Canon 2.0 Mega Pixels MVX3i)
Flow Chamber Perspex Box

1L Calibration Syringe (Koko, Pulmonary Data Service Instrumentation)

Andersen Cascade Impactor (ACI; Andersen Instruments, USA)

Vitalograph (Model DFM2, Copley Scientific, UK)

3.2 Study Population

Ethical approval for this study was obtained from Princess Margaret Hospital Ethics Committee (Registration No. 933/EP) and the Human Ethics Sub-Committee Faculty of Computing Health and Science, Edith Cowan University, Joondalup.

The study involved a cohort of 47 children between 2.5-7.5 years of age with mild, stable asthma who were on daily inhaled anti-inflammatory medication (fluticasone propionate) and did not suffer from any other lung disorders. The 47 patients were recruited from a larger trial (Funhaler Trial) which is currently being undertaken at Princess Margaret Hospital for Children in Perth, Australia. The trial involves monitoring asthma symptoms and compliance therapy in children using either an Aerochamber Plus® (AC+; Trudell Medical International, Canada) or a Funhaler® (FH; InfaMed, Australia) spacer device, over a 12 month period. Of the 47 patients in the present study, 24 were part of the AC+ spacer group (15 male, mean age 63.7 months, range 30-90 months), and 23 were part of the FH (14 male, mean age 60.5 months, range 36-90 months). Four children (AC+: n=2, FH: n=2), with a mean age of 51 months (36-60 months) were identified as nose breathers. These children were analysed as a separate group. All patients had used either the AC+ or FH for a period of three to nine months (depending on the number of visits they had previously attended for the Funhaler Trial). The participants’ parents or caregivers were
provided with both verbal and written information regarding the study on their regular attendance for the Funhaler Trial. Parents were assured they were free to refuse participation or withdraw their child from the study without prejudice to future asthma care. On agreement to take part in the study parents were asked to sign an informed consent (Appendix I p. 87) on their child’s behalf.

3.3 Study Design

The present project was divided into three categories: clinic visit, domiciliary filter study and in vitro procedures (Figure 3.1).

3.3.1 Clinic Visit

3.3.1.1 Spacer Technique Evaluation and Training

Initially parents and children attended a clinic visit where two filter studies were performed. The first study involved a pre-training filter analysis. The parent was asked to administer five single actuations of pMDI salbutamol (100µg/actuation, Ventolin®) while the child breathed for five tidal breaths in between each actuation, using the technique normally employed at home. Each child used the spacer he/she was randomised to. Salbutamol was captured on a low resistance inspiratory filter (Uni-Filter Junior Datex-Ohmeda) with a minimum dead volume (<50ml), which was placed between the child’s mouth and their spacer (Figure 3.2 & 3.3). The aerosol was drawn onto the filter- the child did not inhale any drug into their body. Both the parent and child were video-recorded (using a digital camera which was connected to a desk top computer containing a multi media software program) in their attempt to use the device optimally. As part of the clinic training process, the technique employed by both the parent and child was assessed according to a
criterion checklist (pre-training evaluation; Appendix II p. 91), and any errors in the parent’s administration technique and the child’s inspiration technique were corrected by physical demonstration and verbal instructions.

The number of training sessions the parent and child had received prior to their clinic visit for the present study was dependent on the number of visits they had previously attended for the Funhaler Trial. Children who were recruited at visits one, two and three had received one, two or three training sessions, respectively, before recruitment into this sub-study.
CLINIC VISIT

- Pre-training filter study
- Evaluation of administration procedure and technique training (both parent and child)
- Post-training filter study
- Breathing trace recorded (for in vitro evaluation)
- Domiciliary materials provided

Analysis of drug delivery on pre and post training filters (2 samples collected per child): evaluation of the effects administration technique training on drug delivery in a clinical setting.

DOMICILIARY

- Performed in the child’s home with no study supervisor
- Administration and filter set-up was identical to the clinic filter studies
- A new filter will be used every morning and evening
- Filters were collected at the end of the 1 week period from the child’s home

Analysis of drug delivery over a 1 week period (morning and evening- 14 samples collected per child): evaluation of variability in drug delivery in a home setting.

IN VITRO METHODS

- Breathing pattern transferred to a FVS
- Filter placed between FVS and spacer device (FVS represents child in vitro)
- Administration procedure mimicked the clinic and domiciliary filter studies
- All measurements were taken in duplicates
- Measurement of breathing parameters

Analysis of drug delivery using a FVS: evaluation of the effects of age, height, weight and breathing parameters on drug delivery.

Figure 3.1: Study design. The project was conducted in three areas: clinic visit, domiciliary filter study and in vitro procedures.
**Figure 3.2:** Funhaler spacer attached to a filter. Aerosolised drug is collected on the inspiratory filter, so the child does not inhale any drug.

**Figure 3.3:** Aerochamber Plus spacer attached to a filter with an adaptor. Aerosolised drug is collect on the inspiratory filter, so the child does not inhale any drug.
Subsequently, both the parent and child were asked to watch a one minute educational video featuring either the FH or AC+ spacer, depending on which device the child was randomised to. The FH children did not see the AC+ video and vice versa, however, both videos showed the same caregiver administering medication and the same child performing the breathing manoeuvre. The video demonstrated the optimal breathing technique to be performed by the child (deep slow breathing, five tidal breaths after each actuation) and correct use of a pMDI-spacer by the parent (shaking the canister before each actuation, allowing five tidal breaths before re-actuating). The video also contained information on how to clean the spacer and reduce electrostatic charge by detergent coating. Once the training session was completed a post-training filter analysis was conducted. The same administration procedure was performed as with the pre-training filter study. The parents and children were video-recorded again and their technique was re-assessed (post-training evaluation; Appendix II p. 91). The effects of training were analysed by comparison of the pre- and post-training videos and technique scores (qualitatively) and the total drug recovered on the pre- and post-inspiratory filters (quantitatively; see section 3.4.1 pg. 44).

3.3.1.2 Breathing Recording

Breathing patterns were recorded for all study subjects during the clinic visit using a custom-built transparent flow chamber consisting of a Perspex box and a paediatric pneumotachometer (RSS 100 Hans Rudolph, Kansas, USA). The flow chamber enclosed a small volume spacer and a pMDI (Figure 3.4). These devices were held in position by a special sleeve fitting located on the floor of the box. The front of the Perspex box contained an opening allowing only the mouthpiece of the spacer to
protrude whilst keeping the exhalation valves of the spacer inside the box. The roof and the side of the box also contained small openings. The opening on the side allowed a bias flow of medical air to enter the box via a tube. Medical air was introduced at a constant flow rate of approximately 4 L/min in order to prevent the accumulation of carbon dioxide in the box from exhaled air. The pneumotachometer was placed in the opening on the roof of the flow chamber to record the child’s breathing pattern. The air flow through the two spacer devices is shown in figure 3.5.

**Figure 3.4:** Custom built flow chamber used to record breathing patterns in children using either the Aerochamber Plus (pictured) or Funhaler.
Figure 3.5: A: Air entrainment through the Aerochamber Plus spacer. B: Air entrainment through the Funhaler spacer. Green arrows represent inhalation flow and red arrows represent exhalation flow.

The flow chamber was kept air tight during the recording procedure and changes in air pressure (air inhaled and exhaled through the spacer) were measured through the membrane in the pneumotachometer. The pneumotachometer was connected to a desk top computer which held the controlling software (Research Pneumotach System, KORR Medical Technologies; Windows Software Version 3.07b), designed to record breathing traces. Before each recording the pneumotachometer was calibrated with a 1L syringe (Koko, Pulmonary Data Service Instrumentation) and the temperature and humidity in the clinic room was recorded. Each patient was administered one actuation of a placebo pMDI via an actuation port on the flow chamber at the start of inhalation and was asked to breathe for ten tidal breaths through the spacer whilst their breathing pattern was recoded. Each trace was digitally recorded at a flow range of 0-100L/min at 50Hz via a computer and was stored in a RSS (Really Simple Syndication) file format.
All breathing traces were recorded using the spacer type the study subject was randomised to. A clean detergent coated spacer (Anionic Detergent: Liquid Pyroneg, Diversey, Australia) was used for each new recording. To keep the procedure as natural as possible for the child, the flow chamber was designed to ensure minimal difference in the child’s normal drug administration experience. The breathing pattern from each subject was later simulated in vitro using a Flow-Volume Simulator (FVS) (see section 3.3.3.2 pg. 39).

3.3.2 Domiciliary Filter Study
At the end of the clinic session parents were provided with all the materials needed to perform the domiciliary filter study (instruction sheet, 14 inspiratory filters, a new salbutamol pMDI, filter labels and a storage box).

The domiciliary study was completed by the parent and child in their home, without supervision from the researcher (JM). The filter-inhalation set-up and technique required to perform the study was demonstrated to the parent/s at the clinic visit by the researcher and a take-home instruction sheet with diagrams was also provided. Two filter set-up systems were used in this study, depending on which spacer type the child was randomised to (Figure 3.2 & 3.3 pg. 32).

The filter set-up and administration procedure was identical to the pre- and post-training filter studies performed in the clinic. The aerosolised drug was collected on an inspiratory filter that was placed between the child’s mouth and their spacer - the child did not inhale any drug into their body. When the salbutamol pMDI (100µg/actuation, Ventolin®) was actuated the quantity of drug which would
normally be inhaled is deposited on the filter; this equates to the ‘total body dose’ of drug which would have been inhaled by the child. The domiciliary study was performed using the filters provided and the study medication for a period of one week, after every normal routine administration of anti-inflammatory medication (normally taken twice daily- morning and evening). Parents were asked to administer five single actuations of salbutamol (shaking the pMDI before each actuation), while the child took five tidal breaths from the spacer in synchronization with each actuation. Before each administration, parents attached a new filter to the spacer, thus 14 samples were collected (two samples per day) for each child. After each filter was completed parents were asked to wrap the filter in aluminium foil and store it in the box provided until all filters were completed and collected from their home by the researcher. Each filter was identified by an adhesive label affixed by the parent, detailing filter number and time of day (am/pm).

This section of the study assessed daily variability of drug delivery in a more natural setting. The home filters provide a more realistic representation of the total drug administered as the delivery process takes place in the child’s natural environment. The child’s regular medication regimen was not interfered with during the study as the filter process took place after every prescribed administration and no additional medication was inhaled.
3.3.3 In Vitro Procedures

3.3.3.1 Waveform Conversion

Each original recorded breathing trace stored in a RSS file format was converted to a FVW file format for compatibility with the FVS. Breathing traces were converted using a waveform conversion program (RSS Waveform Editor, Hans Rudolph). The program was able to subtract the bias flow (in L/sec) from the waveform which was introduced during the recording. The same program was used to digitally cut the first five consecutive breaths from each ten-breath breathing trace. The first five breaths were used to keep all in vivo and in vitro procedures consistent (Figure 3.6).

Figure 3.6: A representative five-breath breathing trace. Negative flow represents inhalation and positive flow represents exhalation.
3.3.3.2 Breathing Simulation

All recorded breathing traces from each child were simulated through a Flow-Volume Simulator (FVS) (Series 1120 Hans Rudolph, Kansas, USA). A FVS is a computer-controlled device consisting of a cylindrical piston which displaces air according to the recorded breathing parameters of each breathing trace. An inspiratory filter was placed between the breathing simulator and the spacer to capture the delivered drug (Figure 3.7). The quantity of drug on the filter represented the 'total body dose' of particles inhaled by the child. As with the clinic and domiciliary filter studies, a total of five separate actuations of pMDI salbutamol (100μg/actuation, Ventolin®) were delivered into the spacer. After each actuation the five-breath trace was simulated to 'inhale' the drug (salbutamol was actuated simultaneously with the start of inhalation). The salbutamol pMDI was shaken thoroughly before each actuation. For each breathing trace the procedure was repeated to obtain duplicate measurements. All inspiratory filters, spacers and actuators were assayed as detailed in section 3.4.1.
Figure 3.7: A: Flow-volume simulator used to replicate breathing patterns recorded in children. B: Spacer, Filter, pMDI attached to the FVS; the filter between the breathing simulator captures the delivered drug.
Differences in the ambient conditions between the time of recording and the time of simulation can alter the flow volumes, therefore before each simulation the temperature and humidity of the room was entered into the FVS program which automatically corrected for any differences. Furthermore, prior to use, all spacers were detergent coated in a 1:125 dilution of ionic detergent (Liquid Pyroneg, Diversey, Australia) for 30 minutes and left to drip dry for 24 hours to diminish electrostatic charge. The weight of the canister was measured before and after every trial. The canister was disposed of at a weight of approximately 15g as doses become more unpredictable after this weight.

3.3.3.3 Validation of the Flow-Volume Simulator

The use of a breathing simulator is based on the assumption that it will accurately simulate a real-life human breathing trace and show a correlation between in vivo and in vitro drug delivery. Therefore, an important part of this project was to validate whether the FVS was able to replicate an in vivo measurement of drug dose. Eighteen breathing traces from healthy adult subjects (40% male) aged 21-32 years (mean age 25) were recorded using a transparent flow chamber (the same flow chamber was used to record the study subjects breathing patterns at the clinic visits) whilst in vivo drug filter samples were taken. The airtight flow chamber contained a small volume spacer (AC+) for measurement of in vivo drug delivery and a pneumotachometer to record the subject’s inspiratory parameters. Five individual actuations of pMDI salbutamol were delivered into the spacer. Before each actuation the pMDI was shaken vigorously and the subject’s breathing trace was recorded (i.e. a total of five breathing traces were recorded per subject). Salbutamol was captured on an
inspiratory filter placed between the spacer and the subject’s mouth (one filter was used per subject).

In order for the FVS to recognise the breathing traces, each original recording was converted from an RSS file to a FVW file format where the bias flow was subtracted from the waveform. The breathing traces were then transferred to the FVS (FVS represents the subject *in vitro*). An inspiratory filter was placed between the FVS and the AC+ spacer to capture the drug. As with the breathing recording procedure a total of five actuations of pMDI salbutamol were administered into the spacer device individually. With each actuation the pMDI was shaken and the five separate breathing traces for each subject were simulated in order of recording. One filter was used per subject (i.e. for all five actuations and five breaths). All inspiratory filters were analysed as detailed in section 3.4.1. There was a significant correlation between *in vivo* and *in vitro* drug measurements (Figure 3.8).
Figure 3.8: A regression line showing the mean and ±1.96 SD of FVS drug dose (in vitro) vs. in vivo drug dose. There was a significant correlation ($r^2 = 0.85$, $p < 0.001$) between the two measurements of drug delivery.

3.3.3.4 Measurement of Breathing Parameters

The breathing parameters were measured for each recorded waveform. The original (RSS file format) breathing trace was converted to a SIG file format using the software that was initially used to record the breathing trace. The data from each original waveform was then displayed and the bias flow (L/m) was removed. Each breath from each waveform was analysed separately using a custom made software program (Breathing Simulation Calculation- BSC; Programmer: Brad Zhang, Princess Margaret Hospital) on the following breathing parameters: tidal volume, inhalation volume, inhalation time, exhalation volume, exhalation time, peak inhalation flow, time to peak inhale, peak exhalation flow and time to peak exhale. The influence of these breathing parameters, age, height and weight were assessed on drug delivery.
3.4 Drug Analysis

3.4.1 Drug Recovery

Aerosolised salbutamol was recovered from inspiratory filters, actuators and spacers using HPLC grade methanol. NaOH (0.1M) was added to all samples to increase the absorbance sensitivity, and salbutamol was quantified using an ultraviolet (UV) spectrophotometric method. To wash the filters, each filter was placed over the neck of a Buchner flask, which was connected to a vacuum. Methanol was drawn through the filter membrane, and collected in the flask. The solution was transferred into a 50 ml volumetric flask containing 5 ml of NaOH, and methanol added to achieve a final volume of 50 ml. Actuators used during the breathing simulation procedure were washed with methanol into 25 ml volumetric flasks, each containing 2.5 ml of NaOH. Methanol was added to achieve a final volume of 25 ml. Spacers were washed twice; methanol from each wash was transferred to two separate 50 ml volumetric flasks with 5 ml NaOH, and methanol added to make a final volume of 50 ml.

The salbutamol content of all samples was determined using a UV spectrophotometer (UV-1601, Shimadzu Scientific, Japan) at an optical wavelength of 246 nm, which has been established from a calibrated analysis. All absorbance measures were performed in duplicate and the mean for each was calculated. A five-point standard curve was prepared each day using chemical reference salbutamol, with concentration doses of 0.2, 0.5, 1.0, 1.5 and 2.0 µg/ml. Each standard contained a 10% (v/v) 0.1 M NaOH. Standard curves were linear within the concentration range of 0.2 to 2.0 µg/ml. Methanol containing 10% (v/v) 0.1M NaOH was used as a blank. The amount of salbutamol in each sample was calculated (using the mean absorbance
measure) from the standard curve that was prepared at the time the sample was measured. The standard deviation and %CV for each sample was also calculated.

3.4.2 Validation of Method of Drug Recovery from Inspiratory Filters

The method of recovery and assay of salbutamol from inspiratory filters was validated by placing a known amount of salbutamol on the filter membrane, then extracting and analysing the amount of drug retrieved from the filter. Three different doses of salbutamol were used: low (12.5 μg), medium (50 μg) and high (1250 μg), and each dose was tested in triplicate. Filters were assayed as detailed in section 3.4.1. The mean (range) absolute dose and proportion of drug recovered is shown in Table 3.1.

Table 3.1: Validation filter results performed with salbutamol. The mean drug recovered from the three repeats; expressed in absolute values and as a percentage (%) (range). The standard deviation and percent coefficient of variance (%CV) also shown for each dose.

<table>
<thead>
<tr>
<th>Dose (μg)</th>
<th>Mean Dose Recovered (μg)</th>
<th>Mean % Recovery</th>
<th>STDEV</th>
<th>% CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>25.0 μg</td>
<td>24.86</td>
<td>99.43 (98.3-100.6)</td>
<td>1.18</td>
<td>1.18</td>
</tr>
<tr>
<td>50.0 μg</td>
<td>49.75</td>
<td>99.49 (99.1-100.3)</td>
<td>0.68</td>
<td>0.68</td>
</tr>
<tr>
<td>250 μg</td>
<td>243.07</td>
<td>98.23 (96.8-97.4)</td>
<td>0.34</td>
<td>0.36</td>
</tr>
</tbody>
</table>

3.4.3 Actuator Validation

Inconsistent dosing can be caused by differences in actuator moulds. Moulding can vary from batch to batch; therefore it is important to test different actuator batches for variable dosing. An Andersen Cascade Impactor (ACI; Andersen Instruments,
USA), consisting of eight stages, a jet stage and a throat model (Figure 3.9), was used to test six randomly selected actuators. Each stage of the ACI represents a different particle size fraction with cut-off diameters of 9.0, 5.8, 4.7, 3.3, 2.1, 1.1, 0.7, 0.4 and 0 μm. The particle size distribution was calculated by evaluation of drug impaction on each stage of the ACI. The fine particle fraction (FPF) corresponds to the amount of drug available in particles <4.7 μm in diameter, and are most likely to deposit in the lung. The mass median aerodynamic diameter (MMAD) of an aerosol examines the aerodynamic behaviour of the particles. The MMAD represents the diameter of the aerosol particles at a cumulative distribution of 50%.

Each actuator was adapted to the throat of the ACI; ten actuations of salbutamol pMDI were dispensed into the ACI in total (the pMDI canister was shaken for ten seconds between each actuation), while a constant flow of 28.3 L/minute was drawn through the ACI via a pump. The flow was calibrated using a digital flow meter (Vitalograph; Model DFM2, Copley Scientific, UK). All components of the ACI and actuator were washed separately with methanol in 25 ml volumetric flasks; the drug content was assayed using a UV spectrophotometer as detailed in section 3.4.1. The drug output from each actuator was calculated by analysis of drug particle impaction on each stage, the throat and actuator. There was minimal difference in drug output between the individual actuators. These results are summarised in table 3.2 and figure 3.10.
Figure 3.9: An Andersen Cascade Impactor; consists of a throat, jet-stage, eight-stages and a pump port. Broken arrows represent the flow direction at 28.3 L/min.

Table 3.2: The total recovery, total exiting actuator, particles exiting actuator with <4.7 μm shown in absolute values (μg) and percent of total recovery shown for each actuator. Mass median aerodynamic diameter (MMDA) also shown for each actuator. There were small discrepancies between the individual actuators.

<table>
<thead>
<tr>
<th>Actuator</th>
<th>Total recovery (μg)</th>
<th>Total exiting actuator (μg)</th>
<th>Exiting actuator &lt;4.7 μm (μg)</th>
<th>Total exiting actuator (%)</th>
<th>Exiting actuator &lt;4.7 μm (%)</th>
<th>MMAD (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>93.2</td>
<td>78.2</td>
<td>23.1</td>
<td>83.9</td>
<td>24.8</td>
<td>3.3</td>
</tr>
<tr>
<td>2</td>
<td>91.6</td>
<td>78.6</td>
<td>21.7</td>
<td>85.8</td>
<td>23.7</td>
<td>3.2</td>
</tr>
<tr>
<td>3</td>
<td>92.7</td>
<td>82.9</td>
<td>19.4</td>
<td>89.5</td>
<td>20.9</td>
<td>2.9</td>
</tr>
<tr>
<td>4</td>
<td>92.7</td>
<td>81.3</td>
<td>24.0</td>
<td>87.7</td>
<td>25.9</td>
<td>2.9</td>
</tr>
<tr>
<td>5</td>
<td>91.3</td>
<td>78.5</td>
<td>23.4</td>
<td>85.9</td>
<td>25.7</td>
<td>2.8</td>
</tr>
<tr>
<td>6</td>
<td>92.7</td>
<td>79.3</td>
<td>25.6</td>
<td>85.6</td>
<td>27.6</td>
<td>3.0</td>
</tr>
</tbody>
</table>
Figure 3.10: The cumulative distribution (%) and particle diameter (µm) for each actuator tested. There were minimal differences between the six actuators tested.

3.5 Data Analysis

All statistical analyses were completed using SPSS software program (Version 12). A statistician was also consulted to confirm that all analyses were conducted appropriately. All filter doses were expressed as the amount (µg) of drug deposited on the filter per 100 µg actuation. Nose breathers were excluded from all analyses and were assessed as a separate group. The effect of immediate training was assessed by a two-way analysis of variance (ANOVA). Spacer type (AC+ / FH) was analysed as a between subject factor, and the clinic training filters (pre and post) as within subject factors. In addition, a one-way ANOVA was also performed to assess the effect of repeated training on drug delivery by comparison of post-training filter doses with the number of training sessions.
The mean and standard deviation (SD) was calculated for each of the 14 domiciliary filters collected from each child. The effect of any significant differences in drug delivery in the domiciliary setting was assessed using a three-way ANOVA, comparing spacer type (AC+ FH) with day (1-7 days) and time of day (am/pm). A two-way ANOVA was also used to evaluate if there were any significant differences in drug delivery between the domiciliary setting and clinic setting. Spacer type was used as a between subject factor and the average of the 14 domiciliary filters were compared with the clinic post-training filter as within subject factors. A generalised estimating equation with robust standard errors (weighted analysis) was also performed to validate whether the difference in filter samples between the clinic and home setting influenced the results. Furthermore, an independent t-test was used to compare the age distribution between the two spacer groups in order to validate if age was a confounding factor for any of the between subject comparisons.

Coefficient of variance was used to assess intra- and inter-technique variability for the FVS analysis. Regression analyses were performed to examine the effects of age, height, weight and certain breathing parameter (tidal volume, inhalation volume, inhalation time, exhalation volume, exhalation time, peak inhalation flow, time to peak inhale, peak exhalation flow and time to peak exhale) on drug delivery.
CHAPTER 4

RESULTS

This project was divided into three major categories evaluating the effects of *in vivo* device technique training, *in vivo* drug delivery in the domiciliary setting and the influence of age, height, weight and different breathing parameters on *in vitro* drug delivery.

4.1 Study Population

The demographics of the study population for this project are summarised in table 4.1. A total of 47 children, 24 of whom were allocated to the FH arm and 23 to the AC+ arm, attended a clinic session and underwent drug delivery assessment and training. Of the 47 children recruited, four were analysed separately as these children were identified as nose breathers (Table 4.1; nose breathers), and an additional two withdrew from the domiciliary study after the clinic session was completed. Reasons for withdrawal were non-compliance (n=1; FH) and the child’s daily anti-inflammatory medication being discontinued (n=1; AC+). All study participants were similarly distributed for age and gender between the AC+ group and the FH group (Table 4.1).
Table 4.1: The study population; the mean age (range), gender (percent male) and the spacer used (percent male) of children who attended the clinic session, participated in the domiciliary study and were identified as nose breathers. There were no significant differences in age and gender between the AC+ group and the FH group.

<table>
<thead>
<tr>
<th></th>
<th>AC+ Spacer</th>
<th>FH Spacer</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinic Session (n=43)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (Months)</td>
<td>65.76 (42-90)</td>
<td>60.50 (36-90)</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Gender</td>
<td>33% Male</td>
<td>33% Male</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Domiciliary Study (n=41)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (Months)</td>
<td>66.95 (46-90)</td>
<td>61.33 (36-90)</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Gender</td>
<td>33% Male</td>
<td>33% Male</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Nose Breathers (n=4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (Months)</td>
<td>45 (30-60)</td>
<td>57.5 (55-60)</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Gender</td>
<td>25% Male</td>
<td>25% Male</td>
<td>p&gt;0.05</td>
</tr>
</tbody>
</table>

4.2 Clinic-Based Technique Training

The effect of clinic-based training in pMDI administration and inhalation technique was assessed on drug delivery in this section of the study.

In an overall analysis, the pre-training filter had a higher mean drug dose compared to the post-training filter, however the magnitude of difference did not reach statistical significance (p=0.078). There were no significant differences in technique scores between the pre- and post-training assessments. Also, the type of spacer used (AC+ or FH) had no significant effect on the filter doses (p=0.213). Furthermore, no significant differences were found between the pre- and post-filters within the same spacer group (AC+ p=0.483, FH p=0.105) (Figure 4.1). Finally, repeated training did not result in a significant difference in drug delivery (p=0.151). However, there was a significant difference in pMDI administration and inhalation technique scores at the
baseline visit compared to visits 2 and 3 (p<0.001), but not compared to visit 1 (p>0.05) (Table 4.2).

Figure 4.1: Drug dose (±SD) on the pre and post-training filters within the AC+ and FH spacer groups. The decrease in dose between the pre and post filter was greater in the FH group, but this decrease was not significant.

Table 4.2: Baseline and post-training clinic scores (% of skills performed correctly). There was no significant difference in training scores between baseline and visit one. There was a significant difference between baseline scores and visits three and four.

<table>
<thead>
<tr>
<th>Number of Clinic Visits</th>
<th>Baseline Score (%)</th>
<th>Post-Training Score (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (n=15)</td>
<td>83.9</td>
<td>89.6</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>2 (n=13)</td>
<td>79.7</td>
<td>94.1</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>3 (n=15)</td>
<td>77.4</td>
<td>93.9</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>
4.2.1 Nasal Inhalation

A total of four children, with a mean age 51 months (range 30-60 months) were recognised as nose breathers from both spacer groups (AC+: n=2, FH: n=2). These children were excluded from the overall analyses and were studied as a separate group. The mean of the pre- and post- clinic filter doses for nose breathers and a group of age-matched mouth breathers (n=4) is shown in figure 4.2 (the small numbers didn’t allow demonstration of statistical significance). Despite the distinct discrepancy in drug delivery, technique evaluation scores (percent of correct skills demonstrated) were similar for both mouth breathers and nose breathers (95%, 86% respectively). The effect of nose breathing is further discussed in section 4.5.1.

![Figure 4.2: Clinic pre- and post-training filter doses (±SD). Comparison of drug delivery between patients who performed mouth inhalation (n=4) and nose inhalation (n=4).](image-url)
4.3 Drug Delivery in a Domiciliary Setting

Daily domiciliary inspiratory filters were collected over a period of seven days to evaluate the difference in drug delivery in a more natural, non-clinical setting.

There was no significant difference in drug delivery between the individual days (p=0.331) or the time of day (morning/evening) the medication was administered (p=0.326). There was also no significant effect depending on the type of spacer used and the day it was used (p=0.267), or the type of spacer used and time of day it was used (p=0.131). An overall significant difference was found between morning and evening doses, with evening administration exhibiting significantly higher drug delivery (p=0.001). Within the FH group evening doses were also significantly higher (p=0.015), however, no significant difference was found between morning and evening doses in the AC+ group (p=0.381) (Figure 4.3). Furthermore, a significant difference in drug delivery was found between the AC+ group and the FH group (p=0.032), with the children using the AC+ receiving a higher mean dose (Table 4.3). However, the AC+ group showed greater day-to-day variability, and had a consistently higher standard deviation for both morning and evening doses compared to the FH group (Figure 4.4).
Figure 4.3: Morning and evening doses (±SD) for the seven days and the mean of both morning and evening doses. A: AC+ spacer group (n=20); no significant difference between morning and evening doses. B: FH spacer group (n=21); evening doses were significantly higher.
Table 4.3: The average of the morning and evening doses (µg) for each of the seven days for the AC+ and FH spacer groups. The AC+ group had a significantly higher mean dose than the FH.

<table>
<thead>
<tr>
<th></th>
<th>AC+</th>
<th>FH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>38.02</td>
<td>27.97</td>
</tr>
<tr>
<td>Day 2</td>
<td>38.08</td>
<td>27.33</td>
</tr>
<tr>
<td>Day 3</td>
<td>38.03</td>
<td>28.81</td>
</tr>
<tr>
<td>Day 4</td>
<td>40.02</td>
<td>27.79</td>
</tr>
<tr>
<td>Day 5</td>
<td>35.22</td>
<td>27.70</td>
</tr>
<tr>
<td>Day 6</td>
<td>32.87</td>
<td>28.31</td>
</tr>
<tr>
<td>Day 7</td>
<td>33.39</td>
<td>28.03</td>
</tr>
<tr>
<td>Mean (±SD)</td>
<td>36.52 (2.71)</td>
<td>27.99 (0.47)</td>
</tr>
</tbody>
</table>

Figure 4.4: Morning and evening doses (±SD) for the AC+ and FH spacer. Day-to-day variability was greater in the AC+ group and the standard deviation for each day was consistently higher.
4.4 Drug Delivery in a Domiciliary and Clinical Setting

Overall, there was no significant difference in drug delivery between the domiciliary setting and the clinic setting (p=0.75) (Figure 4.5). The mean drug dose between the two spacer groups in the clinic setting was not significantly different (AC+; 32.11 µg ±14.27, FH; 31.01 µg ±14.27) (p=0.735). On the other hand, when drug delivery was assessed in the domiciliary setting, the AC+ delivered significantly more drug (Figure 4.6). Identical results were obtained using the generalised estimating equation approach (weighted analysis).

![Figure 4.5: Average drug dose (±SD) in the domiciliary and clinic setting. There was no significant difference in drug dose between the domiciliary setting and the clinic setting.](image-url)
Figure 4.6: Average morning and evening doses (±SD) in the domiciliary setting and the post-training filters in the clinical setting. There was a significant difference in drug delivery between spacer groups in the domiciliary setting. However, there was no significant difference in the clinic setting.

4.5 Flow-Volume Simulator Filter Dose Analysis

This section examines *in vitro* the effects of age, height, weight and breathing parameters (tidal volume, inhalation volume, inhalation time, exhalation volume, exhalation time, peak inhalation flow, time to peak inhalation, peak exhalation flow and time to peak exhalation) on drug delivery.

There were no significant differences in the breathing parameters between the AC+ spacer group and the FH spacer group (Table 4.4). Overall, correlations between drug delivery and the analysed parameters were weak ($r^2 = 0.005 - 0.272$). When the two spacer groups were examined separately, significant correlations were found within the AC+ group but not the FH group. In the AC+ group drug delivery was significantly positively associated with peak inhalation flow ($p=0.001$), age ($p=0.002$), tidal volume ($p=0.003$), inhalation volume ($p=0.003$), exhalation volume
(p=0.004), height (p=0.005), weight (p=0.014) and peak exhalation flow (p=0.027) (Table 4.5). Peak inhalation flow and age were the most significantly associated with drug delivery; these two parameters are compared between the two spacer groups in figures 4.7 and 4.8.

Table 4.4: The mean (standard deviation) of the different breathing parameters for the AC+ group and the FH group. There were no significant differences between the two groups.

<table>
<thead>
<tr>
<th>Breathing Parameters</th>
<th>AC+</th>
<th>FH</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tidal volume (mls)</td>
<td>98.81 (65.76)</td>
<td>103.9 (36.36)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Inhalation Volume (mls)</td>
<td>47.88 (31.78)</td>
<td>44.71 (17.27)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Inhalation Time (sec)</td>
<td>0.83 (0.25)</td>
<td>0.93 (0.31)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Peak Inhalation Flow (mls/sec)</td>
<td>5646 (3329)</td>
<td>4537 (1896)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Time to Peak Inhalation</td>
<td>6.41 (8.21)</td>
<td>4.47 (1.34)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Exhalation Volume (mls)</td>
<td>50.73 (34.59)</td>
<td>58.96 (22.20)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Exhalation Time (sec)</td>
<td>1.23 (0.42)</td>
<td>1.02 (0.36)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Peak Exhalation Flow (mls/sec)</td>
<td>4001 (2727)</td>
<td>5052 (1771)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Exhalation Volume (mls)</td>
<td>50.73 (34.59)</td>
<td>58.96 (22.20)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Time to Peak Exhalation (mls/sec)</td>
<td>5.54 (1.57)</td>
<td>5.18 (1.59)</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

Table 4.5: Parameters significantly associated with drug delivery in the AC+ group. Each parameter is shown in order of the strength of correlation ($r^2$) and significance (p-value).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Correlation ($r^2$)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak Inhalation Flow</td>
<td>0.451</td>
<td>0.001</td>
</tr>
<tr>
<td>Age</td>
<td>0.403</td>
<td>0.002</td>
</tr>
<tr>
<td>Tidal volume</td>
<td>0.387</td>
<td>0.003</td>
</tr>
<tr>
<td>Inhalation Volume</td>
<td>0.385</td>
<td>0.003</td>
</tr>
<tr>
<td>Exhalation Volume</td>
<td>0.365</td>
<td>0.004</td>
</tr>
<tr>
<td>Height</td>
<td>0.349</td>
<td>0.005</td>
</tr>
<tr>
<td>Weight</td>
<td>0.278</td>
<td>0.014</td>
</tr>
<tr>
<td>Peak Exhalation Flow</td>
<td>0.231</td>
<td>0.027</td>
</tr>
</tbody>
</table>
Figure 4.7: The effect of peak inhalation flow on drug dose. A: There was a significant correlation between PIF and drug dose in the AC+ group ($r^2 = 0.451$, $p=0.001$). B: There was no significant correlation between PIF and drug dose in the FH group ($r^2 = 0.008$, $p=0.691$).

Figure 4.8: The correlation between age and drug dose. A: There was a significant correlation between age and drug dose in the AC+ group ($r^2 = 0.403$, $p=0.002$). B: There was no significant correlation between age and drug dose in the FH group ($r^2 = 0.005$, $p=0.745$).
4.5.1 Nasal Inhalation

Children who inhaled through their nose were further examined by analysis of individual breathing traces. The difference in breathing trace patterns between a typical mouth breather and a nose breather is shown in figure 4.9. As expected, the drug dose delivered to patients who perform nasal inhalations was extremely low. The difference in mean drug delivery between the nose breathers and a group of age-matched mouth breathers (n=4) is shown in figure 4.10. The small numbers didn’t allow demonstration of statistical significance. This is only preliminary data; further analysis with a larger cohort is needed in order to attain a better understanding of this sub-group of patients.
Figure 4.9: Representative breathing traces. Negative flow represents inhalation and positive flow represents exhalation. A: Breathing trace of a mouth breather. B: Breathing trace of a nose breather; no inhalation is shown on breathing trace, thus the patient is inhaling through their nose and exhaling through their mouth.

Figure 4.10: A difference of 19.89 μg (±SD) in drug delivery in vitro between mouth breathers (n=4) and nose breathers (n=4; mean age 51 months).
Ineffective drug delivery is a common problem in the paediatric age group, resulting in increased symptoms and a decreased quality of life for both children and parents [5-7]. In order to improve future asthma care, it is important to isolate the sources of variability in drug delivery and implement new tactics in an effort to improve drug delivery. The aim of this study was to examine factors that affect delivery of inhaled aerosol medications and investigate whether certain strategies improve drug delivery in pre-school age children.

5.1 Clinic-Based Technique Training

The pMDI-spacer combination is often used incorrectly by children and parents, causing sub-optimal drug delivery to the airways, and thus increasing the risk of adverse systemic side-effects and dangerous asthma exacerbations [5, 6, 129, 130]. The effect of clinic-based technique training on drug delivery was investigated in this section of the project. The population for the present study was recruited from an existing study with a larger cohort, where the children attended regular clinic sessions for 12 months and received device technique training. The number of training sessions received from the larger study was dependent on the number of clinic visits attended, thus the children in the present sub-study had all obtained various amounts of training prior to their clinic session.
In the clinic session two drug delivery measurements were conducted with each child; a pre- and a post-training filter. The pre-filter sample was taken before the parent was trained on pMDI-spacer administration technique and the child on inhalation technique at that visit. Once the training session had occurred and errors were corrected a post-training filter sample was taken.

In order to achieve the full benefits of therapy, effective inhaler technique is essential [15, 26, 124]. Former studies have not previously assessed the effects of clinic-based technique training by integrating a qualitative analysis (check-list score) with a measure of drug delivery. The present study evaluated the parent’s pMDI technique and the child’s inhalation technique, before and after training, according to a criterion check-list of essential procedures, whilst collecting measurements of drug delivery. The effect of immediate training was measured by comparison of the pre- and post-training filters. Overall, there was no significant difference in drug delivery, or technique scores, between pre-training and post-training. Therefore, these results show that clinic-based training had no immediate positive effect on technique or drug delivery. From the qualitative analysis, the most common errors performed were parents not shaking the pMDI canister before every actuation and children taking their mouth away from the spacer after actuation; these findings are in accordance with other studies [103, 129, 132]. The greatest improvement in technique was parents shaking the pMDI canister before every actuation, and as this technique was dependent on the parent it was more easily corrected, as opposed to keeping a tight seal on the mouth piece of the spacer, which was dependent on the child.
Our laboratory has found that shaking the pMDI before every actuation is essential with corticosteroid suspension delivery (i.e. fluticasone), as the drug particles separate rapidly from the propellant, resulting in minimal release of the effective compound (unpublished data). However, previous studies have shown that the drug particles do not separate as rapidly with salbutamol. This was originally shown using CFC salbutamol [144], and has been confirmed in our laboratory using HFA salbutamol (unpublished data). Therefore, once the pMDI canister has been rigorously shaken prior to the initial actuation, shaking between subsequent actuations is not essential. As salbutamol was used as a marker of drug delivery in this study, shaking may not have caused a significant difference in drug dose, however, there may have been a great difference with inhaled corticosteroids. Fluticasone was deliberately not used in the present study due to the masking effect (i.e. not shaking the pMDI within seconds of actuation may result in huge changes in drug delivery), as a range of device technique issues were being examined, not just one. However, since the greatest improvement in technique was shaking of the pMDI canister, it would be worth assessing if this specific change in technique results in a significant improvement in delivery of corticosteroid suspension formulations.

The effect of repeated training was also assessed by comparison of post-training filter doses (i.e. drug dose after training) with the total number of training sessions attended. At the end of the clinic visit all children had acquired two, three or four training sessions in total; this includes any previous training received from the larger study. The results obtained show that repeated pMDI-spacer technique training in pre-school children and their parents had no significant effect on drug delivery. Previous studies have found that regular training improves device technique skills in
both children and parents [17-21]. Based on a standardised check-list of essential
technique steps, Kamps et al. [19] found that 93% of children (mean age 5 years)
who had received at least two training sessions could perform all vital steps
correctly, compared to 58% who had not received repeated training. Foland and
colleagues [20] also assessed the effects of training in older patients (mean age 9.2
years) and found that after repeated training children were able to perform at least
seven out of eight essential steps correctly without prompting. However, these
studies have some limitations, namely, the form of assessment was only qualitative;
thus the patients technique, before and after training, was assessed by the
investigator's perception of competence according to a criterion check-list of
essential device administration procedures and skills. Additionally, these studies
have not shown whether perceived improvement in technique correlates with
improvement in drug delivery and clinical efficacy, which are the most relevant
outcomes. Wilson et al. [145] incorporated an observational analysis (check-list
score) with patient reports of asthma symptoms, and found that technique scores
increased over a one year follow-up and self-reported asthma symptoms decreased.
Nevertheless, it is well established that objective assessment is the most accurate, as
it does not rely on patient reports and observation [13].

The present study integrated both qualitative and quantitative methods of assessment.
Although it was anticipated that there would be a direct correlation between drug
delivery and technique evaluation the results from the present study show that
technique scores improved after three training sessions from baseline, but drug
delivery did not. These results, along with other findings, suggest that while an
observational analysis of technique may be adequate to correct gross errors which
may sufficiently impact on the efficiency of inhaler technique, more objective methods are needed to identify less obvious errors [146]. Pedersen et al. [129] showed that children who had previously been assessed with objective methods, such as lung function measurements, exhibited better technique, as errors were more readily noticed and corrected, compared to children who did not receive this form of training. This issue is of immense importance and has also been highlighted in the present study. By assessing drug delivery, it was possible to identify children who perform nasal inhalation. These children would not have been recognised by a standard observational analysis alone, and consequently the error in technique could not have been corrected. Patients who breathe through their nose inhale very little, if any drug into their body; hence an error that has a huge impact on drug delivery would have been unrecognised if an objective measure was not incorporated in the present study.

This study assessed drug delivery, which is an intermediate measure between an observational analysis and clinical efficacy. Lung function measurements provide a more coherent evaluation of technique performance and clinical efficacy by showing whether the drug is actually inhaled into the lungs, which is the primary aim of training. Future studies should include objective measures based on clinical efficacy, such as lung function tests, to conclusively determine the effects of inhaler technique training and ensure all essential skills are performed optimally.

Qualitative analyses of the clinic-based video-recordings were conducted to closely observe the manner in which the children interacted with the spacer devices. Children using the AC+ spacer appeared to be more focused on their inhalation
technique and the administration procedure, compared to the children using the FH spacer. Children with the FH spacer seemed to treat the spacer more like a toy, and thus were more likely to misbehave and less likely to concentrate on their breathing. Although these results are preliminary, it is plausible to suggest that perhaps children associate the FH spacer with ‘play time’, and as a result may be more inclined to play about during the administration procedure. However, the AC+ spacer may be seen as more of a ‘medical device’, which could possibly encourage children to adopt a more serious attitude during the administration procedure. The behaviour seen with the FH spacer is directly opposite to what was intended with the use of the incentive device.

5.2 Drug Delivery in the Domiciliary Setting

It is not only essential to assess drug delivery in a clinical setting, but also outside the clinic, in a more natural setting. The domiciliary setting provides a more realistic representation of drug delivery, as the ‘white coat’ effect disappears and the child is in a more comfortable environment. This section of the study assessed drug delivery, with use of the AC+ and FH spacer devices, in daily life over a period of one week. In order to keep the home environment as natural as possible a study supervisor was not present during the domiciliary study.

The results obtained showed there was no difference in drug dose between individual days, thus the children did not perform better or worse on certain days. However, the AC+ spacer group exhibited significantly higher drug delivery consistently over the seven days compared to the FH spacer group. In addition, there were no differences between evening and morning doses in the AC+ group; however the FH group had significantly higher evening doses compared to morning doses. These findings
suggest that technique compliance and co-operation was greater with the AC+ spacer compared to the FH spacer. Moreover, the consistency between morning and evening doses in the AC+ group suggests that compliance to good technique was constant with the AC+ spacer regardless of the time of day the spacer was used, but not with the FH spacer. These results are in contradiction to Watt et al. [1] who found that adherence and technique compliance increased in children and parents with the FH spacer, compared to a standard spacer device, in the home setting over a two-week period. However, this study assessed the long-term effects of the FH spacer (all children had been using the FH for a period of three to nine months), using an objective measure, namely on drug delivery. The earlier study was conducted over a shorter period of time (two-weeks) using more subjective measures (parental report via questionnaire). Therefore, even though improvement in adherence and technique was previously seen, the results found here show that when children use the FH spacer over a longer period of time there is no improvement in drug delivery. An explanation for the two opposing findings could be that children are initially excited by the incentive toys and the novel device, however with constant use over time, the novelty begins to fade and children become bored. In addition, even though a study supervisor was not present during the domiciliary study, based on the clinic video evaluations, it is plausible to suggest that children who were using the FH spacer were more likely ‘play about’ in the home, compared to children using the AC+ spacer. Hence, this preliminary data demonstrates that particularly with prolonged use, ‘toy’ incentive devices may actually decrease co-operation and drug delivery to children.
5.3 Flow-Volume Simulator Drug Dose

Isolating factors that are important in drug delivery in young patients is an essential step to improving health outcomes. This component of the project examined the effects of age, height, weight and breathing parameters (tidal volume, inhalation volume, inhalation time, exhalation volume, exhalation time, peak inhalation flow, time to peak inhale, peak exhalation flow and time to peak exhale) on *in vitro* drug delivery. Breathing traces were recorded from all children during their clinic session and were subsequently simulated using a FVS.

The AC+ spacer showed a significant positive association between drug delivery and age, height, weight, tidal volume, peak inhalation flow, inhalation volume, exhalation volume and peak exhalation flow. However, no significant associations were found between any of the parameters investigated with the FH spacer.

Age, height and weight are all indicators of lungs size [147, 148]; thus the positive association between drug delivery and the age, height and weight of a patient suggests that the AC+ spacer provides a form of dose correction for lung size. This means smaller children will inhale less drug compared to larger children when using the AC+ spacer. The advantage of dose correction is that children receive a dose relative to their lung/body size, and as a result fewer side-effects will be experienced. This is especially important with inhaled corticosteroid treatment as there are many potential adverse side-effects associated with over treatment [28, 95].

Drug delivery with the FH spacer was shown to be independent of the child’s age. Furthermore, the non-significant positive association between drug delivery and the
breathing parameters indicates that dose delivery is also independent of the patients breathing parameters. Therefore, the FH spacer would be ideal to use in emergency situations where the child may not be able to perform optimal breathing, but would still receive an adequate dose of medication independent of their age. An example of this could be in situations of airway obstruction, where the child will not be capable of performing effective breathing, but will need a large dose of a beta\textsubscript{2} agonist independent of their age.

5.3.1 Nasal Inhalation

It is difficult to identify patients who perform nasal inhalation by observation, more objective measures are needed. As was the case in this study, children who inhaled through their nose were identified by assessment of drug delivery and analysis of individual breathing traces. There were a total of four children (AC+: n=2, FH: n=2) who were recognized as nose breathers; mean age 51 months (range: 30-60 months). These children were excluded from the overall analyses and were studied as a separate group.

Drug delivery was compared between the identified nose breathers and a group of age-matched mouth breathers, and as expected the dose inhaled by patients who breathed nasally was extremely low. The results show that on average mouth breathers can inhale up to 24 \( \mu \text{g} \) of drug, compared to nose breathers who only inhaled 4 \( \mu \text{g} \). The magnitude of this difference clearly illustrates that with each administration patients who inhale through their nose can receive up to 20 \( \mu \text{g} \) less drug than patients who breathe through their mouth. The use of a nose clip can be incorporated with each administration in an attempt to encourage mouth breathing;
however many children resist this and compliance becomes a problem, especially in the home where children are even less likely to be co-operative. These findings are preliminary and certainly warrant further investigation into this sub-group of patients.

5.4 Comparison of the Two Spacer Devices (AC+ and FH)

No significant difference was found in drug delivery between the two spacers in the clinic setting. However, when tested in the home, the AC+ spacer was shown to provide a significantly higher drug dose compared to the FH spacer. Previous literature has shown that there is considerable variation in drug delivery from different spacer devices in daily life [10, 16]. The domiciliary setting, as opposed to a clinical setting, provides a more accurate representation of drug delivery and device use in a daily life situation, as this is the primary setting where drug administration occurs. Before prescribing an inhaler device, it is important for clinicians to consider that a child's performance in the clinic setting is not always reflected in a daily life situation. By examining the effects of the FH spacer in a clinical and domiciliary setting, it was found that even though the FH would be ideal to use in emergency situations, it would not be ideal for every day use. The children seemed to treat the FH spacer as too much of a toy, which caused the ‘play’ issue, and in turn compromised drug delivery. Hence, with long-term use the incentive effective of the FH spacer appears to vanish.

Drug delivery with the AC+ spacer was shown to be dependent on the patient’s breathing parameters. As children are more likely to show variation in their breathing technique, variability in drug delivery would also be more common with the AC+
spacer. This was evident in the domiciliary study where more variability was seen between doses with the AC+ spacer. However, despite this, the AC+ spacer still delivered a significantly higher dose compared to the FH spacer. This suggests that children exhibit better technique and were more co-operative with the AC+ compared to the FH spacer. Thus, this study has shown that even though the AC+ spacer may have some limitations, children perform better in the home with the AC+ spacer, compared to an incentive spacer such as the FH.

Due to time restrictions, this study was only able to provide preliminary data on inhaler technique training and the use of an incentive spacer device compared to a standard device in pre-school children. These issues will be more comprehensively analysed in the larger longitudinal study. Furthermore, this study was a non-blinded study, thus both investigators and subjects were aware of which spacer type was being used, however as one of study objectives was to evaluate the way children interact with the two different spacer devices, blinding was unsuitable.

5.5 Future Research

Both the present study and the longitudinal study examined drug delivery in terms of the 'total body dose' of drug inhaled by the patients, not drug delivery to the lungs, specifically; therefore future research will involve radio-labelling lung deposition studies, in order to evaluate the deposition of drug particles in the respiratory tract. Furthermore, increasing the sample size and furthering the development of new patient inhaler training strategies, particularly aimed at nose breathers, is another possible area for future research.
REFERENCES


APPENDIX I

INFORMATION LETTER AND CONSENT FORM
Parent Information Sheet

Effect of a paediatric incentive spacer and reinforcement of inhalation technique training on drug delivery to preschool children in both clinical and domiciliary settings.

Randomisation Number: ________  ________  ________  Subject Initials: ________

Date of Birth: ____ / ______ / ________

Introduction:
In addition to your participation in the Funhaler study we would like to invite your child to take part in a filter study that will assess the amount of medication he/she is inhaling. One component of the study will be conducted in the clinic and the other component will take place in your home. We will then compare the amount of medication delivered in a clinic versus a home setting. The reason for this study is to investigate whether the dose of asthma medication received by children is more variable when used daily in the home setting than when used in the hospital clinic setting. This study will involve a sub-group of 40 children from the Funhaler study.

Overview:
This information sheet provides a written overview of the study as well as an explanation of the procedures involved and will also be verbally discussed with you to ensure your complete understanding. Once you feel confident that you understand the study, and if you agree to allow your child to take part, you will be asked to sign a consent form.

Before you learn more about this study, it is important to know that:

- Your child’s participation is entirely voluntary.
- You can continue to participate in the Funhaler Study without taking part in this filter study.
- You can withdraw your child from the study (through verbal notification) at any time without compromising his/her routine medical care in any way.

Background:
Variability in drug delivery due to incorrect inhaler device technique and resistance to treatment is a common problem in paediatric asthma. The effect of clinic-based technique training in young children and their parents has not been extensively researched previously. Assessment of drug delivery in a clinical setting and a home setting will verify if clinical training improves technique and if this improvement correlated with non-variable drug delivery in the home. The Funhaler™ was developed in an attempt to alleviate children's fear of using standard asthma delivery devices. The devices currently available are difficult to use with small children and infants and therefore inefficient. The purpose of the Funhaler™ is to help overcome these difficulties by motivating the child to inhale willingly and effectively by the use of breath-driven toys attached to the device, such as whistles and spinning disks. This study will build on previous research done at Princess Margaret Hospital.
**Procedures:**
In the clinic visit you and your child will be asked to demonstrate your drug delivery technique pre and post training. During the procedure a filter will be placed between the spacer and your child’s mouth so he/she will not receive any drug. The procedure will be videoed taped for qualitative analysis later. The video recordings will be stored electronically on a secure network folder which is password protected and will only be available to the investigator and supervisors. As part of the pre training analysis your administration technique and your child’s breathing technique will be assessed and any errors will be corrected. A 1 minute training video will also be shown. To assess any improvement a post training analysis will then take place.

Following this visit, 14 filters will be dispensed for the home filter study. For a week, you will be asked to give your child their normal prescribed medication first and then repeat the procedure with a filter. The filter will be inserted in between the spacer and your child’s mouth. You will continue to give your child their normal asthma medication, and he/she will not inhale any additional drug when using the filters. You will be shown how to store the filters until we can arrange to collect them.

**Benefits associated with this study:**
By taking part in this study, your child will additionally support the development of a new form of asthma medication delivery from which he/she and other patients might benefit in the future.

**Risks associated with this Study:**
There are no risks involved. Your child’s normal medication will not be interfered with in any way.

**Confidentiality:**
Your child’s research records will be confidential to the extent permitted by law. Your child will be identified by a code, and any personal information from his/her records will not be released. The information will always be treated confidentially and securely stored and you or your child will not be personally identified in any publications about this study. However, representatives of the ethics committee and from the regulatory bodies may check that the information collected during the study is accurate.

**Queries**
If you have any questions or require any further information about this study or your child’s rights, please contact Jasminka Murdzoska on 9340 8452. If you have any complaints regarding the conduct of the study, please contact the Executive Director of Medical Services at Princess Margaret Hospital on 9340 8222.

Thank you for taking the time to find out more about this study.
FORM OF CONSENT

Subject Initials: ____________________  Randomisation Number: ________

I, ........................................................................... have had the study clearly explained
to me
(Given Names)  (Surname)

and I have read and understood the information sheet explaining the study entitled:

Effect of a paediatric incentive spacer and reinforcement of inhalation technique training on
drug delivery to preschool children in both clinical and domiciliary settings.

Any questions I have asked have been answered to my satisfaction.

I agree to allow the participation in this study of

...........................................................................................................  Daughter  /
Son
(Full name of participant) (please circle)

I understand I may decline to enter or withdraw my child from the study at any stage and
without interfering with routine medical care. I have been made aware of my right to access
and request correction of my child's personal data. I acknowledge that I have received a copy
of this form for future reference.

I agree that research data gathered from the results of this study may be published, provided
that my child is not identified. I also give permission for the study investigators, independent
auditors and other regulatory authorities if required to have access to my child's medical
records, in the knowledge that all information will be treated as strictly confidential.

Signature: ........................................................................................................

Dated: .......... day of ................................................. 20 ........

I, ........................................................................................................
(Investigator's full name and signature)

have explained the nature, demands and foreseeable risks and benefits of the study to the
person named above who stated he/she understood the same and have witnessed the
completion of the consent form.
APPENDIX II

TECHNIQUE EVALUATION CHECK-LIST
### TECHNIQUE EVALUATION

#### PRE-TRAINING EVALUATION

**Time:** __________

<table>
<thead>
<tr>
<th>Action</th>
<th>Score</th>
</tr>
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<tbody>
<tr>
<td>Shaking pMDI before each actuation (0=no, 1=sometimes, 2=always)</td>
<td></td>
</tr>
<tr>
<td>Appropriate insertion of pMDI into spacer (0=no, 1=yes)</td>
<td></td>
</tr>
<tr>
<td>Placement of spacer in child's mouth (0=no, 1=yes)</td>
<td></td>
</tr>
<tr>
<td>Single dose actuation (0=no, 1=yes)</td>
<td></td>
</tr>
<tr>
<td>Five tidal breaths through spacer (0=child refuses, 1=uneven/fast breathing, 2=slow even breathing)</td>
<td></td>
</tr>
<tr>
<td>Actuation of appropriate number of doses (0=no, 1=yes)</td>
<td></td>
</tr>
<tr>
<td>Detachment of spacer from mouth after actuation (0=often, 1=sometimes, 2=never)</td>
<td></td>
</tr>
<tr>
<td>Extent of struggling (0=vigorous, 1=slight, 2=none)</td>
<td></td>
</tr>
</tbody>
</table>

**TOTAL SCORE**

**COMMENTS:**

________________________

________________________

________________________

________________________

________________________

________________________

________________________

Signature/Date: ___________________
POST-TRAINING EVALUATION

Was the training video shown?

☐ 1 Yes  ☐ 0 No

If yes, which video?

☐ 1 Funhaler  ☐ 2

Aerochamber

<table>
<thead>
<tr>
<th>Action</th>
<th>Score</th>
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<tbody>
<tr>
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</table>

TOTAL SCORE

COMMENTS: ________________________________________________________________
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Signature/Date: ___________________________________________________________