SPACER INHALATION TECHNIQUE AND DEPOSITION OF EXTRAFINE
AEROSOL IN ASTHMATIC CHILDREN

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ABSTRACT: The aim of this study was to measure airway, oropharyngeal and gastrointestinal deposition of $^{99m}$Tc labelled HFA-BDP, after inhalation via pMDI-spacer (Aerochamber Plus$^{TM}$) in asthmatic children.

A total of 24 children (aged 5-17 yrs) with mild asthma inhaled the labelled drug. 12 children took 5 tidal breaths after each actuation (tidal). 12 children used a slow maximal inhalation followed by a 5-10 s breath hold (breath hold). Simultaneous anterior and posterior planar gamma scintigraphic scans (120 s acquisition) were recorded.

For the ‘tidal’ group, mean (SD) lung deposition (%ex-actuator, attenuation corrected) was 35.4 (18.3)% 47.5 (13.0)% and 54.9 (11.2)% in patients aged 5-7 (n=4), 8-10 (n=4) and 11-17 (n=4) years. Oropharyngeal and gastrointestinal deposition was 24.0 (10.5)%, 10.3 (4.4)% and 10.1 (6.2)%. With the ‘breath hold’ technique, lung deposition was 58.1 (6.7)%, 56.6 (5.2)% and 58.4 (9.2)%. Oropharyngeal and gastrointestinal deposition was 12.9 (3.2)%, 20.1 (9.5)% and 20.8 (8.8)%.

Inhalation of the extrafine formulation with the ‘breath hold’ technique showed significantly improved lung deposition compared with ‘tidal’ breathing across all ages. Oropharyngeal and gastrointestinal deposition was markedly decreased, regardless of which inhalation technique was applied, compared with a previous paediatric study using the same formulation delivered via a breath-actuated MDI.
INTRODUCTION

Asthma is recognised as a chronic inflammatory disease affecting the large and small airways of both adults and children [1-3]. Inhaled corticosteroids (ICS) are recommended as prophylactic treatment of asthma in children with persistent asthma symptoms [4, 5]. Topical airway targeting largely determines the efficacy of ICS [6, 7]. Factors affecting efficacy include the child’s age, the particle size of the aerosol, the delivery device, the inhalation profile and the geometry of the airways [8, 9].

Chlorofluorocarbon propellants are being phased out and replaced with hydrofluoroalkanes (HFA) in pressurised metered dose inhalers (pMDI). Beclomethasone dipropionate (BDP) reformulated with HFA-134a (HFA-BDP or QVAR™, 3M Health Care Ltd, UK) produces an extrafine aerosol as the propellant evaporates, and the aerosol has a mass median aerodynamic diameter (MMAD) of approximately 1.1 µm [10]. The formulation has a lower spray force, a warmer temperature and is in solution, rather than suspension [11]. These changes in the properties of the aerosol are associated with improved lung deposition and improved penetration of the aerosol into the peripheral airways, and this may be associated with improved asthma control and health-related quality of life [12, 13]. Clinical studies have shown efficacy of HFA-BDP at half the dose of CFC-BDP [14-16].

High lung deposition of HFA-BDP delivered after inhalation via a breath-actuated MDI (Autohaler™), has been shown in a previous paediatric deposition study [17]. However, gastrointestinal deposition was up to 60% in children aged 5-14 years after inhalation via Autohaler™. Drug reaching the gastrointestinal tract is unnecessary and may contribute to side-effects [11, 18]. Spacer devices attached to pMDIs are recommended for children using inhaled corticosteroids, to reduce the impaction of the larger drug particles in the oropharynx.
and minimise drug reaching the gastrointestinal tract [19, 20]. Our study aimed to use gamma scintigraphy to assess the deposition of HFA-BDP, delivered via pMDI with attached spacer (Aerochamber Plus™) in children aged 5-17 years. We hypothesized that oropharyngeal and gastrointestinal deposition of HFA-BDP could be markedly reduced, compared with the delivery of HFA-BDP via Autohaler™, while maintaining high lung deposition of the extrafine particles.

Younger children are able to use tidal breathing with spacer devices, thereby minimising problems coordinating their inhalation with actuation. The GINA guidelines suggest that for children who can use the Aerochamber, the optimal inhalation technique is a slow, deep breath in, followed by a breath-hold of about 10 seconds. It is recommended that children who are unable to perform this inhalation technique use tidal breathing [21]. Therefore we also assessed the differences in total body deposition of HFA-BDP delivered via pMDI-spacer with tidal breathing compared with the slow single maximal inhalation technique followed by a 10 second breath hold, where possible. All children included in the study were able to maintain the breath-hold for a minimum of 5 seconds. Both the tidal breathing technique and the breath-hold technique are commonly recommended by clinicians when training children to use pMDI-spacers.

METHOD

Subjects

Twenty five children (all male) aged 5-17 years, with mild, stable asthma were recruited from outpatient clinics at Princess Margaret Hospital for Children. On the study day, each child had weight, height and lung function measured (Table 1). Only those patients with FEV1 > 80% predicted values were enrolled in the study [22]. Children withheld any bronchodilator medication for 4 hours prior to the study. Twenty three children inhaled 2 doses of Ventolin® (GlaxoSmithKlein PtyLtd, Australia) (100 µg/dose) 30 minutes prior to scintigraphy. One
child did not receive Ventolin® prior to scintigraphy, but his FEV1 was 98% predicted. One child was excluded from the study because he could not attain an FEV1 > 80%.

Table 1: Means of height (cm), weight (kg), FEV1 (L) and FVC (L) in the children of ‘tidal’ and ‘breath hold’ groups *

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>N</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>FEV1 (L)</th>
<th>FVC (L)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tidal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-7</td>
<td>4</td>
<td>124.1±4.8</td>
<td>25.1±4.1</td>
<td>1.5±0.2</td>
<td>1.7±0.2</td>
</tr>
<tr>
<td>8-10</td>
<td>4</td>
<td>136.7±8.0</td>
<td>29.3±4.4</td>
<td>1.9±0.3</td>
<td>2.3±0.3</td>
</tr>
<tr>
<td>11-17</td>
<td>4</td>
<td>159.4±17.2</td>
<td>53.9±19.5</td>
<td>3.3±1.0</td>
<td>3.9±1.0</td>
</tr>
<tr>
<td><strong>Breath hold</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-7</td>
<td>4</td>
<td>119.1±5.0</td>
<td>23.6±0.6</td>
<td>1.8±0.3</td>
<td>1.8±0.1</td>
</tr>
<tr>
<td>8-10</td>
<td>4</td>
<td>130.7±14.0</td>
<td>30.4±8.6</td>
<td>1.7±0.5</td>
<td>2.0±0.6</td>
</tr>
<tr>
<td>11-17</td>
<td>4</td>
<td>155.3±8.5</td>
<td>42.9±5.3</td>
<td>2.4±0.3</td>
<td>3.0±0.3</td>
</tr>
</tbody>
</table>

*: Data are presented as mean±SD

Exclusion criteria were past or present diagnoses of cardiovascular, renal or liver disease, known hypersensitivity to beclomethasone dipropionate, previous inclusion in a radiolabel deposition study for research purposes, exacerbation of asthma symptoms within the previous 4 weeks or inability to perform the required breathing technique.

**Inhalation technique**

Each child was trained to perform either tidal breathing (n=12) or a single maximal inhalation followed by a 5-10 second breath hold (n=12). A low resistance filter (Curity®Anesthesia Filter, Kendall, MA) was attached to the mouth-piece of an Aerochamber Plus™ spacer so that the child could rehearse the tidal breathing technique with 5 tidal breaths from the spacer after firing 100 µg BDP. Alternatively the child rehearsed with a single maximal inhalation, followed by a 5-10 second breath-hold. This was repeated 3-5 times, so that the child
understood the correct technique before inhaling the radiolabelled BDP. These groups are referred to as ‘tidal’ and ‘breath hold’ respectively. The children were divided into three subgroups according to age: 5-7 years (n=4), 8-10 years (n=4) and 11-17 years (n=4), in order to compare results with the previous paediatric deposition study which used the Autohaler™ device to deliver the same formulation. Before the deposition study spacers were soaked in a dilute solution of detergent (Pyroneg, DiverseyLever, Australia Pty Ltd) for a minimum of 10 minutes to reduce static and then drip-dried.

Gamma Scintigraphy

A double-headed gamma camera (GCA 7200DI, Toshiba Australia; Perth, Australia) was used for scintigraphic imaging. Each subject had an initial two minute anterior transmission scan in the supine position, using a uniform flood source containing 37 MBq technetium (\(^{99m}\text{Tc}\)). Attenuation factors were derived for each child due to absorption by body tissues as described by Macey and Marshall [23]. After the transmission scan each child inhaled 2- 4 doses of \(^{99m}\text{Tc}-\text{HFA-BDP}(200-400 \mu\text{g})\) so that the dose was within 2-4 MBq, depending on age.

Immediately after inhaling the \(^{99m}\text{Tc}-\text{HFA-BDP}\) each child was instructed to exhale gently into a low resistance filter (Curity®Anesthesia Filter, Kendall, MA), so that the exhaled fraction of radioactive drug could be assessed. The child was then repositioned under the gamma camera and simultaneous anterior and posterior planar scintigraphic images (120 seconds acquisition time) of the chest and abdomen and lateral images of upper airway were obtained. This was followed by a two minute image of the actuator, spacer and filter. Regions of interest were defined for each of the images and total counts were determined for the right and left lungs, stomach, oesophagus, mouth, oropharynx, actuator, spacer and filter. Each total count was corrected for background counts and decay-corrected to the time of the
patient scan. The attenuation factors for each child were derived as well as the geometric means of corresponding anterior and posterior counts. The dose deposited in the lungs was expressed as a percentage of the total dose delivered from the actuator (i.e. % ex-actuator). The pulmonary regional distribution was determined by calculating the ratio of peripherally (P) and centrally (C) deposited activity.

**Ethical Considerations**

Approval for the study was granted by the Princess Margaret Hospital Ethics Committee. Informed consent was obtained from parents and children. The maximum level of radiation dispensed to each patient (2-4 MBq, depending on age) was approved by the Radiation Safety Officer at Royal Perth Hospital and was equivalent to an effective dose of 0.1 mSv. The Australian Radiation Protection and Nuclear Safety Agency (ARPANSA) recommends a limit of 5 mSv for the cumulative effective dose to 18 years for children participating in biomedical research [24].

**Radiolabelling of HFA-BDP**

Radiolabelling of HFA-BDP was performed using a method previously described by Leach [14]. Sodium pertechnetate (Na$^{99m}$TcO$_4$) was extracted into chloroform as tetraphenylarsonium pertechnetate (AsPh$_4$TcO$_4$), followed by evaporation of the chloroform under a gentle stream of nitrogen. A commercial canister of HFA-BDP (QVAR™) was weighed, supercooled in liquid nitrogen, decrimped and the contents rapidly poured into the $^{99m}$Tc-lined canister, recrimped and then reweighed to determine the propellant loss.

Using an eight stage non-viable Anderson Cascade Impactor (Copley Scientific, Nottingham, UK), the particle size distribution before and after radiolabelling confirmed that the contents of the commercial canister were not changed by the radiolabelling procedure. The pMDI was primed and then inserted into the ‘throat’ of the cascade impactor. Twenty doses of
HFA-BDP (100µg/actuation) were drawn into the cascade impactor at a continuous flow of 28.3 L/min, in order to optimise analytical sensitivity and to minimise bounce effects [25]. Particles were either deposited on the standard USP ‘throat’, jet stage, or one of the eight impaction plates and absolute filter, depending on aerodynamic size and were washed off with 25 mL ethanol. The absorbance of BDP (wavelength 238 nm) was measured in each wash by UV spectrophotometry (Shimadzu UV-1601, Kyoto, Japan). The standard curve for BDP was linear ($r^2=1.00$) for concentrations up to 20 µg/mL.

A comparison of the mass of BDP with 99mTc activity levels for each fraction, measured by ionisation chamber (Atomlab 200 dose calibrator; Gammasonics, Sydney, NSW, Australia), confirmed that 99mTc acts as a suitable marker for BDP (Figure 1). It has been shown that BDP levels, determined by high-performance liquid chromatography (HPLC) match the radioactive counts of 99mTc, measured by ionisation chamber, when only three doses of 99mTc-HFA-BDP (100µg/actuation) were sampled and the same radiolabelling procedure was used [14]. The fine particle fraction (FPF) of both radiolabel and drug was calculated as the proportion of the ex-valve dose in particles <4.7 µm in diameter (sum of Anderson plate 3-filter).

The particle size distribution of BDP from each QVAR™ canister used for patient inhalation studies ($n=15$) was measured both pre- and post-labelling. On each study day a comparison was made between the particle size distribution and output of drug (BDP) before and after radiolabelling, with the corresponding 99mTc distribution, to ensure that the contents of the commercial canister were not altered by the radiolabelling procedure. 99mTc output was measured to ensure that the ex-actuator dose of activity delivered to each subject did not exceed 2-4 MBq. After the decay of 99mTc, another particle size distribution of BDP from the labelled canister was made to verify the integrity of the transfer of contents from the commercial canister (Figure 1).
Statistical analysis

With the sample size (12 children in each of experiment groups: tidal breathing and breath hold), the study had more than 80% power to detect 40% of difference in terms of lung doses according to a pre-study calculation. Lung doses, oropharyngeal and gastrointestinal doses and spacer and filter deposition of $^{99m}$Tc-HFA-BDP were presented with means and the corresponding standard deviations (SD). The difference in the regional distribution of $^{99m}$Tc-HFA-BDP was compared between between the ‘tidal’ and ‘breath hold’ groups using Independent Sample T tests and between the three age groups using analysis of variance (ANOVA) respectively. Correlations were estimated between regional distribution and lung function parameters using the Bivariate correlations procedure. Analysis of variance and covariance was further used to compare the means of lung and oropharyngeal and gastrointestinal deposition between ‘breath hold’ and ‘tidal’ groups. In order to minimize the influence of lung function parameters, adjusted means and 95% confidence intervals of lung deposition were presented. The adjusted means were estimated using general linear models assuming that children in ‘breath hold’ and ‘tidal’ groups had the same value of FVC. The adjustment aimed to minimize the influence of the difference in FVC on the lung deposition between the two groups. The interaction on oropharyngeal and gastrointestinal deposition was also explored between age and groups (‘breath hold’ and ‘tidal’) using general linear models. All the statistical analyses were conducted using the SPSS package [26].

RESULTS

During the in-vitro validation procedure the mean (SD) total amount of BDP (ex-valve dose) recovered from the actuator and cascade impactor for these inhalers (n=15) was 96.6 (4.2) µg before radiolabelling (before label), 102.5 (3.0) µg, immediately after radiolabelling (after label) and 95.1(3.8) µg and after radioactive decay (decay label). Mean (SD) FPF was
56.9 (2.5)%, 58.1 (2.5)%, 58.8 (2.7)% and 59.4 (2.1)% for before label, after label, radiolabel ($^{99m}$Tc) and decay label respectively (Figure 1).

Attenuation factors (AF) were generated using the square root of the counts per pixel in the transmission image of the $^{99m}$Tc flood source divided by the counts per pixel in regions of interest (ROI) attenuated by each child [23]. AFs for lung, mouth, throat, oesophagus and stomach ROI ranged from 1.7- 2.7. The regional distribution of $^{99m}$Tc-HFA-BDP in lungs, oropharynx and gastrointestinal tract, spacer and expiratory filter in the ‘tidal’ group is shown in Table 2. The total body distribution is demonstrated in the anterior gamma scintigraphic images in Figure 2. The average proportion of lung deposition for the ‘tidal’ group was 45.9% (range from 14.4 to 67.9%). The coefficient of variation (CV) was 34.0%. The mean (SD) value for the peripheral to central (P:C) ratio for the ‘tidal’ group was 2.3 (0.5). The proportion of deposition in the lungs increased with age and lung function, although it was not statistically significant. Lung deposition tended to increase with age and lung function and was positively correlated with FVC ($r^2$=0.306, $p=0.062$), FEV1 ($r^2$=0.244, $p=0.102$), height ($r^2$=0.304, $p=0.063$) and weight ($r^2$=0.272, $p=0.082$). Since only four children were studied in each of the age groups the statistical power was 0.29 to detect the differences in lung depositions (shown in Table 2) between the age groups.

**Table 2.** Regional distribution (%ex-actuator dose*) of extrafine aerosol $^{99m}$Tc-HFA-BDP (QVAR™) in the tidal breathing groups (tidal): 5-7 years, 8-10 years and 11-17 years

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Lungs  %</th>
<th>Oropharynx + gastrointestinal %</th>
<th>Spacer  %</th>
<th>Expiratory filter %</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-7</td>
<td>35.4±18.3</td>
<td>24.0±10.5</td>
<td>40.2±9.2</td>
<td>0.40±0.26</td>
</tr>
<tr>
<td>8-10</td>
<td>47.5±13.0</td>
<td>10.3±4.4</td>
<td>41.5±15.1</td>
<td>0.66±0.78</td>
</tr>
<tr>
<td>11-17</td>
<td>54.9±11.2</td>
<td>10.1±6.2</td>
<td>30.7±11.5</td>
<td>4.3±4.4</td>
</tr>
</tbody>
</table>

*: Percentage of ex-actuator dose corrected for tissue attenuation and presented as mean±SD.
In the ‘breath hold’ group (Table 3), the average lung deposition of $^{99m}$Tc-HFA-BDP was greater than 50% (range from 45.9% to 68.1%). The coefficient of variation was 11.4%. No significant difference in lung deposition was found between the three age groups. No correlation was found between lung dose, weight, height and lung function parameters FVC and FEV1. The mean (SD) P:C ratio for the ‘breath hold’ group was 2.3 (0.4).

**Table 3.** Regional distribution (%ex-actuator dose*) of extrafine aerosol (QVAR™) in groups using the single maximal inhalation with breath hold (breath hold): 5-7 years, 8-10 years and 11-17 years

<table>
<thead>
<tr>
<th>Age group (yrs)</th>
<th>Lungs %</th>
<th>Oropharynx + gastrointestinal %</th>
<th>Spacer %</th>
<th>Expiratory filter %</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-7</td>
<td>58.1±6.7</td>
<td>12.9±3.2</td>
<td>24.1±7.0</td>
<td>4.9±4.7</td>
</tr>
<tr>
<td>8-10</td>
<td>56.6±5.2</td>
<td>20.1±9.5</td>
<td>18.2±1.6</td>
<td>5.1±4.6</td>
</tr>
<tr>
<td>11-17</td>
<td>58.4±9.2</td>
<td>20.8±8.8</td>
<td>20.3±4.5</td>
<td>0.6±0.6</td>
</tr>
</tbody>
</table>

*: Same as the notes in Table 1

Differences in lung deposition between ‘tidal’ and ‘breath hold’ were compared by adjusting for FVC, so that the difference between the two groups was independent of lung function and directly related to inhalation technique. Figure 3 compares the difference in lung deposition between ‘tidal’ and ‘breath hold’. The total difference in the adjusted means of lung deposition across the three age groups was statistically significant (n=12, p=0.006). In children aged 5-7 years the adjusted mean of lung deposition in ‘breath hold’ was 1.6 times higher than that in ‘tidal’, although the difference was not statistically significant in our small group. In this youngest age group the mean (SD) P:C was 2.5(0.2) for ‘breath-hold’ compared with 2.0(0.5) for tidal breathing.
Figure 4 shows the comparison of the combined oropharyngeal and gastrointestinal deposition of $^{99m}$Tc-HFA-BDP delivered via pMDI-spacer. This was reduced two to four-fold compared to the previously published dose of 40-60% obtained after inhalation of the same formulation via Autohaler™ [17]. For the ‘tidal’ group, children aged 5-7 years had a higher oropharyngeal and gastrointestinal deposition than ‘breath hold’. Conversely, children aged 8-17 years had higher oropharyngeal and gastrointestinal deposition with ‘breath hold’ relative to ‘tidal’ (Figure 4). The crossover interaction between age and ‘tidal’ and ‘breath hold’ groups for oropharyngeal and gastrointestinal deposition was statistically significant ($p=0.016$). We found significantly more drug retained in the spacer with ‘tidal’ compared with ‘breath hold’ across all ages ($p<0.001$, $n=12$).

The exhaled filter dose was difficult to obtain because some children would cough before breathing onto the filter [27]. We measured a mean exhaled filter dose less than 5% across all ages, which is comparable to the mean exhaled filter dose found with the same formulation and the Autohaler™ device.

**DISCUSSION**

Scintigraphic imaging has been widely used to assess pulmonary deposition of inhaled drugs. Lung deposition of extrafine aerosol, delivered to children via pMDI-spacer, using different inhalation techniques, has not been previously reported. The present study supported our hypothesis that inhalation of extrafine particles via pMDI-spacer would result in a high lung dose and show a marked decrease in oropharyngeal and gastrointestinal deposition compared with delivery of the same formulation via Autohaler™[17]. Two-dimensional (2D) planar scintigraphic images were recorded in order to minimise radiation exposure to the children. The study was limited by the small number of subjects within each age group; however, across all ages ($n=12$), the study had an acceptable power of 80%.
Tidal breathing, combined with pMDI and spacer, is a simple inhalation technique for children, as there are no coordination problems associated with inhalation and actuation. Our study has shown that most of the children could obtain lung deposition of more than 30% ex-actuator dose, using tidal breathing with pMDI-spacer. The amount of drug deposited in the lungs of children using tidal breathing tended to increase with both age and lung function, and was remarkably consistent to that shown in children using the same extrafine formulation inhaled via the Autohaler™ device (37-54%) [17]. However, the tidal breathing group showed a greater degree of intersubject variation with a CV 32%. The combined oropharyngeal and gastrointestinal dose deposited in children using pMDI-spacer, was markedly reduced (10-25%) in the tidal breathing technique, compared with the Autohaler™ (40-60%).

With the breath-hold technique, which requires a short training component for children, we have shown high lung dose delivery (over 55% ex-actuator dose on average) of the extrafine formulation QVAR™, independent of age, FEV1, FVC, height and weight and consistent to that shown in adults using the same formulation via pMDI [14, 28]. There was less variability in the dose to the lungs across all ages, shown by a low intersubject CV of 11%. Regarding lung deposition in children 5-7 years, we have shown that the single maximal inhalation technique can improve lung deposition almost twofold (range 51.5-64.8% ex-actuator) when QVAR™ is delivered via pMDI-spacer (Aerochamber Plus™) compared with the Autohaler™ (range 27.7-46.1% ex-actuator).

The children aged 5-7 years tended to have more oropharyngeal and gastrointestinal drug deposition associated with tidal breathing. This observation may be due to reduced laminar flow of the drug particles and more deposition by inertial impaction in the oropharyngeal region. The improved laminar flow and enhanced gravitational sedimentation associated with a slow single maximal inhalation and breath hold would be an advantage for younger
children with smaller airways. This youngest age group also showed a higher mean P:C ratio for the breath-hold technique (2.5) compared with tidal breathing (2.0). This would indicate that there is more peripheral deposition of the extrafine formulation with the breath-hold technique for this age group. The mean (range) P:C ratio in a previous deposition study with children aged 6-16 years inhaling radiolabelled budesonide from Turbuhaler was 1.7(1.0 to 2.4) [29]. Children aged 5-7 years have a lower tidal volume and a lower inspiratory flow rate than children aged 8-17 years, although we did not record these parameters. Inhalations < 60 Lmin\(^{-1}\) have been shown to improve peripheral penetration [8].

Children aged 8-17 years received similar levels of lung deposition of the extrafine QVAR™ formulation, whether using tidal breathing or a single maximal inhalation with a 5-10 s breath-hold. These children also exhibited similar peripheral penetration of the extrafine drug into the airways with either breathing technique. However, there was less variability in dosing associated with the single maximal inhalation technique. The Aerochamber Plus™ has a small chamber volume of 149 mL and was chosen because of its optimal in-vitro characteristics, portability and ease of use. However, the small volume may have been the limiting factor which led to an increase in oropharyngeal and gastrointestinal dose in the children aged 8-17 years, using the ‘breath hold’ technique.

Different modes of inhalation are known to affect drug delivery from both dry powders inhalers and pMDIs [8, 30-32]. Our study has shown that the single maximal inhalation technique, in combination with Aerochamber Plus™, can improve the delivery of HFA-BDP to the peripheral airways of children. The increase in oropharyngeal and gastrointestinal deposition associated with ‘breath-hold’ in patients aged 8-17 years may not be clinically
relevant, whereas the decreased variability of drug delivery via pMDI-spacer with ‘breath-hold’ in all age groups is an important clinical consideration for drug delivery in children. Drug distribution patterns obtained from scintigraphic studies provide information on the effectiveness of aerosol delivery to the lungs and therefore provide an important guide to dosage regimens [33]. We have shown that the extrafine formulation shows an even, diffuse deposition throughout the airways. It has been suggested that high lung deposition, associated with increased absorption via alveolar deposition, may be associated with higher systemic effects and therefore an increased risk / benefit ratio [12]. Efficacy of QVAR™ at half the dose of CFC-BDP [15] means that with regular clinical review and titration of the dose, the improved therapeutic effect associated with targeting the airways could be maintained, while minimising the systemic dose from both lung and oropharyngeal and gastrointestinal deposition. Improved efficacy at a lower dose may result in equivalent control and fewer side effects [4, 12, 34, 35].

Gamma scintigraphy has demonstrated that the extrafine formulation results in an even diffuse distribution of QVAR™ throughout the lungs of adults and children [14, 16] and the increased peripheral deposition may be associated with improved asthma control [3]. Corticosteroid receptors are located throughout the airways [36] and inflammation extends to the alveoli [1-3]. Computed tomography has been used to detect structural changes to the airways of infants and children [37]. Functional high resolution computed tomography (HRCT) imaging has shown that there is reduced air-trapping and improved efficacy when extrafine formulations reach the distal lung [37, 38]. This would indicate the need for more efficient delivery of ICS to the small airways in children with persistent asthma. New inhaled corticosteroid formulations with an extrafine particle size, such as Ciclesonide, should offer both even, diffuse lung deposition, as can be obtained with QVAR™, as well as an improved safety profile [39].
In conclusion, we have shown that spacer inhalation technique can significantly improve lung deposition of the extrafine aerosol delivered via pMDI-spacer in asthmatic children aged 5-17 years. Tidal breathing with pMDI-spacer provided adequate lung deposition of the extrafine formulation, however the slow single maximal inhalation followed by a 5-10 s breath-hold produced less variability in lung dose in all age groups and improved lung deposition in children aged 5-7 years almost two-fold. The degree of variability in dosing is an important consideration when optimising formulation, delivery device and inhalation technique for the specific needs of children. Children from 5 years of age should be encouraged to use this spacer inhalation technique as soon as practicable. Future recommendations for optimising inhaled drug delivery to infants and young children who are unable to perform a slow single maximal inhalation technique could include the combination of pMDI-spacer with an extrafine formulation. Children from 2 years of age could be encouraged to perform a more consistent, regular tidal breathing pattern, perhaps with the aid of an incentive spacer device.
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**Figure 1:** Size distributions of QVAR™ particles before and after radiolabelling (before label, after label), radiolabel (99mTc) in the corresponding size fractions, and QVAR™ particles after radioactive decay (decay label) (n=15). Data are presented as mean (SD) percentages of total dose.
Aerodynamic diameter um

% total drug and % total 99mTc

< 0.4 filter
0.4-0.7 plate 7
0.7-1.1 plate 6
1.1-2.1 plate 5
2.1-3.3 plate 4
3.3-4.7 plate 3
4.7-5.8 plate 2
5.8-9.0 plate 1
9.0-10.0 plate 0
>10.0 jet
throat
actuator

before label
after label
99mTc
decay label
Figure 2: Anterior gamma scintigraphic scans showing regional distribution of radiolabelled QVAR\textsuperscript{TM} in asthmatic children a) age 5-7 'tidal' and b) age 5-7 'breath-hold'; c) age 11-17 ‘tidal’ and d) age 11-17 ‘breath-hold.’
Figure 3: Adjusted means of lung deposition (% ex-actuator, adjusting for FVC) in the two study group: ‘breath hold’ and ‘tidal’.
*: Analysis of variance and covariance was used to compare the means of lung deposition between ‘breath hold’ and ‘tidal’
Figure 4: Mean oropharynx and gastrointestinal (OG) deposition for ‘breath hold’ and ‘tidal’ expressed as a percentage of the ex-actuator dose.