Eur Respir J 2003; 21: 1007–1011
DOI: 10.1183/09031936.03.00087803
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European Respiratory Journal
ISSN 0903-1936

Distribution of technetium-99m-labelled QVAR™ delivered using an Autohaler™ device in children

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ABSTRACT: QVAR™, an extrafine hydrofluoroalkane/beclomethasone dipropionate formulation, has been shown to double lung deposition in adults. The aim of the present study was to assess the total body deposition and distribution of technetium-99m-labelled (^{99m}Tc) QVAR™ in children after inhalation *via* an Autohaler™.

Sixteen male asthmatic children (5–14 yrs) inhaled labelled drug (<4 MBq ^{99m}Tc; 100 μg beclomethasone dipropionate) *via* an Autohaler within 30 min after salbutamol (200 μg) administration. Simultaneous anterior and posterior planar scintigraphic scans (120 s acquisition time) were collected after inhalation of labelled drug.

Mean±SD lung deposition of labelled drug (attenuation-corrected; percentage of ex-actuator dose) was 36.9±9.2, 46.5±11.6 and 54.1±10.7% in children aged 5–7, 8–10 and 11–14 yrs, respectively. Combined oropharyngeal and gastrointestinal deposition was 59.7±8.2, 48.9±12.3 and 40.3±11.8%. Lung deposition positively correlated with the forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC). Gastrointestinal dose negatively correlated with the FEV_1, FVC, height and age.

In older children (11–14 yrs), lung deposition was almost identical to that reported in adults using QVAR™. In children aged 5–10 yrs, lung deposition using QVAR™ was greater than the levels measured using other commercial aerosol delivery systems. Oropharygeal and gastrointestinal deposition was inversely related to age.

Eur Respir J 2003; 21: 1007–1011.

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Keywords: Aerosol delivery to children
lung deposition
paediatric asthma therapy

Received: September 24 2002
Accepted after revision: December 6 2002

This study was funded, in part, by 3M Pharmaceuticals Pty Ltd, Sydney, Australia. S.G. Devadason was supported by a grant from the National Health and Medical Research Council of Australia.

The original devices used for inhalation therapy were designed for adult patients. Although problems with compliance and dose variability with inhaler therapy occur in adults, they are magnified when these devices are used by children. Added to this is a very unique set of considerations associated with choosing an appropriate aerosol device for use by young children. Hence choice of both device and formulation is critical when considering asthma therapy in children.

Children aged ⩾5 yrs can, in theory, be taught specific inhalation techniques, which means that they should be able to use devices such as the Turbuhaler™ (AstraZeneca, Sydney, Australia) and the Autohaler™ (3M Pharmaceuticals, Sydney, Australia), a breath-actuated pressurised metered-dose inhaler (pMDI) requiring a relatively constant inspiratory flow over 2–4 s for optimal use. The Autohaler™ has been shown to improve lung deposition in adults with poor coordination compared to conventional "press-and-breathe" pMDIs [1]. When using the same drug formulation, equivalent clinical efficacy has been shown using the Autohaler™ compared to efficient use of pMDIs in both adults [2, 3] and children [4]. However, the efficacy of these devices and ability to consistently perform the appropriate inhalation technique still needs to be more formally assessed in children aged 5–7 yrs compared to older children.

The reformulation of pMDIs with hydrofluoroalkane (HFA) propellants has resulted in the development of an extrafine form of beclomethasone dipropionate (BDP), known as QVAR™ (3M Pharmaceuticals). The mass median aerodynamic diameter (MMAD) of the QVAR™ formulation is 1.1 μm, which is much smaller than that of the chlorofluorocarbon (CFC)-based formulations (MMAD 3.3 μm) [5]. Use of the QVAR™ formulation has been shown to significantly increase lung deposition in adults compared to other pMDI formulations, when delivered by either pMDI [6] or Autohaler™ [7, 8]. Clinical efficacy studies have also shown that 2.5-times more CFC/BDP is required to achieve the same beneficial improvement in asthma control as obtained using QVAR™ [9]. Since children have a smaller airway diameter than adults, it was postulated that the extrafine formulation would be ideal for use in children with asthma.

Drug delivery to the lungs is likely to be affected by factors such as inspiratory flow, inspiratory volumes and structural aspects of the respiratory system, all of which are likely to change with increasing age. In addition, the pattern of deposition within the body is likely to differ in children using the extrafine QVAR™ formulation compared with adults. In order to determine the efficacy of drug delivery from this device and formulation, a gamma scintigraphic study was undertaken in 16 children aged 5–14 yrs with mild, stable asthma to assess total and regional deposition of technetium-99m-labelled (^{99m}Tc) QVAR™, delivered *via* an Autohaler™.

Methods

Patient selection

Sixteen patients (all male) aged 5–14 yrs with mild, stable asthma were recruited. Each patient was clinically well with

normal respiratory examination results and lung function. Patients were seen prior to the study day for assessment and were instructed in the use of the Autohaler^{TM}. Lung function measurements were carried out on all patients to ensure that only those patients with a forced expiratory volume in one second (FEV1) of >80% of the predicted value [10, 11] were enrolled in the study. Patients were excluded from this study for the following reasons: 1) past or present diagnoses of cardiovascular, renal or liver disease; 2) known hypersensitivity to BDP; 3) inability to demonstrate an adequate inhalation technique using the Autohaler^{TM} after two instruction sessions; and 4) previous inclusion in a radiolabel-deposition study for research purposes.

Approval for this study was granted by the Ethics Committee of Princess Margaret Hospital for Children, Perth, Australia. Informed consent was obtained from parents, and the children who completed the study were willing participants. The maximum level of radiation dispensed to each patient (4 MBq) was approved by the Radiation Safety Officer at Royal Perth Hospital (Perth, Australia), and was equivalent to the additional radiation exposure from a 12-h plane flight, or <3 weeks' natural background radiation.

Radiolabelling of QVAR^{TM} formulation

Radiolabelling of the HFA/BDP formulation was carried out using a previously described method [2]. Briefly, a canister containing the commercial QVAR^{TM} (HFA/BDP) formulation was supercooled in dry ice. ^{99m}Tc in normal saline was eluted from a molybdenum/technetium generator (Australian Radioisotopes, Sydney, Australia) and extracted from the aqueous phase into chloroform using a separating funnel. The chloroform was evaporated to dryness in an empty Autohaler^{TM} canister under a slow stream of nitrogen gas. The Autohaler^{TM} canister, now coated with ^{99m}Tc, was covered and cooled in dry ice. The supercooled commercial canister containing QVAR^{TM} was rapidly decrimped, the contents poured into the Autohaler^{TM} canister containing ^{99m}Tc and a new valve crimped on top. This canister was then allowed to warm up in a water bath to ensure that no leakage of propellant occurred through the crimped valve.

In-vitro *assessment of radiolabelling*

The gamma-scintigraphic technique used in the present study measures the distribution of radiolabel within the body and not drug distribution. Hence, stringent *in-vitro* assessment of the output of radiolabelled BDP from the Autohaler^{TM} device was employed to ensure that the radiolabelling method did not significantly alter the particle size distribution of the aerosol generated by the Autohaler^{TM}, and to confirm that the distribution of ^{99m}Tc reflected that of the drug, thus acting as a suitable marker for BDP. Particle size distribution and total drug delivery was measured using an eight-stage nonviable cascade impactor (Thermo-Andersen, Smyrna, GA, USA) with an inhalation flow of 28 L·min^{-1}. The Autohaler^{TM} was primed and then inserted into the "throat" of the cascade impactor. Twenty doses of radiolabelled BDP were drawn into the cascade impactor with the entraining air flow. Particles were deposited either in the mouthpiece of the Autohaler^{TM} casing or on the "throat", jet stage, one of the eight stages or a filter. The location of particle deposition was determined by the aerodynamic size of the particle.

The mouthpiece and stages of the cascade impactor were washed with 10–25 mL ethanol. Activity was quantified using an ionisation chamber (Atomlab 200 dose calibrator; Gammasonics, Sydney, Australia). The absorbance (at 238 nm) of each sample was measured in duplicate using an ultraviolet spectrophotometric method. The standard curve for BDP was linear (r^2=1.00) for concentrations up to 20 μg·mL^{-1}. The fine particle fraction of both radiolabel and drug was calculated as the proportion of the ex-valve dose of particles <4.7 μm in diameter (sum of Andersen Plate 3-filter). The extrafine particle fraction was calculated as the proportion of the ex-valve dose of particles <3.3 μm in diameter (sum of Andersen Plate 4-filter).

The particle size distribution of drug from each canister used for patient inhalation studies (n=9) was determined both before and after labelling (fig. 1). The distribution of radioactivity from these canisters after labelling was also measured. This was performed to confirm that the labelling procedure had been successfully carried out and to ensure that the ex-actuator dose of activity delivered per actuation did not exceed 4 MBq.

Inhalation procedures

Each patient's inhalation technique was assessed prior to the study, using a Respiratory Training Device (3M Pharmaceuticals). Subjects were taught to exhale to functional residual capacity and then inhale deeply and sustain the inhalation over 2–4 s. Subjects were also asked to breathhold for ⩾10 s after inhalation through the Autohaler^{TM}.

Patients then inhaled a single dose of ^{99m}Tc -labelled HFA/BDP (100 μg nominal dose) from the Autohaler^{TM}. No more than 4 MBq of ^{99m}Tc (exactuator dose) was administered to each patient during the study. During all experiments, the Autohaler^{TM} containing the radiolabelled drug was enclosed in lead sheeting, which allowed air to be entrained through the device as patients inhaled and also permitted measurement of inspiratory flow parameters using the Respiratory Training Device.

Quantification of distribution of activity in patients

An anterior transmission scan of each patient was initially obtained using a flood source containing 37 MBq ^{99m}Tc. Individual values for attenuation of activity due to absorption by body tissues were calculated as described by MACEY and MARSHALL [12].

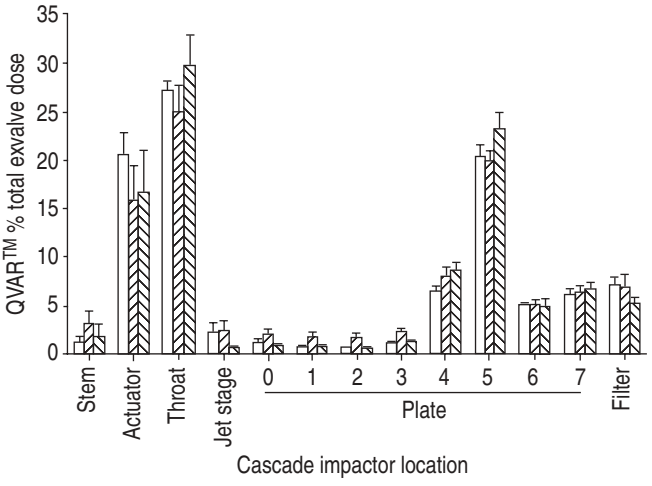

Fig. 1.–Size distribution of QVAR^{TM} particles before (□) and after (▨) radiolabelling and of radiolabel (▩). Data are presented as mean±SD.

Table 1. – Height, weight, postbronchodilator forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) of asthmatic children

Age group yrs	Height cm	Weight kg	FEV_1 L	FVC L
5–7	121.4±6.9	23.1±2.5	1.36±0.14	1.66±0.17
8–10	138.4±6.2	39.7±12.5	2.11±0.23	2.51±0.40
11–14	153.4±10.0	45.6±10.0	2.66±0.43	3.34±0.75

Data are presented as mean±SD.

Immediately after inhaling the ^{99m}Tc-labelled BDP, simultaneous anterior and posterior planar scintigraphic images (120 s acquisition time) of the chest and abdomen together with lateral images of the head and neck were obtained using a double-headed gamma camera (GCA 7200DI; Toshiba Australia, Perth, Australia). Areas of interest were defined for each of the images and separate count rates were determined for the right and left lungs, stomach, oesophagus, mouth and oropharynx. Each count rate was corrected for background counts and tissue attenuation, and the geometric means of the corresponding anterior and posterior count rates were then calculated.

The dose deposited in the lungs was then expressed as a percentage of the total dose deposited in the body or exhaled (*i.e.* the exactuator or emitted dose).

Statistical analysis

Statistical analysis was carried out using analysis of variance for unmatched data. *Post-hoc* analysis was performed using the Fisher protected least significant difference with a significance level of 95% ($p<0.05$), unless otherwise stated. Linear regression analysis was performed to determine significant relationships between variables. All data are presented as mean±SD.

Results

During the *in-vitro* validation procedure, the total amount of drug (ex-valve dose) recovered from the actuator and cascade impactor for these inhalers (n=9) was 95.2±3.9 μg before and 101.0±8.2 μg after labelling. The fine particle fraction was 59.7±1.3, 59.6±1.9 and 60.5±2.4% of the ex-valve dose of drug before and after labelling and of radiolabel, respectively. The extrafine particle fraction was 58.2±1.4, 56.9±1.7 and 58.8±2.4%, respectively, of the ex-valve dose.

Patients were divided into three age groups: 5–7 (n=5), 8–10 (n=7), and 11–14 yrs (n=4). The mean height, weight, FEV_1 and forced vital capacity (FVC) of patients within each age group are shown in table 1.

During inhalation of the labelled drug, time from start of inhalation to actuation of Autohaler^{TM} (*t*a), total inspiratory time (*t*I) and breath-hold time at the end of the inspiratory breath were recorded (table 2).

Table 2. – Time to actuation (*t*a), total inspiratory time (*t*I) and breath-hold time during inhalation of labelled drug *via* Autohaler^{TM} in asthmatic children

Age group yrs	*t*a s	*t*I s	Breath-hold s
5–7	0.29±0.12	2.16±0.94	10.96±1.29
8–10	0.22±0.70	2.66±0.63	10.28±1.89
11–14	0.49±0.19	2.35±0.95	11.60±1.20

Data are presented as mean±SD.

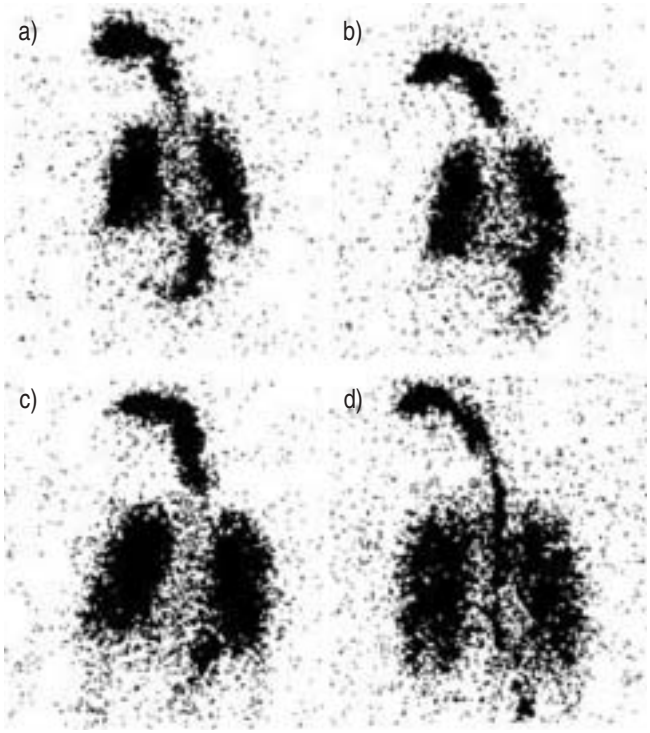

Fig. 2. – Anterior gamma scintigraphic scans showing regional distribution of radiolabelled extrafine beclomethasone dipropionate formulation in asthmatic children aged: a) 5 yrs; b) 7 yrs; c) 11 yrs; and d) 14 yrs.

For comparison to a previous study measuring lung deposition of the QVAR^{TM} formulation in adults [6], the distribution of labelled drug (percentage of exactuator dose), uncorrected for tissue attenuation, was first calculated. The lung dose was 41.1±10.2, 45.0±12.5 and 53.5±11.3% for children aged 5–7, 8–10 and 11–14 yrs, respectively. Combined oropharyngeal and gastrointestinal deposition was 52.3±9.5, 46.8±12.5 and 36.3±12.1%, respectively. Exhaled drug deposited on expiratory filters was 6.6±5.0, 8.2±4.8 and 10.2±5.4% for each of the above age groups, respectively.

Anterior gamma scintigraphic scans illustrate the changes in distribution of radiolabelled drug within the body in children of different ages (fig. 2). The distribution of label within the body (corrected for tissue attenuation), calculated as a proportion of the metered (exactuator) dose, is shown in table 3. All further analyses were performed using the attenuation-corrected data.

The range of lung deposition was 21.7–45.2, 31.2–58.6 and 41.1–68.2% in children aged 5–7, 8–10 and 11–14 yrs, respectively. The coefficient of variation was 24.8, 24.9 and 19.8%, respectively. The proportion of label deposition in the lungs was significantly higher in children aged 11–14 yrs

Table 3. – Regional distribution$^{\#}$ of technetium-99m and deposition on expiratory filter in asthmatic children

Age group yrs	Lung %	Oropharynx/ stomach %	Expiratory filter %
5–7	36.9±9.2	59.7±8.2	3.5±3.1
8–10	46.5±11.6	48.9±12.3	4.6±2.9
11–14	54.1±10.7	40.3±11.8	5.6±2.7

Data are presented as mean±SD. $^{\#}$: percentage of exactuator dose corrected for tissue attenuation.

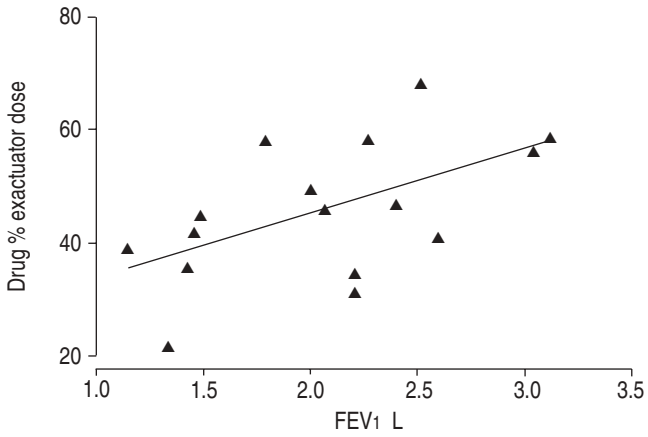

Fig. 3. – Change in lung deposition of labelled drug with forced expiratory volume in one second (FEV1) (r^2=0.306; p=0.026).

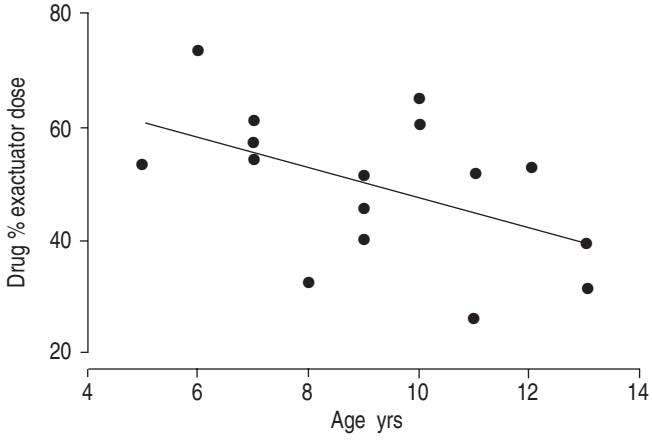

Fig. 4. – Change in oropharyngeal and gastrointestinal deposition of labelled drug with age (r^2=0.249; p=0.043).

compared to 5–7 yrs (p=0.036). The combined oropharyngeal and gastrointestinal dose was significantly lower in children aged 11–14 yrs compared to 5–7 yrs (p=0.025). Lung deposition positively correlated with postbronchodilator FEV1 (p=0.026) (fig. 3) and FVC (p=0.043). The lung dose tended to increase with height (p=0.056) and age (p=0.061). The combined oropharyngeal and gastrointestinal dose negatively correlated with FEV1 (p=0.017), FVC (p<0.001), height (p=0.037) and age (p=0.043) (fig. 4). Neither the lung dose nor the oropharyngeal and gastrointestinal dose correlated with *t*a, *t*I or breath-hold time.

Discussion

This study provides the first direct information regarding the dose delivered to the lungs of children aged from 5 yrs using the extrafine BDP formulation (QVAR™) delivered using an Autohaler™ breath-actuated inhaler. The amount of drug deposited in the lungs of children aged 11–14 yrs was remarkably consistent with that shown in adults using the same formulation *via* pMDI [6, 13] and Autohaler™ [7, 8]. This would indicate that the extrafine aerosol generated with this formulation provides more consistent dose delivery to the lungs than has been shown previously with other corticosteroid formulations. The oropharyngeal and gastrointestinal dose was lower than that found with other inhalers used without spacers or holding chambers, particularly considering that the higher lung dose would necessitate a reduction in the number of inhalations required by asthmatic patients for control of respiratory symptoms [9]. The reduced oropharyngeal dose can be explained by two factors, the extrafine particle size of the QVAR™ formulation and the slower velocity of the aerosol plume emitted from the inhaler.

Although younger children (5–7 yrs) received significantly less drug than older children using this device and formulation, the lung dose was still higher than that found with other devices and formulations in this age group [14–17]. However, the combined oropharyngeal and gastrointestinal dose was higher than that found in older children, and the use of a spacer may still be indicated in this age group. Use of the extrafine BDP formulation delivered *via* pMDI and used with a low-volume spacer has been shown, in adults, to deliver the same amount of drug to the lungs with less drug deposition in the mouth [18]. This is still an important issue to consider when delivering corticosteroid medication to children of all ages. In addition, use of the Autohaler™ requires the ability to perform a slow maximal inhalation, rather than tidal breathing, which makes it unsuitable for infants and very young children. Hence, the efficacy of the extrafine formulation delivered *via* pMDI and low-volume spacer should be tested in this age group.

The issue of greater systemic availability through increased pulmonary absorption is of potential concern, particularly due to increased peripheral lung deposition with the extrafine aerosol. However, inflammation is detected throughout the airways in asthmatic individuals, and a more diffuse application of topical prophylactic therapy within the airways may be advantageous.

At the same dose of CFC/BDP and extrafine HFA/BDP (800 μg), an increase in systemic availability of drug in adults was noted with the extrafine formulation [19]. However, there was no difference in adrenal effects found with the increased systemic levels of BDP after 14 days of treatment.

Owing to the increased drug delivery to the lungs, when switching over to the extrafine BDP formulation, a concomitant reduction in nominal dose (generally halving the dose) is required to maintain equivalent delivery. In children aged 5–11 yrs, no significant difference was noted in height velocity over a period of 1 yr, or in bone density or markers of bone metabolism at half the dose of extrafine HFA/BDP (100–200 μg) compared with CFC/BDP (200–400 μg) [20]. At the same doses, in children of the same age, no difference in 24-h urinary free cortisol or response to low-dose adrenocorticotrophic hormone test was found between the two formulations after 6 months [21].

Hence, as long as the nominal dose is halved when switching over to the extrafine hydrofluoroalkane/beclomethasone dipropionate formulation, the increased efficiency of drug delivery to the lungs, using the extrafine aerosol, makes it ideal for use in children. Even when inhaled with a poor technique, a relatively high dose is still deposited in the lungs, in both adults [22] and children, as shown in the present study. The Autohaler™ combines the convenience and portability of the pressurised metered-dose inhaler (used without a spacer) and also eliminates problems with coordination of actuation and inhalation. This is of particular advantage in children, and should increase compliance in this age group.

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