Lung deposition from the Turbuhaler® in children with cystic fibrosis

S.G. Devadason*, M.L. Everard*, C. MacEarlan**, C. Roller**,
Q.A. Summers+, P. Swift**, L. Borgstrom++, P.N. Le Souëf*

Lung deposition from the Turbuhaler® in children with cystic fibrosis. S.G. Devadason, M.L. Everard, C. MacEarlan, C. Roller, Q.A. Summers, P. Swift, L. Borgstrom, P.N. Le Souëf. ©ERS Journals Ltd 1997.
ABSTRACT: Drug delivery to patients using dry powder inhalers, such as the Turbuhaler®, is believed to be influenced by the inspiratory flow used. Clinical studies have indicated that this delivery system can be used effectively by children. However, it is not known how the total and weight-corrected dose delivered to the airways varies with age. A deposition study using technetium-99m (^{99m}Tc)-labelled budesonide was performed in order to determine the effect of age on delivery.

Twenty one children with cystic fibrosis, aged 4–16 yrs, were recruited. They were clinically stable with normal lung function. Initially, a gamma camera scan was taken in front of a flood source containing 37 MBq of ^{99m}Tc. Subsequently, subjects inhaled through a low resistance inspiratory filter connected to a commercially available Turbuhaler®. Immediately afterwards they inhaled from a noncommercial Turbuhaler® containing budesonide labelled with ^{99m}Tc, and then underwent anterior and posterior gamma camera scans. Both Turbuhaler® inhalers were attached to a portable spirometer and the peak inspiratory flow through the Turbuhaler® was recorded for each inhalation. The total body dose was calculated from the dose deposited on the inspiratory filter connected to the commercial Turbuhaler®. Analysis of the gamma camera images provided information on the proportion of the radiolabel delivered to the lungs compared to that deposited in the upper airway and stomach.

As expected, a highly significant positive correlation was noted between the peak inspiratory flow generated by the patient through the Turbuhaler® and the dose delivered to the lung. Similarly, there was a highly significant positive correlation between age and "total lung dose". However, when total lung dose was corrected for body weight, there was a nonsignificant negative correlation with age.

This study suggests that the "weight-corrected lung dose" achieved when children aged >6 yrs use the Turbuhaler®, is largely independent of age. It would appear that the flow-dependent properties of this device are such that the reduced peak inspiratory flow generated by younger children results in a lower dose to the lungs, but that this is off-set by their lower body weight. This is unlikely to be a property of other devices with different flow/drug delivery characteristics.
Eur Respir J 1997; 10: 2023–2028.

Depts of *Respiratory Medicine and **Nuclear Medicine, Princess Margaret Hospital for Children, Perth, Western Australia. +Royal Perth Hospital, Dept of Paediatrics, The University of Western Australia, Perth, Western Australia. ++Astra Draco, Lund, Sweden.

Correspondence: M.L. Everard
Dept of Respiratory Medicine
Sheffield Children's Hospital
Western Bank
Sheffield S10 2TH
UK

The convenience and ease of use of Turbuhaler®, a multidose dry powder inhaler (DPI), has resulted in its widespread use for the treatment of children with respiratory disease. Scintigraphic and pharmacokinetic deposition studies have indicated that this device is capable of delivering a mean of 20–30% of the nominal dose to the lungs of adults [1, 2]. Although it is difficult to compare results from studies utilizing different methods [3], these results suggest that the device delivers a greater proportion of the nominal dose to the lungs of adult patients than do other DPIs [4, 5], metered-dose inhalers (MDIs) [4, 6, 7], and jet nebulizers [8, 9], and these results are similar to optimal values obtained using certain MDI-spacer combinations [6].

In vitro deposition studies have indicated that the performance of the Turbuhaler®, and other DPIs, can be significantly influenced by the peak inspiratory flow (PIF) achieved through the device [2, 5, 10–16]. The fine particle dose delivered by a Turbuhaler®, measured *in vitro* using multistage liquid impingers, decreases with decreasing flow [16]. Studies assessing effects on pulmonary function [14, 15], and radiolabelled deposition studies [2] in adult subjects have indicated that this decrease in the fine particle dose translates into reduced drug delivery to the lungs as PIF falls. Inevitably, the PIF when inhaling through the device tends to be lower in younger children [14] and, hence, the dose delivered to the lungs of young children is likely to be lower than when used by adults.

It has been suggested that the Turbuhaler® is not suitable for children less than 5 yrs of age [17, 18]. These recommendations have been based on data obtained from measurement of drug on inspiratory filters and measurements of PIF achieved by children inhaling through the device. A study quantifying the total dose of drug on an inspiratory filter indicated that the dose

inhaled increases with age [18]. A study in children aged 7–15 yrs indicated that the clinical response to terbutaline using PIFs below 30 L·min⁻¹ is significantly less than that achieved using flows at and above this value [14]. The same study found little change in response when inhaling at 60 L·min⁻¹ rather than 30 L·min⁻¹. Studies in children have indicated that, above the age of 5 yrs, most children can generate PIFs above 30 L·min⁻¹ when inhaling through the Turbuhaler®, but that below this age PIFs above 30 L·min⁻¹ are less common [14]. Despite this, clinical studies have indicated that useful clinical effects can be demonstrated in pre-school children as young as 3 yrs of age [19, 20].

The conflict between observed clinical benefit and apparent suboptimal use by younger children might be explained if drug delivery is corrected for body weight. That is, the dose of drug depositing in the lungs required to produce a therapeutic effect is likely to be much less for a 3 yr old than for an adult, and, hence, apparent suboptimal use may still be associated with useful clinical responses. The clinical effect noted in older children 7–15 yrs of age, when inhaling at only 13 L·min⁻¹ was still 33% of that at 60 L·min⁻¹ [14], and drug delivery sufficient to achieve this response in an older child produced a good clinical response in a younger child.

Drug delivery to the lungs from a Turbuhaler® is likely to be affected by factors such as morphological aspects of the respiratory system, PIFs and inspiratory volumes, all of which are likely to change with increasing age. In order to improve our understanding of drug delivery from this DPI, a radiolabelled deposition study was undertaken in 21 children aged 4–16 yrs. This study was performed as part of a series of ongoing studies assessing drug delivery to the lungs of patients with cystic fibrosis.

Materials and methods

Patients

Twenty one patients (10 males and 11 females) aged 4–16 yrs and previously diagnosed with cystic fibrosis were recruited. Each patient was clinically well, with normal respiratory examination and lung function. Patients were seen prior to the study day for assessment and were instructed in the use of the Turbuhaler®. Lung function measurements were carried out in all patients aged ≥6 yrs, to ensure that only those patients with a forced expiratory volume in one second (FEV_1) >80% of predicted value were enrolled in the study. Patients were excluded from this study for the following reasons: past or present diagnoses of cardiovascular, renal or liver disease; known hypersensitivity to budesonide; pregnancy or likelihood of pregnancy; inability to demonstrate an adequate inhalation technique using the Turbuhaler® after two instruction sessions; and 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, Western Australia). Informed consent was obtained from the 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 Medical Physics Department at Royal Perth Hospital, and was equated to the additional radiation exposure from a 12 h plane flight, or <3 weeks natural background radiation.

Radiolabelling of budesonide powder

Radiolabelling of budesonide powder was carried out using a method described previously [1, 2]. Briefly, technetium-99m (^{99m}Tc) was extracted from the aqueous phase into butanone using a separating funnel. The butanone was evaporated to dryness using a hot plate and the ^{99m}Tc was redissolved in water. Seventy milligrams of spheronized, micronized budesonide was added to the test tube containing the ^{99m}Tc and thoroughly mixed. The suspension was then placed on dry ice, rapidly freezing the suspension of budesonide. The suspension was then placed in a freeze-drier (Dynavac, Melbourne, Australia) and water was removed over a period of 6–7 h. An empty 200 μg Turbuhaler® was filled with the dry, labelled budesonide and the filling channel sealed with a stopper.

In vitro *assessment of radiolabelling*

In vitro assessment of the output of radiolabelled budesonide from the Turbuhaler® was used to ensure that the radiolabelling method did not significantly alter the particle size distribution of the aerosol generated by the Turbuhaler®, and to confirm that the distribution of ^{99m}Tc reflected that of the drug, thus acting as a suitable marker for budesonide. Particle size distribution and total drug delivery was measured using a multistage liquid impinger (MSLI; Copley, Nottingham, UK) with an inhalation flow of 60 L·min⁻¹. The Turbuhaler® was primed, and then inserted into the inlet of the MSLI. Five doses of radiolabelled budesonide were drawn into the MSLI with the entraining airflow. Particles were either deposited in the Turbuhaler® mouthpiece, or on one of four stages. The location of particle deposition was determined by the aerodynamic size of the particle. The sizes of particles depositing on Stages 1, 2, 3 and 4 were >13, 6.8–13, 3.1–6.8 and <3.1 μm, respectively.

The mouthpiece and stages of the MSLI were washed with 50 mL of ethanol. The absorbance (243 nm) of each sample was measured in duplicate using an ultraviolet spectrophotometric method. The concentration of budesonide in each of the washes was calculated using the absorbance of a solution containing a known concentration of budesonide. The standard curve for budesonide was linear ($r^2 = 1.00$) for concentrations between 0 and 30 μg·mL⁻¹.

Particles reaching Stages 3 and 4 are often referred to as "respirable" particles, though levels of drug on these stages tend to significantly overestimate the proportion of drug that reaches the lungs of patients [1, 2].

The distribution of drug from unlabelled commercial Turbuhalers® (n=10) was compared with the distribution of drug from labelled Turbuhalers® (n=13) and the distribution of radioactivity from the labelled devices was assessed by an ionization chamber.

On the study days, the particle size distribution was assessed prior to the studies to confirm that the labelling was satisfactory and to determine the dose of activity likely to be delivered per actuation.

Inhalation procedures

Each patient's inhalation technique was assessed prior to the study. Subjects were taught to exhale comfortably, and then to inhale with maximal inspiratory effort and to sustain the effort for as long as possible. No breathholding pause was used. This is in line with instructions given in the instruction leaflets. Previous clinical studies [11, 13] and deposition studies [5] have indicated that a breath holding pause does not appear necessary when using DPIs. Previous studies have also indicated that inhaling from functional residual capacity (FRC) is as effective as from residual capacity [13, 15]. Poor inhalation technique was demonstrated by one subject (aged 5 yrs) prior to administration of the radiolabelled drug. The subject was given further instruction on the use of the Turbuhaler® and attended on a second occasion, when his technique appeared acceptable, and the study was completed successfully on this occasion.

Patients initially inhaled five times through a filter (Kendall Curity, Massachusetts, USA) from a commercial 200 µg budesonide Turbuhaler®. The dose that would normally be inhaled was collected on the filter and subsequently assayed. The dose on the inspiratory filter was termed the "delivered" or "total body" dose. Since we did not directly quantify the dose exhaled, this will slightly overestimate the lung dose, but previous studies have indicated that the exhaled dose using high inspiratory flows with DPIs is less than 1% of the nominal dose. Hence, the dose on the inspiratory filter will be very close to the delivered dose [1, 2, 4, 5].

Patients then inhaled 4–12 doses (depending on the activity per actuation) from the radiolabelled Turbuhaler® to give a nominal dose of approximately 4 mBq. During all the experiments the Turbuhaler® (both commercial and radiolabelled) was enclosed in a "spaceship" (Astra, Draco), which allowed air to be entrained through the Turbuhaler® as patients inhaled and also permitted measurement of inspiratory flows using a Vitalograph Compact Spirometer (Vitalograph Ltd, UK) connected to the spaceship. In addition, the radiolabelled Turbuhaler® was enclosed in lead shielding.

Quantifying distribution of deposition of activity in patients

A flood source containing approximately 37 MBq of ^{99m}Tc was used to obtain individual values for attenuation of activity due to absorption by body tissues, as described by MACEY and MARSHALL [21]. This method has recently been assessed in adults and proved to be the most accurate of currently used methods [22]. Because of the great differences in size and body mass, individual attenuation values were needed.

Immediately after inhaling the ^{99m}Tc-labelled budesonide, anterior and posterior images of the chest and abdomen were obtained, together with lateral images of the upper airway using a circular head analogue gamma camera (Siemens ZLC7500). Collection times were 2 min for each of the images. Areas of interest were defined for each of the images and separate count rates were determined for the right and left lungs, stomach, oesophagus, mouth and oropharynx. Each count rate was corrected for background counts and attenuation, and the geometric means of corresponding anterior and posterior count rates were calculated.

The dose deposited in the lungs was then expressed as a percentage of the total dose deposited in the body. Deposition within the lungs was then subdivided into two regions: central and peripheral.

Following imaging, the subjects rinsed their mouths with water and the washings were collected. The subjects then gargled and again the washings were collected. Activity in these washings was quantified using an ionization chamber (Atomlab 200 dose calibrator; Gammasonics, Sydney, Australia).

Of the 21 patients enrolled, 20 patients completed the study. One patient (aged 5 yrs) became distressed during the posterior gamma camera scan, which was discontinued prior to completion. Hence, the data on this patient were not included in the statistical analysis, since geometric means could not be calculated from the anterior images alone.

Assessment of lung dose

Because of the force required to remove the Turbuhaler® from the spaceship and lead shielding, the activity per dose could not reliably be assessed using the MSLI. Furthermore, it was apparent from recovery of drug from the inspiratory filter, that the dose extracted from a Turbuhaler® was often less than the nominal dose, even allowing for the dose retained in the mouthpiece. We therefore chose to use a method advocated by BENNETT [23] and SMALDONE *et al*. [24], in which the lung dose was calculated from the delivered dose defined by the dose on the inspiratory filter and the proportion of the total body dose deposited in the lungs as defined by the gamma camera images.

The peripheral to central deposition (P:C ratio) was quantified using the technique described by O'DOHERTY *et al*. [25] in which deposition in the central region representing half the width of the lung and one third the height was compared with the remaining peripheral region.

Statistical analysis

Statistical analysis was carried out using analysis of variance (ANOVA) for unmatched data. *Post-hoc* analysis was performed using the Fisher protected least significant difference (Fisher PLSD) with a significance level of 95% (p-value less than 0.05), unless otherwise stated. Linear regression analysis was performed to determine significant relationships between variables. All statistical analysis was performed using the Statview 512+ statistical package (Abacus Concepts, Berkeley, CA, USA).

Results

The distribution of drug particles from the commercial and labelled Turbuhalers® were compared with the distribution of the radiolabel (fig. 1). There was a good correlation between label and drug, particularly for Stages 3 and 4, the "respirable dose". The agreement was less good for the mouthpiece and Stage 1, but this is of less importance when measuring lung deposition. This

pattern was consistent with previous work using this method [12].

Demographic data for the patients included in this study are presented in table 1, together with their $FEV1$ and PIF through the commercial Turbuhaler® on the day of the study visit.

There was a significant positive correlation between lung deposition as a proportion (%) of the total body dose and both age ($r^2=0.219$, $p<0.04$) (fig. 2) and PIF ($r^2=0.286$; $p<0.02$) (fig. 3). In addition, there was a negative correlation between PIF and the proportion of the total body dose deposited in the upper airway ($r^2=0.307$; $p<0.01$). Total body dose increased with inspiratory flow ($r^2=0.368$; $p<0.005$), that is slightly less of the nominal dose was delivered to the patient at lower inspiratory flows with more remaining within the mouthpiece of the Turbuhaler®.

The correlation between total lung deposition (µg) both with age ($r^2=0.490$; $p<0.001$) and PIF ($r^2=0.420$;

$p<0.005$) (fig. 4) was also highly significant. There was a good correlation between the amount of radiolabelled budesonide deposited in the lungs and both the height ($r^2=0.460$; $p<0.005$) and weight ($r^2=0.444$; $p<0.005$) of the patient. There was no correlation between the P:C ratio (table 2) and either age or PIF.

Mouth-washing removed 9.9 (SD 14.0)% of the total body dose from the mouth, whilst gargling removed only 0.7 (0.8)% of the total body dose from the throat.

We had difficulty obtaining a consistent optimal inhalation technique from children aged ≤5 yrs using the Turbuhaler®. Only two patients in the 3–5 yr age group completed the study successfully (table 2). Lung deposition in the 13–16 yr age group was significantly higher ($p<0.05$) than in all other age groups (table 3). However, there was no significant difference between the 6–8, 9–12 and 13–16 yr age groups when the lung deposition was corrected either for height or weight (table 3).

The intersubject coefficients of variation for total lung dose in the three age groups were: 6–8 yrs = 40%; 9–12 yrs = 28% and 13–16 yrs = 32%. The coefficient of variation for weight-corrected lung dose for all subjects older than 5 yrs was 39%.
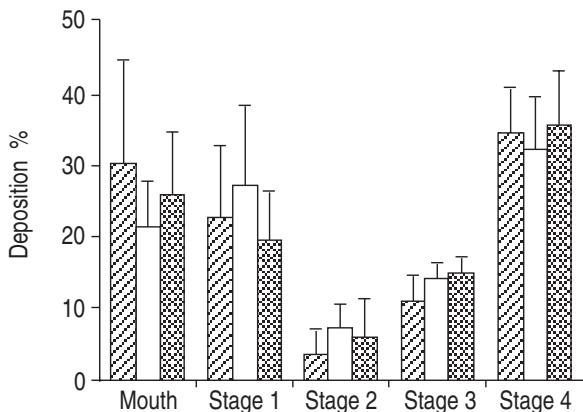

Fig. 1. – The particle size distribution of drug from the commercial (▨) and labelled (▢) Turbuhalers®, and the radiolabel distribution from the labelled Turbuhalers® (▩). Data are presented as mean and SD.

Table 1. – Age and gender of the children included in this study, with their median peak inspiratory flow (PIF) when inhaling through a commercial Turbuhaler®

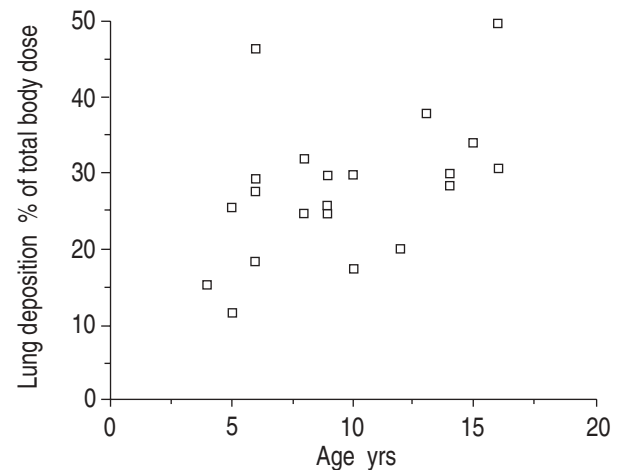| Age yrs	Gender	Median PIF L·min⁻¹
4	M	25
5	M	17
6	M	39
6	F	42
6	M	39
6	M	31
8	F	44
8	M	55
9	F	63
9	F	70
9	M	68
10	F	59
10	F	55
12	M	59
13	F	54
14	F	57
14	M	67
15	F	63
16	F	67
16	F	82

Fig. 2. – Association between lung deposition (% of total body dose) after inhalation through the radiolabelled Turbuhalers® and age ($r^2=0.219$; $p<0.04$).
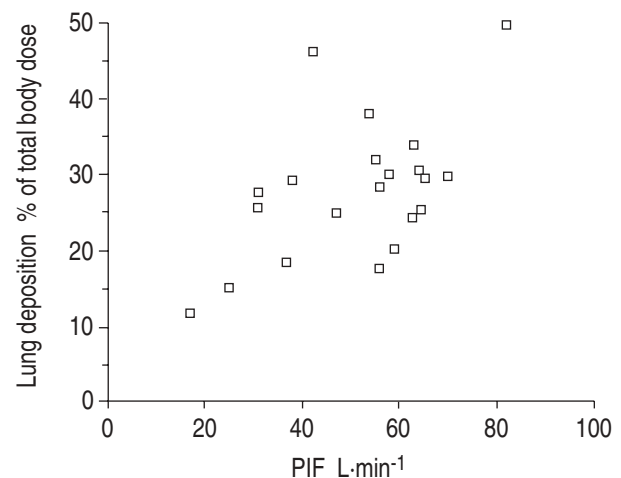

Fig. 3. – Association between lung deposition (% of total body dose) and inhalation through the radiolabelled Turbuhalers® and peak inspiratory flow (PIF) ($r^2=0.286$; $p<0.02$).
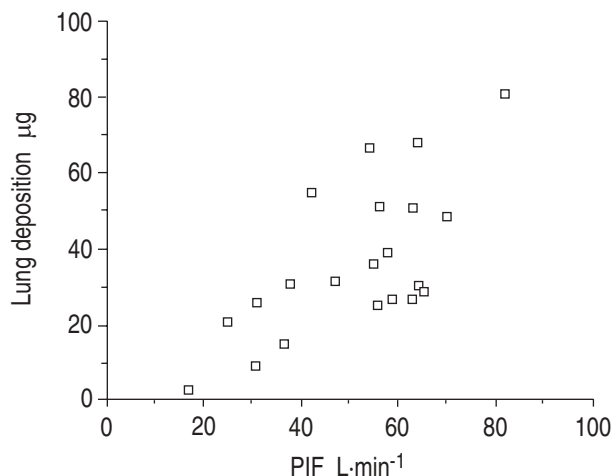
Fig. 4. – Association between lung deposition (µg) (lung deposition (%)/total body deposition (%) × dose on inspiratory filter (µg)) and peak inspiratory flow (PIF) through the radiolabelled Turbuhalers® (r^2=0.420; $p<0.005$).

Table 2. – Lung, oropharyngeal and stomach deposition of radiolabelled budesonide in each age group, expressed as a proportion (%) of the total body dose

Age group yrs	Pts n	Lung %	Oropharynx %	Stomach %	P:C ratio
3–5	2	13.4 (1.7)	48.6 (4.0)	38.0 (25.8)	1.3 (0.1)
6–8	6	29.6 (9.4)	26.9 (15.8)	43.5 (13.0)	1.8 (0.2)
9–12	6	24.4 (5.0)	28.8 (19.1)	46.8 (15.3)	1.6 (0.4)
13–16	6	34.9 (8.0)	39.9 (16.0)	25.2 (13.7)	1.5 (0.3)

Data are presented as mean, and SD in parenthesis, with the exception of the 3–5 yr age group, where data are presented as mean, and range in parenthesis, since only two patients in this group completed the study. Lung deposition was subdivided into peripheral and central deposition, and this is shown as a ratio (P:C ratio). Pts: patients.

Table 3. – Lung dose (µg·inhalation^{-1}) derived for each age group, expressed as the absolute dose (µg), and corrected both for body weight (µg·kg^{-1}) and height (µg·cm^{-1})

Age group yrs	Pts n	Lung dose		
		µg	µg·kg^{-1}	µg·cm^{-1}
3–5	2	12.0 (9.1)	0.66 (0.50)	0.12 (0.09)
6–8	6	32.5 (13.1)	1.61 (0.68)	0.28 (0.11)
9–12	6	32.8 (9.2)	1.23 (0.31)	0.26 (0.07)
13–16	6	57.8 (18.2)	1.14 (0.47)	0.37 (0.12)

Data are expressed as mean, and SD in parenthesis, with the exception of the 3–5 yr age group, where data are presented as mean, and range in parenthesis, since only two patients in this group completed the study.

Discussion

This study provides the first direct information on the dose delivered to the lungs of children from 3 yrs of age when using Turbuhaler®. As expected, there was a positive correlation between lung deposition and PIF. A similar correlation was observed between drug delivery to the lungs and age. However, when the lung dose was corrected for body weight, there were no significant changes between the ages of 6–16 yrs.

The lung dose in adult subjects [2] when inhaling at a mean of 58 L·min^{-1} is approximately twice that achieved in the same subjects at approximately 36 L·min^{-1}, and we found a similar trend of increasing lung dose with increasing PIF. Although there was no significant change in dose delivered to the lungs per kilogram body weight, there was a suggestion that the dose delivered per kilogram fell slightly with age from 6 yrs of age. For adults weighing 75 kg, a lung dose of 50 µg (25% of the nominal 200 µg dose) would be only 0.66 µg·kg^{-1}, a level achieved by all but the youngest subject.

The intersubject coefficients of variation in the three age groups are very similar to those obtained in other studies using aerosol delivery systems in trained adults. These results suggest that drug delivery with this device is at least as reproducible between subjects as that achieved by trained adults using other types of devices [26]. Until further information is available in the paediatric age range, it is unclear whether reproducibility of lung dose in children is going to be generally similar to that seen in adults or will prove to be more variable.

As noted above, patients with cystic fibrosis took part in this study as it formed part of an ongoing series of studies in this group of patients. Information about aerosol delivery in this group is especially important as inhalation therapy is vital for their care. For a DPI, such as the Turbuhaler®, the disease process is unlikely to have a significant impact on the lung dose, since even in healthy individuals, virtually all the inhaled dose is deposited. It will, however, affect the distribution of drug deposition within the lungs. The lack of correlation between the P:C ratio and age noted in this study is likely to reflect two opposing effects. Previous deposition studies [25] and theoretical models of deposition [27] suggest that there is a trend for increased deposition in larger central airways as age decreases. However the pattern of deposition of aerosols is very sensitive to airways obstruction and, indeed, can detect progressive obstructive airways disease long before changes in lung function become apparent [28, 29]. The older subjects with CF are likely to have more significant disease than the younger subjects, hence encouraging more central deposition and obscuring any trend with age due to changes in anatomy. However, this may not be a factor in the present study group, as only subjects with an FEV1 within normal limits were studied.

As in previous studies, the oral deposition was very high and in excess of the pharyngeal deposition in all cases. This is presumably due to the centrifugal momentum of powder as it leaves the device. Our results indicate that powder depositing in the mouth is more accessible for elimination by mouth-washing than powder in the pharynx by gargling. A recent study suggested that mouth-washing is indeed effective in reducing systemic side-effects [30], and the present results supported this, though mouth-washing and gargling removed only a mean of approximately 10% of the total body dose. Large amounts of activity were detected in the stomach immediately after inhalation from the Turbuhaler®, and much of the dose depositing in the upper airway is presumably swallowed soon after deposition and, is, hence, inaccessible to mouth-washing and gargling.

This is the first deposition study using DPIs in children and further studies are required to confirm these findings. The results of this study cannot be generalized to other DPIs since they all have particular performance characteristics. A number of newer DPIs apparently have less flow dependence, *i.e.* the dose delivered is less affected by inspiratory flow. It might be predicted that these devices will deliver significantly more drug to the lungs of young children when corrected for weight than is achieved in adults, and, hence, dose adjustments could be required with these devices.

This study has provided valuable information relating to the performance of the Turbuhaler® in childhood, and suggests that the "weight-corrected dose" delivered to the lungs is essentially unchanged from 6 yrs of age and that this is equivalent to or slightly greater than those achieved by adults using the same dose. These results appear consistent with clinical experience, in that good therapeutic effects have been reported using this dry powder inhaler at doses in the same range as those used by adults. Lung doses in children aged 5 yrs and under were more variable, but results in two children are consistent with clinical studies suggesting that useful clinical effects can be observed when some children as young as 3 yrs of age use this device.

References

1. Borgstrom L, Newman SP, Weisz A, Moren F. Pulmonary deposition of inhaled terbutaline: comparison of scanning gamma camera and urinary excretion methods. *J Pharm Sci* 1992; 81: 753–755.
2. Borgstrom L, Bondesson E, Moren F, Newman SP. Lung deposition of budesonide inhaled *via* Turbuhaler: a comparison with terbutaline sulphate. *Eur Respir J* 1994; 7: 69–73.
3. Everard ML. Studies using radiolabelled aerosols in children. *Thorax* 1994; 49: 1259–1266.
4. Melchor R, Biddiscombe MF, Mak VHF, Short MD, Spiro SG. Lung deposition patterns of directly labelled salbutamol in normal subjects and in patients with reversible airflow obstruction. *Thorax* 1993; 48: 506–511.
5. Newman SP, Hollingworth A, Clark AR. Effect of different modes of inhalation on drug delivery from a dry powder inhaler. *Int J Pharm* 1994; 102: 127–132.
6. Newman SP, Steed KP, Hooper G, Kallen A, Borgstrom L. Lung deposition of pressurised terbutaline sulphate aerosols compared by two techniques. *J Aerosol Med* 1994; 7: 177–179.
7. Hardy JG, Everard ML, Coffiner M, Fossion J. Lung deposition of a Nacystelyn metered-dose inhaler formulation. *J Aerosol Med* 1993; 6: 37–44.
8. Johnson MA, Newman SP, Bloom R, Talaee N, Clarke SW. Delivery of albuterol and ipratropium bromide from two nebuliser systems in chronic stable asthma: efficacy and pulmonary deposition. *Chest* 1991; 99: 1139–1144.
9. Thomas SHL, O'Doherty MJ, Page CJ, Nunan TO, Bateman NT. Which apparatus for inhaled pentamidine? A comparison of pulmonary deposition *via* eight nebulizers. *Eur Respir J* 1991; 4: 616–622.
10. Groth S, Dirken H. Optimal inhalation procedure for the fenoterol powder inhaler. *Eur J Respir Dis* 1983; 130 (Suppl.): 17–24.
11. Pedersen S. How to use a Rotahaler®. *Arch Dis Child* 1986; 61: 11–14.
12. Auty RM, Brown K, Neale M, Snashall PD. Respiratory tract deposition of sodium cromoglycate is highly dependent upon technique of inhalation using the Spinhaler. *Br J Dis Chest* 1987; 81: 371–380.
13. Hansen O, Pedersen S. Optimal inhalation technique with terbutaline Turbuhaler®. *Eur J Respir Dis* 1989; 2: 637–639.
14. Pedersen S, Hansen OR, Fuglsang G. Influence of inspiratory flow rate upon the effect of a Turbuhaler®. *Arch Dis Child* 1990; 65: 308–319.
15. Engel T, Scharling B, Skovsted B, Heinig JH. Effects, side-effects and plasma concentrations of terbutaline in adult asthmatics after inhaling from a dry powder inhaler device at different inhalations and flows and volumes. *Br J Clin Pharmacol* 1992; 33: 439–444.
16. Jaegfeldt H, Andersoon JAR, Trofast E, Wetterlin KIL. Particle size distribution from different modifications of Turbuhaler®. *In*: Newman SP, Moren F, Crompton GK, eds. A New Concept in Inhalation Therapy. Bussum, The Netherlands, Medicom, 1987; pp. 90–99.
17. Pedersen S. Inspiratory capacity through the Turbuhaler® in various patient groups. *J Aerosol Med* 1994; 7: S55–S58.
18. Bisgaard H, Pedersen S, Nikander K. Use of budesonide Turbuhaler® in young children suspected of asthma. *Eur Respir J* 1994; 7: 740–742.
19. Ahlstrom H, Svenonius E, Svensson M. Treatment of asthma in preschool children with inhalation of terbutaline in Turbuhaler® compared with Nebuhaler®. *Allergy* 1989; 44: 525–528.
20. Goren A, Noviski N, Avital A, *et al.* Assessment of the ability of young children to use a powder inhaler device (Turbuhaler®). *Pediatric Pulmonol* 1994; 18: 77–80.
21. Macey DJ, Marshall R. Absolute quantification of radiotracer uptake in the lungs using a gamma camera. *J Nucl Med* 1982; 23: 731–734.
22. Forge NI, Mountford PJ, O'Doherty MJ. Quantification of technetium-99m lung radioactivity from planar images. *Eur J Nucl Med* 1993; 20: 10–15.
23. Bennett WD. Aerosolized drug delivery: fractional deposition of inhaled particles. *J Aerosol Sci* 1991; 4; 223–228.
24. Smaldone GC, Fuhrer J, Steigbigel RT, McPeck M. Factors determining pulmonary deposition in patients with human immunodeficiency virus infection. *Am Rev Respir Dis* 1991; 143: 727–737.
25. O'Doherty MJ, Thomas SHL, Gibb D, *et al.* Lung deposition of nebulised pentamidine in children. *Thorax* 1993; 48: 220–226.
26. Borgström L, Asking L, Beckman O, Bondesson E, Kallen A, Olsson B. Dose variation within and between individuals with different inhalation systems. *In*: Oalby RN, Byron PR, Farr SJ, eds. Respiratory Drug Delivery. Buffalo Grove, USA Interpharm Press Inc., 1996; pp. 19–24.
27. Xu GB, Yu CP. Effects of age on deposition of inhaled aerosols in human lungs. *Aerosol Sci Technol* 1986; 5: 349–357.
28. Dolovich MB, Sanchis J, Rossman C, Newhouse MT. Aerosol penetrance: a sensitive index of peripheral airways obstruction. *J Appl Physiol* 1976; 40: 468–471.
29. Ilowite JS, Gorvoy JD, Smaldone GC. Quantitative deposition of aerosolized gentamycin in cystic fibrosis. *Am Rev Respir Dis* 1987; 136: 1445–1449.
30. Selroos O, Halme M. Effect of a volumatic spacer and mouth-rinsing on systemic absorption of inhaled corticosteroids from a metered-dose inhaler and dry powder inhaler. *Thorax* 1991; 46; 891–894.