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Fine particle mass from the Diskus inhaler and Turbuhaler inhaler in children with asthma

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Fine particle mass from the Diskus inhaler and Turbuhaler inhaler in children with asthma. H. Bisgaard, B. Klug, B.S. Sumby, P.K.P. Burnell. ©ERS Journals Ltd 1998.

ABSTRACT: The study aimed to investigate dose consistency and particle distribution from the dry powder inhalers Diskus and Turbuhaler.

Full profiles of inhalation pressure *versus* time were recorded in 18 4 yr old and 18 8 yr old asthmatic children through Diskus and Turbuhaler inhalers. These data were used in an inhalation profile simulator to assess drug delivery from both a Diskus inhaler and a Turbuhaler inhaler, and in particular to assess the proportion of drug emitted in the coarse (>4.7 μm) and fine (<4.7 μm) particle size range from each type of inhaler. The inhalation profile more accurately represents the changes in flow rate over time through the device than the constant flow rate usually applied with an impactor alone. The aerosol cloud was released before the peak inspiratory effort had been achieved and accordingly the early part and not the peak of the inspiratory performance is a determinant of the quality of the aerosol.

The mean (SD) amount of drug in large particles (>4.7 μm), fine particles (<4.7 μm) and very fine particles (<2.1 μm) in percentage of label claim from the Fluticasone Diskus was 72 (5), 15 (2) and 2 (1) from the 4 yr old children and 71 (3), 18 (2) and 2 (1) from the 8 yr old children, respectively. Similar particle fractions from the Budesonide Turbuhaler were 35 (9), 21 (10) and 7 (5) from 4 yr old children and 30 (7), 32 (9) and 12 (6) from 8 yr old children.

In conclusion, the Diskus inhaler provides an improved dose consistency through the varying age groups and inspiratory flow performances when compared to the Turbuhaler in terms of the proportion of the dose emitted at each particle size. This improvement is at the expense of a low fine particle mass and a high proportion of coarse particles from the Diskus as compared with the Turbuhaler.

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Dry powder inhalers (DPI) are increasingly used for aerosol delivery to the airways for the reasons that they are easy-to-use with no requirements of co-ordination, they are convenient and are without propellants or irritants. In addition, an ideal device should provide a high and predictable airway dose and a low pharyngeal dose. In all DPIs the inspiratory airflow of a patient provides the energy source to disperse the agglomerates of micronized powder and to move the respirable particles from the body of the inhaler to the lung. The drug is drawn from a holding bin of pure drug, or is available as drug particles mixed in a bulking agent such as lactose, which helps dispersion and improves the dose-to-dose reproducibility. It is a fundamental prerequisite for use that the patient can generate enough airflow energy through the device to achieve sufficient dispersion of the drug agglomerates. This interaction between the inhalation effort provided and the aerosolizing property is unique to the different designs of DPIs. The present study was undertaken to examine the likely lung dose, its reproducibility, and the effort dependency in children using two common DPIs: 1) the Turbuhaler is a widely used DPI which is easy-to-use and provides a high lung dose [1, 2], yet apparently with flow dependent drug delivery [3–5]; and 2) the Diskus inhaler is the most recent addition to the range of multidose powder inhalers available for the delivery of β_2-agonists or corticosteroids. It contains 60 factory-dispensed drug doses in a lactose carrier. The Diskus was designed as a low resistance device similar in aerosolizing property to the Diskhaler [6].

We have studied the amount of aerosol obtained from the Diskus and Turbuhaler in asthmatic children of 4 and 8 yrs. The Turbuhaler is in most countries approved for use in children of >5 yrs, while the Diskus is approved for use down to 3 yrs of age. We therefore chose to consider children of 4 yrs as the lower limit for comparison, as this 1 yr difference to the recommended lower age is unlikely to affect the expected flow performance of the children. Our approach has been to record inhalation profiles from asthmatic children. We have used these profiles in an inhalation simulator [7] (fig. 1) to draw doses from both the Diskus and Turbuhaler inhalers and subsequently to assess the particle size distribution of the drug using a cascade impactor. This method has enabled us to measure the emitted dose and the fractions of coarse and fine particles of drug that each child would be capable of drawing from these devices.

Methods

Patients

Twenty children aged 4 yrs and 18 children aged 8 yrs with asymptomatic asthma were recruited to the study. Informed consent was obtained from parents or guardians

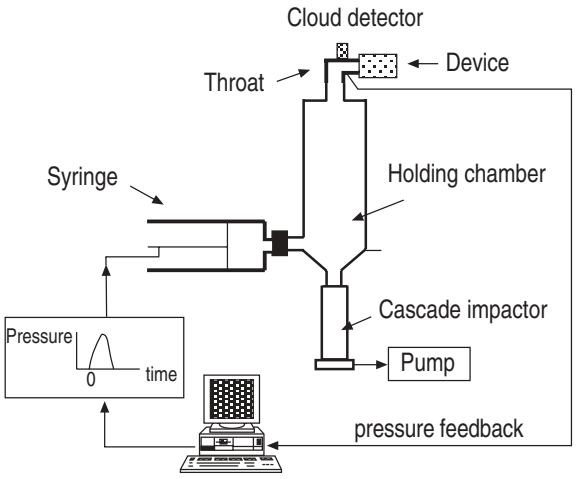

Fig. 1. – The electronic inhalation profile simulator. The computer controlled piston "inhales" through the device mimicking the recorded inhalation profile for flow rate, flow volume and time. The extracted dose is drawn into the sampling chamber as an aerosol cloud and is then drawn by a secondary pump through the cascade impactor. The cloud detector detects the emission of the cloud.

for participation in the study. The study was conducted in accordance with the Declaration of Helsinki.

The children were required to be able to perform measurements of peak expiratory flow rate (PEFR) and/or forced expiratory volume in one second (FEV_1). Children were excluded if they experienced an exacerbation of their airway disease or had a lower respiratory tract infection. None of the 4 yr old children had previously used a powder inhaler, while all the 8 yr old children were regularly using Turbuhaler.

The children were allowed a two week training period to become familiar with the technique for maximum inspiratory performance and to monitor the peak inspiratory flow (PIF) that could be obtained at home through a resistance similar to that of the Diskus (PIF_{DISKUS}). The apparatus used consisted of a Wright peak flow meter adapted with a tube so that the resistance at the inlet was adjusted to equal the resistance of the Diskus inhaler. The children kept a diary card of PIF_{DISKUS} twice daily during the 2 week period. The children were subsequently required to attend the clinic for assessment and to record the full inspiratory profile, with and without each powder inhaler. The children were asked to withhold the use of β_2-agonists prior to their clinic visit: inhaled short acting β_2-agonists for 4 h, long acting β_2-agonists for 12 h and oral β_2-agonists for >24 h before. All other concurrent medication was continued as prescribed. Children were excluded at this stage if they were unable to inhale through either of the powder devices at the clinic (two 4 yr olds were excluded).

Collection of inhalation profiles to determine drug delivery characteristics

Both the Diskus and Turbuhaler inhalers were blinded in a specially constructed enclosure which allowed independent measurement of pressure drops and flow rates (fig. 2; R & D Dept, GlaxoWellcome, Ware, Herts, UK). The inspiratory profile was recorded by a pneumotachograph within the enclosure and loaded onto an IBM computer. Each child recorded three inhalation profiles with each inhaler.

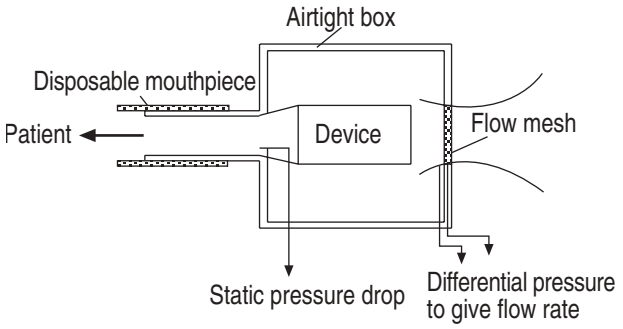

Fig. 2. – Enclosure for measurements of pressure and volume during inhalation through either the Diskus or the Turbuhaler.

Replication of inhalation profiles

For each child, the profile with the highest PIF was used in the inhalation profile simulator (fig. 1). The inhalation profile simulator replicated the recorded inhalation profile in terms of pressure drop, inhaled volume and acceleration. The suction generated extracted a dose from the test inhalers into a large metal holding chamber. The emission of the aerosol cloud was detected in front of the device. An Anderson cascade impactor (Gaseby Anderson Ltd, Orpington, UK) was attached to the metal holding chamber, and the generated standing cloud of particles was subsequently drawn from the spacer into the impactor at its standard flow rate of 28.3 $L \cdot min^{-1}$.

Measurement of emitted dose

Fluticasone propionate Diskus inhalers containing 250 $\mu g \cdot dose^{-1}$ of fluticasone propionate (GlaxoWellcome, UK) and budesonide Turbuhaler inhaler containing 200 $\mu g \cdot dose^{-1}$ of budesonide (Astra, UK) were used. For each patient, a total of 10 doses from fluticasone propionate Diskus and a similar number from budesonide Turbuhaler inhalers were used in each evaluation. The total emitted dose of drug in each portion of the system was assayed by high performance liquid chromatography (HPLC), including throat, sample chamber side filter and cascade impactor.

The cumulative dose of the sampling chamber, glass throat, preseparator and stage 1 of the cascade impactor, was assessed to determine the coarse particle dose, *i.e.* >4.7 μm. The cumulative amount of drug on stages 2–7 plus the filter of the cascade impactor was also assessed and termed fine particle mass (FPM), *i.e.* <4.7 μm. Within the FPM the drug on stages 5–7 plus the filter was termed very fine particle mass, *i.e.* <2.1 μm. The results were expressed as a percentage of the label claim.

Two-sided t-test was used for group comparisons. Mean and SD are used as descriptive statistics. Relative standard deviation (RSD) was estimated as the ratio between SD and mean.

Results

Patient demographics

Twenty patients, mean age 4.5 yrs (range 4.0–4.9 yrs) and 18 patients, mean age 8.4 yrs (range 8.0–9.0 yrs)

Table 1. – Peak inspiratory flow for the Diskus inhaler (PIFDISKUS) for 4 and 8 yr old children recorded at home using an adapted Wright peak flow meter with modified inlet resistance mimicking the resistance of Diskus, or in the laboratory using the test devices in the enclosures depicted in figure 2

Inhalation	4 yr olds	8 yr olds
Lowest PIFDISKUS at home through "Diskus"*	57 (19)	97 (29)
Highest PIFDISKUS at home through "Diskus"*	80 (22)	121 (30)
Laboratory PIFDISKUS through Diskus inhaler†	70 (23)	105 (14)
Laboratory PIF through Turbuhaler inhaler†	53 (23)	76 (10)

Values are presented as mean (SD). *: PIFDISKUS at home was calculated from the group mean of the two lowest individual PIFDISKUS readings and the two highest individual PIFDISKUS readings during the last 7 days of the training period; †: the laboratory reading is taken from the recorded inhalation profiles. SD: standard deviation.

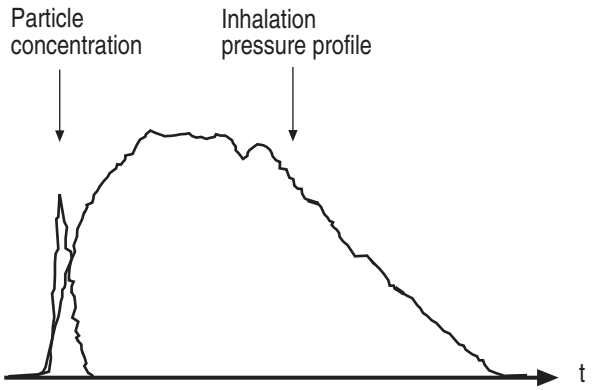

Fig. 3. – Example of individual flow profile *versus* release of aerosol cloud. This shows the release of the aerosol particles from the inhaler before the inhalation pressure has reached its maximum, *i.e.* before the peak inspiratory flow rate had been achieved. Therefore, the early part of the inhalation manoeuvre and not the peak inspiratory flow (PIF) is determinant to the generation of the aerosol. Diskus and Turbuhaler both released the aerosol of particles before the PIF had been achieved.

entered the study. Two 4 yr olds were unable to perform an acceptable inspiratory manoeuvre despite daily training at home for 2 weeks, and consequently collection of inhalation profiles could not be achieved.

The PIFDISKUS at the final test in the laboratory reflected closely the child's PIFDISKUS performance at home: table 1 gives the group mean PIFDISKUS of the highest and lowest performance for both 4 yr olds and 8 yr olds. This has been calculated from the two lowest individual PIFDISKUS and the two highest individual PIFDISKUS readings during the last 7 days of the training period. The group means for laboratory measurements of PIFDISKUS are also given.

Dose emitted and particle size distribution

When the pressure profiles were compared with the release of the aerosol cloud, it appeared that the peak pressure drop was always reached after the aerosol had been released from the device (fig. 3 shows a typical example). The mean (SD) time to peak of the aerosol cloud from the Diskus was 0.16 s (0.14), while the time to peak pressure drop was 0.46 s (0.31). Corresponding figures for the Turbuhaler were 0.19 s (0.03) and 0.36 s (0.23). The PIF reflects the peak pressure drop, and is accordingly achieved after the release of the aerosol cloud. Therefore, the early part and not the peak of the inspiratory effort is determinant to the characteristics of the aerosol.

Table 2 shows the mean (SD) results for each group of children for the amount of drug collected for each particle size range as a percentage of the label claim. The fine particle fraction, as well as the fraction of very fine particles, was significantly increased in the group of 8 yr old children as compared with those of 4 yr olds from both devices. However, the relative difference between the two age groups was less from the Diskus than from the Turbuhaler. Children of 8 yrs compared with the 4 yr olds achieved a 20% increased dose in FPM from the Diskus, but a 50% increased dose in FPM from the Turbuhaler. The scatter of the FPM fraction of the aerosols between patients, expressed as RSD, was 10% in both the 4 and 8 yr olds using the Diskus, compared with 48% and 27% in the 4 and 8 yr olds using the Turbuhaler, respectively. This inter-individual scatter of FPM, together with the age-dependent FPM dose delivery, is depicted in fig. 4.

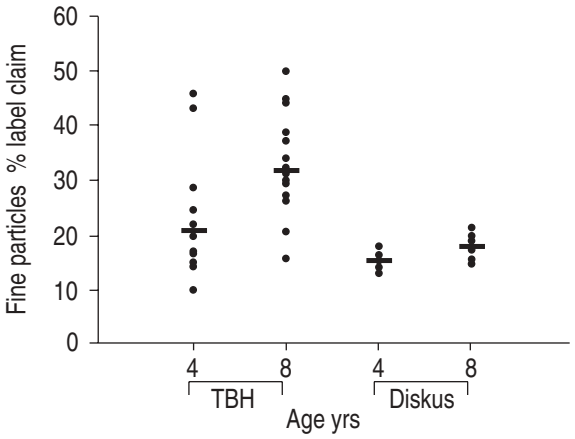

Fig. 4. – Fine particles mass (FPM) as % label claim obtained from the Diskus inhaler and Turbuhaler (TBH) inhaler using inhalation profiles from 4 and 8 yr old children in the electronic inhalation profile simulator. The scatter of FPM from the Turbuhaler is wider as compared with the Diskus and the age dependency more pronounced. The FPM from the Turbuhaler is, however, approximately twice that of the FPM from the Diskus in children of 8 yrs. Data are given as individual data points and the median is indicated. Statistics are given in table 2.

Table 2. – Dose delivered as a percentage label claim

	Diskus inhaler			Turbuhaler inhaler		
Particle size	4 yr olds	8 yr olds	Probability	4 yr olds	8 yr olds	Probability
Large (>4.7 μm)	72 (5)	71 (3)	NS	35 (9)	30 (7)	NS
Fine (<4.7 μm)*	15 (2)	18 (2)	<0.01	21 (10)	32 (9)	<0.01
Very fine (<2.1 μm)	1.8 (1)	2.4 (1)	<0.05	7 (5)	12 (6)	<0.05
Total emitted dose	87 (4)	89 (4)	NS	56 (9)	62 (12)	NS

Values are presented as mean (SD). *: comprises the fraction of very fine particles <2.1 μm. NS: nonsignificant.

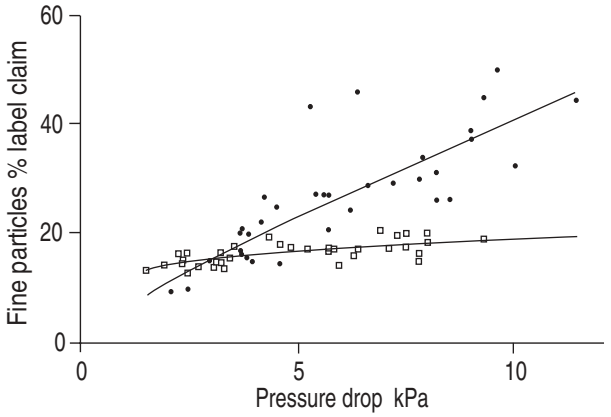

Fig. 5. – The fine particle mass (FPM) *versus* maximal pressure drop during inhalation for the Diskus inhaler (❑) and for the Turbuhaler inhaler (●). The FPM from each patient is related to the corresponding maximal pressure drop, which is reflected by the peak inspiratory flow. This illustrates the effort-dependent FPM generation from the Turbuhaler, with less effort dependency of FPM from the Diskus. Data are given as individual data points, and the least square lines are given to indicate the trend.

Figure 5 presents the FPM as a function of peak pressure drop (reflecting PIF) for each inhaler. The FPM from the Turbuhaler exhibits a pronounced effort dependency, while that from the Diskus exhibits a less pronounced effect.

Discussion

The development of the inhalation profile simulator (or Electronic Lung™) [7] has enabled us to rigorously test powder inhalers in a realistic model of inhalation behaviour by using inhalation profiles collected from our patients. Patient ability to inhale a dose of drug as respirable particles is accounted for by using actual recorded inhalation profiles through each device for subsequent *in vitro* analysis. This pressure profile is replayed *in vitro* and used to control the piston of the inhalation simulator, which activates the dry powder inhaler into a holding chamber from which the aerosol is analysed. Thereby the aerosol that the patient's inhalation would have provided can be accurately analysed from this device. This has enabled us to look closely at the proportions of drug available as fine and large particles and how FPM relates to the patient flow profiles. These assessments therefore closely mimic the *in vivo* situation. Thus, the methodology used in the present study can be considered the first truly comparable estimate of DPI performance, overcoming many of the limitations of earlier work and raising questions over some of the earlier conclusions.

The simplest form of *in vitro* assessment uses an impactor set to operate at a fixed flow rate applied for a specified time period. The sample drawn from the inhaler is collected on stages, which separate particles of differing sizes for analysis. Such cascade impactors are only valid for operation at fixed flow rates, 28.3 or 60 $L \cdot min^{-1}$. However, as devices have different internal resistance, patients making the same maximum inspiratory effort can achieve very different airflow rates through powder inhalers of different internal resistance. Basically, the three-way interaction between the inherent internal resistance to airflow of a powder inhaler, determined by its design; the inspiratory effort that a patient has to make in order to inhale a dose; and the resulting flow of air through a device, makes a direct comparison between the inhalers difficult when only one factor is measured. Therefore, comparison between devices should be based on measures of standardized pressure drop from the patient performance rather than measures at fixed flow rates from the impactors requirements. Recognizing this, OLSSON and ASKING [8] calculated the energy input to a device, and based comparative measurements between devices on such standardized energy input. Still, common to all these approaches is the limitation of the cascade impactor, which applies an abrupt, rising flow remaining constant thereafter. Such a step-function flow is far from the profile of the inhalation the patient performs (fig. 3). Applying an abruptly rising flow provides better aerosol performance than can be expected during rise time performed *in vivo*. Therefore, the cascade impactor assessment is only suited to its primary purpose of quality control within devices, but is not useful for evaluation of the clinical situation.

In the present study we found that the FPM from the Turbuhaler was approximately twice that from the Diskus in 8 yr old children (table 2). If FPM is considered, the aerosol fraction of therapeutic relevance has implications on dose-recommendations as well as cost-effectiveness of treatment [9, 10].

The coarse particle fraction from the Diskus was approximately twice that of the Turbuhaler (table 2). This implies a high pharyngeal deposition from the Diskus. This is of special concern for the administration of steroids, where the coarse particles may carry a risk of local side-effects. The risk of systemic side-effects is also potentially increased, though this concern is less for fluticasone propionate, where the first-pass metabolism is 99% efficient.

Very fine particles constituted <10% of the fine-particle fraction from the Diskus as compared with approximately one-third from the Turbuhaler. This fraction of the very fine particles may carry a risk of increased alveolar deposition detracting from the clinical effect yet with full systemic bioavailability of the drug. However, the behaviour of particles <2 μm in terms of deposition, absorption and elimination from the lung requires further investigation to fully assess potential risks and benefits to patients.

Predictability was better for the Diskus as compared with the Turbuhaler. The RSD for the inter-individual scatter of FPM was approximately 10% in 8 yr olds using the Diskus, but 28% from the Turbuhaler. The RSD was even higher from the Turbuhaler in 4 yr olds, while the RSD in 4 and 8 yr olds using the Diskus were the same. More importantly a pronounced age-dependent dose delivery was shown from the Turbuhaler, with a 50% increase in FPM in 8 yr olds as compared with the 4 yr olds. This was also reflected in a pronounced effort-dependent FPM delivery (fig. 5). In contrast, the FPM from the Diskus increased by only 20% in the 8 yr old children when compared with the 4 yr olds. These results suggest that the Diskus inhaler provides a more consistent dosing in children than the Turbuhaler. More importantly, this good predictability can be extended to its use in older children and adults, as when such a good predictability from the Diskus is found even in the youngest children, it is safe to assume at least as good predictability in older patients.

The PIFDISKUS performance through a resistance comparable to that of the Diskus was quite similar when studied at home and in the laboratory (table 1). Therefore, the inspiratory effort performances recorded in the laboratory, despite its standardized and optimized setting, seem to reflect the performance at home quite well. However, in young children predictability is probably more affected by the child's willingness to co-operate than their physical ability to perform the task adequately. This co-operation may not be reliable in all children at all times. In paediatrics it is important to separate the age at which the child can, and the age at which the child will perform what is required. This argues in favour of the use of a pressurized metered-dose inhaler or a DPI with a paediatric spacer attachment rather than a powder inhaler in young children [10]. Aerosol from a spacer can more reliably be administered to the child by a carer if rescue bronchodilator medication is required and the child is too distressed to co-operate in the use of a powder inhaler.

We found the aerosol is released 0.2–0.3 s before the maximal pressure is achieved, *i.e.* before the PIF in either device (fig. 3). The PIF is therefore a poor reflection of clinical efficacy for powder inhalers and the achievement of a specified PIF through a device is not sufficient basis on which to prescribe it for regular use, although it may be a useful indicator.

In conclusion, the use of inhalation simulation from asthmatic children has allowed us to study the *in vivo* aerosol performance from dry powder inhalers. Our findings have shown that the peak inspiratory flow does not reflect fully the aerosol performance and thus the ability to draw a stated amount from a powder inhaler as fine particles. The reproducibility of the fine particle mass is high for the Diskus and with little flow dependency, yet there is inherent variability in dosing dependent on flow performance for the Turbuhaler, which reduces predictability from this device. The mean fine particle mass of the Turbuhaler inhaler is approximately twice that of the Diskus inhaler, while the coarse particle fraction from the Diskus is twice that of the Turbuhaler. The controversial very fine particle mass is low for the Diskus inhaler but again is higher and more variable with flow rate for the Turbuhaler inhaler.

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