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Emitted dose estimates from Seretide® Diskus® and Symbicort® Turbuhaler® following inhalation by severe asthmatics

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Abstract

The dose emitted from dry powder inhalers may be inhalation flow-dependent. Using an ex vivo method, the Electronic Lung™, we have measured the aerodynamic characteristics of the emitted dose for both active constituents from Seretide® Diskus® (salmeterol xinafoate 50 mcg; fluticasone propionate 500 mcg) and Symbicort® Turbuhaler® (formoterol 6 mcg; budesonide 200 mcg).[1] Electronic inhalation profiles were collected from 20 severe asthmatics (mean PEFR 53% predicted) when they inhaled using a placebo Seretide® Diskus® and a placebo Symbicort® Turbuhaler®. These were replayed in the Electronic Lung™ with the respective active inhaler in situ. Mean(S.D.) peak inhalation flow rates (PIFR) through the Diskus® and Turbuhaler® were 94.7(32.9) and 76.8(26.2) l min^{-1}, respectively. From the Electronic Lung™ the Diskus® inhalation profiles provided a mean(S.D.) fine particle dose (FPD) for fluticasone propionate and salmeterol of 20.4(4.8) and 18.4(4.4)% labelled dose. For Turbuhaler® inhalation profiles the FPD was 23.1(12.9) and 20.7(11.1)% labelled dose for budesonide and formoterol, respectively. The linear ($p < 0.001$) relationships between FPD against PIFR for budesonide and formoterol were 3 ($p = 0.002$) and 2.8 ($p = 0.007$) times steeper than fluticasone propionate and salmeterol, respectively. The results highlight a more significant effect of inspiratory flow on variable dosage emission when using the Symbicort® Turbuhaler® compared with the Seretide® Diskus®.

Keywords: Diskus®; Turbuhaler®; Asthma; Electronic Lung™; Dose

1. Introduction

Inhalation remains the preferred route of administration for many drugs to treat respiratory disease. However, poor inhaler technique with the pressurised metered dose inhaler may lead to sub-optimal drug delivery (Newman et al., 1991). Dry powder inhalers (DPIs) are inherently breath actuated and have been developed to circumvent these difficulties. They have been formulated so that an aerosolisation force is required for the drug to become available to the lungs. The process of creating a 'force' inside the device, to facilitate deaggregation of the powder formulation, depends upon the energy input (inspiratory effort) by the patient and inhaler resistance (Ganderton and Kassem, 1992). The aerodynamic characteristics of the emitted dose provide in vitro data about its potential for deposition in the lungs (Chrystyn, 2003). These aerodynamic characteristics are the fine particle dose and the mass median aerodynamic diameter. It has been shown that for some DPIs the inhalation flow rate has a significant effect on the dose emitted, which is related to the clinical efficacy (Engel et al., 1989; Nielsen et al., 1997; Chrystyn, 2003) and lung deposition (Newman et al., 1991). Additionally, the deposition patterns of aerosolised drugs may be affected by other ventilatory parameters such as the inhaled volume and inhalation flow rates (Martonen and Katz, 1993). To select the most suitable dry powder inhaler for a patient, it would be useful to be aware of the flow rates and the nature of the inhalation profiles that different groups of subjects can generate through various inhalers. This may be particularly important in adults or children with severe asthma who may have less capacity to generate the most desirable inspiratory effort to use different DPIs.

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An ex vivo method, using the Electronic Lung™ has been described (Brindley et al., 1994; Burnell et al., 1998a, 1998b). Use of the Electronic Lung™, an inhalation simulator (Brindley et al., 1994; Burnell et al., 1989a) provides a realistic model of inhaler behaviour by using inhalation profiles collected from patients. The ability of a patient to inhale drug as respirable particles (referred to as the fine particle dose) is assessed by using actual recorded inhalation profiles through each device for subsequent in vitro analysis. The aerosol that the patient's inhalation would have provided can be accurately analysed to look at the proportions of drug available as fine and large particles and how dose emission relates to the patient inhalation flow profiles.

The Electronic Lung™ method has previously been used to determine the dose emission characteristics for different patient inhalation flow rates when they inhaled through a budesonide Turbuhaler® and a fluticasone propionate Diskus® (Bisgaard et al., 1998; Burnell et al., 2001). We have extended the use of this method to combination dry powder inhalers. The aerodynamic characteristics of the dose of drug emitted from two DPIs, the Seretide®/Advair® Diskus® (GlaxoSmithKline), Accuhaler® in the UK, and Symbicort® Turbuhaler® (AstraZeneca) has been characterised using inhalation profiles collected from adults with severe asthma.

Our aim was to determine the ex vivo performance of the combination dry powder inhalers under inhalation conditions that mimic patient use (Bisgaard et al., 1998) rather than determine the emitted dose characteristics using a vacuum pump as recommended by the Pharmacopoeias (USP, 2000). The fine particle dose and the mass median aerodynamic diameter of 50/500 mcg Seretide® Diskus® and 200/6 mcg Symbicort® Turbuhaler® have been determined using this ex vivo method. For the Symbicort® product, the new version of the Turbuhaler® ("Mark 3") with a lower resistance (Assi and Chrystyn, 2001), than the one ("Mark 2") used for formulations with single active drugs, was utilised in this study.

2. Methods

2.1. Patients

Patients were recruited from the Chest Out-Patient Clinic of the Leeds General Infirmary. Twenty adult patients (inclusion criteria ≥18 years) with a diagnosis of severe asthma who were dry powder inhaler naïve and were prescribed, as required β_2-agonist and 800–2000 μg daily of inhaled beclometasone dipropionate or budesonide, or ≥400 μg daily of inhaled fluticasone propionate were recruited. Patients were also required to have a peak expiratory flow rate (PEFR) of 40–60% of their predicted value (Nunn and Gregg, 1989). Patients with evidence of unstable severe asthma or who had an exacerbation that required oral steroids or had been hospitalised due to an exacerbation within the 12 weeks prior to the start of the study, were excluded. Those unable to correctly use the inhalers after instruction or had any other uncontrolled disease were also excluded.

The study protocol was approved by the Local Research Ethics Committee and conducted according to Good Clinical Practice guidelines and the 1996 Declaration of Helsinki. Signed informed consent was obtained from all patients before enrollment.

2.2. Study design

This was a single-centre, randomised, single blind, crossover study designed to record inhalation profiles of pressure drop and inspiratory flow rate versus time using the inhalation profile recorder and pressure transducer (Burnell et al., 1998a) of 20 adult subjects with severe asthma. There were two scheduled clinic visits 7–10 days apart. Each subject was assigned a study code and the order for inhalation by each patient through the Diskus® and Turbuhaler® was randomised.

At the first visit, patients were screened for eligibility into the study. If subjects had taken inhaled short-acting or long-acting β_2-agonist within 4 or 12 h of each clinic visit, respectively, then the visit was rescheduled. All other medication was continued as prescribed. Patients received a demonstration of each inhaler as outlined in the manufacturers' patient information leaflet and were asked to demonstrate the inhalation manoeuvre with a placebo Seretide® Diskus® and a placebo Symbicort® Turbuhaler®. Patients were also familiarised with the inhalation profile recorder by recording two inhalation profiles for each inhaler (thereby mimicking the standard practice of prescribing two doses). Each patient was also trained how to use the In-Check Meter™ (Clement Clark International, UK) and asked to take three peak inhalation flow rate (PIFR) recordings for each of the appropriate settings for the Diskus® and Turbuhaler® once each day between the two clinic visits. The patient recorded these values in a daily record card. The In-Check Meter™ used in this study was modified to take into account the lower resistance of the Mark 3 Turbuhaler® in the Symbicort® product.

At the second visit, patients were asked to demonstrate the use of each inhaler and two inhalation profiles were each recorded for the Diskus® and Turbuhaler®. The order in which the devices were used was randomised according to the randomisation schedule. Patients were allowed to rest for 5–15 min following the inhalation profiles for the first inhaler before beginning the measurement of the inhalation profiles for the second inhaler.

2.3. Collection and replication of inhalation profiles

Placebo inhalers to match standard product batches were enclosed in a specially constructed blinding box (Bisgaard et al., 1998). Inspiratory profiles were recorded by an inhalation profile recorder consisting of a laptop computer and a pressure transducer, which is connected to the mouthpiece of the test inhaler. For each patient, the second inhalation profile from each inhaler recorded at visit 2 was used with the Electronic Lung™ as described previously (Brindley et al., 1994).

2.4. Measurement of the aerodynamic characteristics of the emitted dose using the Electronic Lung™

These were measured using the Electronic Lung™. For each of the 20 individual patient profiles, a total of 10 doses from

each inhaler were used for evaluation. Each selected inhalation profile was replayed using a matched inhaler product attached to the Electronic Lung™. The two products used were Seretide® Diskus® containing salmeterol xinafoate (hereafter referred to as salmeterol) 50 mcg with fluticasone propionate 500 mcg (50/500) in each dose (GlaxoSmithKline, UK) and Symbicort® Mark 3 Turbuhaler® inhaler containing 6 mcg of fomoterol and 200 mcg of budesonide (6/200) per dose (AstraZeneca, UK). The computer controlled piston in the Electronic Lung™ device replays the recorded inhalation profile through the inhaler in situ. A feedback mechanism ensures that the pressure drop that is recorded within the inhaler in situ is identical to that being replayed (Burnell et al., 1998a, 2001).

At the start of the simulated inhalation, the dose from the inhaler containing the active drug was drawn into a sampling chamber by the action of a programmable piston. At the end of the inhalation, valves were switched opened/closed to enable the evacuation of the sample chamber at 28.3 l min^{-1} into an Anderson Cascade Impactor (Graseby Anderson Ltd., Orpington, UK) located at the base of the chamber. Each stage of the cascade impactor and the chamber of the Electronic Lung™ together with its mouthpiece were rinsed with appropriate solvent for quantitative analysis via high performance liquid chromatography to determine the amount of drug collected on each stage of the cascade impactor. The total emitted dose (TED) is defined as the amount of drug deposited in the mouthpiece, Electronic Lung™ chamber and the cascade impactor. The amount of drug on stages 2–7 plus the filter of the cascade impactor is defined as the fine particle dose (FPD), which contains particles with a mass median aerodynamic diameter (MMAD) less than 5.8 μm. From the cascade impactor data, the MMAD and the geometric standard deviation (GSD) of the particles were also calculated (USP, 2000). The closer the geometric standard deviation is to 1, then the more homogenous is the particle size distribution.

2.5. Resistance of the Diskus® and the Turbuhaler®

Resistance of the inhalers was measured as described previously (Clark and Hollingworth, 1993). These values were used in the inhalation profile recorder to convert the pressure drop values across the inhaler, that were measured as the patient inhaled through it, into the respective inhalation flow rates. The fastest rate recorded during each inhalation is the peak inhalation flow rate (PIFR).

2.6. Analysis

Differences between the inhalers in peak pressure drop and PIFR obtained from the electronic inhalation profiles recorded from each patient were analysed using analysis of covariance with factors for subject, inhaler number and inhaler. Pairwise differences between the inhalers were calculated and the 95% confidence interval for each difference constructed. The FPD and MMAD from the subject profiles for each inhaler were analysed in the same manner. A multiple regression analysis was performed to investigate relationships between the PIFR and either the fine particle dose (% labelled dose) or the MMAD for each of the four drugs, used with the Diskus® (salmeterol and fluticasone propionate) and Turbuhaler® (budesonide and formoterol). PIFR measured using the In-Check Meter™ between clinic visits was summarised by presenting descriptive statistics for each day and inhaler. For each inhaler a correlation, together with a Bland and Altman (1986) plot, of the PIFR In-Check Meter™ readings was made to those obtained from the PIFR inhalation profiles.

3. Results

3.1. Patient demographics

Twenty severe asthmatic patients with a mean age of 56.5 years (range 26–74) were recruited and completed the study. Details of demography and inhalation characteristics are shown in Table 1.

3.2. Inhalation parameters

Table 1 shows that the PIFRs were faster using the Diskus® than the Turbuhaler®. The mean difference for the PIFRs through the two inhalers was 17.3 l min^{-1} (95% CI; 10.4, 24.2 l min^{-1}) which was significant ($p < 0.001$). This tables also shows that the inhaled volume through the two inhalers were similar. The mean inhalation time was 2.5 ± 0.9 s for the Diskus® and 2.9 ± 1.1 s for the Turbuhaler®. The mean inhalation flow rate profiles for each inhaler are described in Fig. 1.

The peak pressure drop through the Diskus® was lower than for the Mark 3 Turbuhaler® with a mean of 4.33 and 4.86 kPa for the two inhalers, respectively. The estimated mean difference between the inhalers was −0.53 kPa (95% CI; −1.076, 0.017; $p = 0.057$).

3.3. Characteristics of the emitted dose

The mean(S.D.) aerodynamic characterisation of the emitted doses from the 200/6 mcg Symbicort® Turbuhaler® for budesonide and formoterol and from the 50/500 mcg Seretide® Diskus® for fluticasone propionate and salmeterol is shown in Table 2. From the Diskus® the TED for salmeterol and fluticasone ranged from 74.1 to 106.6% labelled dose and 70.6–95.8%, respectively, according to the PIFR. Similar values from the

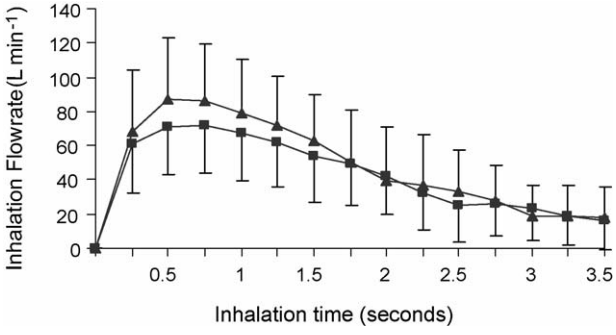

Fig. 1. Mean(±S.D.) inhalation flow rate profile from the 20 severe asthmatics when they used the Diskus® (▲) and Turbuhaler® (■).

Table 1
Patient demographic data

Patient number	Age (years)	M/F	%Predicted PEFR ($l\,min^{-1}$)	PIFR (DKS) ($l\,min^{-1}$)	Inhaled volume (DKS) (l)	PIFR (TBH) ($l\,min^{-1}$)	Inhaled volume (TBH) (l)
1	64	M	42	120.5	3.4	93.1	3.4
2	49	M	58	47.4	1.9	55.2	2.2
3	48	F	53	97.0	2.1	84.3	1.9
4	63	M	53	68.7	2.6	74.4	2.4
5	38	F	54	84.3	1.7	60.0	2.0
6	50	M	40	103.6	3.9	105.3	2.9
7	42	F	59	115.9	2.7	98.6	2.5
8	52	M	59	122.0	4.1	102.7	4.3
9	68	M	51	153.6	4.6	115.8	3.5
10	71	F	44	86.0	2.2	68.2	2.6
11	74	F	49	109.3	2.4	83.1	2.1
12	74	F	50	100.7	1.3	80.2	1.3
13	73	M	58	100.2	5.1	80.2	1.2
14	26	M	57	156.6	3.7	119.1	3.5
15	58	F	53	120.0	2.7	92.4	2.4
16	51	F	58	49.0	1.3	40.6	0.8
17	52	M	59	89.0	3.4	74.2	2.9
18	49	M	58	80.7	2.6	35.5	2.0
19	61	M	53	38.3	2.3	35.8	1.9
20	66	M	45	52.0	2.3	36.7	2.6
Mean	56.5		52.7	94.7	2.8	76.8	2.4
S.D.	13.0		6.01	32.9	1.1	26.2	0.8

DKS = Diskus®; TBH = Turbuhaler®; PEFR = peak expiratory flow; PIFR = peak inhalation flow rate.

Turbuhaler® for budesonide and formoterol were 29.4–93.9 and 28.3–96.7% of the labelled dose, respectively, depending on the flow. The correlation of TED against patients' PIFR, was linear ($p < 0.05$ for formoterol and fluticasone propionate; $p < 0.01$ for budesonide and salmeterol). The gradient of the slope for the TED correlation with PIFR was 2.46 times steeper for formoterol than salmeterol. This difference is significant at the 5% level, with $p = 0.046$ and a mean difference (95% confidence interval) between the gradients of 0.188 (0.003, 0.372). Similarly, for the TED against PIFR budesonide has a 3.47 times steeper slope than fluticasone propionate. This difference is also significant as $p = 0.007$ with a mean difference (95% confidence interval) of 0.256 (0.075, 0.437) between the gradients.

Figs. 2 and 3 demonstrate the performance variation of the aerodynamic characteristics of the emitted dose with the peak inhalation flow rate for the corticosteroid and long-acting β-agonist from both inhalers. The correlations of FPD and for the MMAD, against patient PIFR were all linear ($p < 0.001$). For FPD, budesonide has a 3.08 times steeper gradient than fluticasone propionate on PIFR (Fig. 2). This difference is significant as $p = 0.002$ and a mean difference (95% confidence interval) between the gradients of 0.246 (0.097, 0.394). Fig. 2 also demonstrates that formoterol has a 2.82 times steeper gradient than salmeterol on PIFR. This difference is significant with $p = 0.007$ and a mean difference (95% confidence interval) between the gradients of 0.191 (0.055, 0.327). Fig. 3 shows that the difference in the slopes of the MMAD against PIFR, for both the corticosteroids and the long-acting β-agonists, were not as large as those for the FDP. The budesonide slope was only 1.43 times steeper than that for fluticasone propionate. Similarly, the formoterol slope was only 1.59 times steeper than that for salmeterol.

3.4. Resistance of the inhalers

Measurement of resistance showed that the Diskus® specific resistance was lower than the "Mark 3" Turbuhaler® with

Table 2
Mean(S.D.) aerodynamic dose characterisation from the Seretide® Diskus® for FP (500 μg) and salmeterol (50 μg) and the Symbicort® Turbuhaler® for budesonide (200 μg) and formoterol (6 μg)

	Seretide® Diskus®		Symbicort® Turbuhaler®	
	Fluticasone propionate	Salmeterol	Budesonide	Formoterol
TED (μg)	436.6(40.0)	42.6(3.5)	105.2(32.8)	3.1(1.0)
TED (% labelled dose)	87.2(8.0)	85.1(6.9)	52.6(16.4)	52.3(16.3)
FPD (μg)	101.9(23.8)	9.2(2.2)	46.0(25.9)	1.2(0.7)
FPD (% labelled dose)	20.4(4.8)	18.4(4.4)	23.1(12.9)	20.7(11.1)
MMAD (μm)	3.57(0.48)	3.54(0.47)	3.09(0.55)	3.30(0.64)
GSD	1.46(0.05)	1.49(0.06)	1.56(0.09)	1.57(0.15)

FPD = fine particle dose; MMAD = mass median aerodynamic diameter; GSD = geometric standard deviation.

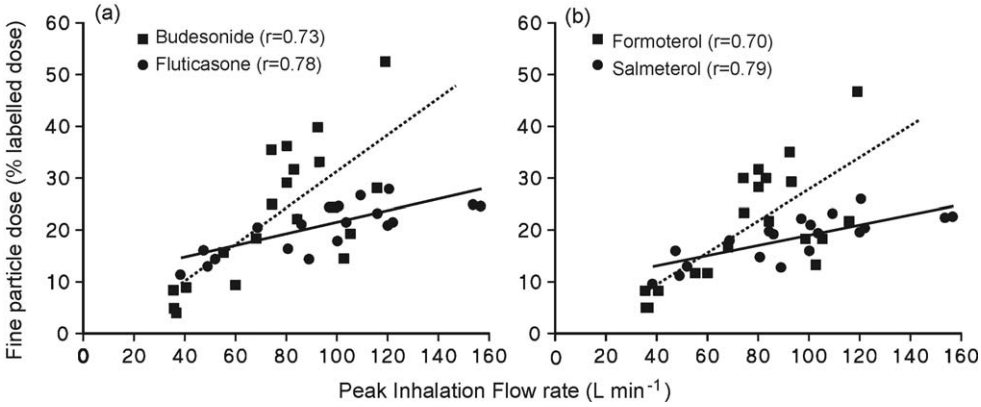

Fig. 2. The performance variation of the fine particle dose (expressed as a % of the labelled dose) with the peak inhalation flow rate for: (a) budesonide and fluticasone propionate and (b) formoterol and salmeterol (the continuous line represent the line of regression for fluticasone and salmeterol, the dashed line for budesonide and formoterol).

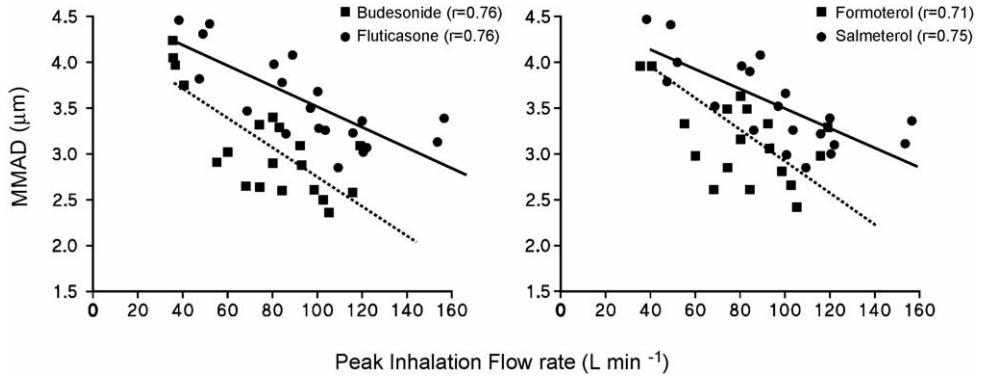

Fig. 3. The mass median aerodynamic diameter with the peak inhalation flow rate for: (a) budesonide and fluticasone propionate and (b) formoterol and salmeterol (the continuous line represent the line of regression for fluticasone and salmeterol, the dashed line for budesonide and formoterol).

values of $0.0208\,\mathrm{kPa}^{0.5}\,(\mathrm{l\,min})^{-1}$ and $0.027\,\mathrm{kPa}^{0.5}\,(\mathrm{l\,min})^{-1}$, respectively.

3.5. *In-Check Meter™ measurement of PIFR*

Fig. 4 demonstrates that there was a significant correlation between the PIFR measured electronically and the PIFR measured by the In-Check Meter™ for the Diskus® ($p<0.001$, $r=0.83$) and the Turbuhaler® ($p<0.001$, $r=0.89$). Two patients inhaled with a PIFR > 150 l min^{-1} through the Diskus® with the inhalation profile recorder and since the In-Check Dial records a maximum of 120 l min^{-1} then these two were excluded from the analysis. A Bland and Altman (1986) plot revealed that for each inhaler when the mean of the two PIFRs (inhalation profile recorder and In-Check Meter™) for each inhaler were plotted against the difference between the PIFRs for each inhaler then all the values fell within two standard deviations of the mean difference. The mean difference (2 standard deviations) between the In-Check Meter™ and inhalation profile recorder measurements were −4.6(36.8) l min^{-1} for the Seretide® Diskus® and −8.4(12.1) l min^{-1} for the Symbicort® Turbuhaler®. A summary of daily PIFR using the In-Check Meter™ during the period between clinic visits shown in Fig. 5 reveals that the PIFRs were higher for the Diskus® than the Turbuhaler® at

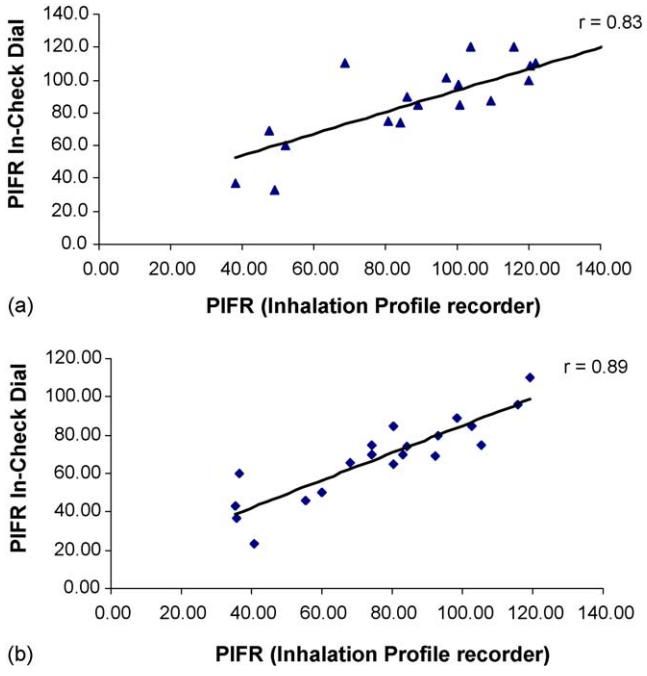

Fig. 4. The relationship between peak inhalation flow rates (PIFR) measured by the In-Check Meter™ and the inhalation profile recorder for: (a) Diskus® ($n=18$) and (b) Turbuhaler® ($n=20$). All values are l min^{-1}.

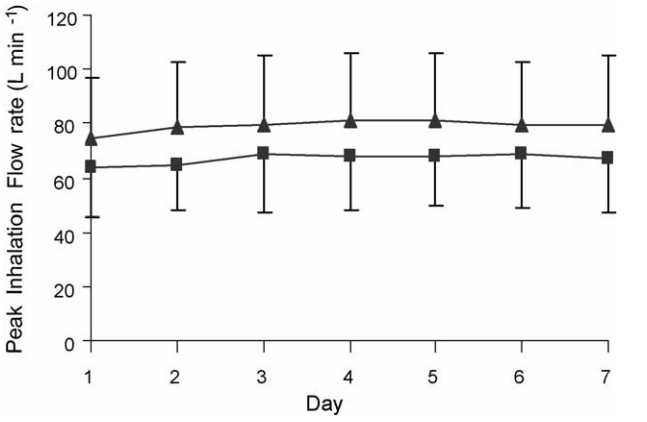

Fig. 5. Mean peak inspiratory flow measured with the In-Check Meter™ at Diskus® (▲) and Turbuhaler® (■) settings over days 1–7 between clinic visits.

each time point. The range of PIFR when they inhaled through the In-Check Meter™ for the Diskus® was 35.7–120 l min^{-1} and 28.3–114.3 l min^{-1} for the Turbuhaler®. The mean(S.D.) intrapatient coefficient of variation of the PIFR, measured on each of the 7 days, for Diskus® was 9.3(3.1)% with a range of 3.8–17.2%. Similar values for the Turbuhaler® were 8.9(3.0)% and a range of 3.9–15%.

4. Discussion

This study demonstrates that adult patients with severe asthma were able to achieve a high inspiratory flow rate through the Diskus® and the Turbuhaler®. The fine particle dose emitted from the Seretide® Diskus® inhaler for both constituent drugs (salmeterol and fluticasone propionate) was relatively consistent irrespective of the patient inhalation profile. In contrast, for the Symbicort® Turbuhaler® inhaler, these characteristics (for both formoterol and budesonide) were more dependent on the patient's inhalation flow rate. The dose emission characteristics of the steroids in both the combination products are similar to previous data generated from the Electronic Lung™ for budesonide in a Turbuhaler® and fluticasone propionate in a Diskus® using asthmatic children (Bisgaard et al., 1998) and patients with chronic obstructive pulmonary disease (Burnell et al., 2001). The Mark 3 Turbuhaler® (Symbicort® product), therefore, has similar flow-dependent dose emission characteristics as the Mark 2 Turbuhaler® (used for the single agent formulations).

Drug delivery from dry powder inhalers depends on the internal resistance of the inhaler and the inspiratory flow by the patient (Selroos et al., 1996; Ganderton, 1997) together with how these forces interact with the formulation inside the inhalation device (Chrystyn, 2003). Consistent and reliable dose emission from an inhaler is essential for the management of patients prescribed inhaled medication. The performance of the Diskus® with different inhalation profiles was more consistent than the Turbuhaler®. The significantly steeper slopes for budesonide and formoterol compared to fluticasone propionate and salmeterol indicates a heightened sensitivity of the budesonide and formoterol in a Turbuhaler® to changes in inhalation technique notably the peak inhalation flow rate used. Gamma scintigraphy has demonstrated that total lung deposition, for some dry powder inhalers, can vary with inhalation flow (Newman et al., 1991) and it has been shown that lung deposition for some dry powder inhalers generally increases at higher inhalation flows (Pauwels, 1997). This is consistent with the higher FPD and lower MMAD with the inhalation flow rate identified in this study. The lower MMAD with fast inhalation flow rates would counteract the greater resulting potential for impaction in the central zones of the lungs.

Pharmacopoeial methods recommend that dose emission from dry powder inhalers should be tested at one flow rate corresponding to a pressure drop of 4 kPa across the device using a vacuum pump (USP, 2000). These are standard methods to demonstrate compliance with specific criteria. The range of peak inhalation flow rates (with corresponding pressure drops) together with the variability of the aerodynamic characteristics of the emitted dose at these flow rates highlights that a range of flows should be tested using the Pharmacopoeial methods. The inhalation flow rates (pressure drops) used should take into account those achieved by patients when they inhale through the dry powder inhaler to be tested.

The Electronic Lung™ method provides more realistic information than using Pharmacopoeial in vitro methods that use a vacuum pump set at a constant rate and allows the Andersen Cascade Impactor to be used at the recommended flow rate of 28.3 l min^{-1}. (Burnell et al., 1998a; Bisgaard et al., 1998). Nevertheless we have used the Pharmacopoeia methods with different flow rates and have shown inhalation flow rate-dependent dose emission of budesonide and formoterol from a Symbicort® inhaler (Tarsin et al., 2004). Similarly others have shown that dose emission of salmeterol and fluticasone propionate from a Diskus® is not affect by flow (Ashurst et al., 1998). These results suggest that although the compendial methods rely on a vacuum pump, that provides a square wave inhalation profile, these methods provide useful data that can be extended to patient data if a range of inhalation flow rates are used.

It has been suggested that the acceleration rate during an inhalation is important in the generation of the fine particle dose (Everard et al., 1997). The feedback mechanism in the Electronic Lung™ ensures that the inhalation profile (with the respective pressure drops) actually occurs within the inhaler in situ (Burnell et al., 1998a, 2001). This comparison between the recorded patient profile and that within the inhaler in situ was made for every determination thus acceleration rates were replicated for each dose emission into the Electronic Lung™. Acceleration rates when a patient inhales through a dry powder inhaler have been shown to be directly related to the peak inhalation flow rate (Broeders et al., 2001). We have therefore reported the results as the inhalation flow rate rather than pressure drops and acceleration rate.

Validation of the Electronic Lung™ methodology has highlighted that some of the emitted dose is deposited on the walls of the sample chamber (Burnell et al., 1998a). In this validation it was shown that the higher the Stokes number of the particle then the more likely it is to deposit in the sample chamber.

Since the budesonide and formoterol MMADs were smaller than those of fluticasone propionate and salmeterol and inhalation rates were slower through the Turbuhaler® then their Stokes number is smaller. Thus less formoterol and budesonide will be deposited in the sample chamber and indeed this was the case. Due to the amounts deposited on walls of the sample chamber the fine particle dose is under estimated but the difference is small (Burnell et al., 1998a). This under estimation will be greater for the Seretide® Diskus® than the Symbicort® Turbuhaler® because the Stokes number of the fluticasone propionate and salmeterol particles were larger. The deposition on the sample chamber explains the smaller fine particle dose of budesonide and formoterol we have determined by this Electronic Lung™ method compared to that we have previously reported from the Symbicort® Turbuhaler® using the Andersen Cascade Impactor (Tarsin et al., 2004).

The results demonstrate that there was a significant correlation between the PIFR measured electronically and the PIFR measured by the In-Check Meter™ for both devices. Overall the correlations were similar to those previously published (Broeders et al., 2003) and support the usefulness of the In-Check Meter™ in assessing the suitability of different marketed dry powder inhalers to various patient groups. Furthermore, the large intra-patient variability in peak inhalation flow rates suggests that if the inhaler used exhibits flow-dependent dose emission then their dose will be different every time they use that device. This inconsistency could be reflected in difficulties, during routine clinical practice, to optimise a dose that provides asthma control.

5. Conclusion

Data from this study clearly indicate a more consistent and reliable dose delivery from the Seretide® Diskus® than the Symbicort® Turbuhaler® to patients with severe asthma regardless of the inhalation profile used by these patients. The lower resistance of the Diskus® makes it easier for patients to generate a sufficient flow for adequate aerosolisation of the dose. The results suggest that the effects of using the Diskus® should be more predictable than those of the Turbuhaler® with each patient's emitted dose characteristics from the Diskus® being almost constant irrespective of the inhalation profile, whereas for the Turbuhaler®, the dose characteristics varied with the peak inspiratory flow rate.

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