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The Inhalation Characteristics of Patients When They Use Different Dry Powder Inhalers

Wahida Azouz, PhD,¹ Philip Chetcuti, MB, ChB, FRCP,² Harold S.R. Hosker, MB, ChB, FRCP,³
Dinesh Saralaya, MD, FRCP,⁴ John Stephenson, PhD,⁵ and Henry Chrystyn, PhD¹

Abstract

Background: The characteristics of each inhalation maneuver when patients use dry powder inhalers (DPIs) are important, because they control the quality of the emitted dose.

Methods: We have measured the inhalation profiles of asthmatic children [CHILD; $n=16$, mean forced expiratory volume in 1 sec (FEV₁) 79% predicted], asthmatic adults (ADULT; $n=53$, mean predicted FEV₁ 72%), and chronic obstructive pulmonary disease (COPD; $n=29$, mean predicted FEV₁ 42%) patients when they inhaled through an Aerolizer, Diskus, Turbuhaler, and Easyhaler using their “real-life” DPI inhalation technique. These are low-, medium-, medium/high-, and high-resistance DPIs, respectively. The inhalation flow against time was recorded to provide the peak inhalation flow (PIF; in L/min), the maximum pressure change (ΔP ; in kPa), acceleration rates (ACCEL; in kPa/sec), time to maximum inhalation, the length of each inhalation (in sec), and the inhalation volume (IV; in liters) of each inhalation maneuver.

Results: PIF, ΔP , and ACCEL values were consistent with the order of the inhaler’s resistance. For each device, the inhalation characteristics were in the order ADULT > COPD > CHILD for PIF, ΔP , and ACCEL ($p < 0.001$). The results showed a large variability in inhalation characteristics and demonstrate the advantages of ΔP and ACCEL rather than PIFs. Overall inhaled volumes were low, and only one patient achieved an IV > 4 L and $\Delta P > 4$ kPa.

Conclusion: The large variability of these inhalation characteristics and their range highlights that if inhalation profiles were used with compendial *in vitro* dose emission measurements, then the results would provide useful information about the dose patients inhale during routine use. The inhalation characteristics highlight that adults with asthma have greater inspiratory capacity than patients with COPD, whereas children with asthma have the lowest. The significance of the inhaled volume to empty doses from each device requires investigation.

Key words: inhaled therapy, dry powder inhalers, asthma, COPD, inhalation profiles

Introduction

EACH DRY POWDER INHALER (DPI) has its own unique dose preparation and inhalation procedure, and many patients have problems with this.⁽¹⁾ After a dose has been prepared for inhalation, the formulation has to be deaggregated and dispersed into the conducting airstream inside the device so that the emitted dose contains particles with the likelihood for deposition in the airway. During each inhalation, a turbulent energy is created inside the inhalation channel, of each DPI, by the interaction between the patient’s

inhalation maneuver and the resistance inside the inhalation channel of the DPI. This turbulent energy (which can be measured as a pressure change) breaks up (deaggregates) the formulation.⁽²⁾

To ensure adequate deaggregation, patients should use a forceful and deep inhalation that begins from the start of their inhalation.^(3–5) It has been shown that the peak inhalation flow (PIF) achieved by patients through each DPI is related to clinical efficacy,^(6–8) and some patients have problems achieving a fast inhalation rate.⁽⁹⁾ Asthmatic children⁽¹⁰⁾ and chronic obstructive pulmonary disease (COPD) patients⁽⁹⁾

¹Department of Pharmacy, School of Applied Sciences, University of Huddersfield, Huddersfield, HD1 3DH, United Kingdom.

²Paediatrics, Leeds General Infirmary, Leeds, LS1 3EX, United Kingdom.

³Respiratory Airedale Hospital, Steeton, Keighley, BD20 6TD, United Kingdom.

⁴Respiratory, Bradford Royal Infirmary, Bradford, BD9 6RJ, United Kingdom.

⁵School of Human and Health Sciences, University of Huddersfield, Huddersfield, HD1 3DH, United Kingdom.

especially during acute exacerbations^(11,12) are most likely to have problems achieving sufficient turbulent energy inside a DPI.

For each DPI, there is a minimum turbulent energy threshold for sufficient deaggregation to occur during an inhalation.⁽⁵⁾ Hence, more attention needs to be directed to the minimum acceptable PIF achieved through each DPI rather than to the optimal flow. Also, it has been suggested that the pressure changes that occur inside the inhalation channel of each DPI⁽¹³⁾ and the initial acceleration rate of the inhalation maneuver^(14,15) are more important than PIF in the generation of the fine particle dose. Similarly, inhaled volume is also considered an important parameter of the inhalation profile and can govern the quality of the emitted dose,⁽¹⁵⁾ particularly in a capsule formulation^(10,16) because of the need to empty the capsule.

Information on the characteristics of an inhalation maneuver when patients use different types of DPIs is limited. The main aim of this study was to identify the inhalation characteristics of different groups of patients (children with asthma, asthmatic adults, and COPD patients) when they inhaled through DPIs with a different resistance.

Materials and Methods

This was an open-label, single-visit study measuring inhalation profiles of patients when they inhaled through four different DPIs. Local research ethics approval (Yorkshire and Humber REC: 09/H/1302/64) was obtained for this study, and all participants gave signed informed consent. For children, the parent/carer also gave consent.

Patients

Children with asthma (CHILD; aged 5 to 17 years), adults with asthma (ADULT; aged 18 to 55 years), and those with COPD (over 55 years of age) attending an outpatient appointment and prescribed a DPI for their inhaled medication were eligible for inclusion. Those not eligible either had been using a DPI for less than 4 weeks, were pregnant females, or had an acute exacerbation or were prescribed a short course of oral prednisone in the past 4 weeks.

Measurement of inhalation characteristics

A Micro-Loop Spirometer (Cardinal Health, Swinden, UK) was modified so that adapters could be fitted onto the air inlet end of the spirometer. For each DPI, a specially designed adapter was used to ensure airtight seals between the adapter, the spirometer inlet, and the empty DPI. The mouthpiece adapters were the same as those used for *in vitro* dose emission measurements to insert an inhaler into the USP induction port. Inhalation flow profiles were measured by asking patients to make their normal (real-life) DPI inhalation. The DPIs used were the Aerolizer™ (AERO; Novartis, Basel, Switzerland), Diskus™ (DSK; GlaxoSmith-Kline, Brentford, UK), Easyhaler™ (EASY; Orion, Espoo, Finland), and the Turbuhaler™ (TBH; Symbicort® version, AstraZeneca, Södertälje, Sweden). Each device was the empty placebo version. For the Diskus, the placebo version containing the foil strips was used. As the blisters in this placebo device contain lactose, this was discharged before each inhalation profile measurement. Also, the Aerolizer

contained a pierced empty capsule for each inhalation, because the resistance is lower without it.

The data from each inhalation flow profile was transported into Microsoft Access (Microsoft Corporation, Redwood, WA) for data analysis. Flow rates were converted into pressure changes using the resistance of the DPI. The resistance of AERO, DSK, EASY, and TBH, measured according to the method described by Clark and Hollingworth,⁽²⁾ was 0.0207, 0.0249, 0.0424, and 0.0335 (kPa)^{0.5}(min L⁻¹), respectively.

The inhalation characteristics obtained from each inhalation profile were the PIF (in L min⁻¹), the time post start of the inhalation when PIF occurred (Tp; in seconds), the maximum pressure change that occurred inside the DPI (ΔP ; in kPa), the initial acceleration of the inhalation flow (ACCEL; in kPa sec⁻¹), the inhalation volume (IV; in liters), and the duration of the inhalation (Ti; in seconds).

Study design

Each patient's age, gender, height, and weight were recorded. Spirometry was measured using a ONEFLOW Spirometer (Clement Clark International, Harlow, UK), and the adults with asthma completed the Asthma Control Questionnaire (ACQ).⁽¹⁷⁾

The order of DPI used was randomized, and all patients were instructed to make the same inhalation maneuver that they made when using their DPI during routine use (no training was given). The patient was seated when making the measurements, because this was the most common position that they all used. Each patient made two separate inhalations through each device, and the profile with the fastest PIF was chosen for data analysis. Patients were given a 5-min rest between the two separate inhalations through each device.

Data analysis

All analyses were performed using SPSS (Version 20.0; IBM Corporation, Armonk, NY, USA). Demographic data of patients in the three patient groups and outcome measures obtained due to the use of all four devices were summarized descriptively. A series of repeated-measures analyses of variance (ANOVA) was carried out, considering each of the six outcome measures in turn. Patient group was included in all models as a between-subjects factor. Although some evidence of a significant effect of age on certain outcome measures was indicated, this variable was confounded with patient group (as groups comprising adults and groups comprising children were both included in the study), and hence was not included as a covariate. Further demographic variables did not indicate any relationship with the outcome measures and were also not included. The Greenhouse-Geisser correction factor was applied in cases of violation of sphericity assumptions. In the case of significant findings, *post hoc* tests were conducted to identify the source of any significant differences between patient groups or device types for any outcome measure. Sidak corrections for multiple comparisons were applied as appropriate.

Results

Sixteen children with asthma, 53 adults with asthma, and 29 patients with COPD completed all the inhalation

TABLE 1. PATIENT DETAILS

	CHILD	ADULT	COPD
Number (<i>n</i>)	16	53	29
Sex [M/F] (<i>n</i>)	13/3	11/42	15/14
Age in years	8.8 (3.08)	48.7 (16.03)	66.0 (9.6)
Height in cm	132.8 (20)	165.7 (9.67)	168.5 (10.2)
Weight in kg	34.8 (16.2)	75.5 (16.8)	78.0 (12.5)
FEV ₁ in liters	1.34 (0.67)	2.01 (0.62)	1.25 (0.8)
FEV ₁ % predicted	78.5 (19.5)	72.0 (17)	41.5 (16.1)
PEF in L/min	182.8 (84.7)	301 (115.0)	173.3 (89.7)
PEF % predicted	65.1 (21.57)	71.8 (24)	44.9 (18.5)
FVC in liters	1.58 (0.73)	2.5 (0.8)	2.02 (0.6)
Disease severity (<i>n</i>)			
Mild	8	17	12
Moderate	5	22	10
Severe	3	14	7
Very severe	N/A	N/A	0

All values are means (SD) unless indicated otherwise. FEV₁, forced expiratory volume; PEF, peak expiratory flow; FVC, forced vital capacity.

maneuvers through the four DPIs. A summary of the demographic data, lung function [presented as forced expiratory volume in 1 sec (FEV₁) % predicted], and disease severity classification (according to GINA⁽¹⁸⁾ and GOLD⁽¹⁹⁾ Guidelines) is presented in Table 1. The mean (SD) ACQ of the 53 adults with asthma was 1.95 (1.01) with only four indicating well-controlled asthma (ACQ <0.75), whereas 19 were classified as partly controlled

(0.75–1.5), and the remaining 30 poorly controlled (ACQ >1.5). All participants were using either a Diskus or a Turbuhaler. Twelve of the children with asthma, 23 of the adults, and 18 COPD patients were using a Diskus with the remainder a Turbuhaler. Twenty-seven of the COPD patients were also using a Handihaler.

The mean (SD) inhalation parameters of the inhalation maneuvers through each DPI are presented in Table 2, and the ranges of the PIFs, the pressure changes, and the inhaled volumes are presented in the box plots in Figures 1, 2, and 3, respectively. Table 2 shows that the acceleration rates of the inhalation maneuvers were generally slower for the Diskus, similar between the Aerolizer and Turbuhaler, and faster through the Easyhaler (mean rates of 8.8, 10.6, 10.7, and 13.2 kPa sec⁻¹), respectively. Classification of patients with respect to their PIF, the maximum pressure change, and their inhaled volumes is shown in Table 3, and the relationships between the inhaled volumes and the maximum pressure changes is shown in Figure 4.

p values associated with each outcome measure arising from repeated measures ANOVA mixed models, using patient group as a between-subject factor and device type as a within-subject factor, are summarized in Table 4. There were significant differences between the patient groups with respect to the PIF, ΔP, ACCEL, and Tp outcome measures, and significant differences between device types with respect to the PIF, ΔP, and IV outcome measures.

Post hoc testing analysis of specific patient group comparisons, incorporating a Sidak correction for multiple comparisons, indicated that with respect to the PIF and ΔP outcome variables, adult and child asthmatic patients were

TABLE 2. MEAN (SD) INHALATION PARAMETERS

	AERO	DSK	TBH	EASY
ALL PATIENTS				
PIF (L min ⁻¹)	86.5 (26.3)	68.3 (25.0)	54.9 (17.3)	53.6 (15.2)
ΔP (kPa)	3.50 (2.07)	3.28 (2.24)	3.76 (2.29)	5.66 (3.11)
Tp (sec)	0.38 (0.19)	0.44 (0.22)	0.42 (0.17)	0.45 (0.16)
ACCEL (kPa sec ⁻¹)	10.6 (8.8)	8.8 (8.2)	10.7 (10.8)	13.2 (10.1)
IV (L)	1.77 (0.81)	1.71 (0.82)	1.49 (0.78)	1.52 (0.79)
Ti (sec)	1.61 (0.39)	1.56 (0.47)	1.59 (0.35)	1.60 (0.48)
CHILD				
PIF (L min ⁻¹)	71.4 (21.5)	53.3 (24.2)	44.8 (16.0)	45.5 (13.2)
ΔP (kPa)	2.37 (1.33)	2.10 (1.70)	2.55 (1.79)	4.02 (2.21)
Tp (sec)	0.41 (0.13)	0.49 (0.19)	0.46 (0.20)	0.52 (0.18)
ACCEL (kPa sec ⁻¹)	7.2 (6.7)	5.4 (5.5)	6.7 (5.9)	8.9 (7.2)
IV (L)	1.22 (0.68)	1.19 (0.76)	1.00 (0.73)	1.00 (0.46)
Ti (sec)	1.69 (0.38)	1.50 (0.46)	1.52 (0.17)	1.62 (0.23)
ADULT				
PIF (L min ⁻¹)	93.7 (25.9)	76.3 (23.8)	60.2 (17.0)	58.3 (14.4)
ΔP (kPa)	4.05 (2.19)	3.96 (2.39)	4.44 (2.39)	6.67 (2.28)
Tp (sec)	0.34 (0.14)	0.42 (0.25)	0.39 (0.14)	0.43 (0.17)
ACCEL (kPa sec ⁻¹)	12.6 (9.8)	11.0 (8.8)	13.2 (13.0)	15.9 (11.5)
IV (L)	1.96 (0.77)	1.89 (0.74)	1.63 (0.74)	1.68 (0.81)
Ti (sec)	1.54 (0.34)	1.61 (0.56)	1.63 (0.45)	1.55 (0.47)
COPD				
PIF (L min ⁻¹)	81.8 (25.4)	62.0 (22.4)	50.9 (15.3)	49.6 (15.0)
ΔP (kPa)	3.13 (1.88)	2.68 (1.80)	3.19 (1.94)	4.8 (2.71)
Tp (sec)	0.43 (0.28)	0.44 (0.16)	0.44 (0.20)	0.46 (0.14)
ACCEL (kPa sec ⁻¹)	8.7 (6.8)	6.7 (7.3)	8.5 (6.7)	10.7 (6.9)
IV (L)	1.71 (0.83)	1.79 (0.87)	1.50 (0.80)	1.52 (0.80)
Ti (sec)	1.71 (0.46)	1.53 (0.24)	1.57 (0.20)	1.68 (0.60)

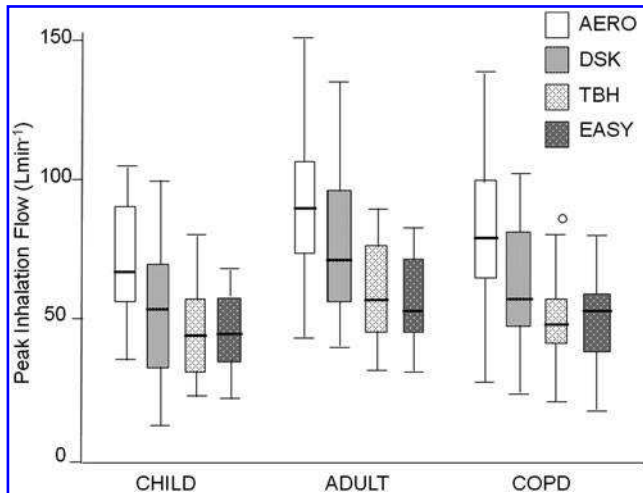


FIG. 1. Peak inhalation flow (PIF) distributions from the inhalation maneuvers through each DPI. The boxes represent the interquartile range with the median, and the whiskers represent the full range of the data (excluding the outliers, which are shown as open circles).

significantly different ($p < 0.001$ for PIF; $p = 0.003$ for ΔP), and the asthmatic children and the COPD patients were significantly different ($p = 0.024$ for PIF; $p = 0.020$ for ΔP); however, the adult asthmatic and COPD patients were not significantly different ($p = 0.469$ for PIF; $p = 0.629$ for ΔP). For the ACCEL outcome measure, analysis of specific patient group comparisons indicated a significant difference between adult and child asthmatic patients ($p = 0.010$), and between the adult asthmatic and COPD patients ($p = 0.023$), but a nonsignificant difference between the children with asthma and COPD patients ($p = 0.851$). For the T_p outcome

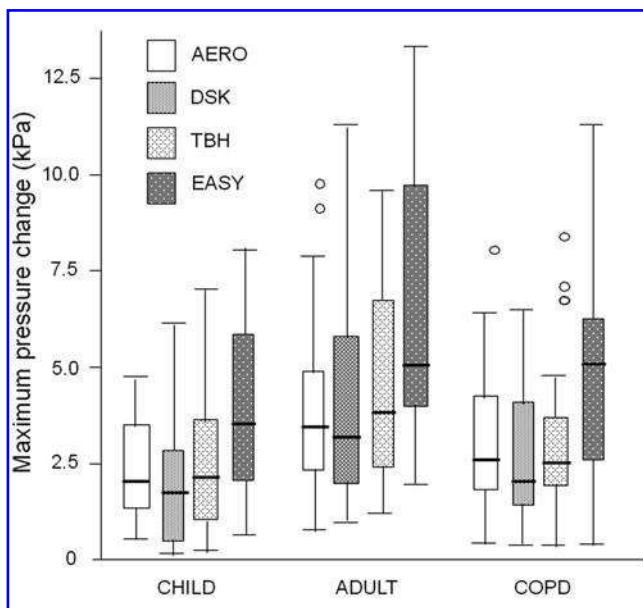


FIG. 2. Maximum pressure change distributions, during each inhalation maneuver through each DPI. The boxes represent the interquartile range with the median, and the whiskers represent the full range of the data (excluding the outliers, which are shown as open circles).

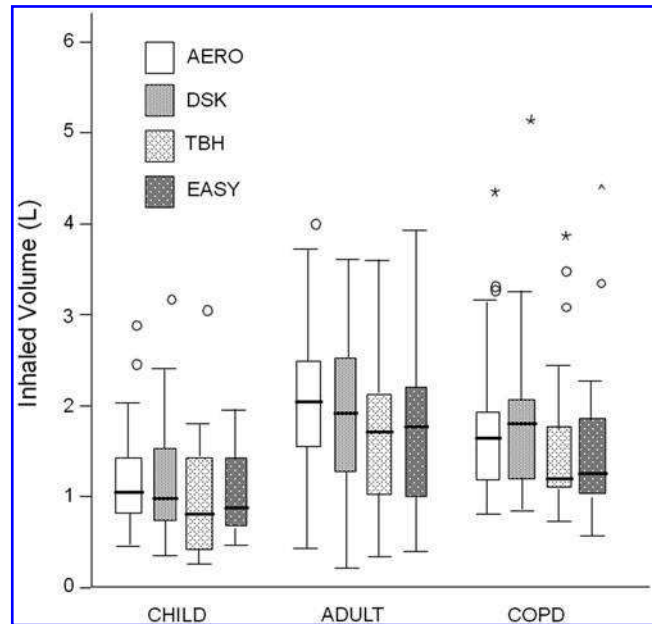


FIG. 3. The inhaled volume distributions of each inhalation maneuver through the DPIs. The boxes represent the interquartile range with the median, and the whiskers represent the full range of the data (excluding the outliers, which are shown as open circles).

measure, analysis of specific patient group comparisons indicated a significant difference between the adult and child asthmatic patients ($p = 0.028$), but nonsignificant differences between the adult asthmatics and the COPD patients ($p = 0.105$), and between the children with asthma and the COPD patients ($p = 0.780$).

Analysis of specific device type comparisons, incorporating a Sidak correction for multiple comparisons, indicated that for the PIF outcome variable, all devices were significantly different from each other ($p < 0.001$ in most cases), except Turbuhaler and Easyhaler ($p = 0.955$). For the ΔP outcome variable, the Easyhaler device was significantly different from all other devices ($p < 0.001$ in all cases). Additionally, the Turbuhaler device was significantly different from the Diskus device ($p = 0.006$). No other pairs of devices were significantly different from each other. For the IV outcome measure, all devices were significantly different from each other ($p < 0.001$ in most cases), except the Aerolizer and the Diskus ($p = 0.863$) and the Turbuhaler and the Easyhaler ($p = 0.633$).

Due to the high correlations observed between the PIF, ΔP , IV, and ACCEL variables, it was not considered appropriate to apply any further corrections to the p values for multiple comparisons.

Discussion

The results show that, as expected, adults with asthma generate the most favorable inhalation maneuver characteristics, and children with asthma the weakest, with COPD patients slightly better than the children. The inhalation characteristics between the DPIs were different, with the high-resistance DPIs providing the most favorable set of inhalation characteristics for formulation deaggregation and delivery of

TABLE 3. THE NUMBER OF PATIENTS ACHIEVING DIFFERENT INHALATION FLOWS THROUGH EACH DPI

	CHILD				ADULTS				COPD			
(a) Peak inhalation flow ($L \text{ min}^{-1}$)												
	<30	30–59	60–89	>90	<30	30–59	60–89	>90	<30	30–59	60–89	>90
AERO	Nil	4	8	4	0	3	21	29	1	4	13	11
DSK	3	6	6	1	0	17	17	19	3	14	5	7
TBH	2	11	3	0	0	29	23	1	2	21	6	Nil
EASY	1	11	4	0	0	31	22	Nil	2	22	5	Nil
(b) Maximum pressure change (kPa)												
	<1	1–1.99	2–3.99	>4	<1	1–1.99	2–3.99	>4	<1	1–1.99	2–3.99	>4
AERO	3	5	5	3	2	7	18	26	2	8	11	8
DSK	6	6	1	3	0	13	16	24	3	9	9	8
TBH	2	5	6	3	0	9	20	24	2	7	14	6
EASY	1	1	8	6	0	0	15	38	1	3	9	16
(c) Inhaled volume (L)												
	<1	1–1.99	2–3.99	>4	<1	1–1.99	2–3.99	>4	<1	1–1.99	2–3.99	>4
AERO	8	6	2	0	8	18	28	0	5	17	6	1
DSK	8	6	2	0	6	22	25	0	2	19	7	1
TBH	9	6	1	0	13	22	18	0	7	17	5	0
EASY	9	7	0	0	15	19	19	0	8	17	3	1

the emitted dose into the lungs. The results highlight that the importance of these inhalation maneuver characteristics, reflecting real-life use when using a DPI, needs to be investigated. The patients were not trained before the measurements, and so the inhalation profiles are not maximum values.

Each inhaler was empty because any lactose in the air-stream would have affected the measurements. This would not alter the inhalation profile with a Turbuhaler. To our knowledge, the presence of lactose does not affect a patient’s inhalation maneuver when using a DPI, and so any affect on the inhalation profile for the other three inhalers would be negligible. We measured inhalation profiles

without training so that real-life use data were obtained rather than the maximum values each patient could achieve. All participants were DPI users. Most COPD patients also used the Handihaler, and so they would be familiar with different levels of resistance between each type of DPI.

Traditionally, PIF has been the focus of attention when patients use DPIs. However, this is only useful when considering the flows through each DPI rather than comparing devices, because it is the generated turbulent energy, which is a product of the flow and the resistance, that deaggregates the formulation.^(3,13) When the PIF was faster, the turbulent flow generated in the inhalation channel of

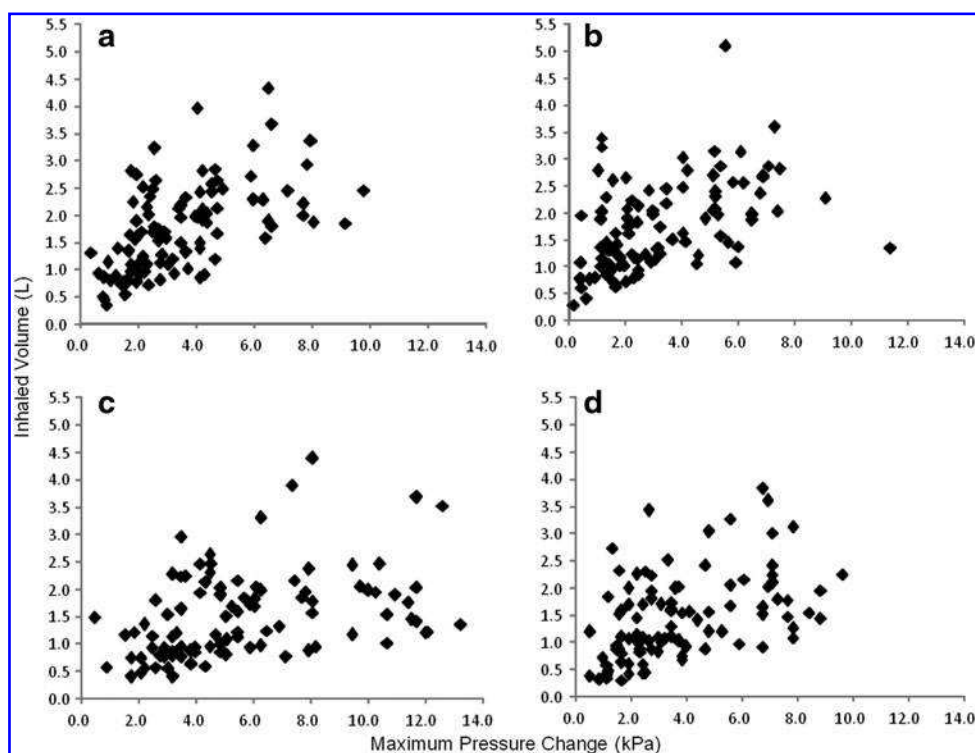


FIG. 4. The relationship between the inhaled volume and the maximum pressure change achieved by every patient when inhaling using each of the DPIs ($n=98$). (a) Aerolizer. (b) Diskus. (c) Easyhaler. (d) Turbuhaler.

TABLE 4. *P* VALUES FROM REPEATED MEASURES ANOVA MODELS: ALL OUTCOME MEASURES

Variable	<i>p</i> values from outcome measure					
	<i>PIF</i>	ΔP	<i>IV</i>	<i>ACCEL</i>	<i>T_p</i>	<i>T_i</i>
Patient group	0.001	0.001	0.094	0.001	0.013	0.871
Device type	<0.001	<0.001	0.036	0.138	0.083	0.739

each device was greater, thereby confirming why each DPI has flow-dependent dose emission.⁽²⁰⁾ For each DPI, there will be a minimum threshold turbulent energy (corresponding to a measured pressure change) for efficient deaggregation of the dose.⁽⁵⁾ It has been shown that, below 30 L min^{-1} , the turbulent energy generated inside a Turbuhaler is not sufficient to efficiently deaggregate the dose,⁽²¹⁾ and that the clinical effect sharply decreases.⁽⁷⁾ This flow is also considered to be the minimum for the Diskus,⁽²²⁾ whereas that for the Easyhaler is slightly lower,⁽²³⁾ but that for the Aerolizer is much faster.⁽⁸⁾

Overall, the inhalation flows with the Turbuhaler are higher than values previously reported in COPD,^(24,25) adults,⁽²⁶⁾ and children^(7,27) with asthma, but lower than others in COPD^(28–30) and asthma.^(29,31) The number of patients inhaling with an inhalation flow of $<30 \text{ L min}^{-1}$ through the Turbuhaler is similar to that in other studies.^(7,24,25,27) When using the Diskus, similar numbers of COPD patients^(25,29) and children with asthma⁽²²⁾ achieved inhalation flow compared with those in this study. This also applies to previous reports of inhalation flows through the Easyhaler by children with asthma⁽³²⁾ and COPD patients.⁽³³⁾

The Aerolizer has low resistance, and so the minimum flow for efficient deaggregation will be faster. It has been reported that this flow could be $>90 \text{ L min}^{-1}$.⁽⁸⁾ Table 3 shows that only 44 out of 98 participants achieved this minimum flow, which is a lower proportion than previously reported in adults and children with asthma.⁽³⁴⁾ This, together with the Diskus data (6 out of 98 inhaling $<30 \text{ L min}^{-1}$), suggests that less efficient deaggregation occurs with low-resistance DPIs. Also, when the flow is fast (due to the lower resistance), there will be a tendency for more oropharyngeal and central lung deposition. When using a DPI, this is counterbalanced by the flow-dependent dose emission from a DPI. However, dose emission from an Aerolizer⁽³⁵⁾ and a Diskus⁽²⁰⁾ is less flow-dependent than that from other DPIs. Hence, the low resistance of these devices, together with the resultant fast inhalation flows, will tend to provide low lung deposition and high oropharyngeal impaction. Reduced peripheral lung deposition has been reported when salbutamol was inhaled from a low-resistance DPI.⁽³⁶⁾ In contrast, it has been shown that, when using a Turbuhaler, which has pronounced flow-dependent dose emission,⁽²⁰⁾ there is no change in the peripheral:central lung deposition ratio when using faster flows.⁽³⁷⁾ Furthermore, it has been reported that high-resistance DPIs do provide greater lung deposition than those with a lower resistance,⁽³⁸⁾ which could be related to the greater pressure changes shown in Figure 2.

In contrast to *PIF* values, the pressure changes (hence the turbulent energy) that occur inside each DPI during an inhalation allow a comparison to be made between different devices.⁽¹³⁾ The results show that the pressure changes were

greater for the DPIs with a higher resistance than those with a lower resistance, which explains why *PIF* measurements should only be used to confirm that a patient can achieve the threshold minimum flow for efficient deaggregation. Figure 2 shows that when the resistance is low-to-medium high (Aerolizer, Diskus, and Turbuhaler), there is little difference between the inhalers, and that for high-resistance inhalers the pressure changes are much greater. This is due to the nonlinear relationship between this pressure change with flow and the resistance.⁽²⁾

The acceleration of the flow, like the pressure change, has been shown to be critical for deaggregation of the formulation in a DPI,^(14,15) because the dose is emitted in the first part of an inhalation. Overall, when the *PIF* was fast, then the acceleration rates were steeper than when the *PIF* was slow.⁽³⁹⁾ Previously, only the acceleration rates when asthmatics and COPD patients inhaled through a Diskus and a Turbuhaler have been reported.⁽²⁹⁾ Our results show that acceleration rates were lower in children than in COPD patients, whereas adults with asthma produced the steepest rates.

The inhaled volume has two functions. First, the dose has to be emptied from the device, and then the airstream delivers the particles into the airways. The inhaled volume has to be sufficient for both to occur. Some DPIs require a higher volume to empty the dose than others. It has been reported that capsule-based DPI inhalers require 4 L to completely empty their dose,^(10,16) the Turbuhaler at least 1 L,⁽¹⁵⁾ and the Diskus only 150 mL.⁽¹⁵⁾ These differences are due to the design of the devices. Capsules have to be emptied. The inhalation channel in the Turbuhaler is relatively long and includes a cyclone, whereas the inhalation channels of the Diskus and the Easyhaler are very short.⁽¹³⁾ Overall within the groups, the inhaled volumes were similar for the different devices, with a tendency for a slightly larger volume for DPIs with lower resistance. Table 3 shows that many subjects could be using an inhaled volume that is too small. Overall in COPD^(29,30) and asthma^(29,31) studies, the volumes reported were higher than those in this study, but one study using a Turbuhaler by adult asthmatics reported similar volumes.⁽²⁶⁾ This difference, like those of the other inhalation parameters, could be due to the amount of inhalation technique training that had previously been provided to each patient.

Overall, the inhalation profiles indicate that the inhalation volume could be more of a problem, and this has not previously been identified. Also, the pressure changes and the acceleration of the inhalation maneuver should be considered. These parameters should replace the traditional focus put on inhalation flow when using a DPI. The inhalation volume results indicate that during training there should be an emphasis that patients exhale before each inhalation maneuver. Participants with low inhalation flow, suggesting

that they need to use a more forceful inhalation through their DPI, were retrained before they left the study. The results in Table 3 highlight that it is the DPIs with low resistance where retraining is important. The results also suggest that the way forward could be to design DPIs with high resistance.

Compendial methods recommend that dose emission and the aerodynamic characteristics of the emitted dose should be measured using a ΔP of 4 kPa and an inhaled volume of 4 L.^(40,41) Figure 4 shows that only one patient achieved these values. Furthermore, no individual replicated an inhalation profile that was the same as a square wave produced by a vacuum pump. Overall, the time of the PIF was 0.4–0.5 sec, but some were up to 1.5 sec; hence, the shape of the profiles was more sinusoidal. This highlights the need to focus on using an inhalation that is as fast as possible from the start when training patients how to use a DPI.⁽⁵⁾ A preliminary study has shown that the *in vitro* compendial methods can be adapted, so that the square profile produced by a vacuum pump can be replaced by inhalation profiles like the real-life ones generated by the patients in this study.⁽⁴²⁾ We have developed this methodology, and so studies with these inhalation profiles are ongoing. Dose emission data using these profiles would provide the regulatory authorities and others with information about the quality of the dose patients would receive, and identify those that would have problems generating an adequate dose during their inhalation maneuver.

Conclusion

The results have provided an insight into the inhalation maneuvers when patients use DPIs. As expected, the inhalation characteristics of children with asthma were lower than those of adults and slightly less than those of COPD patients. The importance of these inhalation maneuver characteristics needs to be investigated with respect to the dose that would have been emitted, as well as the likelihood for lung deposition.

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WA generated all the data and contributed to the analysis. PC, HH, and DS were involved with study design and implementation, patient recruitment, and their management. JS analyzed all the data. HC was the Principal Investigator and wrote the manuscript. All authors have contributed to the writing of the manuscript and have read, provided comments, and approved the final version.

Author Disclosure Statement

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Reviewed by:
Anthony Hickey
Kurt Nikander
Martyn Biddiscombe

Address correspondence to:
Dr. Henry Chrystyn
Division of Pharmacy and Pharmaceutical Sciences
University of Huddersfield
Queensgate
Huddersfield
HD1 3DH
United Kingdom

E-mail: h.chrystyn@hud.ac.uk